Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV

Developed by the National Institutes of Health, the HIV Medicine Association, and the Infectious Diseases Society of America Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV—A Working Group of the NIH Office of AIDS Research Advisory Council (OARAC)

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It is emphasized that concepts relevant to HIV management evolve rapidly. The Panels have a mechanism to update recommendations on a regular basis, and the most recent information is available on the Clinicalinfo website (https://clinicalinfo.hiv.gov/).

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What's New in the Guidelines

The *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV* document is published in an electronic format and updated as relevant changes in prevention and treatment recommendations occur.

All changes are developed by the subject-matter groups listed in the document. (Changes in group composition also are posted promptly.) These changes are reviewed by the editors and relevant outside reviewers before the document is altered. Major revisions within the last 6 months are as follows:

July 14, 2025

Cytomegalovirus Disease

- Expanded the discussion on the diagnosis and treatment of non-ocular cytomegalovirus end-organ disease.
- Updated guidance on monitoring response to therapy and drug adverse effects.

Herpes Simplex Virus

- Provided more detailed information on diagnosing diseases associated with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2).
- Added recommendations on the management of HSV epithelial keratitis and stromal keratitis.
- Added treatment recommendations for central nervous system, visceral, and disseminated HSV-1 and HSV-2 disease.

Immunizations for Preventable Diseases in Adults and Adolescents With HIV

- Updated pneumococcal vaccine recommendations to include the use of 21-pneumococcal conjugate vaccine (PCV21).
- Updated mpox vaccine recommendations with new information on data supporting their use.
- Added a second pentavalent meningococcal conjugate vaccine (MenABCWY) recommendation and updated the dosing intervals for meningococcal group B vaccines.

Mpox

- Updated treatment recommendations to reflect new trial data suggesting limited benefit of tecovirimat monotherapy; clarified eligibility for use under an expanded-access investigational new drug protocol.

Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

- Expanded the discussion on rifamycin- and azole-related interactions, as well as therapeutic drug monitoring.

Talaromycosis (Formerly Penicilliosis)

- Updated and expanded the Diagnosis section, with a focus on non–culture-based diagnostics.
- Provided more detailed recommendations regarding the use of primary prophylaxis.

April 23, 2025

Cystoisosporiasis (Formerly Isosporiasis)

- Updated the epidemiology information, including adding new regions endemic for *Cystoisospora belli*.
- Updated the Diagnosis section, including new information on the use of polymerase chain reaction, or PCR, for diagnosing cystoisosporiasis.
- Provided more detailed recommendations regarding the use of primary prophylaxis.
- Updated preferred and alternative regimens for treatment and chronic maintenance therapy.

Human Herpesvirus-8 Disease

- Provided more detailed information on diagnosing diseases associated with human herpesvirus-8 (HHV-8).
- Updated recommended treatment regimens for Kaposi sarcoma (KS), multicentric Castleman's disease, primary effusion lymphoma, and HHV-8 diffuse large B-cell lymphoma.
- Added information on the treatment of KS inflammatory cytokine syndrome.

Table 6

- Updated to incorporate clinical discretion when adjusting doses of lamivudine and emtricitabine for renal insufficiency, now aligning with dosing recommendations found in the Adult and Adolescent Antiretroviral Guidelines from the U.S. Department of Health and Human Services.

Introduction

Updated: December 16, 2024
Reviewed: January 8, 2025

Opportunistic infections (OIs), which in the context of HIV have been defined as infections that are more frequent or more severe because of HIV-mediated immunosuppression,[1] were the first clinical manifestations that alerted clinicians to the occurrence of AIDS. *Pneumocystis* pneumonia (PCP), *Toxoplasma* encephalitis, cytomegalovirus retinitis, cryptococcal meningitis, tuberculosis, disseminated *Mycobacterium avium* complex (MAC) disease, and pneumococcal respiratory disease, as well as Kaposi sarcoma and central nervous system lymphoma cancers, have been hallmarks of AIDS. These OIs occurred, on average, 7 to 10 years after infection with HIV.[2,3] Until effective antiretroviral therapy (ART) was developed, patients generally survived only 1 to 2 years after the initial clinical manifestation of AIDS.[4]

Since the late 1980s, the use of chemoprophylaxis, immunization, and better strategies for managing OIs have improved the quality of life and lengthened the survival of people with HIV.[5] Profound reduction in OI-related morbidity and mortality in people with HIV resulted from the introduction of highly effective combination ART in the mid-1990s.[6-12]

Despite the availability and wide use of safe, effective, and simple ART regimens that have led to corresponding population-level declines in the incidence of OIs,[10,13,14] the Centers for Disease Control and Prevention (CDC) estimates that in 2022, 13% of people with HIV in the United States were unaware of their positive HIV status and 43% of Americans with HIV who were aware of their positive HIV status were not effectively virally suppressed (see Figure 14 and Table 5 in the CDC HIV Surveillance report).[15,16] As a result, OIs continue to cause preventable morbidity and mortality in the United States.

Achieving and maintaining durable viral suppression in all people with HIV and preventing or substantially reducing the incidence of HIV-related OIs remains challenging for three main reasons:

- *Not all HIV infections have been diagnosed, and once HIV is diagnosed, many people have already experienced substantial immunosuppression.* The CDC estimates that in 2022, among those with diagnosed HIV, approximately 21% had a CD4 T lymphocyte (CD4) cell count <200 cells/mm^3 (or <14%) at the time of diagnosis (see Figure 2 and Table 1a in the CDC HIV Surveillance report).[15]
- *Not all people with diagnosed HIV receive timely, continuous HIV care or are prescribed ART.* The CDC estimates that in 2022, 82% of people with newly diagnosed HIV had been linked to care within 1 month (see Figure 3 and Table 2a in the CDC HIV Surveillance report). However, only 47% of people with HIV were adequately engaged in continuous care (see Figure 14 in the CDC HIV Surveillance report).[15]
- *Not all people who are treated for HIV achieve durable viral suppression.* The CDC estimates that in 2022, only 65% of people were both engaged in care and had durable viral suppression within 6 months of HIV diagnosis (see Figure 11 in the CDC HIV Surveillance report).[15] Causes for the suboptimal response to treatment include challenges with adherence, unfavorable pharmacokinetics, or unexplained biologic factors.[17]

Thus, some people with HIV will continue to present with an OI as the sentinel event (leading to a diagnosis of HIV) or present with an OI as a complication of unsuccessful viral suppression.[15]

Durable viral suppression eliminates most but not all OIs. Tuberculosis, pneumococcal disease, and dermatomal zoster are examples of infectious diseases that occur at higher incidence in people with HIV regardless of CD4 count. The likelihood of each of these OIs occurring does vary inversely with the CD4 count, however.[18-24] Certain OIs—most notably tuberculosis and syphilis—can increase plasma viral load,[25-29] which both accelerates HIV progression and increases the risk of HIV transmission if patients are not virally suppressed by ART.

Therefore, clinicians continue to need to be knowledgeable about the prevention and management of HIV-related OIs.

History of These Guidelines

In 1989, the Guidelines for Prophylaxis Against *Pneumocystis carinii* Pneumonia for Persons Infected with the Human Immunodeficiency Virus became the first HIV-related treatment guideline published by the U.S. government.[30] This guideline was published in the *Morbidity and Mortality Weekly Report (MMWR)*, which was the most rapid mode of publication at the time. It was followed by a guideline on prevention of MAC disease in 1993.[31] In 1995, these guidelines were expanded to include the treatment of 18 HIV-related OIs. In 2004, information about the prevention of HIV-related OIs was incorporated into the guidelines. The National Institutes of Health (NIH), the HIV Medicine Association (HIVMA), and the Infectious Diseases Society of America (IDSA) jointly co-sponsor these guidelines,[1,32,33] which have been published in peer-reviewed journals and/or the *MMWR* in 1997, 1999, 2002, 2004, and 2009.[33-44] Since 2009, these OI guidelines have been managed as a living document on the web, with each chapter reviewed quarterly by the guidelines committee. Updates are published as often and as promptly as deemed appropriate by the guidelines committee.

In 2023, there were nearly 566,000 online page views and approximately 17,400 PDF downloads, which demonstrate that the Adult and Adolescent OI Guidelines continue to be a valuable resource to clinicians, other health care providers, people with HIV, and policymakers in the United States. Guidelines pertinent to other regions of the world, especially resource-limited countries, may differ with respect to the spectrum of relevant OIs and the diagnostic and therapeutic options that are available to clinicians.

All guideline recommendations related to prevention or treatment are rated based on rigorous criteria that include the quality of supporting evidence. These ratings allow readers to assess the relative importance of each recommendation.

These guidelines address the prevention and treatment of HIV-related OIs in adults and adolescents. Guidelines addressing the prevention and treatment of HIV-related OIs in pediatric populations can be found on the Clinicalinfo website.

Snapshot of Guidelines Development Process

These guidelines were prepared by the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) under the auspices of the Office of AIDS Research Advisory Council (OARAC), an authorized Federal Advisory Committee

to the U.S. Department of Health and Human Services established in 1994. Co-chairs who are selected and appointed by their respective agencies or organizations (i.e., NIH, IDSA, HIVMA) convene OI-specific working groups of clinicians and scientists with subject matter expertise in specific OIs.

The working groups review in real time the relevant literature published since the last review, with the help of quarterly literature searches for articles relevant to their section that are provided by guidelines support staff. The working groups propose revisions to their section as appropriate. The co-chairs, representatives from HIVMA and IDSA, and other Panel working groups with special expertise (e.g., pharmacology, pregnancy) review proposed revisions.

The co-chairs and working group leaders have quarterly teleconferences to discuss section updates. In addition, the co-chairs convene an annual meeting with members of the Panel to discuss guidelines content and strategic planning.

The names and affiliations of all contributors, as well as their financial disclosures, are provided in Appendix B: Panel Roster and Financial Disclosures.

Guidelines Development Process	
Topic	**Comment**
Goal of the guidelines	Provide guidance to HIV care practitioners and others on the optimal prevention and management of HIV-related opportunistic infections (OIs) for adults and adolescents in the United States.
Panel members	The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) is composed of co-chairs who represent the National Institutes of Health (NIH), the HIV Medicine Association (HIVMA), and the Infectious Diseases Society of America (IDSA), plus Panel members with expertise in HIV clinical care, infectious disease management, and research. Co-chairs are selected by their respective agencies or organizations. Each working group is led by a Panel member selected by the co-chairs. Panel members are selected from government, academia, and the health care community by the co-chairs and working group leaders based on the member's area of subject matter expertise. Members serve on the Panel for a 4-year term, with an option to be reappointed for additional terms. Prospective Panel members may self-nominate at any time. When specific or unique subject matter expertise is required, the co-chairs, together with working group leaders, may solicit advice from individuals with such specialized knowledge. The list of the current Panel members can be found in Appendix B: Panel Roster and Financial Disclosures.
Financial disclosure and management of conflicts of interest	All members of the Panel submit a written financial disclosure annually reporting any associations with manufacturers of drugs, vaccines, medical devices, or diagnostics used to manage HIV-related OIs. A list of these disclosures and their last update is available in Appendix B: Panel Roster and Financial Disclosures. The co-chairs review each reported association for potential conflicts of interest and determine the appropriate action: disqualification from the Panel, disqualification or recusal from topic review and discussion, or no disqualification needed. A conflict of interest is defined as any direct financial interest related to a product addressed in the section of the guideline to which a Panel member contributes content. Financial interests include direct receipt by the Panel member of payments, gratuities, consultancies, honoraria, employment, grants, support for travel or accommodation, or gifts from an entity having a commercial interest in that product. Financial interests also include direct compensation for membership on an advisory board, data safety monitoring board, or speakers' bureau. Compensation and support provided to a Panel member's university or institution (e.g., grants, research funding) is not considered a financial conflict of interest. The co-chairs strive to ensure that 50% or more of the members of each working group have no conflicts of interest.
Primary users of the guidelines	HIV treatment providers
Developer	Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV, a working group of the Office of AIDS Research Advisory Council (OARAC). See Appendix B: Panel Roster and Financial Disclosures.
Funding source	Office of AIDS Research (OAR), NIH
Evidence collection	The recommendations in the guidelines are based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or information prepared by the U.S. Food and Drug Administration or manufacturers (e.g., warnings to the public) may be used as evidence to revise the guidelines. Members of each working group are responsible for identifying relevant literature and conducting a systematic comprehensive review of literature that is provided to them on a quarterly basis.

Guidelines Development Process	
Topic	Comment
Method of synthesizing data and formulating recommendations	Each section of the guidelines is assigned to a working group of Panel members with expertise in the area of interest. The members of the working group synthesize the available data. Recommendations are reviewed and updated by each working group after an assessment of the quality and impact of the existing and any new data. Types of evidence that are considered include but are not necessarily limited to case series, prospective cohort trials, and randomized controlled trials, with consideration of the quality and appropriateness of the methods, and the number of participants and effect sizes observed. Finally, all proposed recommendations and supporting evidence are reviewed by the co-chairs before final approval and publication. OAR reviews all proposed recommendations and gives final approval.
Recommendation rating	Recommendations are rated according to the information in the table below, "Rating System for Prevention and Treatment Recommendations," and accompanied, as needed, by explanatory text that reviews the evidence and the working group's assessment. All proposed changes are discussed during teleconferences and by email and then assessed by the Panel's co-chairs and reviewed by OAR, HIVMA, and IDSA before being endorsed as official recommendations.
Other guidelines	These guidelines focus on prevention and treatment of HIV-related OIs for adults and adolescents. A separate guideline outlines similar recommendations for children who have HIV. These guidelines are also available on the Clinicalinfo website.
Update plan	Each working group leader and the co-chairs meet every 3 months by teleconference to review interim data that may warrant modification of the guidelines. Updates may be prompted by approvals of new drugs, vaccines, medical devices, or diagnostics; new information regarding indications or dosing; new safety or efficacy data; or other information that may affect prevention and treatment of HIV-related OIs.

How to Use the Information in These Guidelines

Recommendations in this report address—

- Preventing exposure to opportunistic pathogens;
- Preventing disease;
- Discontinuing primary prophylaxis after immune reconstitution;
- Treating disease;
- When to start ART in the setting of an acute OI;
- Monitoring for adverse effects (including immune reconstitution inflammatory syndrome);
- Managing treatment failure;
- Preventing disease recurrence (secondary prophylaxis or chronic maintenance therapy);
- Discontinuing secondary prophylaxis or chronic maintenance therapy after immune reconstitution; *and*
- Special considerations during pregnancy.

Recommendations are rated according to the criteria in the table below and accompanied, as needed, by explanatory text that reviews the evidence and the working group's assessment. In this system, the letters A, B, or C signify the strength of the recommendation for or against a preventive or therapeutic measure, and the Roman numerals I, II, or III indicate the quality of the evidence supporting the recommendation.

Rating System for Prevention and Treatment Recommendations	
Strength of Recommendation	**Quality of Evidence for the Recommendation**
A: Strong recommendation for the statement B: Moderate recommendation for the statement C: Weak recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, non-randomized trials or observational cohort studies with long-term clinical outcomes* III: Expert opinion*

* In cases where there are no data for the prevention or treatment of an opportunistic infection based on studies conducted in people with HIV but there are data derived from studies in people without HIV that could plausibly guide management of patients with HIV, the recommendation is rated II or III but is assigned A, B, or C depending on the strength of the recommendation.

This document also includes tables in each section pertinent to the prevention and treatment of the OI(s) in that section, as well as six summary tables at the end of the document (Tables 1–6).

References

1. Kaplan JE, Masur H, Holmes KK, et al. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: an overview. USPHS/IDSA Prevention of Opportunistic Infections Working Group. *Clin Infect Dis*. 1995;21 Suppl 1:S12-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8547500.

2. Bacchetti P, Moss AR. Incubation period of AIDS in San Francisco. *Nature*. 1989;338(6212):251-253. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2922052.

3. Alcabes P, Munoz A, Vlahov D, Friedland GH. Incubation period of human immunodeficiency virus. *Epidemiol Rev*. 1993;15(2):303-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8174659.

4. Bacchetti P, Osmond D, Chaisson RE, et al. Survival patterns of the first 500 patients with AIDS in San Francisco. *J Infect Dis*. 1988;157(5):1044-1047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3258900.

5. Detels R, Munoz A, McFarlane G, et al. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA*. 1998;280(17):1497-1503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9809730.

6. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet*. 1998;352(9142):1725-1730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9848347.

7. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. Adult/Adolescent Spectrum of Disease Group. *AIDS*. 1999;13(13):1687-1695. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10509570.

8. Miller V, Mocroft A, Reiss P, et al. Relations among CD4 lymphocyte count nadir, antiretroviral therapy, and HIV-1 disease progression: results from the EuroSIDA study. *Ann Intern Med*. 1999;130(7):570-577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10189326.

9. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362(9377):22-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12853195.

10. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000–2010. *J Infect Dis*. 2016;214(6):862-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27559122.

11. Gardner EM, McLees MP, Steiner JF, Del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis*. 2011;52(6):793-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21367734.

12. Ives NJ, Gazzard BG, Easterbrook PJ. The changing pattern of AIDS-defining illnesses with the introduction of highly active antiretroviral therapy (HAART) in a London clinic. *J Infect*. 2001;42(2):134-139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11531320.

13. Coelho L, Veloso VG, Grinsztejn B, Luz PM. Trends in overall opportunistic illnesses, *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis and *Mycobacterium avium* complex incidence rates over the 30 years of the HIV epidemic: a systematic review. *Braz J Infect Dis*. 2014;18(2):196-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24275372.

14. Rubaihayo J, Tumwesigye NM, Konde-Lule J. Trends in prevalence of selected opportunistic infections associated with HIV/AIDS in Uganda. *BMC Infect Dis*. 2015;15:187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25879621.

15. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 territories and freely associated states, 2022. *HIV Surveillance Supplemental Report*. 2024;29(2). Available at: https://www.cdc.gov/hiv-data/nhss/national-hiv-prevention-and-care-outcomes.html.

16. Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2018–2022. *HIV Surveillance Supplemental Report*. 2024;29(1). Available at: https://www.cdc.gov/hiv-data/nhss/estimated-hiv-incidence-and-prevalence.html.

17. Kelly C, Gaskell KM, Richardson M, Klein N, Garner P, MacPherson P. Discordant immune response with antiretroviral therapy in HIV-1: a systematic review of clinical outcomes. *PLoS One*. 2016;11(6):e0156099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27284683.

18. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis*. 2005;191(2):150-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15609223.

19. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. 2000;23(1):75-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10708059.

20. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997;155(1):72-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9001292.

21. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. 1995;333(13):845-851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7651475.

22. Engels EA, Rosenberg PS, Biggar RJ. Zoster incidence in human immunodeficiency virus-infected hemophiliacs and homosexual men, 1984–1997. District of Columbia Gay Cohort Study. Multicenter Hemophilia Cohort Study. *J Infect Dis*. 1999;180(6):1784-1789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10558932.

23. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. *J Acquir Immune Defic Syndr*. 2005;40(2):169-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16186734.

24. Vanhems P, Voisin L, Gayet-Ageron A, et al. The incidence of herpes zoster is less likely than other opportunistic infections to be reduced by highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2005;38(1):111-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15608535.

25. Toossi Z, Mayanja-Kizza H, Hirsch CS, et al. Impact of tuberculosis (TB) on HIV-1 activity in dually infected patients. *Clin Exp Immunol*. 2001;123(2):233-238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11207653.

26. Sadiq ST, McSorley J, Copas AJ, et al. The effects of early syphilis on CD4 counts and HIV-1 RNA viral loads in blood and semen. *Sex Transm Infect*. 2005;81(5):380-385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16199736.

27. Bentwich Z. Concurrent infections that rise the HIV viral load. *J HIV Ther*. 2003;8(3):72-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12951545.

28. Kublin JG, Patnaik P, Jere CS, et al. Effect of *Plasmodium falciparum* malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. *Lancet*. 2005;365(9455):233-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15652606.

29. Abu-Raddad LJ, Patnaik P, Kublin JG. Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa. *Science*. 2006;314(5805):1603-1606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17158329.

30. Centers for Disease Control and Prevention. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. *MMWR Suppl*. 1989;38(5):1-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2524643.

31. Masur H. Recommendations on prophylaxis and therapy for disseminated *Mycobacterium avium* complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for *Mycobacterium avium* Complex. *N Engl J Med*. 1993;329(12):898-904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8395019.

32. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *MMWR Recomm Rep*. 1995;44(RR-8):1-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7565547.

33. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: disease-specific recommendations. USPHS/IDSA Prevention of Opportunistic Infections Working Group. *Clin Infect Dis*. 1995;21 Suppl 1:S32-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8547510.

34. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with HIV: part I. prevention of exposure. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. *Am Fam Physician*. 1997;56(3):823-834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9301575.

35. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Recomm Rep*. 1999;48(RR-10):1-59, 61-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10499670.

36. Kaplan JE, Masur H, Holmes KK, U.S. Public Health Service, Infectious Disease Society of America. Guidelines for preventing opportunistic infections among HIV-infected persons—2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2002;51(RR-8):1-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12081007.

37. Kaplan JE, Masur H, Jaffe HW, Holmes KK. Preventing opportunistic infections in persons infected with HIV: 1997 guidelines. *JAMA*. 1997;278(4):337-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9228443.

38. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 2000;30 Suppl 1:S29-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10770913.

39. USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: a summary. *Ann Intern Med*. 1996;124(3):349-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8554235.

40. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Ann Intern Med*. 1997;127(10):922-946. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9382373.

41. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with HIV: part I. prevention of exposure. *Am Fam Physician*. 2000;61(1):163-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10643957.

42. Benson CA, Kaplan JE, Masur H, et al. Treating opportunistic infections among HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. *MMWR Recomm Rep*. 2004;53(RR-15):1-112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15841069.

43. Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep*. 2009;58(RR-4):1-207; quiz CE201-204. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19357635.

44. Mofenson LM, Brady MT, Danner SP, et al. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-exposed and HIV-infected children: recommendations from CDC, the National Institutes of Health, the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR Recomm Rep*. 2009;58(RR-11):1-166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19730409.

Bacterial Enteric Infections

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Epidemiology

HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase the risk of enteric bacterial infections. Rates of Gram-negative bacterial enteric infections are at least 10 times higher among adults with HIV than in the general population, but these rates are lower among people with HIV who are treated with antiretroviral therapy (ART).[1] The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) cell count and is greatest in individuals with clinical AIDS or CD4 counts <200 cells/mm^3.

The bacteria most frequently isolated by culture from adults with HIV in the United States are *Shigella*, *Campylobacter*, and nontyphoidal *Salmonella* spp. (particularly *Salmonella enterica* serotypes Typhimurium and Enteritidis).[1-6] Diarrheagenic *Escherichia coli*, particularly enteroaggregative *E. coli*, may contribute to the burden of diarrheal disease,[7] but their role is understood poorly because reporting to public health systems is not required. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in people with HIV.[8]

Clostridioides difficile–associated infection (CDI) is common in people with HIV[9]; in addition to traditional risk factors, such as exposure to a health care facility or to antibiotics, data[10] suggest that low CD4 count (<50 cells/mm^3) is an independent risk factor. Incidence of community-onset CDI is increasing, and clinicians also should consider CDI in the evaluation of outpatient diarrheal illnesses in people with HIV.

Other enteric infections that may cause diarrhea—such as *Mycobacterium avium* complex (MAC), cytomegalovirus, and various protozoa—are discussed elsewhere in these guidelines.

As with bacterial enteric infections in people without HIV, the probable source for most bacterial enteric infections in people with HIV is ingestion of contaminated food or water.[11] Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with *Shigella*[12] and *Campylobacter*.[3,13-16]

Clinical Manifestations

Three major clinical syndromes of infection are associated with Gram-negative enteric bacteria among people with HIV:

- Self-limited gastroenteritis;
- Severe and prolonged diarrheal disease, potentially associated with fever, bloody diarrhea, and weight loss; *and*
- Bacteremia associated with extra-intestinal involvement, with or without concurrent or preceding gastrointestinal (GI) illness.[6,17,18]

Severe community-associated diarrhea often is defined as six or more loose stools (loose stool is defined as defecated material that takes the shape of a container) per day with or without other signs of systemic illness, such as fecal blood, orthostatic hypotension, or fever. In people with HIV, the risk of more profound illness increases with the degree of immunosuppression but risk diminishes

with ART therapy.[1,4,5,11,18,19] Relapses in infection with *Salmonella* and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in people with HIV.[11,20,21] As in other populations, CDI can cause a variety of syndromes, from watery diarrhea to toxic megacolon.[10]

Although enteric pathogens can be associated with clinical proctitis (e.g., pain with defecation, tenesmus, bloody discharge),[22] other infections that may be transmitted during intimate contact (e.g., *Chlamydia trachomatis* including lymphogranuloma venereum, *Neisseria gonorrhoeae,* herpes simplex virus, *Treponema pallidum,* and mpox) more commonly cause this syndrome, especially in those with relevant exposures (e.g., condomless receptive anal intercourse).[23] Proctocolitis with diarrhea caused by STIs is less common but may occur; relevant exposures should be queried.[24]

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (i.e., ingestion of contaminated food or water, including through recreational exposure to water, sexual history or other fecal-oral exposures, animal/pet exposures, travel-related exposures, exposure to antibiotics or chemotherapies, use of acid-suppressing medications, recent hospitalization); a medication review, because diarrhea is a common side effect of some ART and antibiotics; quantification of the diarrheal illness by stool frequency, consistency, volume, duration, and presence of blood; and associated signs and symptoms, such as presence and duration of fever. Physical examination should include measurement of temperature and assessment of intravascular volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood or stool molecular methods (i.e., culture-independent diagnostic tests [CIDTs]), ideally before antibiotics are given. Although stool molecular methods rapidly diagnose enteric infections, stool cultures are required to obtain phenotypic antibiotic sensitivity testing for isolated enteric pathogens and may also be helpful during outbreak investigations to identify the source. Thus, the Centers for Disease Control and Prevention (CDC) recommends reflex stool cultures and antibiotic sensitivity testing for specimens with positive CIDT reports given increasing resistance detected in enteric bacterial infections.[25] Because incidence of bacteremia associated with *Salmonella* gastroenteritis is high in people with HIV—particularly those with advanced disease—blood cultures should be obtained from any patient who has diarrhea and fever. For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.[18]

Other infections for which people with HIV are at risk, albeit at a lower rate, are non-*jejuni,* non-*coli Campylobacter* spp.—such as *C. fetus, C. upsaliensis,* and *C. lari*—and the enterohepatic *Helicobacter* spp. (*H. cineadi* and *H. fennelliae),* which were described originally as *Campylobacter* spp. Blood culture systems typically will grow these bacteria, but they are unlikely to be identified on routine stool cultures performed by most laboratories because growing these fastidious organisms requires special stool culture conditions.

The diagnosis of CDI can be made only through careful selection of the correct population for testing and a correlation of clinical and laboratory findings. Populations at risk for *C. difficile* diarrhea include individuals who recently received or currently are receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy; those who have been hospitalized in the past 4 to 6 weeks (or currently are hospitalized); those who reside in a long-term care facility; those with CD4 counts <200 cells/mm^3; those taking acid-suppressive medications; and those with moderate-to-severe community-acquired diarrhea.[26] Only people with diarrhea (defined as three or more loose stools in 24 hours) should be tested for CDI to limit detection of asymptomatic colonization, and only stool samples that take the shape of the container (i.e., diarrheal) should be tested.[27] Detection of

either the *C. difficile* toxin B gene (using nucleic acid amplification testing [NAAT]) or the *C. difficile* toxin B protein (using an enzyme immunoassay [EIA]) is required for diagnosis. Current EIAs suffer from low sensitivity, whereas polymerase chain reaction (or PCR) assays have high sensitivity and can detect asymptomatic carriers. Glutamate dehydrogenase (GDH) antigen enzyme immunoassays, which detect an antigen common to *C. difficile* strains, whether or not toxigenic, must be combined with a second confirmatory test for stool *C. difficile* toxin B.[28,29] Based on the criteria above (i.e., person meets the definition of diarrhea and the stool sample is diarrhea, taking the shape of the container), Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (or SHEA) guidelines for CDI support using an NAAT alone or a multiple-step algorithm (e.g., GDH plus toxin B assay) versus an EIA alone for *C. difficile* testing.[29]

Endoscopy generally should be reserved for patients in whom stool culture, microscopy, *C. difficile* toxin B assay, and blood culture fail to reveal an etiology or in whom treatment for an established diagnosis fails. Endoscopy with biopsy may be required for diagnosing etiologies other than bacterial enteric infections—including cryptosporidiosis, microsporidiosis, cytomegalovirus, or MAC gastroenteritis—and noninfectious causes of GI symptoms.

Clinicians should remain alert to the possibility of sexually transmitted infections (STIs). In patients with relevant exposures and symptoms of proctitis or proctocolitis, diagnostic evaluation and treatment for STIs should are recommended.[30]

Preventing Exposure

Multiple epidemiologic exposures can place people at risk for enteric illnesses. The most common are ingestion of contaminated food or water and fecal-oral exposures. Providing advice and education about such exposures is the responsibility of the health care provider. The clinical condition and CD4 count of a person with HIV can help the provider determine what prevention recommendations are most appropriate. People with HIV with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness[31] are at the greatest risk of enteric illnesses; however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Individuals in the community should be advised to wash their hands regularly with soap and water or alcohol-based cleansers to reduce the risk of enteric infection **(AIII).** To prevent enteric infections, soap and water are preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are active only partially against norovirus and *Cryptosporidium* **(AIII).** People with HIV should be advised to wash their hands with soap and water after potential contact with human feces (e.g., through defecation, sexual exposures, cleaning feces from infants, contact with a person who has diarrhea), after handling pets or other animals, after gardening or other contact with soil, and before preparing food and eating **(AIII).** In addition to handwashing, use of barriers (e.g., condoms, dental dams, and gloves) can reduce exposure to feces when engaging in sex practices such as anal sex and oral-anal contact **(AIII).**[22,30,32] Avoiding sex while any partner has diarrhea may further reduce risk of transmission. Travelers to relevant locations may be counseled on food and water hygiene (see the CDC Travelers' Health webpage).[33]

Preventing Disease

Recommendations for Preventing Bacterial Enteric Infections
Preventing Bacterial Enteric Illness
• Immunizations (e.g., against *Salmonella serotype* Typhi) should be recommended in advance of travel to relevant locations (see Immunizations for Preventable Diseases in Adults and Adolescents With HIV in the Adult and Adolescent Opportunistic Infection Guidelines) (AIII).
• Antimicrobial prophylaxis to prevent bacterial enteric illness is not routinely recommended, including for travelers (AIII).
• In rare cases—such as for immunosuppressed travelers (depending on their level of immunosuppression, the region of travel, and the trip's duration)—antimicrobial prophylaxis with rifaximin or azithromycin should be offered (CIII).
• Because of toxicity associated with fluoroquinolone use (e.g., CDI, tendinitis) and increasing rates of antimicrobial resistance among enteric bacterial pathogens outside of the United States, routine use of fluoroquinolones for prophylaxis is discouraged (AIII).
• During pregnancy, azithromycin is the preferred agent for prophylaxis (BIII).

Key: CDI = *Clostridioides difficile*–associated infection

Antimicrobial prophylaxis to prevent bacterial enteric illness **is not routinely recommended,** including for travelers **(AIII).** Prophylactic antimicrobial treatment can elicit adverse reactions, promote the emergence of resistant organisms, and increase the risk of CDI. In rare cases, however, antimicrobial prophylaxis (e.g., with rifaximin or azithromycin) should be considered—such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration **(CIII).**[34,35] In addition, immunizations, (e.g., against *Salmonella* serotype Typhi), should be recommended in advance of travel to relevant locations (see Immunizations for Travel in the Immunizations section of the Adult and Adolescent Opportunistic Infection Guidelines) **(AIII).**

For people with HIV already taking trimethoprim-sulfamethoxazole (TMP-SMX) (e.g., for *Pneumocystis jirovecii* pneumonia prophylaxis), TMP-SMX may offer limited protection against traveler's diarrhea.[36] During pregnancy, azithromycin would be the preferred agent for prophylaxis **(BIII).** Clinicians should be aware of concerns about fluoroquinolone safety. Given increased recognition of fluoroquinolone toxicities, as well as increasing rates of antimicrobial resistance among enteric bacterial pathogens outside the United States, routine use of fluoroquinolones for prophylaxis is discouraged **(AIII).**[37]

Treating Disease

Recommendations for Treating Bacterial Enteric Infections
General Considerations When Managing Patients With Bacterial Enteric Infections
• Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhea (AIII).
• Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists (BIII).
• Diagnostic fecal specimens should be obtained before initiation of empiric antimicrobial therapy.
• If a pathogen is identified in stool, antibiotic susceptibilities should be performed to confirm and inform antibiotic choice given increased reports of antibiotic resistance. Reflexively culturing the stool of patients diagnosed using PCR-based methods can facilitate antibiotic susceptibility testing among these patients.

- Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in people with CD4 counts <200 cells/mm^3. Risk of bacteremia also increases with decreasing CD4 count. If no clinical response occurs after 3 to 4 days of therapy, consider follow-up stool culture with antibiotic susceptibility testing and other methods to detect enteric pathogens (e.g., toxin assays, molecular methods), alternative diagnosis, antibiotic resistance, or drug–drug interactions (BIII).
- Effective ART may reduce the frequency, severity, and recurrence of bacterial enteric infections.

Empiric Treatment of Bacterial Enteric Infections (Pending Diagnostic Studies and Antimicrobial Resistance Testing)

For People With HIV and CD4 >500 cells/mm^3, With 1–2 Days of Loose Stools Without Fever or Blood

- Oral hydration; no further work-up and no treatment is needed.

For People With HIV and CD4 Count 200–500 cells/mm^3, With Diarrhea Severe Enough to Compromise Quality of Life or Ability to Work

- Azithromycin 500 mg PO daily for 5 days (BIII), *or*
- Ciprofloxacin 500–750 mg PO every 12 hours for 5 days (BIII)

For People With HIV and Severe Disease (e.g., people with CD4 count <200 cells/mm^3 or concomitant AIDS-defining illnesses), With Clinically Severe Diarrhea (**≥6 liquid stools/day or bloody stool and/or accompanying fever or chills)**

- Hospitalization for inpatient diagnostic evaluation and IV antibiotics
- Ceftriaxone 1–2 g IV every 24 hours (BIII)[a] until antimicrobial susceptibility is available, then treatment can be changed based on sensitivity results.
  - If *Campylobacter* or *Shigella* bacteremia is suspected, a carbapenem is preferred for empiric therapy (BIII).

Duration of Therapy

- Therapy and its duration should be adjusted depending on stool microbiology results and antibiotic sensitivity testing. See recommendations for specific bacteria below. If no pathogen is identified and the patient recovers quickly, 5 days of therapy is recommended.

Other Considerations

- MSM may be at increased risk for antibiotic-resistant enteric infections.
- Diarrhea is a common illness of international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is common. Clinicians should consider the possibility of resistant infections when prescribing empiric antibiotic therapy for travelers with HIV while traveling or upon return to the United States, particularly among travelers to South and Southeast Asia or Africa.
- For patients with persistent diarrhea (>14 days) but no other severe clinical signs (e.g., dehydration, blood in stool), antibiotic therapy can be withheld until a diagnosis is confirmed. Noninfectious etiologies of persistent diarrhea (e.g., inflammatory bowel disease) also can be considered in the differential diagnosis (BIII).
- Azithromycin should not be used to treat bacteremia.
- Before susceptibilities are known, empiric IV ceftriaxone is recommended, although given the rise of antimicrobial resistance in enteric pathogens, updated outbreak information, local susceptibility patterns, and travel history should always be considered.

Treating Nontyphoidal Salmonellosis

All people with HIV and salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia (by 20- to 100-fold) and mortality (by as much as sevenfold) compared with people without HIV (AIII).

For Invasive Disease (Suspected or Confirmed) Pending Susceptibilities

- Ceftriaxone 1–2 g IV every 24 hours pending susceptibilities (BIII)

Preferred Therapy for Nontyphoidal Salmonella Gastroenteritis With or Without Bacteremia (If Susceptible)

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (AIII)

Alternative Therapy (If Susceptible)

- Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), *or*
- Moxifloxacin 400mg (PO or IV) every 24 hours (BIII), *or*
- Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) every 12 hours (BIII), *or*
- Ceftriaxone 1–2 g IV every 24 hours (BIII)

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count ≥200 cells/mm^3: 7–14 days (BIII)
- If CD4 count <200 cells/mm^3, minimum of 2 weeks (may extend to up to 6 weeks if with severe disease or bacteremia) (BIII)

Duration of Therapy for Gastroenteritis With Bacteremia

- If CD4 count ≥200 cells/mm^3: 14 days; longer duration if bacteremia persists or if the infection is complicated (e.g., metastatic foci of infection are present) (BIII)
- If CD4 count <200 cells/mm^3: 2–6 weeks (BIII)

Secondary Prophylaxis

- The role of long-term, secondary prophylaxis for patients with recurrent bacteremia or gastroenteritis is not well established. Clinicians must weigh the benefit against the risks of long-term antibiotic exposure (BIII). Antibiotic choices for secondary prophylaxis are the same as for primary treatment and are dependent on the sensitivity of the *Salmonella* isolate.
- HIV suppression with ART is expected to decrease the risk of recurrent illnesses.
- Clinicians should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Indication

- Patients with recurrent bacteremia (BIII), *or*
- Patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 and severe diarrhea (BIII)

Discontinuing Secondary Prophylaxis

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm^3, secondary prophylaxis likely can be discontinued (CII).

Treating Shigellosis

Therapy should be considered because it may slightly shorten the duration of illness and help prevent spread of the infection to others (AIII); however, antibiotic selection should be guided by the results of antibiotic susceptibility testing. Because antimicrobial resistance of *Shigella* spp. is increasing and limited data demonstrate that antibiotic therapy limits transmission, antibiotic treatment may be withheld in people with HIV and CD4 >500 cells/mm^3 whose diarrhea resolves before culture confirmation of *Shigella* infection (CIII).

In Severely Ill Patients R**equiring** Empiric Parenteral Therapy While Awaiting Susceptibility

- Initiate a carbapenem until antimicrobial susceptibilities are available (BIII).

Preferred Therapy (If Susceptible)

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours if MIC <0.12 μg/mL for 5 to 10 days (AIII)

Alternative Therapy (If Susceptible)

- Levofloxacin 750 mg (PO or IV) every 24 hours if MIC <0.12 ug/mL for 5 to 10 days (BIII), *or*
- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV every 12 hours for 5 to 7 days (BIII), *or*
  - Note: TMP-SMX is not recommended for bacteremia.
- Azithromycin 500 mg PO daily for 5 days (BIII)
  - Note: Azithromycin is not recommended for bacteremia (AIII)
- Ceftriaxone 1–2 g IV every 24 hours (BIII)

Duration of Therapy

- Gastroenteritis: 5–7 days (AIII) (except ciprofloxacin [5 to 10 days] and azithromycin [5 days])
  - 7–10 days of therapy may be reasonable in patients who are severely immunosuppressed with poor clinical response to antibiotics.
- Bacteremia: ≥14 days (BIII)
- Recurrent infections: up to 6 weeks (BIII)

Chronic Maintenance or Suppressive Therapy

- Not recommended for first-time *Shigella* infections (BIII)

Treating Campylobacteriosis

- Optimal treatment is poorly defined and multidrug resistance may occur.
- Antimicrobial therapy should be modified based on susceptibility reports.

Mild Disease If CD4 Count >200 cells/mm^3

- If diarrhea resolves before culture confirmation of *Campylobacter* infection, antibiotic treatment can be withheld (CIII). If symptoms persist for more than several days, consider antibiotic therapy (CIII).

Mild-to-Moderate Disease

- *Preferred Therapy (If Susceptible)*
  - Azithromycin 500 mg PO daily for 5 days (BIII) (not recommended for bacteremia [AIII]), *or*
  - Ciprofloxacin[b] 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days (BIII) (if susceptible)
- *Alternative Therapy (If Susceptible)*
  - Levofloxacin[c] 750 mg PO or IV every 24 hours (BIII), *or*

Bacteremia

- Ciprofloxacin[b] 500–750 mg PO (or 400 mg IV) every 12 hours for ≥14 days (BIII) (if susceptible) plus an aminoglycoside (BIII) to limit the emergence of antibiotic resistance

Duration of Therapy

- Gastroenteritis: 7–10 days (except azithromycin, which is 5 days) (BIII)
- Bacteremia: ≥14 days (BIII)
- Recurrent disease: 2–6 weeks (BIII)

Chronic Maintenance or Suppressive Therapy

- Not recommended for first-time *Campylobacter* infections (BIII)

[b] The rate of fluoroquinolone resistance in the United States is increasing (29% resistance in 2018 among *C. jejuni* isolates). Third generation cephalosporins are not reliably active and use of alternative cell-wall active agents such as carbapenems may be necessary in severely ill people requiring empiric parenteral therapy until antimicrobial susceptibilities return.

Treating *Clostridioides difficile*–Associated Infection

Preferred Therapy (Severe or Nonsevere CDI[c])

- Fidaxomicin 200 mg PO two times per day for 10 days (AI)

Alternative Therapy

- Vancomycin 125 mg PO four times per day for 10 days (AI)
- For severe, life-threatening CDI, see *C. difficile* and references for additional information.

Alternative Therapy for Nonsevere CDI[c]

- If neither fidaxomicin nor vancomycin is available: metronidazole 500 mg PO three times per day for 10 days (CI).

Note: Based on clinical trials, vancomycin is superior to metronidazole for therapy of CDI (discussed in text).

Recurrent CDI

- Use of fidaxomicin over oral vancomycin is recommended, in agreement with the 2021 IDSA CDI Guidelines, as it has a greater likelihood for a sustained clinical response at 30 days (AI).
- Vancomycin is an acceptable option (see IDSA Guideline for tapered and pulsed regimens) (AI).
- FMT may be considered after three CDI episodes (i.e., an initial and two recurrent episodes) (CIII).

[c] Severe CDI: white blood cell count ≥15,000 cells/mL or serum creatinine concentrations >1.5 mg/dL; nonsevere CDI: white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL

Treating Bacterial Enteric Infections During Pregnancy

- Based on their safety profile, expanded-spectrum cephalosporins (such as ceftriaxone and cefotaxime) or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing (BIII).
- Other commonly prescribed antimicrobials during pregnancy include vancomycin and metronidazole. Fidaxomicin, quinolones, and TMP-SMX should be prescribed using shared decision-making.
- Quinolones can be used for bacterial enteric infections during pregnancy if indicated by susceptibility testing or failure of first-line therapy (BIII).
- TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects (BIII). As soon as possible during the first trimester of pregnancy, or when anticipating or attempting conception, any administration of TMP-SMX should be supplemented with 4 mg/day of folic acid (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDI = *Clostridioides difficile*–associated infection; FMT = fecal microbiota therapy; IDSA = Infectious Diseases Society of America; IV = intravenously; MIC = minimum inhibitory concentration; MSM = men who have sex with men; PCR = polymerase chain reaction; PO = orally; TMP-SMX = trimethoprim-sulfamethoxazole

Empiric Therapy

In most situations, treatment of diarrheal disease in people with HIV does not differ significantly from that in immunocompetent individuals. Decisions on therapy are based on an assessment of diarrhea severity and hydration status. Patients should be informed of the importance of maintaining

hydration and be given oral or intravenous (IV) rehydration, if indicated **(AIII).** Because diarrheal disease can produce temporary malabsorption or lactose intolerance, consuming a bland diet and avoiding fat, dairy, and complex carbohydrates are likely to be useful and are therefore recommended **(BIII).** The effectiveness and safety of probiotics or antimotility agents have not been studied adequately in people with HIV who have diarrheal illnesses.[38] Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists **(BIII).**

After obtaining stool samples for diagnostic evaluation, the initiation and duration of empiric antimicrobial therapy depend on the patient's CD4 count and clinical appearance. If stool samples are obtained, antibiotic susceptibility testing should be performed to confirm and inform antibiotic choice. For example, in patients with CD4 counts >500 cells/mm^3 who have had 1 to 2 days of loose stools without fever or blood, no further work-up and no treatment other than oral rehydration may be required. However, a short course of antibiotics (e.g., ciprofloxacin for 5 days **[BIII]**) may be indicated in people with HIV and CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with severe disease (advanced HIV disease [i.e., CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness] and clinically severe diarrhea [i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease]) should undergo inpatient diagnostic evaluation to determine the etiology of the diarrheal illness and receive parenteral antimicrobial treatment **(AIII).** In stable patients, empiric therapy with oral ciprofloxacin **(BIII)** or azithromycin **(BIII)** is recommended, particularly if the infection is not associated with international travel. However, even in the United States, all patients should have careful follow-up since rates of resistance to ciprofloxacin and (to a lesser extent) azithromycin in common enteric pathogens are substantial, and therefore treatment failure may occur. In patients with severe disease, treatment with empiric IV ceftriaxone is recommended until antimicrobial susceptibility results are available **(BIII).** Given the rise of antimicrobial resistance in enteric pathogens, however, updated outbreak information, local susceptibility patterns and travel history always should be considered. For example, if *Campylobacter* or *Shigella* bacteremia is suspected, a carbapenem is preferred for empiric therapy **(BIII).**

Therapy should be adjusted based on the results of the diagnostic work-up. For diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity—such as bloody stool or dehydration—antibiotic therapy can be withheld and directed therapy initiated once a diagnosis is confirmed. Noninfectious etiologies of persistent diarrhea (e.g., inflammatory bowel disease) also should be considered in the differential diagnosis **(BIII).**

International travel: Diarrhea is one of the most common illnesses affecting international travelers. Antimicrobial resistance among enteric bacterial pathogens outside the United States is an important public health problem. For example, traveler's diarrhea caused by fluoroquinolone-resistant *C. jejuni* in South and Southeast Asia or Africa is common.[39,40] Clinicians should consider the possibility of a resistant infection when prescribing empiric therapy for travelers with HIV who experience diarrhea or a syndrome consistent with a systemic infection while traveling or upon returning to the United States, given reports of multidrug-resistant *Enterobacteriaceae* acquisition during travel.[41-45]

Pathogen-Specific Therapy

Nontyphoidal *Salmonella* Species

Immunocompetent hosts who do not have HIV often do not require antibiotic treatment for *Salmonella* gastroenteritis (typically caused by nontyphoidal *Salmonella* spp.) because the condition is usually self-limited, and treatment may prolong the carrier state. In contrast, all people with HIV

and salmonellosis should be treated **(AIII),** even though no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of *Salmonella* bacteremia 20 to 100 times and mortality as much as seven times compared to people who do not have HIV.[19,46]

The treatment of choice for susceptible nontyphoidal *Salmonella* spp. infection is a fluoroquinolone **(AIII).** Ciprofloxacin is the preferred agent **(AIII).**[47] Other fluoroquinolones—such as levofloxacin and moxifloxacin are recommended as alternatives to ciprofloxacin **(BIII).** Although they have not been well evaluated in clinical trials, they likely would be effective in treating salmonellosis in people with HIV**.** Depending on antibiotic susceptibility, alternatives to the fluoroquinolones include TMP-SMX or expanded-spectrum cephalosporins, such as ceftriaxone **(BIII).** Fluoroquinolone resistance in nontyphoidal *Salmonella* spp. appears to be increasing, with preliminary CDC data showing genetic markers of fluoroquinolone resistance among 19% of 20,831 nontyphoidal *Salmonella* spp. isolates tested in the United States in 2023.[48] In agreement with IDSA guidelines, the Panel recommends ceftriaxone over ciprofloxacin if invasive disease is suspected or confirmed, at least until susceptibilities return **(BIII).**[47,48]

The optimal duration of therapy for HIV-related nontyphoidal *Salmonella* infection has not been defined. For patients with CD4 counts ≥200 cells/mm^3 who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is recommended **(BIII).** For the same patients with bacteremia, 14 days is appropriate provided clearance of bacteremia is documented. Longer treatment is recommended if bacteremia persists or if the infection is complicated (i.e., if metastatic foci are present) **(BIII).**

For any patients with advanced HIV disease (CD4 count <200 cells/mm^3) and *Salmonella* infection, a minimum of 2 weeks with extension up to 6 weeks of antibiotics in severe disease or bacteremia is often recommended **(BIII).**[49]

People with HIV and *Salmonella* bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment **(BIII).** As people with HIV age, it is also important to remember that rates of invasive *Salmonella* infections increase with age in each age group beyond infancy.[50,51] Recurrence may present as bacteremia or as an anatomically localized infection, including intraabdominal, endothelial, urinary tract, soft tissue, bone and joint, lung, or meningeal foci. Secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII),** and it also might be considered for patients with recurrent gastroenteritis (with or without bacteremia), and in those with CD4 counts <200 cells/mm^3 with severe diarrhea **(BIII).** The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure. Recurrent *Salmonella* bacteremia constitutes an AIDS-defining illness,[31] and HIV suppression with ART appears to decrease the risk of recurrent illnesses.

In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm^3, secondary prophylaxis for salmonellosis likely can be discontinued **(CII).** Clinicians also should be aware that recurrence may indicate development of antimicrobial resistance during therapy.

Shigella Species

Therapy for *Shigella* infections should be considered because it may slightly shorten the duration of illness and help prevent transmission to others **(AIII);** however, because antimicrobial resistance of *Shigella* spp. is increasing and limited data demonstrate that antibiotic therapy limits transmission,

antibiotic treatment may be withheld in people with HIV and CD4 >500 cells/mm^3 with mild symptoms or whose diarrhea is resolving before culture confirmation of *Shigella* infection **(CIII).** When treatment is offered, antibiotic selection should be guided by the results of antibiotic susceptibility testing.[43,52-55]

Preferred treatment for susceptible shigellosis is a fluoroquinolone, preferably ciprofloxacin, for 5 to 10 days **(AIII)** with levofloxacin serving as an alternative **(BIII).** Importantly, preliminary CDC data estimate 60% of *Shigella* spp. isolated among the general U.S. population in 2023 harbored genetic markers of resistance to ciprofloxacin, and 55% of such isolates tested in 2022 had a ciprofloxacin minimum inhibitory concentration (MIC) of ≥0.12 µg/mL.[48] Although current Clinical and Laboratory Standards Institute criteria categorize *Shigella* isolates with a ciprofloxacin MIC of 0.12 and 0.25 µg/mL as susceptible and a MIC of 0.5 µg/mL as intermediate, these isolates typically harbor a fluoroquinolone resistance gene or mutation. Until the clinical significance of these findings can be determined, alternative antibiotics should be considered to treat patients whose isolates have ciprofloxacin MICs ≥0.12 µg/mL **(BIII).**[56] In general, automated antimicrobial susceptibility test panels do not have doubling dilutions that span the MIC range to determine susceptibility to ciprofloxacin based on the CDC recommendation of ≤0.06. As such, a clinically validated manual antimicrobial susceptibility testing method such as reference broth microdilution or a gradient diffusion method would be required to confirm susceptibility at the lower MIC range. Ciprofloxacin-resistant *S. sonnei* and *S. flexneri* infections in the United States are associated with international travel, homelessness, and men who have sex with men (MSM); ciprofloxacin-resistant shigellosis among MSM appears to be acquired predominantly within the United States, rather than during travel.[43]

Depending on antibiotic susceptibilities, in stable patients without concern for bacteremia, azithromycin (5 days) or TMP-SMX (5–7 days) may be alternatives **(BIII).** Azithromycin has not been evaluated in people with HIV and shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[56] Azithromycin susceptibility testing is not widely available in clinical laboratories but can be performed by many state public health laboratories. Preliminary CDC data estimate 34% of *Shigella* spp. isolated among the general U.S. population in 2023 harbored genetic markers of resistance to azithromycin.[48] Azithromycin-resistant *Shigella* spp. infections in MSM with HIV have been reported.[57-59]

Multidrug resistance is common among shigellae, and clinicians should be aware that rates of infections caused by extensively drug resistant *Shigella* strains (strains resistant to azithromycin, ciprofloxacin, ceftriaxone, trimethoprim-sulfamethoxazole, and ampicillin) are increasing in the United States.[60] Therefore, while IV ceftriaxone is recommended therapy for susceptible *Shigella*, in severely ill people requiring empiric parenteral therapy, carbapenems can be initiated before antimicrobial susceptibilities are available **(BIII).**

Treatment for people with *Shigella* bacteremia is less well defined but extending treatment to at least 14 days is recommended **(BIII).** Azithromycin **is not recommended** for treatment of *Shigella* spp. bacteremia **(AIII).** Chronic suppressive or maintenance therapy **is not recommended** for first-time *Shigella* infections **(BIII).** Recurrent infections can occur, particularly in individuals with CD4 counts <200 cells/mm^3, in which case, extending antimicrobial therapy for up to 6 weeks is recommended **(BIII).** Because of *Shigella's* extremely low infectious dose, patients with shigellosis should be counseled about transmission prevention. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

Campylobacter Species

The optimal treatment of campylobacteriosis in people with HIV is poorly defined and multidrug resistance might occur.[61,62] Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended **(BIII).** In the United States in 2018, 29% of *C. jejuni* isolates were resistant to ciprofloxacin, and 2% were resistant to azithromycin; among *C. coli* isolates, 41% of isolates were resistant to fluoroquinolones, and 13% were resistant to azithromycin.[48]

For people with mild disease and CD4 counts >200 cells/mm^3, therapy should be withheld unless symptoms persist for more than several days **(CIII).** For mild-to-moderate campylobacteriosis, initiating therapy with azithromycin for 5 days or a fluoroquinolone—such as ciprofloxacin—for 7 to 10 days (if the organism is sensitive) is recommended **(BIII).** Azithromycin has not been evaluated in people with HIV and campylobacteriosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[39] Azithromycin susceptibility testing, however, is not widely available in clinical laboratories but can be performed by many state public health laboratories. *Campylobacter* bacteremia should be treated for at least 14 days using a fluoroquinolone if the isolate is sensitive **(BIII).**[63] Adding a second active agent—such as an aminoglycoside—may be prudent in patients with bacteremia to limit the emergence of antibiotic resistance **(BIII).** Third generation cephalosporins are not reliably active and use of alternative cell-wall active agents such as carbapenems may be necessary in severely ill people requiring empiric parenteral therapy until antimicrobial susceptibilities return. Antibiotic choice should be guided by antibiotic susceptibility tests. Azithromycin **is not recommended** for treatment of *Campylobacter* bacteremia **(AIII).** Chronic suppressive or maintenance therapy **is not recommended** for first-time *Campylobacter* infections in people with HIV **(BIII).** However, recurrent infections can occur, particularly in people with CD4 counts <200 cells/mm^3. In recurrent disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable **(BIII).** As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent *Campylobacter* spp. infections.[64]

Clostridioides difficile

No randomized controlled trials have been conducted for CDI therapy in people with HIV. Available data suggest that people with HIV respond to treatment of CDI similarly to people without HIV.[9] Thus, treatment of CDI in people with HIV is the same as in people without HIV. Guidelines and subsequent updates for treatment of CDI have been published[29,65] and should be consulted for further information.

Treatment of an Initial Episode of Clostridioides difficile–Associated Infection

Four randomized clinical trials all conducted in the general population (two identical studies with ~60% hospitalized patients; two studies restricted to hospitalized patients)[66-69] have revealed that, when compared to oral vancomycin, fidaxomicin increased the likelihood of a sustained clinical response of CDI (at 28 days) in the initial therapy of CDI (relative risk [RR] 1.16; 95% confidence interval [CI], 1.09–1.24).[65] Fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events and all-cause mortality. Given these data, the 2021 IDSA CDI Clinical Practice Guideline update[65] for adults suggests treatment with fidaxomicin rather than oral vancomycin, for initial CDI whether CDI is severe or nonsevere. Fidaxomicin remains very expensive but should be considered in people with HIV and CDI, if available **(AI).** Oral vancomycin is also an acceptable option for initial CDI **(AI).** Earlier multicenter, randomized, double-blind studies identified that oral vancomycin is superior to metronidazole for treatment of CDI.[70,71] Thus, metronidazole is to be considered as an alternative drug for CDI therapy only if fidaxomicin or

vancomycin are unavailable and CDI is nonsevere (white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL) **(CI).**[29]

Treatment of Recurrent Clostridioides difficile–Associated Infection

Treatment of recurrent CDI is complex and, in part, defined by the specific circumstances of the patient with recurrent CDI and the number of prior CDI episodes. Brief guidance is provided here; the 2017 and 2021 IDSA CDI guidelines should be consulted for a full discussion of this topic.[29,65] Risk factors for CDI recurrence are age ≥65 years, history of CDI, compromised immunity, severe CDI, and certain virulent strains (ribotypes 027/078/244). Similar to an initial episode of CDI and also based on the randomized clinical trials cited above,[66-69] the Panel recommends administering fidaxomicin, instead of oral vancomycin, to adults with recurrent CDI **(AI),** consistent with the 2021 IDSA CDI Clinical Practice Guideline update.[65] Fidaxomicin therapy increased the likelihood of a sustained clinical response for recurrent CDI at 30 days (RR 1.27; 95% CI, 1.05–1.54). For treatment of an initial CDI recurrence, fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events, and all-cause mortality. Vancomycin is also an acceptable option for recurrent CDI (see the IDSA Guideline for tapered and pulsed regimens) **(AI).**

Bezlotoxumab is a humanized monoclonal antibody against *C. difficile* toxin B approved for prevention of recurrent CDI in high-risk adults when used in conjunction with standard-of-care (SOC) antibiotic therapy. The 2021 IDSA CDI Clinical Practice Guideline update suggests use of bezlotoxumab as a cointervention along with vancomycin as the SOC antibiotic in patients with a history of CDI in the last 6 months or other risk factors for recurrence (i.e., age ≥65 years, compromised immunity, severe CDI, or certain virulent strains (ribotypes 027/078/244).[65] However, data on the benefit of bezlotoxumab therapy when fidaxomicin is used as the SOC antibiotic are limited. Limited case reports suggest that fecal microbiota therapy (FMT) (i.e., fecal transplant) may be successful and safe to treat recurrent CDI in people with HIV.[72-74] However, it is important to note that complications of FMT, including transmission of enteric pathogens and antibiotic-resistant bacteria with deaths, have been reported.[75,76] FMT for treatment of recurrent CDI may be considered after three total CDI episodes (initial and two recurrent CDI episodes) **(CIII).**[29,65] The effect of ART on recurrence of CDI is unknown, but ART initiation should follow standard guidelines, similar to other enteric infections (see the Special Considerations Regarding ART Initiation section below).

Special Considerations Regarding ART Initiation

ART initiation should follow standard guidelines. The presence of an enteric infection should not delay ART initiation **(AIII).** The presence of a diarrheal illness is relevant only in terms of a patient's ability to ingest and absorb ART. If recurrent enteric infections are documented or *Salmonella* bacteremia occurs, prompt initiation of ART should be considered regardless of CD4 count.

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome)

Patients should be monitored closely for response to treatment, defined clinically by improvement in systemic signs and symptoms, resolution of diarrhea, and sterilization of infected tissues or body fluids, such as blood. Follow-up stool testing may be required when public health considerations and state policies dictate the need to ensure microbiologic cure, such as in health care or food service workers. Follow-up stool culture and antibiotic susceptibility testing should be considered for patients with incomplete clinical response to appropriate antimicrobial therapy. In patients with persistent or recurrent diarrhea despite therapy, clinicians should consider other enteric infections (including STIs; see the Diagnosis section above) in the context of the patient's immune status and

exposures, as well as the possibility of *C. difficile* or the development of antimicrobial resistance **(BIII).**

Observational studies suggest that plasma drug concentrations in people with HIV may be decreased as a result of severe diarrhea or malabsorption.[77,78] Coadministration of fluoroquinolones with magnesium- or aluminum-containing antacids or with calcium, zinc, or iron should be avoided because these agents interfere with fluoroquinolone absorption **(AII).**[79] Although larger prospective studies are needed to determine the impact of severe diarrhea on antibiotic absorption, it is prudent to use IV antibiotics in clinically unstable patients **(AIII).**

Immune reconstitution inflammatory syndrome has not been described in association with treatment for typical bacterial enteric pathogens.

Preventing Recurrence

The pharmacologic approach to recurrent enteric infections is covered in the section on directed therapy for each bacterial species. As noted above, secondary prophylaxis should be considered for patients with recurrent *Salmonella* bacteremia **(BIII)** and, in some circumstances, for those with recurrent shigellosis **(BIII)** or campylobacteriosis **(BIII).**

Special Considerations During Pregnancy

During pregnancy, the diagnosis and management of bacterial enteric infection are the same as for other people with HIV, with several considerations. **Based on their safety profile, expanded-spectrum cephalosporins or azithromycin should be the first-line therapy for bacterial enteric infections during pregnancy if antimicrobials are required, depending on the organism and the results of susceptibility testing (BIII).**[80] Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating quinolone use during pregnancy did not find an increased risk of birth defects or musculoskeletal abnormalities.[81-83] Thus, quinolones can be used for bacterial enteric infections if indicated by susceptibility testing or failure of first-line therapy, as listed above with a shared medical decision-making decision model in discussion with the patient. **(BIII).** TMP-SMX use in the first trimester should be avoided, if possible, because of an association with an increased risk of birth defects, specifically neural tube, cardiovascular, and urinary tract defects **(BIII).**[84-86] However, a review of potential risks related to TMP-SMX use cites the low quality of current data and supports the use of TMP-SMX during pregnancy as clinically indicated.[87] As soon as possible during the trimester of pregnancy, or when anticipating or attempting conception, any administration of TMP-SMX should be supplemented with folic acid 4 mg/day **(BIII).**[84,85,88] Neonatal care providers should be informed if maternal sulfa therapy was used near delivery because of the theoretical increased risk of hyperbilirubinemia and kernicterus in the newborn. Because oral rifaximin and fidaxomicin are not absorbed systemically, they can be used during pregnancy. However, this should be a shared decision made between providers and patients ensuring that patients are made aware of the limited data about fidaxomicin in pregnancy **(BIII).**

Vancomycin and metronidazole are two antimicrobials that have been utilized in the perinatal period in the United States. Intravenous vancomycin has been utilized as intrapartum prophylaxis in the penicillin allergic patient colonized with group B streptococcus,[89] and minimal absorption is expected with oral therapy. Although vancomycin for enteric disease is recommended for use only in its oral formulation, which is not absorbed in meaningful concentrations from the gastrointestinal tract,[90] it should be noted that with intravenous use, vancomycin readily crosses the placenta.[91] A study of 10 infants evaluated after the second or third trimester for *in utero* exposure of maternal

intravenous vancomycin therapy for serious staphylococcal infections found no hearing loss or renal toxicity attributed to vancomycin.[91] A review of metronidazole use in pregnancy for treatment of trichomoniasis or bacterial vaginosis found no increase in risk of birth defects.[92] Studies on the use of metronidazole for CDI in pregnancy were not found.

References

1. Sanchez TH, Brooks JT, Sullivan PS, et al. Bacterial diarrhea in persons with HIV infection, United States, 1992–2002. *Clin Infect Dis*. 2005;41(11):1621-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16267735.

2. Newman KL, Newman GS, Cybulski RJ, Fang FC. Gastroenteritis in men who have sex with men in Seattle, Washington, 2017–2018. *Clin Infect Dis*. 2020;71(1):109-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31621824.

3. Verma A, Hine AM, Joelson A, et al. The influence of hospitalization and HIV severity on gastrointestinal PCR panel evaluation of HIV-related acute diarrhea in New York City: a retrospective, cross-sectional study. *Therap Adv Gastroenterol*. 2022;15:17562848221092593. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35509422.

4. Chou YJ, Lin HW, Yang CJ, et al. Risk of recurrent nontyphoid *Salmonella* bacteremia in human immunodeficiency virus-infected patients with short-term secondary prophylaxis in the era of combination antiretroviral therapy. *J Microbiol Immunol Infect*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26316009.

5. Hung CC, Hung MN, Hsueh PR, et al. Risk of recurrent nontyphoid *Salmonella* bacteremia in HIV-infected patients in the era of highly active antiretroviral therapy and an increasing trend of fluoroquinolone resistance. *Clin Infect Dis*. 2007;45(5):e60-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17682981.

6. Taramasso L, Tatarelli P, Di Biagio A. Bloodstream infections in HIV-infected patients. *Virulence*. 2016;7(3):320-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26950194.

7. Huang DB, Mohanty A, DuPont HL, Okhuysen PC, Chiang T. A review of an emerging enteric pathogen: enteroaggregative *Escherichia coli*. *J Med Microbiol*. 2006;55(Pt 10):1303-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17005776.

8. Nevin DT, Morgan CJ, Graham DY, Genta RM. *Helicobacter pylori* gastritis in HIV-infected patients: a review. *Helicobacter*. 2014;19(5):323-329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24773336.

9. Revolinski SL, Munoz-Price LS. *Clostridium difficile* in immunocompromised hosts: a review of epidemiology, risk factors, treatment, and prevention. *Clin Infect Dis*. 2019;68(12):2144-2153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30281082.

10. Haines CF, Moore RD, Bartlett JG, et al. *Clostridium difficile* in a HIV-infected cohort: incidence, risk factors, and clinical outcomes. *AIDS*. 2013;27(17):2799-2807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23842125.

11. Angulo FJ, Swerdlow DL. Bacterial enteric infections in persons infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21 Suppl 1:S84-93. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8547518.

12. Aragon TJ, Vugia DJ, Shallow S, et al. Case-control study of shigellosis in San Francisco: the role of sexual transmission and HIV infection. *Clin Infect Dis*. 2007;44(3):327-334. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17205436.

13. Quinn TC, Goodell SE, Fennell C, et al. Infections with *Campylobacter jejuni* and *Campylobacter*-like organisms in homosexual men. *Ann Intern Med*. 1984;101(2):187-192. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6547580.

14. Mitchell HD, Thomson NR, Jenkins C, et al. Linkage of whole genome sequencing, epidemiological, and clinical data to understand the genetic diversity and clinical outcomes of *Shigella flexneri* among men who have sex with men in England. *Microbiol Spectr*. 2021;9(3):e0121321. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34908501.

15. Mohan K, Hibbert M, Rooney G, et al. What is the overlap between HIV and shigellosis epidemics in England: further evidence of MSM transmission? *Sex Transm Infect*. 2018;94(1):67-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28490580.

16. Kuhn KG, Hvass AK, Christiansen AH, Ethelberg S, Cowan SA. Sexual contact as risk factor for *Campylobacter* infection, Denmark. *Emerg Infect Dis*. 2021;27(4):1133-1140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33754996.

17. Tee W, Mijch A. *Campylobacter jejuni* bacteremia in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients: comparison of clinical features and review. *Clin Infect Dis*. 1998;26(1):91-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9455515.

18. Tobin-D'Angelo M, Oosmanally N, Wilson SN, Anderson EJ, Segler S, Poventud L. *Shigella* bacteremia, Georgia, USA, 2002–2012(1). *Emerg Infect Dis*. 2020;26(1):122-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31855540.

19. Celum CL, Chaisson RE, Rutherford GW, Barnhart JL, Echenberg DF. Incidence of salmonellosis in patients with AIDS. *J Infect Dis*. 1987;156(6):998-1002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3680999.

20. Kristjansson M, Viner B, Maslow JN. Polymicrobial and recurrent bacteremia with *Shigella* in a patient with AIDS. *Scand J Infect Dis*. 1994;26(4):411-416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7984973.

21. Casado JL, Valdezate S, Calderon C, et al. Zidovudine therapy protects against *Salmonella* bacteremia recurrence in human immunodeficiency virus-infected patients. *J Infect Dis*. 1999;179(6):1553-1556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10228081.

22. Williamson DA, Chen MY. Emerging and reemerging sexually transmitted infections. *N Engl J Med*. 2020;382(21):2023-2032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32433838.

23. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries - April–June 2022. *N Engl J Med*. 2022;387(8):679-691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35866746.

24. Arnold CA, Limketkai BN, Illei PB, Montgomery E, Voltaggio L. Syphilitic and lymphogranuloma venereum (LGV) proctocolitis: clues to a frequently missed diagnosis. *Am*

J Surg Pathol. 2013;37(1):38-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23095509.

25. Huang JY, Henao OL, Griffin PM, et al. Infection with pathogens transmitted commonly through food and the effect of increasing use of culture-independent diagnostic tests on surveillance–Foodborne Diseases Active Surveillance Network, 10 U.S. sites, 2012–2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(14):368-371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27077946.

26. Pulvirenti JJ, Mehra T, Hafiz I, et al. Epidemiology and outcome of *Clostridium difficile* infection and diarrhea in HIV infected inpatients. *Diagn Microbiol Infect Dis*. 2002;44(4):325-330. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12543536.

27. Kociolek LK, Gerding DN, Carrico R, et al. Strategies to prevent *Clostridioides difficile* infections in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol*. 2023;44(4):527-549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37042243.

28. Mizusawa M, Carroll KC. The future of *Clostridioides difficile* diagnostics. *Curr Opin Infect Dis*. 2021;34(5):483-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34524199.

29. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*. 2018;66(7):987-994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29562266.

30. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34292926.

31. Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. *MMWR Recomm Rep*. 2008;57(RR-10):1-12. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19052530.

32. de Vries HJC, Nori AV, Kiellberg Larsen H, et al. 2021 European guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens. *J Eur Acad Dermatol Venereol*. 2021;35(7):1434-1443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34057249.

33. Centers for Disease Control and Prevention. Healthcare Resources. 2024. Available at: https://www.cdc.gov/c-diff/hcp/resources/?CDC_AAref_Val=https://www.cdc.gov/cdiff/clinicians/resources.html#cdc_listing_res2-resources.

34. Advice for travelers. *Med Lett Drugs Ther*. 2019;61(1582):153-160. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31599872.

35. Riddle MS, Connor BA, Beeching NJ, et al. Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. *J Travel Med*. 2017;24(suppl_1):S57-S74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28521004.

36. Diptyanusa A, Ngamprasertchai T, Piyaphanee W. A review of antibiotic prophylaxis for traveler's diarrhea: past to present. *Trop Dis Travel Med Vaccines*. 2018;4:14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30455974.

37. Food and Drug Administration. FDA drug safety communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. 2018. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-updates-warnings-oral-and-injectable-fluoroquinolone-antibiotics.

38. Nwachukwu CE, Okebe JU. Antimotility agents for chronic diarrhoea in people with HIV/AIDS. *Cochrane Database Syst Rev*. 2008(4):CD005644. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18843696.

39. Kuschner RA, Trofa AF, Thomas RJ, et al. Use of azithromycin for the treatment of Campylobacter enteritis in travelers to Thailand, an area where ciprofloxacin resistance is prevalent. *Clin Infect Dis*. 1995;21(3):536-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8527539.

40. Tribble DR, Sanders JW, Pang LW, et al. Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis*. 2007;44(3):338-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17205438.

41. Kantele A, Laaveri T, Mero S, et al. Antimicrobials increase travelers' risk of colonization by extended-spectrum betalactamase-producing Enterobacteriaceae. *Clin Infect Dis*. 2015;60(6):837-846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25613287.

42. Barlow RS, Debess EE, Winthrop KL, Lapidus JA, Vega R, Cieslak PR. Travel-associated antimicrobial drug-resistant nontyphoidal Salmonellae, 2004–2009. *Emerg Infect Dis*. 2014;20(4):603-611. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24655581.

43. Centers for Disease Control and Prevention. Importation and domestic transmission of *Shigella sonnei* resistant to ciprofloxacin — United States, May 2014–February 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(12):318-320. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6412a2.htm?s_cid=mm6412a2_w.

44. Ruppe E, Andremont A, Armand-Lefevre L. Digestive tract colonization by multidrug-resistant Enterobacteriaceae in travellers: an update. *Travel Med Infect Dis*. 2018;21:28-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29155322.

45. Tribble DR. Resistant pathogens as causes of traveller's diarrhea globally and impact(s) on treatment failure and recommendations. *J Travel Med*. 2017;24(suppl_1):S6-S12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28520997.

46. Cummings PL, Sorvillo F, Kuo T. Salmonellosis-related mortality in the United States, 1990–2006. *Foodborne Pathog Dis*. 2010;7(11):1393-1399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20617938.

47. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017;65(12):e45-e80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29053792.

48. Centers for Disease Control and Prevention. National Antimicrobial Resistance Monitoring System (NARMS) Now: human data. 2023. Available at: https://wwwn.cdc.gov/narmsnow.

49. Gordon MA, Banda HT, Gondwe M, et al. Non-typhoidal *Salmonella* bacteraemia among HIV-infected Malawian adults: high mortality and frequent recrudescence. *AIDS*. 2002;16(12):1633-1641. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12172085.

50. Hsu RB, Tsay YG, Chen RJ, Chu SH. Risk factors for primary bacteremia and endovascular infection in patients without acquired immunodeficiency syndrome who have nontyphoid salmonellosis. *Clin Infect Dis*. 2003;36(7):829-834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12652381.

51. Nielsen H, Gradel KO, Schonheyder HC. High incidence of intravascular focus in nontyphoid *Salmonella* bacteremia in the age group above 50 years: a population-based study. *APMIS*. 2006;114(9):641-645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16948817.

52. Eikmeier D, Talley P, Bowen A, et al. Decreased susceptibility to azithromycin in clinical *Shigella* isolates associated with HIV and sexually transmitted bacterial diseases, Minnesota, USA, 2012–2015. *Emerg Infect Dis*. 2020;26(4):667-674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32186495.

53. Hoffmann C, Sahly H, Jessen A, et al. High rates of quinolone-resistant strains of *Shigella sonnei* in HIV-infected MSM. *Infection*. 2013;41(5):999-1003. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23852945.

54. Murray K, Reddy V, Kornblum JS, et al. Increasing antibiotic resistance in *Shigella* spp. from infected New York City residents, New York, USA. *Emerg Infect Dis*. 2017;23(2):332-335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28098543.

55. Gharpure R, Friedman CR, Fialkowski V, et al. Azithromycin and ciprofloxacin treatment outcomes during an outbreak of multidrug-resistant *Shigella sonnei* infections in a retirement community-Vermont, 2018. *Clin Infect Dis*. 2022;74(3):455-460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33993224.

56. Centers for Disease Control and Prevention. CDC recommendations for diagnosing and managing *Shigella* strains with possible reduced susceptibility to ciprofloxacin. 2017. Available at: https://emergency.cdc.gov/han/han00401.asp.

57. Heiman KE, Karlsson M, Grass J, et al. Notes from the field: *Shigella* with decreased susceptibility to azithromycin among men who have sex with men - United States, 2002–2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(6):132-133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24522098.

58. Hassing RJ, Melles DC, Goessens WH, Rijnders BJ. Case of *Shigella flexneri* infection with treatment failure due to azithromycin resistance in an HIV-positive patient. *Infection*. 2014. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24488332.

59. Baker KS, Dallman TJ, Ashton PM, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. *Lancet Infect Dis*. 2015;15(8):913-921. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25936611.

60. Centers for Disease Control and Prevention. Increase in extensively drug-resistant shigellosis in the United States. 2023. Available at: https://emergency.cdc.gov/han/2023/han00486.asp.

61. Gaudreau C, Rodrigues-Coutlee S, Pilon PA, Coutlee F, Bekal S. Long-lasting outbreak of erythromycin- and ciprofloxacin-resistant *Campylobacter jejuni* subspecies *jejuni* from 2003 to 2013 in men who have sex with men, Quebec, Canada. *Clin Infect Dis*. 2015;61(10):1549-1552. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26187024.

62. Greninger AL, Addetia A, Starr K, et al. International spread of multidrug-resistant *Campylobacter coli* in men who have sex with men in Washington state and Quebec, 2015–2018. *Clin Infect Dis*. 2020;71(8):1896-1904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31665255.

63. Fernandez-Cruz A, Munoz P, Mohedano R, et al. *Campylobacter* bacteremia: clinical characteristics, incidence, and outcome over 23 years. *Medicine (Baltimore)*. 2010;89(5):319-330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20827109.

64. Larsen IK, Gradel KO, Helms M, et al. Non-typhoidal *Salmonella* and *Campylobacter* infections among HIV-positive patients in Denmark. *Scand J Infect Dis*. 2011;43(1):3-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20849366.

65. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis*. 2021;73(5):e1029-e1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34164674.

66. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med*. 2011;364(5):422-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21288078.

67. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22321770.

68. Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis*. 2018;18(3):296-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29273269.

69. Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of *Clostridioides (Clostridium) difficile* infection in a randomized, double-blind, comparative phase III study in Japan. *J Infect Chemother*. 2018;24(9):744-752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29934056.

70. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014;59(3):345-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24799326.

71. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302-307. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17599306.

72. Di Bella S, Gouliouris T, Petrosillo N. Fecal microbiota transplantation (FMT) for *Clostridium difficile* infection: focus on immunocompromised patients. *J Infect Chemother*. 2015;21(4):230-237. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25703532.

73. Serrano-Villar S, Talavera-Rodriguez A, Gosalbes MJ, et al. Fecal microbiota transplantation in HIV: a pilot placebo-controlled study. *Nat Commun*. 2021;12(1):1139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33602945.

74. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. *Am J Gastroenterol*. 2014;109(7):1065-1071. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24890442.

75. Food and Drug Administration. Fecal microbiota for transplantation: safety alert - risk of serious adverse events likely due to transmission of pathogenic organisms. 2020. Available at: https://www.fda.gov/safety/medical-product-safety-information/fecal-microbiota-transplantation-safety-alert-risk-serious-adverse-events-likely-due-transmission.

76. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant *E. coli* bacteremia transmitted by fecal microbiota transplant. *N Engl J Med*. 2019;381(21):2043-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31665575.

77. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Malabsorption of rifampin and isoniazid in HIV-infected patients with and without tuberculosis. *Clin Infect Dis*. 2004;38(2):280-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14699462.

78. Sahai J, Gallicano K, Swick L, et al. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Ann Intern Med*. 1997;127(4):289-293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9265429.

79. Highlights of prescribing information. CIPRO® (ciprofloxacin hydrochloride) tablet, for oral use CIPRO® (ciprofloxacin), for oral suspension [package insert]. U.S. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/019537s092lbl.pdf.

80. Bérard A, Sheehy O, Zhao J, Nordeng H. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. *Pharmacoepidemiology and Drug Safety*. 2015;24(12):1241-1248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26513406.

81. Padberg S, Wacker E, Meister R, et al. Observational cohort study of pregnancy outcome after first-trimester exposure to fluoroquinolones. *Antimicrob Agents Chemother*. 2014;58(8):4392-4398. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24841264.

82. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. 1996;69(2):83-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8902438.

83. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42(6):1336-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9624471.

84. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. 2001;15(6):637-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11738517.

85. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 2000;343(22):1608-1614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11096168.

86. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001;153(10):961-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11384952.

87. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2014;66(5):512-521. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24853309.

88. Bortolus R, Filippini F, Cipriani S, et al. Efficacy of 4.0 mg versus 0.4 mg folic acid supplementation on the reproductive outcomes: a randomized controlled trial. *Nutrients*. 2021;13(12). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34959975.

89. Puopolo KM, Lynfield R, Cummings JJ, et al. Management of infants at risk for group B streptococcal disease. *Pediatrics*. 2019;144(2). Available at: https://publications.aap.org/pediatrics/article/144/2/e20191881/38546/Management-of-Infants-at-Risk-for-Group-B?autologincheck=redirected.

90. Rao S, Kupfer Y, Pagala M, Chapnick E, Tessler S. Systemic absorption of oral vancomycin in patients with *Clostridium difficile* infection. *Scand J Infect Dis*. 2011;43(5):386-388. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21198337.

91. Bourget P, Fernandez H, Delouis C, Ribou F. Transplacental passage of vancomycin during the second trimester of pregnancy. *Obstet Gynecol*. 1991;78(5 Pt 2):908-911. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1923224.

92. Sheehy O, Santos F, Ferreira E, Berard A. The use of metronidazole during pregnancy: a review of evidence. *Curr Drug Saf*. 2015;10(2):170-179. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25986038.

Bartonellosis

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Epidemiology

Bartonella species cause infections that include cat scratch disease, retinitis, trench fever, relapsing bacteremia, culture-negative endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.[1] The latter two manifestations occur almost exclusively in individuals who are immunocompromised. Thirty-seven species and three subspecies of *Bartonella* have been described and are officially recognized (see Bartonella on the List of Prokaryotic Names with Standing in Nomenclature); fourteen of these *Bartonella* species have been implicated in human infections.

BA most often occurs late in HIV infection[2] in patients with median CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. In people with HIV, bartonellosis is often a chronic illness, lasting for months to more than a year, with BA lesions and intermittent bacteremia. Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in people with HIV.[2] In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness.[2] The body louse serves as the vector of *B. quintana* to humans. To avoid exposure to *B. quintana*, people with HIV should avoid body lice exposure and have prompt eradication of lice if infestation occurs. The cat flea is the vector of *B. henselae* in cats. Cats are the most common vector (via a scratch) responsible for transmitting *B. henselae* to humans, most likely when their claws become contaminated with feces from *B. henselae*-infected fleas. In some areas of the United States, the prevalence of *B. henselae* bacteremia in pet cats approaches 50%;[3] infection is more common among kittens and feral cat populations. Controlling cat flea infestation and avoiding cat scratches are therefore critical strategies for preventing *B. henselae* infections in people with HIV.

Clinical Manifestations

BA lesions have been associated with nearly every organ system, but cutaneous lesions are the most readily identified. These lesions can be clinically indistinguishable from Kaposi sarcoma, pyogenic granuloma, and other skin conditions. BA also can cause subcutaneous nodules. Osteomyelitis is usually caused by *B. quintana*, and only *B. henselae* causes bacillary peliosis hepatis.[2] Although isolated organs can appear to be the principal focus of disease, BA represents a hematogenously disseminated infection, and systemic symptoms of fever, night sweats, and weight loss often accompany BA. *Bartonella* infection is a major cause of unexplained fever in patients with advanced HIV and should be considered in the differential diagnosis of patients with CD4 counts <100 cells/mm^3 and fever.[4] *Bartonella* is a frequent cause of culture-negative endocarditis in immunocompetent and immunocompromised humans and is most commonly caused by *B. quintana*, less frequently by *B. henselae*, and rarely by other *Bartonella* species.[5] Immune complex disease (such as glomerulonephritis) may complicate endocarditis or other systemic *Bartonella* infections; assessment for immune complex formation may be warranted in such cases so that nephrotoxic agents can be avoided.

Diagnosis

Diagnosis of BA can be confirmed by histopathologic examination of biopsied tissue.[6] BA lesions are characterized by vascular proliferation, and a modified silver stain (such as Warthin-Starry stain) usually demonstrates numerous bacilli. Tissue Gram staining and acid-fast staining are negative.

A well-characterized indirect fluorescent antibody (IFA) serologic test was developed at the Centers for Disease Control and Prevention (CDC)[7] and is available at the CDC Infectious Diseases Laboratories. In addition, several private laboratories offer IFA serological testing, but the performance characteristics of these tests have not been validated for people with HIV. In immunocompetent patients, anti-*Bartonella* antibodies might not be detectable for 6 weeks after acute infection; in contrast, by the time *Bartonella* infection is suspected in patients with late-stage HIV infection, they usually have been infected with *Bartonella* for months or even >1 year. However, as many as 25% of *Bartonella* culture-positive patients never develop antibodies in the setting of advanced HIV infection.[4] In those patients who do develop anti-*Bartonella* antibodies, monitoring of antibody levels can be useful in following treatment response of *Bartonella* infection to antibiotics, reflecting resolution[8] or recrudescence. Because of interlaboratory variability, longitudinal testing should be conducted at the same laboratory to enable direct comparison of titers over time.

Because of their fastidious nature, *Bartonella* organisms can be isolated only with difficulty from blood (drawn into ethylenediaminetetraacetic acid [EDTA] tubes, centrifuged, and then plated directly onto fresh chocolate agar). *Bartonella* has been cultured directly from tissue in only a few laboratories.[2] Removing samples from blood culture bottles after 8 days of incubation, followed by staining with acridine orange, has facilitated identification and subsequent culture of *Bartonella* species.[9] Additionally, the CDC can perform polymerase chain reaction (PCR) amplification with universal and/or specific primers to detect *Bartonella* in EDTA blood samples (see *Bartonella quintana* Molecular Detection); these molecular detection tests also are increasingly available through private laboratories. Finally, molecular detection of *Bartonella* in BA skin lesions or other vascular lesions, lymph nodes, or resected cardiac valves from unfixed tissue biopsy samples (at the University of Washington) or from formalin-fixed tissue (at the CDC Infectious Disease Pathology Branch) can be performed.[8,10] *Bartonella* species may also be detected from blood or plasma using metagenomic next generation sequencing.[11-13] Clinicians should be aware that results from the CDC may take longer—several weeks to months—for serologic and molecular testing, respectively, compared with some private laboratories. A notable update was published in the 2023 Duke-ISCVID Criteria for Infective Endocarditis, indicating that an IFA immunoglobulin G (IgG) titer of ≥1:800 for *B. quintana* or *B. henselae* or identification of a *Bartonella sp.* by PCR or other nucleic acid–based techniques (including metagenomic sequencing) from blood are now considered major criteria for the diagnosis of *Bartonella* endocarditis.[14]

In summary, diagnosis of bartonellosis may require multiple testing modalities, including serologic testing (which is the most accessible test, and when positive, is helpful both for diagnosis and subsequent monitoring of treatment response), histopathology, and, especially, molecular testing for biopsied or resected tissue (e.g., BA lesion tissue or heart valve tissue).

Preventing Exposure

People with HIV, specifically those who are severely immunocompromised (CD4 counts <100 cells/mm^3), are at high risk of severe disease when infected by *B. quintana* or *B. henselae*. The

major risk factors for acquisition of *B. henselae* are contact with cats infested with fleas and receiving cat scratches. Immunocompromised individuals should consider the potential risks of cat ownership **(AIII).** People with HIV who want cats should acquire animals that are older than 1 year of age and in good health **(BII).** Cats should be acquired from a known environment, have a documented health history, and be free of fleas. Stray cats and cats with flea infestation should be avoided. Declawing is not advised, but individuals with HIV should avoid rough play with cats and situations in which scratches are likely **(AII).** People with HIV should avoid contact with flea feces (i.e., flea dirt), and any cat-associated wound should be washed promptly with soap and water **(BIII).** Care of cats should include a comprehensive, ongoing flea-control program under the supervision of a veterinarian **(BIII).** No evidence indicates any benefits to cats or their owners from routine culture or serologic testing of the pet for *Bartonella* infection or from antibiotic treatment of healthy, serologically positive cats **(BII).** The major risk factor for *B. quintana* infection is body lice infestation. People with HIV who are experiencing homelessness or are in marginal housing should be informed that body louse infestation can be associated with serious illness and should be provided with appropriate measures to eradicate body lice, if present **(AII).** Regardless of CD4 count, people with both HIV and solid organ transplantation may be at risk of developing more severe *Bartonella* infections, similar to transplant recipients without HIV.[15]

Preventing Disease

Primary chemoprophylaxis for *Bartonella*-associated disease is not recommended **(BIII).** However, note that in a retrospective case-control study, use of a macrolide (such as for *Mycobacterium avium* complex prophylaxis) was protective against developing *Bartonella* infection.[2]

Treating Disease

Recommendations for Treating *Bartonella* Infections
Preferred Therapy
For Cat Scratch Disease, Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis
o Doxycycline 100 mg PO or IV every 12 hours (AII), *or*
o Erythromycin 500 mg PO or IV every 6 hours (AII)
For Infections Involving the CNS
o Doxycycline 100 mg PO or IV every 12 hours +/– rifampin 300 mg PO or IV every 12 hours (AIII)
For Confirmed Bartonella Endocarditis
o (Doxycycline 100 mg IV every 12 hours + rifampin 300 mg IV or PO every 12 hours) for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months (BII), *or*
For Other Severe Infections (Multifocal Disease or with Clinical Decompensation)
o Doxycycline 100 mg PO or IV every 12 hours + rifampin 300 mg PO or IV every 12 hours (BIII), *or*
o Erythromycin 500 mg PO or IV every 6 hours + rifampin 300 mg PO or IV every 12 hours (BIII)
Note: IV therapy may be needed initially (AIII).
Alternative Therapy
For Confirmed Bartonella Endocarditis

- (Doxycycline 100 mg IV every 12 hours + gentamicin 1 mg/kg IV every 8 hours) for 2 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months (BII)

For Bartonella Infections Other than Endocarditis or CNS Infections

- Azithromycin 500 mg PO daily (BIII), *or*
- Clarithromycin 500 mg PO twice daily (BIII)

Duration of Therapy

- At least 3 months for all manifestations of *Bartonella* infection in patients with HIV

Long-Term Suppressive Therapy

Indication for Long-Term Suppressive Therapy

If a relapse occurs after a ≥3-month course of primary treatment:

- A macrolide or doxycycline as long as the CD4 count remains <200 cells/mm^3 (AIII)

Indications for Discontinuing Long-Term Suppressive Therapy (CIII)

- Received at least 3–4 months of treatment, *and*
- CD4 count >200 cells/mm^3 for at least 6 months
- Some specialists would discontinue therapy only if *Bartonella* titers have also decreased by 4-fold (CIII).

Other Considerations

- Rifamycin class antibiotics are potent hepatic enzyme inducers and may lead to significant interaction with many drugs, including ARV agents (see the Dosing Recommendations for Anti-TB Drugs table in the Mycobacterium tuberculosis Infection and Disease section for dosing recommendations).
- In pregnancy, erythromycin or an alternative macrolide should be used as first-line therapy (AIII) rather than tetracyclines (such as doxycycline) due to toxicity profile; third-generation cephalosporins may have efficacy but are second line. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* (AII).

Key: +/− = with or without; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CNS = central nervous system; IV = intravenously; PO = orally

All patients with HIV and *Bartonella* infection should receive antibiotic treatment **(AII).** No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in patients with HIV. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis; either drug is considered first-line treatment for bartonellosis on the basis of reported experience in case series **(AII).**[1,2] Anecdotal and limited published case reports[16] suggest that other macrolide antibiotics (such as azithromycin or clarithromycin) are effective in treating *Bartonella* infections in patients with HIV and may be better tolerated than erythromycin; either of these can be an alternative therapy for *Bartonella* infections (except for endocarditis or central nervous system [CNS] infections) **(BIII).** Therapy should be administered for at least 3 months **(AII).** Doxycycline, preferably in combination with a rifamycin class antibiotic, is the treatment of choice for bartonellosis infection involving the CNS **(AIII).** For severe *Bartonella* infections (i.e., patients with multifocal disease or evidence of clinical decompensation), combination therapy using erythromycin or doxycycline with a rifamycin class antibiotic is recommended **(BIII);** intravenous therapy may be needed initially **(AIII).** Treatment of *Bartonella* endocarditis should include doxycycline with the addition of a rifamycin class antibiotic for a minimum of 6 weeks **(BII).** Doxycycline for 6 weeks plus gentamicin for the first 2 weeks may also be considered but is less

preferred due to the intrinsic nephrotoxicity of gentamicin and the frequency of vasculitis-induced renal dysfunction complicating *Bartonella* endocarditis **(BII).**[17]

Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(AII).**[18] *Bartonella* species have been isolated from patients with HIV during documented treatment or prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX);[2] quinolones and TMP-SMX also have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended **(AIII).**

Monitoring of Response to Therapy and Adverse Effects (Including IRIS)

The potential exists for immune reconstitution inflammatory syndrome (IRIS) in association with bartonellosis treatment and initiation of antiretroviral therapy (ART) in people with HIV. In ART-naive patients, ART generally can be initiated at the same time as *Bartonella*-directed treatment; however, patients with *Bartonella* CNS or ophthalmic lesions probably should be treated with doxycycline and a rifamycin class antibiotic for 2 to 4 weeks before instituting ART **(CIII).**

Because of the propensity for relapse of *Bartonella* infection, patients should have anti-*Bartonella* IFA IgG antibody titers checked at the time of diagnosis (Note: It is important to specify to the receiving lab that the sample must be diluted to endpoint.) and, if positive, should be followed with sequential endpoint titers every 6 to 8 weeks during treatment, preferably until at least a fourfold decrease is documented **(CIII).**[8] Patients treated with oral doxycycline should be cautioned about pill-associated esophagitis and photosensitivity. Adverse effects associated with macrolides include nausea, vomiting, abdominal pain, and elevations of liver transaminase levels; potential QT interval prolongation also should be considered. Serious side effects can occur during treatment with rifamycin class antibiotics, including hypersensitivity reactions (thrombocytopenia, interstitial nephritis, and hemolytic anemia) and hepatitis. Administration of rifamycin class antibiotics strongly induces the cytochrome P450 enzyme system, which is an important consideration when other medications, including many antiretroviral drugs, are taken simultaneously.

Managing Treatment Failure

Relapse of *Bartonella* infections occurs frequently, especially in patients with BA. Among patients who fail to respond to initial treatment, switching to a different preferred regimen (for example, from doxycycline to erythromycin) may be considered, again with treatment duration of ≥3 months **(AIII).** For severe infections, the addition of a rifamycin class antibiotic is indicated **(AIII).** For patients with positive or increasing antibody titers, but with clinical improvement, treatment should continue until at least a fourfold decrease in the antibody titers is documented **(CIII).**[8]

Preventing Recurrence

After a primary course of treatment (minimum of 3 months), treatment may be discontinued, with close monitoring for evidence of relapse (e.g., symptoms, increase in antibody titers).

If a relapse occurs, an additional course of treatment is recommended, followed by long-term suppression of infection with doxycycline or a macrolide **(AIII).**

Long-term suppression can be discontinued after the patient has received at least 3 to 4 months of therapy and when the CD4 count remains >200 cells/mm^3 on effective ART for ≥6 months **(CIII).**[8]

Some specialists would discontinue therapy only if the *Bartonella* titers also have decreased at least fourfold **(CIII).**

Special Considerations During Pregnancy

Infection with *B. bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk of death, but no data are available on the effect of *B. quintana* or *B. henselae* infection during pregnancy.

During pregnancy, the diagnosis and management of *Bartonella* infections are the same as for other people with HIV. Erythromycin treatment (or an alternative macrolide) should be used as first-line therapy **(AIII)** rather than tetracyclines (such as doxycycline) during pregnancy because of the increased risk of hepatotoxicity and the accumulation of tetracycline in fetal teeth and bones, resulting in dark, permanent staining of fetal teeth. Third-generation cephalosporins, such as ceftizoxime[19] or ceftriaxone, may have efficacy against *Bartonella* during pregnancy, but it should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins are not recommended because of their lack of efficacy against *Bartonella* **(AII).**

References

1. Rose SR, Koehler J. Bartonella, including cat-scratch disease. In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease. J. E. Bennett, R. Dolin and M. J. Blaser. 9th ed. Philadelphia, PA: Elsevier Press; 2020.

2. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis. *N Engl J Med*. 1997;337(26):1876-1883. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9407154.

3. Koehler JE, Glaser CA, Tappero JW. Rochalimaea henselae infection. A new zoonosis with the domestic cat as reservoir. *JAMA*. 1994;271(7):531-535. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8301768.

4. Koehler JE, Sanchez MA, Tye S, et al. Prevalence of Bartonella infection among human immunodeficiency virus-infected patients with fever. *Clin Infect Dis*. 2003;37(4):559-566. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12905141.

5. Fournier PE, Thuny F, Richet H, et al. Comprehensive diagnostic strategy for blood culture-negative endocarditis: a prospective study of 819 new cases. *Clin Infect Dis*. 2010;51(2):131-140. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20540619.

6. LeBoit PE, Berger TG, Egbert BM, Beckstead JH, Yen TS, Stoler MH. Bacillary angiomatosis. The histopathology and differential diagnosis of a pseudoneoplastic infection in patients with human immunodeficiency virus disease. *Am J Surg Pathol*. 1989;13(11):909-920. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2802010.

7. Regnery RL, Olson JG, Perkins BA, Bibb W. Serological response to "Rochalimaea henselae" antigen in suspected cat-scratch disease. *Lancet*. 1992;339(8807):1443-1445. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1351130.

8. Lee SA, Plett SK, Luetkemeyer AF, et al. Bartonella quintana aortitis in a man with AIDS, diagnosed by needle biopsy and 16S rRNA gene amplification. *J Clin Microbiol*. 2015;53(8):2773-2776. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26063867.

9. Larson AM, Dougherty MJ, Nowowiejski DJ, et al. Detection of Bartonella (Rochalimaea) quintana by routine acridine orange staining of broth blood cultures. *J Clin Microbiol*. 1994;32(6):1492-1496. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7521357.

10. Dumler JS, Carroll KS, Patel R. Bartonella. In: Manual of Clinical Microbiology. K. C. Carroll, M. A. Pfaller and M. Landry. 12th ed. Washington, DC: American Society for Microbiology; 2019.

11. Li M, Yan K, Jia P, Wei E, Wang H. Metagenomic next-generation sequencing may assist diagnosis of cat-scratch disease. *Front Cell Infect Microbiol*. 2022;12:7. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36189365.

12. Flurin L, Wolf MJ, Fisher CR, et al. Pathogen detection in infective endocarditis using targeted metagenomics on whole blood and plasma: a prospective pilot study. *J Clin Microbiol*. 2022;60(9):e0062122. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36040200.

13. Downey RD, Russo SM, Hauger SB, et al. Identification of an emergent pathogen, *Bartonella vinsonii*, using next-generation sequencing in a patient with culture-negative endocarditis. *J Pediatric Infect Dis Soc*. 2021;10(2):213-216. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32092135.

14. Fowler VG, Durack DT, Selton-Suty C, et al. The 2023 Duke-ISCVID Criteria for infective endocarditis: updating the modified Duke Criteria. *Clin Infect Dis*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/37138445.

15. Psarros G, Riddell Jt, Gandhi T, Kauffman CA, Cinti SK. Bartonella henselae infections in solid organ transplant recipients: report of 5 cases and review of the literature. *Medicine (Baltimore)*. 2012;91(2):111-121. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22391473.

16. Guerra LG, Neira CJ, Boman D, et al. Rapid response of AIDS-related bacillary angiomatosis to azithromycin. *Clin Infect Dis*. 1993;17(2):264-266. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8399879.

17. Raybould JE, Raybould AL, Morales MK, et al. Bartonella endocarditis and Pauci-immune glomerulonephritis: a case report and review of the literature. *Infect Dis Clin Pract (Baltim Md)*. 2016;24(5):254-260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27885316.

18. Koehler JE, LeBoit PE, Egbert BM, Berger TG. Cutaneous vascular lesions and disseminated cat-scratch disease in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. *Ann Intern Med*. 1988;109(6):449-455. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3415105.

19. Riley LE, Tuomala RE. Bacillary angiomatosis in a pregnant patient with acquired immunodeficiency syndrome. *Obstet Gynecol*. 1992;79(5, Part 2):818-819. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1565376.

Candidiasis (Mucocutaneous)

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Epidemiology

Oropharyngeal and esophageal candidiasis are common in people with HIV.[1] The vast majority of such infections are caused by *Candida albicans*, although infections caused by non–*C. albicans* species have been increasingly reported worldwide, in part due to increased selection pressure from increased use of azoles.[2-9] The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in people with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.[10,11] In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy adults and does not suggest HIV.

Clinical Manifestations

Oropharyngeal candidiasis (oral thrush) is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, gums, oropharynx, or tongue surface. In many cases, lesions can be scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilosis also can be caused by *Candida*. Because a proportion of people with HIV who have oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in people with oropharyngeal candidiasis.

Esophageal candidiasis generally presents with retrosternal burning pain or discomfort along with odynophagia; occasionally, esophageal candidiasis can be asymptomatic. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease. On occasion, the plaques may progress to superficial ulcerations of the esophageal mucosa with central or peripheral whitish exudates.

In contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common in people with HIV and when it occurs, it is uncommonly refractory to azole therapy unless caused by non-*C. albicans* species. In people with HIV, *Candida* vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In those with advanced immunosuppression, episodes may be more severe and recur more frequently.

Diagnosis

Oropharyngeal candidiasis is usually diagnosed clinically based on the characteristic appearance of lesions. In contrast to oral hairy leukoplakia, the white plaques of oropharyngeal candidiasis can be scraped off the mucosa. If laboratory confirmation is required, scrapings can be examined microscopically for characteristic yeast or hyphal forms, using a potassium hydroxide preparation. Cultures of clinical exudative material yield the species of *Candida* present.

Esophageal candidiasis should be suspected in people with low CD4 count with substernal chest pain, dysphagia, and odynophagia, especially if there is oral thrush present (though the absence of oral thrush does not rule out esophageal involvement). The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy. The definitive diagnosis of esophageal candidiasis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and confirmation by fungal culture and speciation.

Vulvovaginal candidiasis usually is diagnosed based on clinical presentation coupled with the demonstration of characteristic blastosphere and hyphal yeast forms in vaginal secretions when examined microscopically after potassium hydroxide preparation. Culture confirmation is rarely required but may provide supportive information. Self-diagnosis of vulvovaginitis is unreliable; microscopic and culture confirmation is required to avoid unnecessary exposure to treatment and to assess for other potential pathogens including those that cause sexually transmitted infections (STIs).

Preventing Exposure

Candida organisms are common commensals on mucosal surfaces in healthy individuals. No measures are available to reduce exposure to these fungi.

Preventing Disease

Routine primary prophylaxis **is not recommended** because mucosal disease is associated with very low attributable morbidity and mortality and, moreover, acute therapy is highly effective.[12,13] Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* strains and introduce significant drug–drug interactions and QTc (QT corrected for heart rate) prolongation. In addition, long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII).** Administration of antiretroviral therapy (ART) and immune restoration is the most effective means to prevent disease.

Treating Disease

Treating Mucosal Candidiasis
Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 Days) *Preferred Therapy* • Fluconazole 200-mg loading dose, followed by 100–200 mg PO once daily (AI) *Alternative Therapy* • One 50-mg miconazole mucoadhesive buccal tablet once daily: Apply to mucosal surface over the canine fossa (do not swallow, chew, or crush tablet). Refer to the product label for more detailed application instructions. (BI), *or* • One 10-mg clotrimazole troche PO five times a day (BI), *or* • Nystatin suspension 4–6 mL PO four times daily (BII), *or* • Itraconazole oral solution 200 mg PO daily (BI), *or* • Posaconazole oral suspension 400 mg (10 mL) PO twice daily for 1 day, then 400 mg daily (BI), *or*

- Posaconazole tablet 300 mg PO twice daily for 1 day, then 300 mg daily (BI)

Esophageal Candidiasis (Duration of Therapy: 14–21 Days)

Note: Systemic antifungals are required for effective treatment of esophageal candidiasis (AI); topical therapy alone is not recommended (AI).

Preferred Therapy

- Fluconazole 200-mg loading dose, followed by 100–200 mg (up to 400 mg) PO or IV daily (AI); consider oral suspension for people with severe symptoms and difficulty swallowing.

Alternative Therapy

- Itraconazole oral solution 200 mg PO daily (AI), *or*
- Isavuconazole 400 mg PO as a loading dose, followed by isavuconazole 100 mg PO daily (BI), *or*
- Isavuconazole 400 mg PO once weekly (BI), *or*
- Voriconazole 200 mg PO or IV twice daily (BI), *or*
- Posaconazole oral suspension 400 mg (10 mL) PO twice daily for 1 day, then 400 mg daily (BI), *or*
- Posaconazole tablet 300 mg PO twice daily for 1 day, then 300 mg daily (BI), *or*
- Lipid formulation of amphotericin B 3–4 mg/kg IV daily (BI)
- Caspofungin 70-mg loading dose IV, followed by 50 mg IV daily (BI), *or*
- Micafungin 150 mg IV daily (BI), *or*
- Anidulafungin 100 mg IV for one dose, then anidulafungin 50 mg IV daily (BI)

Note: A higher rate of esophageal candidiasis relapse has been reported with echinocandins than with fluconazole.

Uncomplicated Vulvovaginal Candidiasis

- Fluconazole 150 mg PO for one dose (AII), *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (AII), *or*
- Ibrexafungerp 300 mg PO twice daily for 1 day (BI), *or*
- For azole-refractory *Candida glabrata* vaginitis, boric acid 600 mg vaginal suppository once daily for 14 days (BII)

Severe or Recurrent Vulvovaginal Candidiasis

- Oral fluconazole (100–200 mg) PO daily or topical antifungals for ≥7 days (AII)
- *For recurrent only (the following regimens include treatment for the acute episode plus treatment to reduce incidence of recurrent episodes):*
  - Oteseconazole 600 mg PO at Day 1, 450 mg at Day 2, followed by once weekly 150 mg dosing starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or*
  - Fluconazole 150 mg PO at Days 1, 4, and 7, followed by oteseconazole 150 mg PO daily at Days 14 through 20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); or
  - Fluconazole 150 mg PO every 72 hours x 3 doses, followed by ibrexafungerp 300 mg PO twice daily 1 day per month for 6 months (BI) (use an effective form of contraception during treatment and for 4 days after the last dose)

Other Considerations
• Systemic azoles may have significant drug–drug interactions with ARV drugs (refer to Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines) and other drugs used for the treatment of opportunistic infections (refer to Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections). Consider TDM if prolonged use is indicated. • Fluconazole, itraconazole, posaconazole, and voriconazole can increase the risk for QTc prolongation, especially when co-administered with other QTc prolonging drugs that are cleared by CYP3A4. • Chronic or prolonged use of azoles might promote development of resistance.
Considerations During Pregnancy and Lactation
• Topical therapy is preferable for treatment of oral candidiasis and vulvovaginal candidiasis in pregnancy. Oral fluconazole should be avoided when treating vulvovaginal candidiasis in the first trimester (AIII). • During pregnancy, substitution of amphotericin B for fluconazole in the first trimester is recommended for invasive or refractory esophageal *Candida* infections (AIII). • Human data are not available for micafungin, anidulafungin, caspofungin, thus their use in human pregnancy is not recommended (AIII). Human data on the use of voriconazole are also not available, so its use is not recommended. • Oteseconazole is contraindicated during pregnancy and when lactating as animal studies have shown fetal malformations including ocular toxicity. Due to its long half-life, it is also contraindicated in females of reproductive potential despite the use of oral or other contraception. • Ibrexafungerp is teratogenic in animal studies. Use during pregnancy and when lactating is contraindicated.

Key: ARV = antiretroviral; CYP = cytochrome P450; IV = intravenous; PO = orally; QTc = QT corrected for heart rate; TDM = therapeutic drug monitoring

Oropharyngeal Candidiasis

Oral fluconazole is as effective as or superior to topical therapy for oropharyngeal candidiasis.[14] In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Oral therapy has the additional benefit over topical regimens of being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 to 200 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy **(AI).**[14] One to 2 weeks of therapy until resolution of infection is recommended for oropharyngeal candidiasis.[14]

Using topical agents to treat oropharyngeal candidiasis includes several advantages: it reduces systemic drug exposure, diminishes the risk of drug–drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. As an alternative to oral fluconazole, once-daily miconazole in 50-mg mucoadhesive buccal tablets **(BI)** or five-times-per-day clotrimazole troches can be used to treat oropharyngeal candidiasis **(BI);** these regimens were shown to be equivalent in a multicenter, randomized study. Nystatin suspension four times daily remains an additional alternative **(BII).**[15] Unfavorable taste and multiple daily dosing, such as in the cases of clotrimazole and nystatin, may lead to decreased tolerability of and adherence to these topical therapies. If esophageal involvement is suspected, topical therapy alone is not recommended **(AI).**

Itraconazole is formulated as an oral solution or capsules, which differ in dosing and efficacy. Oral itraconazole for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated.[16] Posaconazole oral suspension[17] is also as effective as fluconazole and generally better tolerated than itraconazole solution, but it is more expensive. Although both posaconazole and

itraconazole have more drug–drug interactions than fluconazole, there are a few situations, such as *in vitro* resistance or poor clinical response, that would suggest these drugs be used in preference to fluconazole solely to treat mucosal candidiasis **(BI).** In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.[17] A oral delayed-release tablet formulation of posaconazole, which exhibits less variable absorption than the oral suspension, has been available.[18] Whether it offers any advantage for the treatment of oropharyngeal candidiasis has not been formally tested; however, it has been shown that switching from the oral suspension to the tablet formulation of posaconazole results in greater serum concentrations.[19] Itraconazole capsules are less effective than fluconazole because of their more variable absorption, and they are associated with more drug–drug interactions than fluconazole.

Esophageal Candidiasis

Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI).** A 14-day to 21-day course of either fluconazole (oral or intravenous [IV]) or oral itraconazole solution is highly effective and therefore recommended **(AI).** As with oropharyngeal candidiasis, however, itraconazole capsules for esophageal candidiasis may be less effective than fluconazole because of variable absorption Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis **(AI).** People with severe symptoms initially may have difficulty swallowing oral drugs; oral fluconazole suspension is available and should be considered in such patients. A 2-week course of isavuconazole, given orally at an initial loading dose of 400 mg followed by 100 mg once daily **(BI)** or 400 mg once weekly, is as effective as fluconazole for uncomplicated esophageal candidiasis and is recommended as an alternative regimen **(BI);** however, a higher rate of gastrointestinal adverse effects was seen with the 100-mg, once-daily isavuconazole regimen than with fluconazole and the other isavuconazole regimens.[20] Posaconazole, voriconazole, amphotericin B (lipid formulations), and the echinocandins caspofungin, micafungin, and anidulafungin all effectively treat esophageal candidiasis and also can be administered as alternatives **(BI);** however, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.[21,22] Cost and insurance coverage also might be issues for the newer therapies.

Although infection with other pathogens that can cause esophagitis (e.g., cytomegalovirus, herpes simplex virus) can result in symptoms that mimic those of esophageal candidiasis, a diagnostic and therapeutic trial of antifungal therapy is usually warranted before endoscopy. In those who do not respond to antifungal therapy within 7 days, endoscopy is recommended to identify other potential causes of esophagitis or drug-resistant *Candida* **(AII).**

Vulvovaginal Candidiasis

In most people with HIV, vulvovaginal candidiasis is uncomplicated and responds readily to short-course oral or topical treatment with any of several therapies, including the following:

- Oral fluconazole **(AII)**
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) **(AII)**
- Oral ibrexafungerp **(BI)**

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for ≥7 days **(AII).**

There are now additional options for recurrent vulvovaginal candidiasis that include treatment for the acute episode plus treatment to reduce incidence of recurrent episodes. One option for people who are not of reproductive potential is oteseconazole, a new tetrazole antifungal that was U.S. Food and Drug Administration (FDA)–approved in 2022. It exhibited efficacy when administered as 600 mg on Day 1 and 450 mg on Day 2, followed by once-weekly 150 mg dosing starting at Day 14 for 11 weeks or when it was administered after three fluconazole 150-mg doses administered at Days 1, 4, and 7, followed by oteseconazole 150 mg daily dosing at Days 14 through 20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4 through 14) **(AI).**[23,24]

Ibrexafungerp is an oral b-glucan synthase inhibitor that belongs in the class of triterpenoids. It was effective in Phase 2 and Phase 3 clinical trials of uncomplicated vulvovaginal candidiasis and was approved by the FDA in 2021.[25,26] In December 2022, ibrexafungerp was approved by the FDA for women with recurrent vulvovaginal candidiasis. Specifically, administration of fluconazole 150 mg every 72 hours for three doses, followed by ibrexafungerp 300 mg twice daily 1 day per month for 6 months was associated with absence of recurrent infection through week 24 in 65.4% of women compared to 53.1% of women who received placebo. These findings have been reported only in a press release,[27] with results available at ClinicalTrials.gov and on the FDA label,[28] and are thereby less compelling than peer-reviewed publication. Therefore, ibrexafungerp can be administered for recurrent vulvovaginal candidiasis **(BI).** Given the potential teratogenic effects of ibrexafungerp, treatment of women with recurrent vulvovaginal candidiasis who may become pregnant requires institution and documentation of effective contraception during treatment and for 4 days after the last dose.[29] For additional advice on managing Vulvovaginal Candidiasis, see the section in the STI Treatment Guidelines from the Centers for Disease Control and Prevention.

Special Considerations with Regard to Starting ART

There are no special considerations regarding initiation of ART in people with mucocutaneous candidiasis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed. For information about drug–drug interactions between azoles and ARV agents, see the Drug–Drug Interactions section in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. For information about drug–drug interactions between azoles and other drugs used for the treatment of opportunistic infections, see Table 4: Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

For most people with mucocutaneous candidiasis, response to antifungal therapy is rapid; signs and symptoms improve within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although people may experience cutaneous hypersensitivity reactions characterized by rash and pruritus. Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. Liver function and the QTc interval should be monitored if azole therapy is anticipated for >21 days, especially in people with other hepatic comorbidities or on concomitant hepatotoxic drugs **(AII).** The echinocandins appear to be associated with very few adverse reactions: histamine-related infusion toxicity, transaminase elevations, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.[30]

Immune reconstitution inflammatory syndrome (IRIS) with ART has rarely been reported for mucocutaneous candidiasis in people with HIV. Indeed, ART is associated with a markedly reduced incidence of candidiasis.[31,32]

Managing Treatment Failure

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis within 7 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of people with HIV who have oral or esophageal candidiasis, typically those with CD4 counts <50 cells/mm^3 who have received multiple courses of azole antifungals.[4] Confirmatory culture with drug susceptibilities and, in the case of esophageal candidiasis, endoscopy, are necessary to assess for treatment failure due to azole resistance or other causes of esophagitis, especially if these procedures were not initially performed.

Posaconazole immediate-release oral suspension (400 mg twice daily for 28 days) is effective in 75% of people with azole-refractory oropharyngeal or esophageal candidiasis and is therefore recommended **(AI).**[33] Again, although the delayed-release tablet formulation of posaconazole is now available, it is not known whether it offers an advantage over the suspension for treating this particular disease. Alternatively, oral itraconazole solution is effective, at least transiently, in approximately two-thirds of people with fluconazole-refractory mucosal candidiasis and can be used as alternative therapy **(BII).**[16] If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin **(BII),** caspofungin **(BII),** micafungin **(BII),** or voriconazole **(BII).**[21,22,34,35]

IV amphotericin B **(BII),** amphotericin B deoxycholate **(BII),** and the lipid preparations of amphotericin B **(BII)** are usually effective for treating azole-refractory disease and are therefore recommended. Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension four times daily) can be administered to people with refractory oropharyngeal candidiasis who cannot take other oral options **(BII),** but this product is not commercially available in the United States and requires compounding by pharmacies.[36]

Patients with refractory vaginal candidiasis may benefit from intravaginal boric acid suppositories, which are commercially available at 600 mg.[37,38]

Preventing Recurrence

Preventing Recurrence
• Chronic suppressive therapy for recurrent oropharyngeal or vulvovaginal candidiasis is usually not recommended unless people have frequent or severe recurrences (CIII). • If used, it is reasonable to discontinue therapy if CD4 count increased to >200 cells/mm^3 following initiation of ART (AIII).
If the Decision Is to Use Suppressive Therapy Because of Frequent or Severe Recurrences
Oropharyngeal Candidiasis
• Fluconazole 100 mg PO once daily or three times weekly (BI)
Esophageal Candidiasis
• Fluconazole 100–200 mg PO daily (BI), *or*

- Posaconazole oral suspension 400 mg PO twice daily (BII), *or*
- Posaconazole tablet 300 mg PO daily (BII)

Vulvovaginal Candidiasis

- Fluconazole 150 mg PO once weekly (BII) *or*
- Oteseconazole 600 mg at Day 1, 450 mg at Day 2 for treatment of the acute episode, followed by once-weekly 150-mg doses starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or*
- Fluconazole 150 mg at Days 1, 4, and 7 for treatment of the acute episode, followed by oteseconazole 150 mg daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); *or*
- Ibrexafungerp 300 mg twice daily 1 day per month for 6 months (BI) (use an effective form of contraception during treatment and for 4 days after the last dose.)

Considerations During Pregnancy and Lactation

- Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles should not be initiated during pregnancy (AIII). Furthermore, prophylaxis with systemic azoles should be discontinued during pregnancy (AIII).
- Oteseconazole is contraindicated during pregnancy and when lactating as animal studies have shown fetal malformations including ocular toxicity. Due to its long half-life, it is also contraindicated in females of reproductive potential despite the use of oral or other contraception.
- Ibrexafungerp is teratogenic in animal studies. Use during pregnancy or when lactation is contraindicated.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

When to Start Suppressive Therapy

A randomized clinical trial[39] of people with HIV who had CD4 counts <150 cells/mm^3 documented significantly fewer episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (three times a week) than with episodic fluconazole treatment for recurrences. This clinical trial also demonstrated no difference in the risk of developing clinically significant fluconazole resistance between the two fluconazole-treated groups among patients who were receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) for recurrent oropharyngeal or vulvovaginal candidiasis **is not recommended** by most HIV specialists unless people have frequent or severe recurrences **(CIII)** because therapy for acute disease is effective, mortality associated with mucocutaneous disease is low, potential exists for drug interactions and for the development of antifungal-resistant *Candida*, and prophylaxis is costly.

If recurrences are frequent or severe, oral fluconazole can be used as suppressive therapy for oropharyngeal **(BI),** esophageal **(BI),** or vulvovaginal **(AII)** candidiasis.[40-42] Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII).**[43] The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in people with HIV who are severely immunocompromised.[44] Several important factors should be considered when making the decision to use secondary prophylaxis. These factors include the effect of recurrences on the person's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events, and, most importantly, drug–drug interactions.[45]

Rates of relapse are high in people with azole-refractory oropharyngeal or esophageal candidiasis who have initially responded to echinocandins, voriconazole, or posaconazole therapy. In such people, secondary prophylaxis should be instituted until immune reconstitution is achieved with the use of ART **(AIII).**

For information regarding oteseconazole and ibrexafungerp, see the Vulvovaginal Candidiasis Treatment Section above.

When to Stop Suppressive Therapy

In situations where secondary prophylaxis has been instituted, no data exist to guide recommendations regarding its discontinuation. Based on experience with other opportunistic infections, it would be reasonable to discontinue secondary prophylaxis when the CD4 count has increased to >200 cells/mm^3 following initiation of ART **(AIII).**

Special Considerations During Pregnancy

Pregnancy increases the risk of vaginal colonization with *Candida* species. During pregnancy, diagnosis and management of oropharyngeal, esophageal, and vulvovaginal candidiasis are the same as for other people with HIV, with several considerations.

Topical therapy is preferable for treatment of oral candidiasis and vulvovaginal candidiasis in pregnancy. Oral fluconazole should be avoided when treating vulvovaginal candidiasis in the first trimester **(AIII).** Data derived from women with vulvovaginal candidiasis suggest that fluconazole should not be used at any dose (including a single 150-mg dose) in the first trimester due to the risk of spontaneous abortion, while higher exposures (>150 mg dosing) during the first trimester are associated with cardiac septal closure defects.[46-50] A recent analysis of registry data from Sweden and Denmark did not find any increase in stillbirth or neonatal death associated with exposure to fluconazole at any dose during pregnancy.[51] Five cases of a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures (fluconazole embryopathy) have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[48] A report from a national cohort register in Denmark found an increased hazard ratio (HR) of 1.48 for spontaneous pregnancy loss with any exposure to oral fluconazole from 7 to 22 weeks of pregnancy compared to unexposed, matched controls.[49] An increased HR of 1.47 was also noted with low-dose (150–300-mg cumulative dose) exposure. No increase in stillbirth was seen with fluconazole exposure broadly, but an increase in risk of stillbirth (HR, 4.10) was noted with fluconazole doses >300 mg.

Based on these data, substitution of amphotericin B for fluconazole in the first trimester is recommended for invasive or refractory esophageal *Candida* infections **(AIII).** Neonates born to those receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Other azoles are similarly not recommended in pregnancy. Itraconazole at high doses has been shown to be teratogenic in animals,[52] but the metabolic mechanism accounting for these defects is not present in humans, so the data supporting this finding are of uncertain significance to human pregnancy. Case series in humans do not suggest an increased risk of birth defects with itraconazole,[53] but experience is limited. Human data are not available for posaconazole; however, the drug was associated with skeletal abnormalities in rats and was embryotoxic in rabbits when

given at doses that produced plasma levels equivalent to those seen in humans.[54] Evidence is inconclusive or inadequate for determining fetal risk associated with voriconazole use during pregnancy. An association with cleft palate and renal defects has been seen in rats, as well as embryotoxicity seen in rabbits.[55] Human data on the use of voriconazole are not available, so its use **is not recommended.** In animals, multiple anomalies have been seen with exposure to micafungin, and ossification defects have been seen with the use of anidulafungin and caspofungin.[56] Human data are not available for these drugs, thus their use in human pregnancy **is not recommended (AIII).**

The recently FDA-approved drugs for the treatment of vulvovaginal candidiasis, ibrexafungerp and oteseconazole, are **contraindicated** in pregnancy as animal studies have shown fetal malformations including ocular toxicity from oteseconazole.[29,57]

Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles **should not be initiated** during pregnancy **(AIII).** Furthermore, prophylaxis with systemic azoles **should be discontinued** during pregnancy **(AIII).**

References

1. Boesecke C, Schellberg S, Schneider J, Schuettfort G, Stocker H. Prevalence, characteristics and challenges of late HIV diagnosis in Germany: an expert narrative review. Infection. 2023;51(5):1223-1239. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37470977.

2. Martins MD, Lozano-Chiu M, Rex JH. Point prevalence of oropharyngeal carriage of fluconazole-resistant *Candida* in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1997;25(4):843-846. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9356799.

3. Maenza JR, Merz WG, Romagnoli MJ, Keruly JC, Moore RD, Gallant JE. Infection due to fluconazole-resistant *Candida* in patients with AIDS: prevalence and microbiology. *Clin Infect Dis*. 1997;24(1):28-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8994752.

4. Fichtenbaum CJ, Koletar S, Yiannoutsos C, et al. Refractory mucosal candidiasis in advanced human immunodeficiency virus infection. *Clin Infect Dis*. 2000;30(5):749-756. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10816143.

5. Rex JH, Rinaldi MG, Pfaller MA. Resistance of *Candida* species to fluconazole. *Antimicrob Agents Chemother*. 1995;39(1):1-8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7695288.

6. Patel PK, Erlandsen JE, Kirkpatrick WR, et al. The changing epidemiology of oropharyngeal candidiasis in patients with HIV/AIDS in the era of antiretroviral therapy. *AIDS Res Treat*. 2012;2012:262471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22970352.

7. Thanyasrisung P, Kesakomol P, Pipattanagovit P, Youngnak-Piboonratanakit P, Pitiphat W, Matangkasombut O. Oral *Candida* carriage and immune status in Thai human immunodeficiency virus-infected individuals. *J Med Microbiol*. 2014;63(Pt 5):753-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24591706.

8. Mushi MF, Mtemisika CI, Bader O, et al. High oral carriage of non-*albicans Candida* spp. among HIV-infected individuals. *Int J Infect Dis*. 2016;49:185-188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27401585.

9. Clark-Ordóñez I, Callejas-Negrete OA, Aréchiga-Carvajal ET, Mouriño-Perez RR. *Candida* species diversity and antifungal susceptibility patterns in oral samples of HIV/AIDS patients in Baja California, Mexico. *Med Mycol*. 2016. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27630251.

10. Klein RS, Harris CA, Small CB, Moll B, Lesser M, Friedland GH. Oral candidiasis in high-risk patients as the initial manifestation of the acquired immunodeficiency syndrome. *N Engl J Med*. 1984;311(6):354-358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6738653.

11. Bonacini M, Young T, Laine L. The causes of esophageal symptoms in human immunodeficiency virus infection. A prospective study of 110 patients. *Arch Intern Med*. 1991;151(8):1567-1572. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1651690.

12. Brion LP, Uko SE, Goldman DL. Risk of resistance associated with fluconazole prophylaxis: systematic review. *J Infect*. 2007;54(6):521-529. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17239952.

13. Salem M, Reichlin T, Fasel D, Leuppi-Taegtmeyer A. Torsade de pointes and systemic azole antifungal agents: analysis of global spontaneous safety reports. *Glob Cardiol Sci Pract*. 2017;2017(2):11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29644223.

14. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):e1-50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26679628.

15. Vazquez JA, Patton LL, Epstein JB, et al. Randomized, comparative, double-blind, double-dummy, multicenter trial of miconazole buccal tablet and clotrimazole troches for the treatment of oropharyngeal candidiasis: study of miconazole Lauriad(R) efficacy and safety (SMiLES). *HIV Clin Trials*. 2010;11(4):186-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20974574.

16. Vazquez JA. Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection. *HIV AIDS (Auckl)*. 2010;2(1):89-101. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22096388.

17. Vazquez JA, Skiest DJ, Nieto L, et al. A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. *Clin Infect Dis*. 2006;42(8):1179-1186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16575739.

18. Krishna G, Ma L, Martinho M, Preston RA, O'Mara E. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. *J Antimicrob Chemother*. 2012;67(11):2725-2730. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22833639.

19. Jung DS, Tverdek FP, Kontoyiannis DP. Switching from posaconazole suspension to tablets increases serum drug levels in leukemia patients without clinically relevant hepatotoxicity. *Antimicrob Agents Chemother*. 2014;58(11):6993-6995. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25199774.

20. Viljoen J, Azie N, Schmitt-Hoffmann AH, Ghannoum M. A phase 2, randomized, double-blind, multicenter trial to evaluate the safety and efficacy of three dosing regimens of isavuconazole compared with fluconazole in patients with uncomplicated esophageal candidiasis. *Antimicrob Agents Chemother*. 2015;59(3):1671-1679. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25561337.

21. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. *Clin Infect Dis*. 2004;39(6):842-849. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15472817.

22. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis*. 2004;39(6):770-775. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15472806.

23. Martens MG, Maximos B, Degenhardt T, et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. *Am J Obstet Gynecol*. 2022;227(6):880 e881-880 e811. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35863457.

24. Sobel JD, Donders G, Degenhardt T, et al. Efficacy and safety of oteseconazole in recurrent vulvovaginal candidiasis. *NEJM Evid*. 2022;1(8):1-13. Available at: https://evidence.nejm.org/doi/full/10.1056/EVIDoa2100055.

25. Schwebke JR, Sobel R, Gersten JK, et al. Ibrexafungerp versus placebo for vulvovaginal candidiasis treatment: a phase 3, randomized, controlled superiority trial (VANISH 303). *Clin Infect Dis*. 2022;74(11):1979-1985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34467969.

26. Nyirjesy P, Schwebke JR, Angulo DA, Harriott IA, Azie NE, Sobel JD. Phase 2 randomized study of oral ibrexafungerp versus fluconazole in vulvovaginal candidiasis. *Clin Infect Dis*. 2022;74(12):2129-2135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34555149.

27. SCYNEXIS presents positive data from its pivotal phase 3 CANDLE study of oral ibrexafungerp for prevention of recurrent vaginal yeast infections during the 2022 IDSOG annual meeting [press release]. Jersey City, NJ. SCYNEXIS, Inc. 2022. Available at: https://d1io3yog0oux5.cloudfront.net/_b74ab29ee08f7c716ae5e6710e5dba4b/scynexis/news/2022-08-04_SCYNEXIS_Presents_Positive_Data_from_Its_Pivotal_298.pdf.

28. BREXAFEMME® (ibrexafungerp tablets), for oral use [package insert]. U.S. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214900s002lbl.pdf.

29. Sucher AJ, Thai A, Tran C, Mantena N, Noronha A, Chahine EB. Ibrexafungerp: a new triterpenoid antifungal. *Am J Health Syst Pharm*. 2022;79(24):2208-2221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36083109.

30. Chang YL, Yu SJ, Heitman J, Wellington M, Chen YL. New facets of antifungal therapy. *Virulence*. 2017;8(2):222-236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27820668.

31. Thambuchetty N, Mehta K, Arumugam K, Shekarappa UG, Idiculla J, Shet A. The epidemiology of IRIS in southern India: an observational cohort study. *J Int Assoc Provid AIDS Care*. 2017;16(5):475-480. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28399724.

32. Ramirez-Amador V, Patton LL, Naglik JR, Nittayananta W. Innovations for prevention and care of oral candidiasis in HIV-infected individuals: are they available?-A workshop report. *Oral Dis*. 2020;26 Suppl 1:91-102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32862535.

33. Skiest DJ, Vazquez JA, Anstead GM, et al. Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. *Clin Infect Dis*. 2007;44(4):607-614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17243069.

34. Villanueva A, Gotuzzo E, Arathoon EG, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med*. 2002;113(4):294-299. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12361815.

35. Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis*. 2001;33(9):1447-1454. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11577374.

36. Dentinger PJ, Swenson CF, Anaizi NH. Stability of amphotericin B in an extemporaneously compounded oral suspension. *Am J Health Syst Pharm*. 2001;58(11):1021-1024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11402476.

37. Powell A, Ghanem KG, Rogers L, et al. Clinicians' use of intravaginal boric acid maintenance therapy for recurrent vulvovaginal candidiasis and bacterial vaginosis. *Sex Transm Dis*. 2019;46(12):810-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31663976.

38. Nyirjesy P, Brookhart C, Lazenby G, Schwebke J, Sobel JD. Vulvovaginal candidiasis: a review of the evidence for the 2021 Centers for Disease Control and Prevention of sexually transmitted Infections treatment guidelines. *Clin Infect Dis*. 2022;74(Suppl_2):S162-S168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35416967.

39. Goldman M, Cloud GA, Wade KD, et al. A randomized study of the use of fluconazole in continuous versus episodic therapy in patients with advanced HIV infection and a history of oropharyngeal candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40. *Clin Infect Dis*. 2005;41(10):1473-1480. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16231260.

40. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):700-705. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7854376.

41. Schuman P, Capps L, Peng G, et al. Weekly fluconazole for the prevention of mucosal candidiasis in women with HIV infection. A randomized, double-blind, placebo-controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *Ann Intern Med*. 1997;126(9):689-696. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9139554.

42. Havlir DV, Dube MP, McCutchan JA, et al. Prophylaxis with weekly versus daily fluconazole for fungal infections in patients with AIDS. *Clin Infect Dis*. 1998;27(6):1369-1375. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9868644.

43. Vazquez JA, Skiest DJ, Tissot-Dupont H, Lennox JL, Boparai N, Isaacs R. Safety and efficacy of posaconazole in the long-term treatment of azole-refractory oropharyngeal and

esophageal candidiasis in patients with HIV infection. *HIV Clin Trials*. 2007;8(2):86-97. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17507324.

44. Johnson EM, Warnock DW, Luker J, Porter SR, Scully C. Emergence of azole drug resistance in *Candida* species from HIV-infected patients receiving prolonged fluconazole therapy for oral candidosis. *J Antimicrob Chemother*. 1995;35(1):103-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7768758.

45. Marty F, Mylonakis E. Antifungal use in HIV infection. *Expert Opin Pharmacother*. 2002;3(2):91-102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11829723.

46. Alsaad AM, Kaplan YC, Koren G. Exposure to fluconazole and risk of congenital malformations in the offspring: a systematic review and meta-analysis. *Reprod Toxicol*. 2015;52:78-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25724389.

47. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369(9):830-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23984730.

48. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol*. 2005;73(11):919-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16265639.

49. Molgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26746458.

50. Berard A, Sheehy O, Zhao JP, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ*. 2019;191(7):E179-E187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30782643.

51. Pasternak B, Wintzell V, Furu K, Engeland A, Neovius M, Stephansson O. Oral fluconazole in pregnancy and risk of stillbirth and neonatal death. *JAMA*. 2018;319(22):2333-2335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29896619.

52. SPORANOX® (itraconazole) oral solution [package insert]. U.S. Food and Drug Administration. 2003. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/020657s038lbl.pdf.

53. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19338381.

54. NOXAFIL Highlights of prescribing information [package insert]. U.S. Food and Drug Administration. 2015. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022003s018s020,0205053s002s004,0205596s001s003lbl.pdf.

55. VFEND® [package insert]. U.S. Food and Drug Administration. 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021266s032lbl.pdf.

56. Pilmis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: an updated review. *J Antimicrob Chemother*. 2015;70(1):14-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25204341.

57. Oteseconazole. *Am J Health Syst Pharm*. 2022;79(23):2083-2085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36173878.

Chagas Disease

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Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*. It is transmitted to humans by infected triatomine bugs ("kissing bugs"), and less commonly by transfusion, organ transplant, from mother to infant, and, in rare instances, by ingestion of contaminated food or drink.[1-4]

Vector-borne transmission occurs only in the Americas, where an estimated 6 million people have Chagas disease.[5,6] Historically, transmission occurred largely in rural areas in Latin America, where houses built of mud brick are vulnerable to colonization by the triatomine vectors.[4] In such areas, Chagas disease usually is acquired in childhood. In the last several decades, successful vector control programs have substantially decreased transmission rates in much of Latin America.[4,7,8]

Infected triatomine vectors and *T. cruzi*–infected domestic and wild animals are found across the southern half of the United States, and rare cases of autochthonous vector-borne transmission have been documented.[9-11] However, the risk of vector-borne infection within the United States appears to be very low.[12] *T. cruzi* can also be transmitted in blood; screening of blood donations for anti-*T. cruzi* antibodies was introduced in 2007 after the U.S. Food and Drug Administration approved a serological test for that purpose.[13,14]

In people chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (e.g., due to advanced HIV) may lead to reactivation of the disease, characterized by parasitemia, which is associated with increased intracellular parasite replication and lack of immunological control of the infection.[15-17]

Clinical Manifestations

Acute Phase. The acute phase of *T. cruzi* infection, which typically goes unrecognized, lasts up to 90 days and is characterized by circulating trypomastigotes detectable on microscopy of fresh blood or buffy coat smears.[2,4] If the portal of infection was the conjunctiva, patients may develop the characteristic Romaña's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.[2,4] At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective antitrypanosomal treatment, *T. cruzi* infection passes into the chronic phase.[2,4]

Chronic Phase. Most patients with chronic *T. cruzi* infection have no signs or symptoms and are said to have the indeterminate form of the disease. Over the course of their lives, 20% to 30% of these patients will progress to clinically evident Chagas disease—most commonly, cardiomyopathy.[2,4] The earliest manifestations are usually conduction system abnormalities, such as right bundle branch block, alone or in combination with frequent premature ventricular contractions, which may develop years to decades after infection.[4,18] Over time, the disease may progress to

higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, poor prognostic factors include congestive heart failure, ventricular aneurysm, and complete heart block; these are associated with short-term mortality, including sudden death.[19] Chagas digestive disease is much less common than cardiomyopathy.[20] Dysphagia is the characteristic symptom of megaesophagus, and prolonged constipation is the most common complaint associated with megacolon.

T. cruzi reactivation during the chronic phase of Chagas disease is characterized by a return to high levels of parasite replication and parasitemia, which are usually detectable by microscopy. Reactivation can occur in individuals on immunosuppressive medications or cancer chemotherapy and in people with HIV.[16,21-25] Even in the absence of symptoms, people with HIV and chronic Chagas disease have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.[24] Most cases of clinically apparent reactivation occur with CD4 T lymphocyte cell counts <200 cells/mm^3, a history of prior opportunistic infections, or both.[16]

The clinical features of reactivated Chagas disease in people with HIV differ from those observed in individuals who are immunosuppressed for other reasons. The most common manifestations consist of *T. cruzi* meningoencephalitis, with or without brain abscesses (chagomas).[15,16,26,27] The presentation in people with HIV may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in people with HIV is acute myocarditis, sometimes superimposed on pre-existing chronic Chagas heart disease.[16,17] Patients may present with new arrhythmias, pericardial effusion, acute cardiac decompensation, or rapid progression of existing chronic cardiomyopathy.[16,28] Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach, or intestine.[16,28]

Diagnosis

Screening with serological testing is recommended for all individuals who have lived in Mexico or Central or South America for greater than 6 months.[29]

Most persons infected with *T. cruzi* are in the chronic phase and are typically unaware of their infection. Screening for infection to identify persons with the indeterminate or early clinical forms of chronic Chagas disease is important to identify those who might benefit from antiparasitic treatment and counseling regarding potential transmission of *T. cruzi* to others (e.g., blood donation, organ donation). This is particularly important for people with HIV because of the risk of reactivation disease.

Diagnosis of chronic infection relies on serological methods to detect immunoglobulin G antibodies to *T. cruzi*, most commonly enzyme-linked immunosorbent assay (ELISA) and immunofluorescent antibody assay (IFA). No available assay has sufficient sensitivity and specificity to be used alone; a single positive result does not constitute a confirmed diagnosis. Two serological tests based on different antigens (i.e., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA) should be used for individuals with suspected Chagas. In some cases, the infection status remains difficult to resolve even after a third test, because there is no true gold standard assay for chronic *T. cruzi* infection.[29,30]

Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.[31,32] Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.[29,33] In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection, as its sensitivity is highly variable.[30,34,35]

In people with HIV and epidemiologic risk factors for Chagas disease, coinfection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.[16,25,26] The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than *Toxoplasma* lesions.[17,26,27] Computed tomography and magnetic resonance imaging show subcortical hypodense lesions that enhance with contrast or gadolinium. These lesions most often involve brain white matter. Histopathology shows inflammation and the presence of *T. cruzi* amastigotes in glial cells and, less often, in neurons. Cerebrospinal fluid (CSF) typically shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.[16,17,26,27] In a case series that included 15 people coinfected with HIV and *T. cruzi* with clinical meningoencephalitis, trypomastigotes were visualized in CSF in 85%.[36]

A definitive diagnosis of reactivation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF, or in blood.[16] In chronically infected patients who are immunocompetent or who have HIV coinfection in the absence of reactivation, trypomastigotes typically are undetectable in the circulating blood.[24] If observed in a coinfected patient, circulating parasites suggest reactivation and the need for treatment.

Testing to identify *T. cruzi* should be considered in all at-risk individuals with suspected reactivation of chronic Chagas disease. Initial assessment can be done by evaluation of a peripheral blood smear. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.[34] In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Parasites also may be observed in lymph nodes, bone marrow, skin lesions, or pericardial fluid. Hemoculture is somewhat more sensitive than direct methods but takes 2 to 8 weeks to demonstrate parasites. Quantitative PCR assays performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.[37,38] As such, clinicians should consider obtaining PCR testing in all individuals in whom there is high clinical suspicion and blood and/or tissue tests are negative.

In people with HIV who have suspected CNS Chagas disease, centrifugation and microscopic examination of CSF should be conducted. Few published data exist on PCR of CSF, but it would be expected to have high sensitivity for the diagnosis of reactivation in the CNS.[39]

In the United States, Chagas disease molecular detection (PCR testing for *T. cruzi* DNA) is available at the Centers for Disease Control and Prevention (CDC); consultations and testing requests should be addressed to Parasitic Diseases Hotline for Healthcare Providers (404-718-4745, parasites@cdc.gov, hours: 8 a.m.–4 p.m. ET/Monday–Friday) or through the CDC Emergency Operations Center (770-488-7100) for emergencies after business hours, on weekends, and federal holidays.

Preventing Exposure

Travelers to endemic countries may be at risk of infection with *T. cruzi* if they visit rural areas and stay in rustic lodging. The triatomine vector typically infests cracks in walls and roofing of poor-quality buildings that are constructed of adobe brick, mud, or thatch.[40] Because the insects feed at night, individuals who live in or visit Chagas disease–endemic areas should avoid sleeping in such dwellings or outdoors. Control programs in endemic areas rely on spraying infested dwellings with residual-action insecticide. If sleeping outdoors or in suspect dwellings cannot be avoided, sleeping under insecticide-treated bed nets provides significant protection.[41]

In the United States, all blood donors are screened for Chagas disease when they first donate blood. Universal screening of blood donors has been implemented in 21 Chagas disease–endemic Latin American countries.[42] Although transfusion-acquired cases have been uncommon in the United States, transfusion with infected blood products remains a risk for acquiring Chagas disease. No drugs or vaccines for preventing *T. cruzi* infection are available.

Preventing Disease

All people with HIV with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.[29,43]

For people living with HIV, a single course of treatment with benznidazole or nifurtimox should be offered to individuals with *T. cruzi* infection who have not been previously treated and who do not have advanced Chagas cardiomyopathy, with a discussion of potential risks and benefits and shared decision making **(BIII).** However, the efficacy of currently available drugs in the chronic phase is suboptimal, there is no useful test of cure, and treated individuals are still considered at risk for reactivation.[32,44] There are no direct studies evaluating interactions between antiretroviral medications and either benznidazole or nifurtimox. However, as benznidazole may be partially metabolized by the cytochrome P450 (CYP) system, medications that inhibit this system may increase benznidazole toxicity and those that induce CYP enzymes may reduce benznidazole efficacy.[43,45]

Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in coinfected patients**.** Most symptomatic reactivation cases have occurred in people with HIV who were not virologically suppressed on ART.[16,43]

Treating Disease

Therapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute and reactivated disease.[44,46] These drugs have limited efficacy, however, in achieving parasitological cure. As both drugs are U.S. Food and Drug Administration (FDA)–approved only for children, use for the treatment of adults in the United States is off-label. Individuals with advanced Chagas cardiomyopathy will not benefit from treatment. Consultation with a specialist should be sought. Consultations with experts at the CDC can be addressed to the Parasitic Diseases Hotline for Healthcare Providers (404-718-4745, parasites@cdc.gov).

Benznidazole (commercially available at http://www.benznidazoletablets.com/en) is approved by the FDA for use in children 2 to 12 years of age. The use of benznidazole to treat a patient outside of the

FDA-approved age range is based on clinical diagnosis and decision by a treating physician under practice of medicine. The regimen of 5 to 8 mg/kg/day in two divided doses taken with or without food for 60 days is the recommended treatment **(BIII);** a daily maximum dose of 300 mg is recommended by most experts.[47,48]

Nifurtimox (Lampit®) is also FDA approved for children less than 18 years of age and is available from retail sources.[49,50] Use of nifurtimox to treat a patient outside of the FDA-approved age range is based on clinical diagnosis and decision by the treating physician under practice of medicine. The recommended regimen is 8 to 10 mg/kg/day in three divided doses with food for 60 days **(BIII).**[51]

Treatment of patients outside of the FDA-approved age ranges for either drug is based on clinical diagnosis and decision by the treating physician under practice of medicine. The duration of therapy with either of these agents has not been studied in people with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection, even in patients who receive chemotherapy.[16,26] Limited data suggest that early recognition and treatment of reactivation may improve prognosis.[16]

Special Considerations with Regard to Starting Antiretroviral Therapy

As with other parasitic infections that localize in the CNS, the decision to initiate ART must be carefully considered in people with HIV and reactivated *T. cruzi* infection involving the brain. Only anecdotal information exists on the consequences of starting ART after a diagnosis of CNS Chagas disease, but there are no cases of Chagas-related immune reconstitution inflammatory syndrome (IRIS) that have been well described. Therefore, there is no known contraindication to starting or optimizing ART in patients with CNS Chagas disease. ART should be initiated in all patients with concomitant *T. cruzi* **(AIII).** In general, as IRIS is not recognized as a common manifestation in the setting of coinfection, treatment of *T. cruzi* does not warrant delay in ART.

Monitoring for Adverse Events

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.[46]

Benznidazole-associated adverse drug reactions include abdominal symptoms (abdominal pain, nausea, vomiting, diarrhea), reversible peripheral neuropathy, rash, and granulocytopenia. Comprehensive metabolic panel (CMP) and complete blood count (CBC) should be monitored before initiation and during therapy. Co-administration of benznidazole with disulfiram, alcohol, and products that contain propylene glycol should be avoided.

Nifurtimox-associated adverse drug reactions include anorexia, nausea, vomiting, abdominal pain and weight loss, rash, restlessness, tremors, and dose-dependent peripheral neuropathy. Alcohol consumption with nifurtimox should be avoided. CMP and CBC should be monitored before initiation and during treatment with nifurtimox.

The frequency of monitoring CMP and CBC during treatment, though not standardized, is generally every 2 weeks. The adverse effects of both drugs wane when the drugs are discontinued. For more information, refer to the Adverse Drug Reactions table.

As stated above, there are no reports at this time regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

People with HIV are at risk for clinical manifestations because of intermittent reactivation of chronic infection.[43] Benznidazole and nifurtimox are only partially effective in the chronic phase of *T. cruzi* infection and may be suppressive rather than curative.[44] Because the drugs are toxic and experience with their use in people with HIV is limited, expert advice should be sought.[46] Whether secondary prophylaxis or chronic maintenance therapy should be used in people with HIV with latent Chagas disease is unclear, particularly when potent ART is used.

There are no current recommendations for monitoring for reactivation after treatment. *T. cruzi* antibodies may persist after treatment. Reactivation after treatment is diagnosed based on compatible clinical symptoms and identification of the parasite in blood or CNS fluid/tissue by microscopy or PCR. Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for people with HIV and *T. cruzi* reactivation who fail to respond or who reactivate again after initial antitrypanosomal therapy **(AIII).**

Special Considerations During Pregnancy

Anyone who has lived in endemic areas should be screened for Chagas disease, particularly if pregnant, to identify maternal infection and possible risk of infection in their offspring.. See the CDC resource for congenital Chagas disease for more information.

Between 1% to 10% of infants of mothers with *T. cruzi* are born with acute *T. cruzi* infection.[52] Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases.[53] In a small proportion of patients, congenital infection causes severe morbidity, including low birthweight, hepatosplenomegaly, anemia, meningoencephalitis, and/or respiratory insufficiency, with high risk of mortality.[52,54] Limited data suggest that the rate of congenital transmission is higher for women with HIV than in immunocompetent women.[16,55] Infants with HIV and concomitant *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.[56,57]

Minimal data are available on the potential reproductive toxicity of benznidazole and nifurtimox, although both drugs have been associated with increased detection of chromosomal aberrations in children being treated for Chagas disease.[58,59] Benznidazole crosses the placenta in rats.[60] Due to the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection during pregnancy should only be undertaken in consultation with a specialist in this area, and treatment of chronic disease should be considered only after completion of the pregnancy and breastfeeding. In cases of symptomatic reactivation of *T. cruzi* infection during pregnancy, ART should be initiated **(AIII)** as initial treatment. Only two cases of treatment of Chagas disease in pregnancy with benznidazole have been reported in people with HIV.[61,62] One infant was born with a low birthweight.[62] All infants born to women with *T. cruzi* should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.[63,64] Refer to the Opportunistic Infection Drugs During Pregnancy table for additional information.

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Manifestations of Chagas Disease

- All people with HIV who have epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* using at least two serological tests based on different antigens (e.g., whole parasite lysate and recombinant antigens) and/or techniques (e.g., ELISA and IFA).

Indication

- Individuals with epidemiological risk factors for Chagas disease who have tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy

Therapy

- A single course of benznidazole or nifurtimox is recommended by some experts (doses and duration same as for treatment of acute or reactivated infection).
  - Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 60 days (BIII) (commercially available at http://www.benznidazoletablets.com/en). Most experts recommend a daily maximum of 300 mg.
  - Nifurtimox (Lampit®) 8–10 mg/kg/day PO in 3 divided doses for 60 days (BIII) (commercially available through retail sources)

Note: Efficacy of both therapies is suboptimal, and treated patients are still at risk of reactivation.

Treating Acute or Reactivated *T. cruzi* Infection

Indication

- Individuals with acute or reactivated *T. cruzi* infection as manifested by presence of parasitemia should be treated (AII).

Therapy

- Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 60 days (BIII) (commercially available at http://www.benznidazoletablets.com/en). Most experts recommend a daily maximum of 300 mg.
- Nifurtimox (Lampit®) 8–10 mg/kg/day PO in 3 divided doses for 60 days (BIII) (commercially available through retail sources)
- Initiation or optimization of ART is recommended for all people with HIV with concomitant *T. cruzi* (AIII).

Note: Treatment is not recommended for patients with advanced chagasic cardiomyopathy.

Key: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; ELISA = enzyme-linked immunosorbent assays; IFA = immunofluorescence assays; PO = orally

References

1. Messenger LA, Bern C. Congenital Chagas disease: current diagnostics, limitations and future perspectives. *Curr Opin Infect Dis*. 2018;31(5):415-421. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30095485.

2. Maguire J. *Trypanosoma*. Vol. 2nd ed. Philadelphia, PA: Lippincott, Williams, & Wilkins; 2004.

3. Benchimol Barbosa PR. The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks. *Int J Cardiol*. 2006;112(1):132-133. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16600406.

4. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. 2010;375(9723):1388-1402. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20399979.

5. World Health Organization. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. *Wkly Epidemiol Rec*. 2015;90(6):33-43. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25671846.

6. Pan American Health Organization. Chagas disease. 2022. Available at: https://www.paho.org/en/topics/chagas-disease.

7. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. *Acta Trop*. 2010;115(1-2):22-27. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19646412.

8. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. *Mem Inst Oswaldo Cruz*. 2003;98(5):577-591. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12973523.

9. Lynn MK, Bossak BH, Sandifer PA, Watson A, Nolan MS. Contemporary autochthonous human Chagas disease in the USA. *Acta Trop*. 2020;205:105361. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32006523.

10. Bern C, Messenger LA, Whitman JD, Maguire JH. Chagas disease in the United States: a public health approach. *Clin Microbiol Rev*. 2019;33(1). Available at: https://www.pubmed.ncbi.nlm.nih.gov/31776135.

11. Kjos SA, Snowden KF, Craig TM, Lewis B, Ronald N, Olson JK. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol*. 2008;152(3-4):249-256. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18255233.

12. Klotz SA, Dorn PL, Klotz JH, et al. Feeding behavior of triatomines from the southwestern United States: an update on potential risk for transmission of Chagas disease. *Acta Trop*. 2009;111(2):114-118. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19524078.

13. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the U.S. blood supply. *Curr Opin Infect Dis*. 2008;21(5):476-482. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18725796.

14. Centers for Disease Control Prevention. Blood donor screening for chagas disease—United States, 2006-2007. *MMWR*. 2007;56(7):141-143. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17318113.

15. Rocha A, de Meneses AC, da Silva AM, et al. Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. 1994;50(3):261-268. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8147485.

16. Sartori AM, Ibrahim KY, Nunes Westphalen EV, et al. Manifestations of Chagas disease (American trypanosomiasis) in patients with HIV/AIDS. *Ann Trop Med Parasitol*. 2007;101(1):31-50. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17244408.

17. Vaidian AK, Weiss LM, Tanowitz HB. Chagas' disease and AIDS. *Kinetoplastid Biol Dis*. 2004;3(1):2. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15142278.

18. Nunes MCP, Beaton A, Acquatella H, et al. Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. *Circulation*. 2018;138(12):e169-e209. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30354432.

19. Rassi A, Jr., Rassi SG, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol*. 2001;76(1):75-96. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11175486.

20. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. *Am J Gastroenterol*. 1998;93(6):884-889. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9647012.

21. Radisic MV, Repetto SA. American trypanosomiasis (Chagas disease) in solid organ transplantation. *Transpl Infect Dis*. 2020;22(6):e13429. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32738158.

22. Czech MM, Nayak AK, Subramanian K, et al. Reactivation of Chagas disease in a patient with an autoimmune rheumatic disease: case report and review of the literature. *Open Forum Infect Dis*. 2021;8(2):ofaa642. Available at: https://www.pubmed.ncbi.nlm.nih.gov/33575423.

23. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. *Clin Infect Dis*. 1999;29(3):561-567. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10530448.

24. de Freitas VL, da Silva SC, Sartori AM, et al. Real-time PCR in HIV/*Trypanosoma cruzi* coinfection with and without Chagas disease reactivation: association with HIV viral load and CD4 level. *PLoS Negl Trop Dis*. 2011;5(8):e1277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21912712.

25. Sartori AM, Lopes MH, Benvenuti LA, et al. Reactivation of Chagas' disease in a human immunodeficiency virus-infected patient leading to severe heart disease with a late positive direct microscopic examination of the blood. *Am J Trop Med Hyg*. 1998;59(5):784-786. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9840598.

26. Almeida EA, Ramos Junior AN, Correia D, Shikanai-Yasuda MA. Co-infection *Trypanosoma cruzi*/HIV: systematic review (1980–2010). *Rev Soc Bras Med Trop*. 2011;44(6):762-770. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22231251.

27. Diazgranados CA, Saavedra-Trujillo CH, Mantilla M, Valderrama SL, Alquichire C, Franco-Paredes C. Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. *Lancet Infect Dis*. 2009;9(5):324-330. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19393962.

28. Ferreira MS, Nishioka Sde A, Silvestre MT, Borges AS, Nunes-Araujo FR, Rocha A. Reactivation of Chagas' disease in patients with AIDS: report of three new cases and review of the literature. *Clin Infect Dis*. 1997;25(6):1397-1400. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9431385.

29. Forsyth CJ, Manne-Goehler J, Bern C, et al. Recommendations for screening and diagnosis of Chagas disease in the United States. *J Infect Dis*. 2021. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34623435.

30. Whitman JD, Bulman CA, Gunderson EL, et al. Chagas disease serological test performance in U.S. blood donor specimens. *J Clin Microbiol*. 2019;57(12). Available at: https://www.pubmed.ncbi.nlm.nih.gov/31511333.

31. Sosa-Estani S, Gamboa-Leon MR, Del Cid-Lemus J, et al. Use of a rapid test on umbilical cord blood to screen for *Trypanosoma cruzi* infection in pregnant women in Argentina, Bolivia, Honduras, and Mexico. *Am J Trop Med Hyg*. 2008;79(5):755-759. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18981518.

32. Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gurtler RE. The challenges of Chagas disease—grim outlook or glimmer of hope. *PLoS Med*. 2007;4(12):e332. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18162039.

33. Verani JR, Seitz A, Gilman RH, et al. Geographic variation in the sensitivity of recombinant antigen-based rapid tests for chronic Trypanosoma cruzi infection. *Am J Trop Med Hyg*. 2009;80(3):410-415. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19270291.

34. Gorlin J, Rossmann S, Robertson G, et al. Evaluation of a new *Trypanosoma cruzi* antibody assay for blood donor screening. *Transfusion*. 2008;48(3):531-540. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18067497.

35. Junqueira AC, Chiari E, Wincker P. Comparison of the polymerase chain reaction with two classical parasitological methods for the diagnosis of Chagas disease in an endemic region of north-eastern Brazil. *Trans R Soc Trop Med Hyg*. 1996;90(2):129-132. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8761570.

36. Cordova E, Boschi A, Ambrosioni J, Cudos C, Corti M. Reactivation of Chagas disease with central nervous system involvement in HIV-infected patients in Argentina, 1992-2007. *Int J Infect Dis*. 2008;12(6):587-592. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18337139.

37. Ramirez JD, Guhl F, Umezawa ES, et al. Evaluation of adult chronic Chagas' heart disease diagnosis by molecular and serological methods. *J Clin Microbiol*. 2009;47(12):3945-3951. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19846646.

38. Duffy T, Bisio M, Altcheh J, et al. Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in chagas disease patients. *PLoS Negl Trop Dis*. 2009;3(4):e419. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19381287.

39. Schijman AG, Vigliano C, Burgos J, et al. Early diagnosis of recurrence of *Trypanosoma cruzi* infection by polymerase chain reaction after heart transplantation of a chronic Chagas' heart disease patient. *J Heart Lung Transplant*. 2000;19(11):1114-1117. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11077230.

40. Qvarnstrom Y, Schijman AG, Veron V, Aznar C, Steurer F, da Silva AJ. Sensitive and specific detection of *Trypanosoma cruzi* DNA in clinical specimens using a multi-target real-time PCR approach. *PLoS Negl Trop Dis*. 2012;6(7):e1689. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22802973.

41. Mott KE, Muniz TM, Lehman JS, Jr., et al. House construction, triatomine distribution, and household distribution of seroreactivity to *Trypanosoma cruzi* in a rural community in northeast Brazil. *Am J Trop Med Hyg*. 1978;27(6):1116-1122. Available at: https://www.pubmed.ncbi.nlm.nih.gov/103445.

42. Kroeger A, Villegas E, Ordonez-Gonzalez J, Pabon E, Scorza JV. Prevention of the transmission of Chagas' disease with pyrethroid-impregnated materials. *Am J Trop Med Hyg*. 2003;68(3):307-311. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12685636.

43. Perez-Molina JA, Rodriguez-Guardado A, Soriano A, et al. Guidelines on the treatment of chronic coinfection by *Trypanosoma cruzi* and HIV outside endemic areas. *HIV Clin Trials*. 2011;12(6):287-298. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22189148.

44. Rodriques Coura J, de Castro SL. A critical review on Chagas disease chemotherapy. *Mem Inst Oswaldo Cruz*. 2002;97(1):3-24. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11992141.

45. Perez Montilla CA, Moroni S, Moscatelli G, et al. Major benznidazole metabolites in patients treated for Chagas disease: mass spectrometry-based identification, structural analysis and detoxification pathways. *Toxicol Lett*. 2023;377:71-82. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36775077.

46. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. *JAMA*. 2007;298(18):2171-2181. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18000201.

47. U.S. Food and Drug Administration. Benznidazole tablets [package insert]. Exeltis USA, Inc. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209570s002lbl.pdf.

48. Altcheh J, Moscatelli G, Mastrantonio G, et al. Population pharmacokinetic study of benznidazole in pediatric Chagas disease suggests efficacy despite lower plasma

concentrations than in adults. *PLoS Negl Trop Dis*. 2014;8(5):e2907. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24853169.

49. Abbott A, Montgomery SP, Chancey RJ. Characteristics and adverse events of patients for whom nifurtimox was released through CDC-sponsored investigational new drug program for treatment of Chagas disease—United States, 2001–2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(10):371-374. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35271563.

50. Falk N, Berenstein AJ, Moscatelli G, et al. Effectiveness of nifurtimox in the treatment of Chagas disease: a long-term retrospective cohort study in children and adults. *Antimicrob Agents Chemother*. 2022;66(5):e0202121. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35416710.

51. U.S. Food and Drug Administration. LAMPIT (nifurtimox) tablets, for oral use [package insert]. Bayer HealthCare Pharmaceuticals Inc. 2023. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213464s004lbl.pdf.

52. Torrico F, Alonso-Vega C, Suarez E, et al. Maternal *Trypanosoma cruzi* infection, pregnancy outcome, morbidity, and mortality of congenitally infected and non-infected newborns in Bolivia. *Am J Trop Med Hyg*. 2004;70(2):201-209. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14993634.

53. Klein MD, Proano A, Noazin S, Sciaudone M, Gilman RH, Bowman NM. Risk factors for vertical transmission of Chagas disease: a systematic review and meta-analysis. *Int J Infect Dis*. 2021;105:357-373. Available at: https://www.pubmed.ncbi.nlm.nih.gov/33618005.

54. Chancey RJ, Edwards MS, Montgomery SP. Congenital Chagas disease. *Pediatr Rev*. 2023;44(4):213-221. Available at: https://www.pubmed.ncbi.nlm.nih.gov/37002357.

55. Scapellato PG, Bottaro EG, Rodriguez-Brieschke MT. Mother-child transmission of Chagas disease: could coinfection with human immunodeficiency virus increase the risk? *Rev Soc Bras Med Trop*. 2009;42(2):107-109. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19448923.

56. Freilij H, Altcheh J. Congenital Chagas' disease: diagnostic and clinical aspects. *Clin Infect Dis*. 1995;21(3):551-555. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8527542.

57. Freilij H, Altcheh J, Muchinik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. *Pediatr Infect Dis J*. 1995;14(2):161-162. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7746707.

58. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Assessment of cytogenetic damage in chagasic children treated with benznidazole. *Mutat Res*. 1988;206(2):217-220. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3140001.

59. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res*. 1989;224(2):263-267. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2507913.

60. de Toranzo EG, Masana M, Castro JA. Administration of benznidazole, a chemotherapeutic agent against Chagas disease, to pregnant rats. Covalent binding of reactive metabolites to fetal and maternal proteins. *Arch Int Pharmacodyn Ther*. 1984;272(1):17-23. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6440493.

61. Correa VR, Barbosa FG, Melo Junior CA, D'Albuquerque e Castro LF, Andrade Junior HF, Nascimento N. Uneventful benznidazole treatment of acute Chagas disease during pregnancy: a case report. *Rev Soc Bras Med Trop*. 2014;47(3):397-400. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25075496.

62. Bisio M, Altcheh J, Lattner J, et al. Benznidazole treatment of chagasic encephalitis in pregnant woman with AIDS. *Emerg Infect Dis*. 2013;19(9):1490-1492. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23965334.

63. Oliveira I, Torrico F, Munoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther*. 2010;8(8):945-956. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20695749.

64. Edwards MS, Stimpert KK, Bialek SR, Montgomery SP. Evaluation and management of congenital Chagas disease in the United States. *J Pediatric Infect Dis Soc*. 2019;8(5):461-469. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31016324.

Coccidioidomycosis

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Epidemiology

Coccidioidomycosis is caused by either of two soil-dwelling dimorphic fungi: *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in people with HIV have been reported in the areas in which the disease is highly endemic.[1] Cases also may be identified outside of these areas when a person gives a history of having traveled through an endemic region. In the United States, the endemic areas include the lower San Joaquin Valley and other arid regions in California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas and Northern Mexico.[2] Several cases of coccidioidomycosis in individuals who acquired the infection in eastern Washington state have been reported and phylogenetically linked to local *Coccidioides immitis* isolates in nature.[2] These observations and others suggest that the coccidioidal endemic range may be expanding outside the traditional endemic range.

The risk of developing symptomatic coccidioidomycosis after infection is increased in people with HIV who have CD4 T lymphocyte (CD4) cell counts <250 cells/mm^3 and who are not virologically suppressed.[3,4] The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[3,5]

Clinical Manifestations

Four common clinical syndromes of coccidioidomycosis have been described: focal pneumonia; diffuse pneumonia; extrathoracic involvement, including meningitis, osteoarticular infection, and other extrathoracic sites; and positive coccidioidal serology tests without evidence of localized infection.[6] In people with HIV, lack of viral suppression and CD4 count <250 cells/mm^3 are associated with increased severity of the presentation of coccidioidomycosis.[7]

Focal pneumonia is most common in people with CD4 counts ≥250 cells/mm^3. Focal pneumonia can be difficult to distinguish from bacterial or viral community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[7,8] However, symptoms such as hilar or mediastinal adenopathy, upper lobe infiltrates, nodules, peripheral blood eosinophilia, or rash—all of which are uncommon in bacterial pneumonia—may point towards coccidioidomycosis, particularly in patients who reside in, previously resided in, or have traveled to a known endemic area.

Diffuse pneumonia and extrathoracic disease usually occur in more apparently immunocompromised patients. Diffuse pulmonary disease presents with fever and dyspnea with a diffuse reticulonodular pattern on chest imaging, and in some instances may be difficult to distinguish clinically from *Pneumocystis* pneumonia.[9] Hypoxemia may be severe. Furthermore, serological tests may be negative at early presentation of infection.

Patients with meningitis present with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile in meningitis demonstrates low glucose levels, elevated protein levels, and a lymphocytic pleocytosis. Eosinophils may also be present on CSF analysis.

Elevated coccidioidal antibody titers even without symptoms can indicate risk of subsequent symptomatic diseases in people with HIV and advanced immunosuppression when CD4 count decreases to 10 cells/mm^3 or less.[10]

Diagnosis

The diagnosis of coccidioidomycosis is based on serology, histology, culture, and clinical presentation. Culture of the organism from clinical specimens or by demonstration of typical spherules on histopathological examination of infected tissue—such as sputum, bronchoalveolar lavage fluid, joint aspirate, or tissue biopsy—proves the diagnosis. Positive blood cultures are rare and usually found only in those with diffuse pulmonary disease. CSF cultures are positive in fewer than one-third of patients with coccidioidal meningitis.

Unlike other endemic fungi, *Coccidioides* species grow relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a nonpigmented mold may be observed in as few as 3 to 7 days. *Coccidioides* growth on an agar plate is a significant laboratory biosafety hazard because of the risk of inhalation of dislodged arthroconidia. When a specimen is sent for culture, laboratory personnel should be alerted to the possibility of suspected coccidioidomycosis; in the laboratory, the culture plate lid should be kept secured with tape.[11] Identification of the fungus should be performed only in a biosafety level 3 or 2+ containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test and a compatible clinical syndrome. However, it may take several weeks for antibodies to develop in normal hosts and probably longer in immunocompromised hosts. Negative serology cannot be used to rule out disease, and therefore, tissue biopsy may be necessary. Repeat testing every 1 to 2 weeks should be considered if the patient is ill and the diagnosis has not been established.

On the other hand, patients with past coccidioidal infection and without disease activity usually revert to negative serological tests over 1 to 2 years. Thus, screening with an enzyme immunoassay (EIA) for immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody is recommended to detect the possibility of active disease. The EIA has a rapid turnaround time and is available in many clinical laboratories. These tests are very sensitive but occasionally have been associated with false positive results, particularly for IgM.[12] If either EIA test is positive, antibody assays by immunodiffusion (ID) and by complement fixation (CF) should be obtained to confirm the result and be used for further follow-up **(AI).** In cases of EIA positivity with negative ID, the clinical context needs to be carefully considered, as well as the value of further diagnostic workup. CF has been particularly useful in cerebrospinal fluid. A lateral flow assay has become available, but it is far less sensitive than EIA.[13]

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[14] serum,[15] and other body fluids, such as CSF,[16,17] in samples from individuals with active coccidioidomycosis.[18] The assay is most useful in diagnosing disseminated coccidioidomycosis. Detection of coccidioidal antigen in CSF has been reported to have a very high sensitivity and specificity for diagnosing coccidioidal meningitis, but assessing therapeutic responses with this method is more difficult.[19]

In addition, real-time polymerase chain reaction (RT-PCR) testing, if available, can be used on unfixed clinical specimens and on formalin-fixed tissue to aid in the diagnosis of

coccidioidomycosis. A *Coccidioides* RT-PCR assay is commercially available, but it has neither been U.S. Food and Drug Administration–approved nor tested in people with HIV.[20]

Preventing Exposure

People with HIV living in or visiting areas in which *Coccidioides* spp. are endemic cannot avoid exposure to the fungus. They should, however, avoid extensive exposure to disturbed native soil, such as at building excavation sites, without wearing proper N95 masks. Furthermore, in endemic areas, they should stay inside during dust storms **(BIII),** although the exact risk remains controversial.[21-23] However, no evidence indicates that gardening in cultivated soil in a coccidioidal endemic region increases the risk of acquiring coccidioidomycosis.

Preventing Disease

Preventing Coccidioidomycosis
Yearly or twice-yearly serological testing for coccidioidomycosis should be considered for serologically negative individuals with HIV who live in endemic areas (BIII). Primary antifungal prophylaxis or pre-emptive therapy is not recommended for individuals with HIV and low CD4 counts who live in endemic areas and who have negative serologic tests for *Coccidioides* (AIII). Indications for Primary Prophylaxis/Pre-Emptive Therapy (AIII): • Previously tested negative and with a new positive IgM or IgG test for *Coccidioides*, *and* • No signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis, *and* • CD4 count <250 cells/mm^3 Preferred Therapy • Fluconazole 400 mg PO once daily (AIII) Discontinuation of Primary Prophylaxis/Pre-Emptive Therapy • CD4 count ≥250 cells/mm^3 with virologic suppression on ART (BIII)

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IgG = immunoglobulin G; IgM = immunoglobulin M; PO = orally

Primary antifungal prophylaxis (i.e., prophylaxis for individuals with negative results on serological tests for *Coccidioides*) does not appear to benefit people with HIV who have low CD4 counts and live in regions in which *Coccidioides* spp. are endemic,[5] and it **is not recommended (AIII).** Yearly or twice-yearly serological testing for coccidioidomycosis should be considered for serologically negative individuals with HIV who live in endemic areas **(BIII).** Testing is advised also for individuals who have previously traveled to or lived in endemic areas. Both IgM and IgG antibody testing using either an EIA or ID technique are recommended **(BIII).** In people who have CD4 counts <250 cells/mm^3 and who previously tested negative for *Coccidioides*, a new positive serological test suggests possible active disease[10] and should prompt further clinical evaluation. If no signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis are identified, pre-emptive antifungal therapy with fluconazole 400 mg daily is recommended without definitive trials for those with a new positive serological test and CD4 counts <250 cells/mm^3 **(AIII).** This regimen should be continued until the CD4 count is ≥250 cells/mm^3 and virologic suppression is documented **(BIII).** For those with CD4 counts already ≥250 cells/mm^3 and with viral suppression on

antiretrovirals (ARVs), close clinical follow-up without antifungal therapy is recommended **(BIII).** For asymptomatic patients who have not lived in or traveled to endemic regions, routine testing does not appear useful and **should not be performed (AIII).**

Treating Disease

Treating Coccidioidomycosis

Mild-to-Moderate Pulmonary Infections

Indications for Treatment

- Clinically mild infection, such as focal pneumonia

Preferred Therapy

- Fluconazole 400 mg PO once daily (AII), *or*
- Itraconazole 200 mg PO three times daily for 3 days then twice daily (AII)

Alternative Therapy (For Patients Who Failed to Respond to Fluconazole or Itraconazole)

- Voriconazole loading dose of 400 mg PO twice daily on Day 1, followed by 200 mg PO twice daily (BIII), *or*
- Posaconazole delayed-release tablet 300 mg PO twice daily on Day 1, followed by 300 mg once daily (BIII), *or*
- Isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO every 8 hours for six doses, followed by isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO once daily (BIII)

Severe Pulmonary or Extrapulmonary Infection (Except Meningitis)

Preferred Therapy

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII), *or*
- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), particularly for those with underlying renal dysfunction

Use until clinical improvement, then switch to triazole (fluconazole 400 mg PO daily or itraconazole 200 mg PO twice daily) (BIII).

Alternative Therapy

- Some specialists recommend combining amphotericin B deoxycholate or lipid formulation amphotericin B (see above dosing) with a triazole (fluconazole or itraconazole 400 mg daily) as initial therapy and continue the triazole once amphotericin B is stopped (CIII).

Meningeal Infections (Consultation With a Specialist Is Advised [AIII])

Preferred Therapy

- Fluconazole 800–1,200 mg PO once daily (AII)

Alternative Therapy

- Itraconazole 200 mg PO two to three times daily (BII), *or*
- Voriconazole 200–400 mg PO twice daily (BIII), *or*
- Posaconazole delayed-release tablet 300 mg PO twice on Day 1, followed by 300 mg PO once daily (CIII), *or*
- Isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO every 8 hours for six doses, followed by isavuconazole sulfate 372 mg (isavuconazole 200 mg) PO once daily (CIII), *or*

- Intrathecal amphotericin B deoxycholate (AIII) when triazole antifungals are not effective. Use in consultation with a specialist and ensure administration by a clinician experienced in this drug delivery technique.

Treatment in Pregnancy

Preferred Therapy During the First Trimester

- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII)
- Note: In general, azole antifungal agents should be avoided in the first trimester of pregnancy because of potential teratogenic effect unless benefit is thought to outweigh risk (BIII).
- After the first trimester or when disease is diagnosed after the first trimester, treatment with fluconazole or itraconazole could be considered (AIII).

Discontinuing Therapy

Focal Coccidioidal Pneumonia (AII)

- Discontinuation can be considered after the following:
  - Clinical response to 3–6 months of antifungal therapy, *and*
  - CD4 count ≥250 cells/mm^3, *and*
  - Virologic suppression on ART, *and*
- Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis

- Relapse can occur in 25% to 33% of people without HIV and in people with HIV who have CD4 count ≥250 cells/mm^3.
- Discontinuation may be considered after ≥12 months of therapy based on clinical and serological response, and the decision should be made in consultation with experts (BIII).
- For diffuse pulmonary disease, continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Coccidioidal Meningitis

- Relapse has been reported in 80% of patients after stopping triazoles; suppressive therapy at treatment doses should be lifelong. Discontinuation of therapy is not recommended (AII).

Other Considerations

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy. Use of corticosteroids is not recommended.
- All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines list these interactions and recommend dosage adjustments where feasible.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; CSF = cerebrospinal fluid; DDI = drug–drug interaction; IV = intravenous; PO = orally

Treatment of mild-to-moderate pulmonary coccidioidal infection: Therapy with an oral triazole antifungal agent is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII).** Fluconazole should be given as 400 mg daily **(AII);** itraconazole should be given in divided doses of 200 mg three times daily for 3 days, followed by 200 mg twice daily **(AII).**[24,25]

Itraconazole is preferred for those who have bone or joint disease **(AI).**[26] Serum itraconazole concentrations should be measured after the drug reaches steady state at 2 weeks to ensure adequate absorption. Target random serum concentrations (the sum of the parent itraconazole and hydroxyl itraconazole metabolite levels), measured by high-performance liquid chromatography, should be between 1.0 to 2.0 μg/mL.[27]

Data to support clinical efficacy for treatment with posaconazole,[28,29] voriconazole,[30] or isavuconazole[31] are limited, but these agents are recommended for patients who do not respond to fluconazole or itraconazole **(BIII).** Voriconazole is given as a loading dose of 400 mg twice on Day 1, followed thereafter by 200 mg twice daily. Trough serum voriconazole concentrations should be measured to ensure efficacy and avoid toxicity; a concentration of 1 to 5 μg/mL is desired. Several dosage formulations of posaconazole have been studied for coccidioidomycosis. A dose of 400 mg twice daily of the older liquid formulation of posaconazole has been used,[29] but the current delayed-release tablet formulation of posaconazole at a dosage of 300 mg twice on the first day and then 300 mg once daily is better tolerated by people and provides more reliable serum concentrations and is therefore recommended **(BIII).** A syndrome of mineralocorticoid excess manifesting as hypertension with hypokalemia was reported in some patients taking posaconazole.[32] Monitoring of blood pressure and serum potassium levels is appropriate in patients taking posaconazole.

Data supporting isavuconazole treatment in people with HIV are limited; however, in a cohort of 82 patients that included three people with HIV and CD4 ≥200 cells/mm^3, improvement occurred in 70% of patients.[31] Isavuconazole is given as isavuconazole sulfate 372 mg (equivalent to isavuconazole 200 mg) every 8 hours for six doses then isavuconazole sulfate 372 mg (equivalent to isavuconazole 200 mg) once daily. Target serum isavuconazole levels are not always measured, but concentrations of 1 to 4.6 μg/mL are preferred, with adverse events increasingly common in concentrations exceeding 4.6 μg/mL.[33]

All triazole antifungals have the potential for complex and possibly bidirectional interactions with certain ARV agents and other anti-infective agents. The Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines and Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections list such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

Treatment of severe pulmonary coccidioidal infection or extrapulmonary infection:
Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or who are severely ill with extrathoracic disseminated disease **(AII).**[25] Most experience has been with the deoxycholate formulation using a dose of amphotericin B of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are only retrospective reports from studies that used lipid formulations of amphotericin B for the treatment of coccidioidomycosis.[34] Lipid formulations are likely to be as effective as the deoxycholate formulation and should be favored initial therapy, particularly in patients with underlying renal dysfunction **(AIII).** For lipid formulations, a daily dose of amphotericin B of 3 to 5 mg/kg IV is appropriate. Therapy with amphotericin B should continue until clinical improvement is observed and then changed to an oral triazole antifungal **(BIII).**

Some specialists recommend combining amphotericin B with a triazole antifungal (400 mg of fluconazole or itraconazole daily) at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII).**[25] No experience has been reported with single-dose liposomal amphotericin at 10 mg/kg combined with azoles as used in cryptococcosis.[35]

Treatment of patients with coccidioidal meningitis: Treatment of coccidioidal meningitis requires consultation with a specialist in the treatment of coccidioidal meningitis **(AIII).**[36] Intravenous amphotericin B alone is ineffective as treatment for coccidioidal meningitis. Treatment with a triazole antifungal is recommended instead with the early addition of the polyene. Fluconazole (800 to 1,200 mg daily) is the preferred regimen **(AII),**[24,37] but itraconazole 400 to 600 mg daily also has been successfully used **(BII).**[38] Therapy with voriconazole **(BIII),**[39-41] posaconazole **(CIII),**[29,42] and isavuconazole **(CIII)**[43] has been limited and described in individual case reports but has been successful and is generally used with expert opinions. Despite appropriate antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B deoxycholate is recommended **(AIII).**[44] When required, intrathecal therapy should be administered by someone very experienced in this drug delivery technique.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Monitoring the CF antibody titer is useful to assess response to therapy, which should be measured every 12 weeks. More than a twofold rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. Immune reconstitution inflammatory syndrome (IRIS) has been reported infrequently in people with HIV and coccidioidomycosis.[45-47] In general, delaying initiation of ART while treating coccidioidomycosis **may not be necessary (BIII).** However, in highly immunosuppressed patients (i.e., CD4 counts <100 cells/mm^3) with disseminated disease, clinical decline may occur with initiation of ART.[48] It might be prudent to delay ART for 4 to 6 weeks after initiating antifungal therapy in severely immunosuppressed patients who have disseminated or central nervous system (CNS) disease **(CIII).** On the other hand, ART delay may not always prevent IRIS, as reported in at least one patient with disseminated disease and who received treatment with fluconazole for 28 days but still had worsening symptoms within a week after starting ART.[49] Thus, close monitoring for clinical worsening, particularly if meningitis is present, is essential when treating highly immunosuppressed people who have HIV and disseminated coccidioidomycosis.

Managing Treatment Failure

Therapeutic random itraconazole concentrations of 1.0 μg/mL to 2.0 μg/mL should be the goal in patients with severe coccidioidomycosis who do not respond to treatment with itraconazole. In the case of confirmed treatment failure with adequate serum concentrations of the azole, treatment should be changed to IV amphotericin B, either deoxycholate or a lipid formulation for patients who are severely ill **(AIII).** For those who are not severely ill, posaconazole **(BIII),** voriconazole **(BIII),** or isavuconazole **(BIII)** are appropriate alternatives. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir- or cobicistat-boosted regimens (see the Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines). Posaconazole and voriconazole have known drug–drug interactions with ARVs.[50] In certain situations, surgical intervention may be indicated and is a bedside decision.[24]

Therapy After Immune Reconstitution

People with HIV and peripheral blood CD4 counts ≥250 cells/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[51] Moreover, a prospective study has demonstrated that coccidioidomycosis is less severe in those with lower HIV RNA and higher CD4 counts.[3] Given these facts, in people with HIV who have undetectable HIV RNA on potent ART and

who have CD4 count ≥250 cells/mm^3, coccidioidomycosis should be managed no differently than it is in patients in the general population **(AII).**

For patients with focal pulmonary disease who meet the above criteria, treatment with a triazole antifungal agent should continue for a minimum of 3 to 6 months **(AII).** For patients with diffuse pulmonary disease or those with extrathoracic dissemination, antifungal therapy should continue for at least 12 months and usually much longer. Therapy should be discontinued based on clinical and immunological response and in consultation with an expert **(BIII).** For people with detectable HIV viremia or CD4 count <250 cells/mm^3, antifungal therapy at full dose should continue **(BIII).**

Preventing Relapse

Relapse of coccidioidomycosis occurs in 25% to 33% of individuals without HIV who have diffuse pulmonary coccidioidomycosis or non-meningeal disseminated coccidioidomycosis[52,53] and may occur in people with HIV who have CD4 counts ≥250 cells/mm^3 and are virologically suppressed on ARVs.[1,54] Patients with diffuse or focal coccidioidal pneumonia should have serial chest radiographs and coccidioidal serology tests every 3 to 6 months during coccidioidomycosis therapy and for 2 to 3 years after therapy discontinuation **(BIII).** Relapses have been reported in ≥80% of patients with meningitis in whom triazoles have been discontinued.[55] Therefore, therapy for coccidioidal meningitis with treatment doses of the azole should be continued for life even in those with immune reconstitution **(AII).**

Special Considerations During Pregnancy

During pregnancy, coccidioidomycosis should be considered in the differential diagnosis of a consistent clinical presentation and the presence of epidemiological risk such as living in an endemic region or having an appropriate travel history. Reactivation during pregnancy in individuals with prior coccidioidomycosis but without active disease is uncommon, though the risk may be somewhat higher with a history of disseminated coccidioidomycosis.[56] When coccidioidomycosis is acquired later in pregnancy (e.g., during the second or third trimester) the infection is more likely to be more severe and potentially disseminated, with the greatest severity occurring during the immediate postpartum period.[56] There is no evidence that maternal coccidioidomycosis increases risk for pregnancy loss or premature delivery. Perinatal infection is uncommon and most likely acquired during delivery.[56]

Intravenous amphotericin B, formulated with deoxycholate or as a lipid preparation, is the preferred treatment for non-meningeal coccidioidomycosis during the first trimester of pregnancy **(AIII).** Extensive clinical use of amphotericin B has not been associated with teratogenicity. There remain significant gaps in determining optimal dosing regimens in pregnancy; a recent review of dosing strategies in pregnancy recommended use of ideal body weight rather than total body weight to minimize risk of adverse effects to the fetus while maintaining efficacy.[57] Neonates born to women on chronic amphotericin B at delivery may be at increased risk for renal toxicity and electrolyte abnormalities and should be appropriately evaluated as newborns.[58]

For coccidioidal meningitis in the first trimester, for which the only alternative treatment to triazole antifungals is intrathecal amphotericin B, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the patient, the infectious diseases consultant, and the obstetrician.[56]

In general, azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit is felt to outweigh the risk **(BIII).** Fluconazole has teratogenic potential in the first trimester. After the first trimester or when disease is diagnosed after the first trimester, treatment with fluconazole or itraconazole could be considered **(AIII).**[24] Congenital malformations, including craniofacial and limb abnormalities similar to those observed in animals exposed to fluconazole, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[56,59] Furthermore animal data suggest that moderate alcohol consumption during pregnancy may increase the potency of fluconazole resulting in increased risk of craniofacial defects.[60]

Most studies on the effects of fluconazole in pregnancy have involved low doses and short-term exposure. A meta-analysis of literature describing birth defects in infants exposed to fluconazole during the first trimester evaluated nine cohort, case-control or randomized controlled studies, including 53,407 pregnancies with fluconazole exposure and 3,319,353 without fluconazole exposure.[61] Maternal fluconazole use was correlated with an increased prevalence of heart defects in infants for both a low dose (≤150 mg) (odds ratio [OR] 1.95; 95% confidence interval [CI], 1.18–3.21; *P*=0.01) and any dose (OR 1.79; 95% CI, 1.18–2.71; *P*=0.01). No association was found between fluconazole exposure and orofacial, CNS, genitourinary, musculoskeletal, or gastrointestinal defects at either low- or high-dose exposure to fluconazole. One registry-based cohort study of 7,352 women reported a threefold increase in incidence of Tetralogy of Fallot,[62] and a large population-based case-control study specifically noted an increase in transposition of the great arteries (OR 7.56; 95% CI, 1.22–35.45).[63] The latter study also suggested an increase in cleft lip with cleft palate (OR 5.53; 95% CI, 1.68–18.24). In three nested case-control studies using data from the Quebec Prescription Drug Insurance database, there was an increased prevalence of cardiac septal closure anomalies for maternal fluconazole doses greater than 150 mg during pregnancy (OR 1.81; 95% CI, 1.04–3.14).[64] A recent population-based cohort study (included in the meta-analysis) of 1,969,954 pregnancies, including 37,650 pregnancies exposed to fluconazole, found an increased risk of musculoskeletal malformations following exposure to fluconazole during the first trimester of pregnancy (risk of 52.1 per 10,000 pregnancies exposed to fluconazole versus 37.3 per 10,000 pregnancies exposed to topical azoles).[65]

A systematic review and meta-analysis of 6 cohort or case-control studies that analyzed more than 16,000 exposures and reported fetal outcomes after exposure to fluconazole used in the first trimester of pregnancy found a marginal association with increased risk of congenital malformations (OR 1.09; 95% CI, 0.99–1.2, *P* = 0.088), including heart defects, as well as spontaneous abortion; exposure to more than 150 mg was associated with an overall increase in congenital malformations.[61]

A nationwide cohort study in Denmark found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies (n = 16,561; hazard ratio [HR] 1.48; 95% CI, 1.23–1.77) or those with topical azole exposure only (n = 5,646; HR 1.62; 95% CI, 1.26–2.07).[66] Similarly, the nested case-control studies in Canada (n = 320,868 pregnancies) found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies and that risk was greater with higher dose of fluconazole exposure (adjusted OR for ≤150 mg fluconazole 2.23; 95% CI, 1.96–2.54; adjusted OR for >150 mg fluconazole 3.20; 95% CI, 2.73–3.75).[64] However, a cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use during pregnancy and risk of stillbirth or neonatal death.[67] The meta-analysis noted above also found no association between fluconazole exposure and risk of

abortion or stillbirth. On the basis of reported birth defects, the use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks.

Although case reports of birth defects in infants exposed to itraconazole have occurred, a recent systematic review and meta-analysis of four cohort studies involving 971,450 pregnant women with 1,311 exposures found no significant difference in the overall risk of birth defects between those with maternal exposure to itraconazole and non-exposure.[68] Although limb and congenital heart defects were the most common defects seen, they were within the rates of these defects published by EUROCAT (the European network of population-based registries for epidemiological surveillance of congenital anomalies). However, the rate of eye defects was higher than that published by EUROCAT. No difference was found in rates of in spontaneous abortion or stillbirth based on itraconazole exposure. In sum, itraconazole should be used in pregnancy depending on a cost-benefit analysis.

Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animal studies; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans. Voriconazole, posaconazole, and isavuconazole **are not recommended** for use during pregnancy, especially in the first trimester **(AIII).**

References

1. 1. Jones JL, Fleming PL, Ciesielski CA, Hu DJ, Kaplan JE, Ward JW. Coccidioidomycosis among persons with AIDS in the United States. *J Infect Dis*. 1995;171(4):961-966. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7706825.
2. 2. Litvintseva AP, Marsden-Haug N, Hurst S, et al. Valley fever: finding new places for an old disease: Coccidioides immitis found in Washington State soil associated with recent human infection. *Clin Infect Dis*. 2015;60(1):e1-3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25165087.
3. 3. Masannat FY, Ampel NM. Coccidioidomycosis in patients with HIV-1 infection in the era of potent antiretroviral therapy. *Clin Infect Dis*. 2010;50(1):1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19995218.
4. 4. Ampel NM, Dols CL, Galgiani JN. Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. *Am J Med*. 1993;94(3):235-240. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8095771.
5. 5. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994-1997: incidence, risk factors, and prevention. *J Infect Dis*. 2000;181(4):1428-1434. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10753734.
6. 6. Fish DG, Ampel NM, Galgiani JN, et al. Coccidioidomycosis during human immunodeficiency virus infection. A review of 77 patients. *Medicine (Baltimore)*. 1990;69(6):384-391. Available at: https://pubmed.ncbi.nlm.nih.gov/2146461/.
7. 7. Valdivia L, Nix D, Wright M, et al. Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerg Infect Dis*. 2006;12(6):958-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16707052.
8. 8. Kim MM, Blair JE, Carey EJ, Wu Q, Smilack JD. Coccidioidal pneumonia, Phoenix, Arizona, USA, 2000-2004. *Emerg Infect Dis*. 2009;15(3):397-401. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19239751.
9. 9. Mahaffey KW, Hippenmeyer CL, Mandel R, Ampel NM. Unrecognized coccidioidomycosis complicating Pneumocystis carinii pneumonia in patients infected with the human immunodeficiency virus and treated with corticosteroids. A report of two cases. *Arch Intern Med*. 1993;153(12):1496-1498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8512440.
10. 10. Arguinchona HL, Ampel NM, Dols CL, Galgiani JN, Mohler MJ, Fish DG. Persistent coccidioidal seropositivity without clinical evidence of active coccidioidomycosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;20(5):1281-1285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7620011.
11. 11. Stevens DA, Clemons KV, Levine HB, et al. Expert opinion: what to do when there is Coccidioides exposure in a laboratory. *Clin Infect Dis*. 2009;49(6):919-923. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19663562.
12. 12. Blair JE, Ampel NM, Hoover SE. Coccidioidomycosis in selected immunosuppressed hosts. *Med Mycol*. 2019;57(Supplement_1):S56-s63. Available at: https://pubmed.ncbi.nlm.nih.gov/29669037/.
13. 13. Donovan FM, Ramadan FA, Khan SA, et al. Comparison of a Novel Rapid Lateral Flow Assay to Enzyme Immunoassay Results for Early Diagnosis of

Coccidioidomycosis. *Clin Infect Dis*. 2021;73(9):e2746-e2753. Available at: https://pubmed.ncbi.nlm.nih.gov/32818956/.
14. 14. Durkin M, Connolly P, Kuberski T, et al. Diagnosis of coccidioidomycosis with use of the Coccidioides antigen enzyme immunoassay. *Clin Infect Dis*. 2008;47(8):e69-73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18781884.
15. 15. Durkin M, Estok L, Hospenthal D, et al. Detection of Coccidioides antigenemia following dissociation of immune complexes. *Clin Vaccine Immunol*. 2009;16(10):1453-1456. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19675225.
16. 16. Grill FJ, Grys TE, Grill MF, Roeder A, Blair JE, Lake DF. Development of a Quantitative Antigen Assay to Detect Coccidioidal Chitinase-1 (CTS1) in Human Serum. *Open Forum Infect Dis*. 2021;8(7):ofab344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34337097.
17. 17. McHardy IH, Barker B, Thompson GR, 3rd. Review of Clinical and Laboratory Diagnostics for Coccidioidomycosis. *J Clin Microbiol*. 2023;61(5):e0158122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36883820.
18. 18. Bamberger DM, Pepito BS, Proia LA, et al. Cerebrospinal fluid Coccidioides antigen testing in the diagnosis and management of central nervous system coccidioidomycosis. *Mycoses*. 2015;58(10):598-602. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26393436.
19. 19. Kassis C, Zaidi S, Kuberski T, et al. Role of Coccidioides Antigen Testing in the Cerebrospinal Fluid for the Diagnosis of Coccidioidal Meningitis. *Clin Infect Dis*. 2015;61(10):1521-1526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26209683.
20. 20. Dizon D, Mitchell M, Dizon B, Libke R, Peterson MW. The utility of real-time polymerase chain reaction in detecting Coccidioides immitis among clinical specimens in the Central California San Joaquin Valley. *Med Mycol*. 2019;57(6):688-693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30462288.
21. 21. Comrie AC. No consistent link between dust storms and Valley Fever (Coccidioidomycosis). *Geohealth*. 2021;5(12):e2021GH000504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34877441.
22. 22. Freedman M, Jackson BR, McCotter O, Benedict K. Coccidioidomycosis outbreaks, United States and worldwide, 1940-2015. *Emerg Infect Dis*. 2018;24(3):417-423. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29460741.
23. 23. Tong DQ, Gorris ME, Gill TE, Ardon-Dryer K, Wang J, Ren L. Dust storms, Valley Fever, and public awareness. *Geohealth*. 2022;6(8):e2022GH000642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35949254.
24. 24. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of coccidioidomycosis. *Clin Infect Dis*. 2016;63(6):e112–e146. Available at: https://www.idsociety.org/practice-guideline/coccidioidomycosis.
25. 25. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis*. 2005;41(9):1217-1223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16206093.
26. 26. Galgiani JN, Catanzaro A, Cloud GA, et al. Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. *Ann Intern Med*. 2000;133(9):676-686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11074900.

27. 27. Wiederhold NP, Schwartz IS, Patterson TF, Thompson GR, 3rd. Variability of hydroxy-itraconazole in relation to itraconazole bloodstream concentrations. *Antimicrob Agents Chemother*. 2021;65(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33468480.
28. 28. Anstead GM, Corcoran G, Lewis J, Berg D, Graybill JR. Refractory coccidioidomycosis treated with posaconazole. *Clin Infect Dis*. 2005;40(12):1770-1776. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15909265.
29. 29. Stevens DA, Rendon A, Gaona-Flores V, et al. Posaconazole therapy for chronic refractory coccidioidomycosis. *Chest*. 2007;132(3):952-958. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17573510.
30. 30. Kim MM, Vikram HR, Kusne S, Seville MT, Blair JE. Treatment of refractory coccidioidomycosis with voriconazole or posaconazole. *Clin Infect Dis*. 2011;53(11):1060-1066. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22045955.
31. 31. Heidari A, Sharma R, Shakir Q, et al. Isavuconazole in the treatment of chronic forms of coccidioidomycosis. *Clin Infect Dis*. 2023;76(12):2196-2199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36905151.
32. 32. Thompson GR, 3rd, Beck KR, Patt M, Kratschmar DV, Odermatt A. Posaconazole-Induced Hypertension Due to Inhibition of 11beta-Hydroxylase and 11beta-Hydroxysteroid Dehydrogenase 2. *J Endocr Soc*. 2019;3(7):1361-1366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31286100.
33. 33. Kosmidis C, Otu A, Moore CB, Richardson MD, Rautemaa-Richardson R. Isavuconazole therapeutic drug monitoring during long-term treatment for chronic pulmonary aspergillosis. *Antimicrob Agents Chemother*. 2020;65(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33077653.
34. 34. Sidhu R, Lash DB, Heidari A, Natarajan P, Johnson RH. Evaluation of amphotericin B lipid formulations for treatment of severe coccidioidomycosis. *Antimicrob Agents Chemother*. 2018;62(7). Available at: https://www.ncbi.nlm.nih.gov/pubmed/29686150.
35. 35. Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *N Engl J Med*. 2022;386(12):1109-1120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35320642.
36. 36. Thompson GR, Ampel NM, Blair JE, et al. Controversies in the management of central nervous system coccidioidomycosis. *Clin Infect Dis*. 2022;75(4):555-559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35717645.
37. 37. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med*. 1993;119(1):28-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8498760.
38. 38. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med*. 1990;112(2):108-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2153012.
39. 39. Cortez KJ, Walsh TJ, Bennett JE. Successful treatment of coccidioidal meningitis with voriconazole. *Clin Infect Dis*. 2003;36(12):1619-1622. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12802765.
40. 40. Proia LA, Tenorio AR. Successful use of voriconazole for treatment of Coccidioides meningitis. *Antimicrob Agents Chemother*. 2004;48(6):2341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15155250.

41. 41. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. 2009;53(4):1648-1651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139290.
42. 42. Schein R, Homans J, Larsen RA, Neely M. Posaconazole for chronic refractory coccidioidal meningitis. *Clin Infect Dis*. 2011;53(12):1252-1254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21987729.
43. 43. Heidari A, Quinlan M, Benjamin DJ, et al. Isavuconazole in the Treatment of Coccidioidal Meningitis. *Antimicrob Agents Chemother*. 2019;63(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30559134.
44. 44. Johnson RH, Einstein HE. Coccidioidal meningitis. *Clin Infect Dis*. 2006;42(1):103-107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16323099.
45. 45. Mortimer RB, Libke R, Eghbalieh B, Bilello JF. Immune reconstitution inflammatory syndrome presenting as superior vena cava syndrome secondary to Coccidioides lymphadenopathy in an HIV-infected patient. *J Int Assoc Physicians AIDS Care (Chic)*. 2008;7(6):283-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18948432.
46. 46. D'Avino A, Di Giambenedetto S, Fabbiani M, Farina S. Coccidioidomycosis of cervical lymph nodes in an HIV-infected patient with immunologic reconstitution on potent HAART: a rare observation in a nonendemic area. *Diagn Microbiol Infect Dis*. 2012;72(2):185-187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22104185.
47. 47. Trible R, Edgerton N, Hayek S, Winkel D, Anderson AM. Antiretroviral therapy-associated coccidioidal meningitis. *Emerg Infect Dis*. 2013;19(1):163-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23260018.
48. 48. Mu A, Shein TT, Jayachandran P, Paul S. Immune Reconstitution Inflammatory Syndrome in patients with AIDS and disseminated coccidioidomycosis: a case series and review of the literature. *J Int Assoc Provid AIDS Care*. 2017;16(6):540-545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28911256.
49. 49. Lin AY, Chun V, Dhamija A, Bordin-Wosk T, Kadakia A. Immune reconstitution inflammatory syndrome in an HIV-infected patient with disseminated coccidioidomycosis. *Int J STD AIDS*. 2019;30(9):923-926. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31159717.
50. 50. Vadlapatla RK, Patel M, Paturi DK, Pal D, Mitra AK. Clinically relevant drug-drug interactions between antiretrovirals and antifungals. *Expert Opin Drug Metab Toxicol*. 2014;10(4):561-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24521092.
51. 51. Ampel NM. Delayed-type hypersensitivity, in vitro T-cell responsiveness and risk of active coccidioidomycosis among HIV-infected patients living in the coccidioidal endemic area. *Med Mycol*. 1999;37(4):245-250. Available at: https://pubmed.ncbi.nlm.nih.gov/10421859/.
52. 52. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NAIAD Mycoses Study Group. *Am J Med*. 1990;89(3):282-290. Available at: https://pubmed.ncbi.nlm.nih.gov/2168126/.
53. 53. Catanzaro A, Galgiani JN, Levine BE, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med*. 1995;98(3):249-256. Available at: https://pubmed.ncbi.nlm.nih.gov/7872341/.

54. 54. Mathew G, Smedema M, Wheat LJ, Goldman M. Relapse of coccidioidomycosis despite immune reconstitution after fluconazole secondary prophylaxis in a patient with AIDS. *Mycoses*. 2003;46(1-2):42-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12588482.
55. 55. Dewsnup DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for Coccidioides immitis meningitis? *Ann Intern Med*. 1996;124(3):305-310. Available at: https://pubmed.ncbi.nlm.nih.gov/8554225/.
56. 56. Bercovitch RS, Catanzaro A, Schwartz BS, Pappagianis D, Watts DH, Ampel NM. Coccidioidomycosis during pregnancy: a review and recommendations for management. *Clin Infect Dis*. 2011;53(4):363-368. Available at: https://pubmed.ncbi.nlm.nih.gov/21810749/.
57. 57. O'Grady N, McManus D, Briggs N, Azar MM, Topal J, Davis MW. Dosing implications for liposomal amphotericin B in pregnancy. *Pharmacotherapy*. 2023;43(5):452-462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36862037.
58. 58. AmBisome®(amphotericin B) liposome for injection [Type]. Northbrook, IL: Astellas Pharma US, Inc. ; 2018.
59. 59. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22(2):336-340. Available at: https://pubmed.ncbi.nlm.nih.gov/8838193/.
60. 60. Metruccio F, Battistoni M, Di Renzo F, Moretto A, Menegola E. Moderate alcohol consumption during pregnancy increases potency of two different drugs (the antifungal fluconazole and the antiepileptic valproate) in inducing craniofacial defects: prediction by the in vitro rat whole embryo culture. *Arch Toxicol*. 2023;97(2):619-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36385218.
61. 61. Budani MC, Fensore S, Di Marzio M, Tiboni GM. Maternal use of fluconazole and congenital malformations in the progeny: A meta-analysis of the literature. *Reprod Toxicol*. 2021;100:42-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33383164.
62. 62. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369(9):830-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23984730.
63. 63. Howley MM, Carter TC, Browne ML, Romitti PA, Cunniff CM, Druschel CM. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2016;214(5):657.e651-659. Available at: https://pubmed.ncbi.nlm.nih.gov/26640069/.
64. 64. Berard A, Sheehy O, Zhao JP, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ*. 2019;191(7):E179-E187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30782643.
65. 65. Zhu Y, Bateman BT, Gray KJ, et al. Oral fluconazole use in the first trimester and risk of congenital malformations: population based cohort study. *BMJ*. 2020;369:m1494. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32434758.
66. 66. Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Spontaneous Abortion and Stillbirth. *Jama*. 2016;315(1):58-67. Available at: https://pubmed.ncbi.nlm.nih.gov/26746458/.

67. 67. Pasternak B, Wintzell V, Furu K, Engeland A, Neovius M, Stephansson O. Oral Fluconazole in Pregnancy and Risk of Stillbirth and Neonatal Death. *Jama*. 2018;319(22):2333-2335. Available at: https://pubmed.ncbi.nlm.nih.gov/29896619/.
68. 68. Liu D, Zhang C, Wu L, Zhang L, Zhang L. Fetal outcomes after maternal exposure to oral antifungal agents during pregnancy: A systematic review and meta-analysis. *Int J Gynaecol Obstet*. 2020;148(1):6-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31691277.

69.

Update coming soon. See Immunization chapter for the most current vaccine recommendations.

Community-Acquired Pneumonia

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Epidemiology

Bacterial respiratory diseases, including sinusitis, bronchitis, otitis, and pneumonia, are among the most common infectious complications in people with HIV, occurring with increased frequency at all CD4 T lymphocyte cell (CD4) counts.[1] This chapter will focus on the diagnosis, prevention, and management of bacterial community-acquired pneumonia (CAP) in people with HIV. While viral pneumonias are a frequent cause of CAP, particularly influenza and severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the management of coronavirus-19 (COVID-19) disease is outside the scope of these guidelines (refer to NIH COVID-19 Treatment Guidelines for updated treatment recommendations). These guidelines also do not consider hospital acquired pneumonia and ventilator-associated pneumonia; limited data suggest that these do not differ in terms of microbiology, clinical course, treatment, or prevention in people with HIV as compared to in people without HIV with similar HIV-unrelated comorbidities.

Bacterial pneumonia is a common cause of HIV-associated morbidity. Recurrent pneumonia, considered two or more episodes within a 1-year period, is an AIDS-defining condition. The incidence of bacterial pneumonia in individuals with HIV has decreased progressively with the advent of combination antiretroviral therapy (ART).[2-7] In one study, the incidence of bacterial pneumonia declined from 22.7 episodes per 100 person-years before the introduction of ART to 9.1 episodes per 100 person-years by 1997 after ART was introduced. Since then, the incidence of bacterial pneumonia among people with HIV in developed countries has continued to drop. In the Strategic Timing of AntiRetroviral Treatment (START) study, the incidence rate of serious bacterial infections overall was 0.87 per 100 person-years, and approximately 40% of these infections were due to bacterial pneumonia.[4] Recurrent bacterial pneumonia as an AIDS-defining illness is also less frequently encountered in individuals on ART; however, its exact incidence is hard to evaluate because surveillance data for it are not collected systematically as for other opportunistic infections (OIs).[8]

Risk Factors

Yet despite ART, bacterial pneumonia remains more common in people with HIV than in those who do not have HIV.[9-11] Bacterial pneumonia may be the first manifestation of underlying HIV infection and can occur at any stage of HIV disease and at any CD4 count. Bacterial pneumonia in individuals with HIV results from multiple risk factors, particularly immune defects. A CD4 count decrease, especially when below 100 cells/mm^3, continues to be a major risk factor for pneumonia due to routine bacterial pathogens. Other immune defects include quantitative and qualitative B-cell abnormalities that result in impaired pathogen-specific antibody production, abnormalities in neutrophil function or numbers, and abnormalities in alveolar macrophage function.[12,13] Lack of ART or intermittent use of ART increases the risk for pneumonia, likely due to uncontrolled HIV viremia.[14]

Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include chronic viral hepatitis, tobacco, alcohol, injection drug use and prescribed opioid

use, particularly higher doses and opioids with immunosuppressive properties.[3,10,15,16,17] Chronic obstructive pulmonary disease (COPD), malignancy, renal insufficiency, and congestive heart failure (CHF) are emerging as risk factors for pneumonia, particularly in the population of older adults with HIV.[18] Risk for CAP can also increase with obesity[4], an emerging health problem in people living with HIV.

Microbiology

In individuals with HIV, *Streptococcus pneumoniae* (*S. pneumoniae)* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia, the same as in individuals without HIV.[19-25] *Staphylococcus aureus* (*S. aureus)* and *S. pneumoniae* are among the most common etiologies of pneumonia in association with influenza infection.[26,27] Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila* species have been reported as infrequent causes of CAP in individuals with HIV.[22,28] However, when more extensive testing such as serology to detect IgM antibodies (IgM) antibodies and/or positive polymerase chain reaction (PCR) of respiratory secretions was performed, additional infections due to *Mycoplasma* and *Chlamydia* were detected.[29]

Additional microbial etiologies of CAP that should be considered in people with HIV include *Mycobacterium tuberculosis, Pneumocystis*, other opportunistic infections, and respiratory viruses. The incidence of these different organisms will vary depending on geographic region and patient risk factors including degree of immunocompromise when considering opportunistic infections. For example, in a recent prospective study from South Africa of 284 patients with HIV and suspected pneumonia, sputum real-time multiplex PCR testing found that tuberculosis was more common than bacterial causes of CAP in this setting; viruses were detected in 203 patients, with the most common being human metapneumovirus, although the pathogenic significance of the viral pathogens was uncertain.[30] As noted, respiratory viruses, influenza and SARS-CoV-2 are also common causes of CAP in people with HIV. While influenza and COVID-19 generally present similarly in people with and without HIV, some studies suggest mortality may be increased among people with HIV for these viral infections, particularly in low-and-middle income country settings.[31-36]

Risk Factors for Pseudomonas aeruginosa *and Methicillin-Resistant* Staphylococcus aureus

The frequency of *Pseudomonas aeruginosa* (*P. aeruginosa)* and *S. aureus* as community-acquired pathogens is higher in individuals with HIV than in those without HIV based on studies in the early combination ART era.[23,37] Many of these patients often had poorly controlled HIV or the presence of other concomitant risk factors that contributed to risk for *P. aeruginosa* or *S. aureus*. Patients with advanced HIV disease (CD4 count ≤50 cells/mm^3) or underlying neutropenia, as well as pre-existing lung disease such as bronchiectasis or severe COPD have an increased risk of infection with *P. aeruginosa*. Other risk factors for infection include the use of corticosteroids, severe malnutrition, hospitalization within the past 90 days, residence in a health care facility or nursing home, and chronic hemodialysis.[38]

S. aureus should be considered in patients with recent viral infection (particularly influenza), a history of injection drug use, or severe, bilateral, necrotizing pneumonia. Risk factors for *S. aureus* pneumonia in patients with HIV include receipt of antibiotics prior to hospital admission, comorbid illnesses, and recent healthcare contact.[39] Community outbreaks of methicillin-resistant *S. aureus* (MRSA) infection have also been seen among men who have sex with men.[40] Studies of patients

without HIV have identified hemodialysis, known prior colonization or infection with MRSA, as well as recurrent skin infections to be risk factors for MRSA pneumonia.[38] Notably, nasal carriage and colonization of skin sites with MRSA is more common in individuals with HIV than in those without HIV, and is more likely in patients recently incarcerated and/or hospitalized.[41,42]

Clinical Manifestations

Clinical and Radiographic Presentation

The clinical and radiographic presentation of bacterial pneumonia in individuals with HIV, particularly in those with higher CD4 count and HIV viral suppression, is similar to that in individuals without HIV.[43] Patients with pneumonia caused by bacteria such as *S. pneumoniae* or *Haemophilus* species characteristically have acute onset (3 to 5 days) of symptoms, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum, and dyspnea.[44] The presence of fever, tachycardia, and/or hypotension can be indicators of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia, and in such cases, clinicians should strongly consider hospitalizing the patient.

Patients with bacterial pneumonia typically have signs of focal consolidation, such as egophony, and/or pleural effusion on lung examination. In contrast, lung examination often is normal in those with *Pneumocystis* pneumonia (PCP), and if abnormal, reveals inspiratory crackles. In patients with bacterial pneumonia, the white blood cell (WBC) count usually is elevated. The elevation may be relative to baseline WBC count in those with advanced HIV. Neutrophilia or a left shift in WBC differential may be present.

Individuals with bacterial pneumonia characteristically exhibit unilateral, focal, segmental, or lobar consolidation on chest radiograph. The frequency of these typical radiographic findings, however, may depend on the underlying bacterial pathogen. Those with pneumonia due to *S. pneumoniae* or *Haemophilus* typically present with consolidation, whereas cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*.

Risk Factors for Bacteremia

In individuals with HIV the incidence of bacteremia accompanying pneumonia is greater than in individuals without HIV, especially when infection is due to *S. pneumoniae*.[45] In data from the CDC, the incidence of invasive pneumococcal disease, inclusive of bacteremia, was significantly higher in individuals with HIV: rates were 173 cases per 100,000 in those with HIV infection, compared to 3.8 per 100,000 in younger adults aged 18–34 years and 36.4 per 100,000 among those aged ≥65 years in the general population.[46] Similarly, in a study from Kenya, the rate of pneumococcal bacteremia was significantly higher in individuals with HIV infection (rate ratio of HIV-infected versus HIV-negative adults, 19.7, 95% CI 12.4-31.1).[47] With the introduction of ART and pneumococcal conjugate vaccines for both the general pediatric population and individuals living with HIV, this disparity in incidence rates of bacteremia between people with and without HIV has narrowed but has not been eliminated.[48-52] In one recent study of invasive pneumococcal disease (IPD), which includes bacteremia, IPD was more common in people with HIV who had CD4 counts < 500 cells/mm^3, but even those with counts > 500 cells/mm^3, had a higher incidence than in the general population.[53] Risk factors associated with bacteremia include lack of ART, low CD4 count (particularly <100 cells/mm^3), as well as alcohol abuse, current smoking, and comorbidities, particularly liver disease.[49]

Severity of Illness

Disease severity and arterial oxygenation should be assessed in all patients with pneumonia. Noninvasive measurement of arterial oxygen saturation by pulse oximetry is an appropriate screening test. Arterial blood gas analysis is indicated for patients with evidence of hypoxemia suggested by noninvasive assessment and for patients who have tachypnea and/or respiratory distress. Assessment of additional clinical features and the use of severity scoring systems for pneumonia such as the Pneumonia Severity Index (PSI) and CURB-65 and their application to patients with HIV are discussed in the Treating Disease section.

Outcomes

Although some studies suggest that bacterial pneumonia is associated with increased mortality in individuals with HIV,[23,54,55] others do not.[43,56-58] Independent predictors of increased mortality in a prospective, multicenter study of individuals with HIV with community-acquired bacterial pneumonia were CD4 count <100 cells/mm^3, radiographic progression of disease, and presence of shock.[59] In that study, multilobar infiltrates, cavitary infiltrates, and pleural effusion on baseline imaging were all independent predictors of radiographic progression of disease. However, in patients on ART with controlled HIV viremia, and high CD4 counts (>350 cells/mm^3), the clinical courses and outcomes of pneumonia appear to be similar to those in patients without HIV.[43]

As in patients without HIV, pneumonia may have an impact on longer term outcomes of patients with HIV. This includes greater long-term mortality, as hospitalization for pneumonia has been associated with increased mortality up to one year later.[60] One factor that may add to this long-term mortality is cardiovascular disease associated with CAP, which occurs at a similar rate in those with HIV infection , as those without, even though in one retrospective cohort study of 4,384 patients, people with HIV were younger, had less severe CAP and fewer traditional cardiovascular risk factors than those without HIV infection.[61] Pneumonia has also been associated with impaired lung function and risk of subsequent lung cancer in individuals with HIV.[62-64]

Diagnosis

General Approach

Patients with clinical symptoms and signs suggestive of CAP should have posteroanterior and lateral chest radiographs; evidence of pneumonia can also be found on chest computed tomography (CT) scan, but routine use of chest CT scan for this purpose is not recommended. Lung ultrasound can also be used to aid in the diagnosis pneumonia. If previous radiographs are available, they should be reviewed to assess for new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate by chest radiograph or other imaging technique in conjunction with compatible clinical symptoms and signs.

The differential diagnosis of pneumonia in individuals with HIV is broad and a confirmed microbiologic diagnosis should be pursued. Microbial identification can allow clinicians to target the specific pathogen(s) and discontinue broad spectrum antibiotic therapy and/or empiric therapy that targets non-bacterial pathogens. Microbiologic testing should include evaluation of the upper respiratory tract for SARS-CoV-2, influenza in the appropriate season, and may include testing other respiratory viruses.[65] Given the increased incidence of *Mycobacterium tuberculosis* (*M. tuberculosis*) in individuals with HIV, a tuberculosis (TB) diagnosis should always be considered in patients with

HIV who have pneumonia, particularly in high incidence areas. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (i.e., airborne precautions for hospitalized patients), and two to three sputum specimens should be obtained for acid fast bacilli evaluation (including TB PCR; see *Mycobacterium tuberculosis* Infection and Disease section). Bronchoscopy with bronchoalveolar lavage should be considered, especially if the differential diagnosis includes opportunistic pathogens such as *Pneumocystis jirovecii*.

Procalcitonin (PCT) testing has been proposed as a tool to distinguish between bacterial and viral respiratory infections. One study from Africa specifically evaluated the usefulness of PCT testing to distinguish CAP due to bacteria (non-TB), *M. tuberculosis*, and PCP in people with HIV. In general, PCT levels associated with bacterial pneumonia are higher than those associated with viral or fungal pneumonias, but levels can also be elevated in non-bacterial pulmonary infections.[66] Specific PCT thresholds have not been established or validated in HIV-associated bacterial pneumonia. Thus, given the lack of data, the use of PCT to guide decisions regarding etiology of pneumonia, initiation of anti-bacterial treatment, or duration of treatment in patients with HIV is not recommended.

Recommended Diagnostic Evaluation in CAP

American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) guidelines for microbiologic testing for diagnosis of CAP in individuals without HIV generally also apply to people with HIV.[67]

- In patients with HIV with CAP who are well enough to be treated as outpatients, routine diagnostic tests to identify a bacterial etiologic diagnosis are optional, especially if the microbiologic studies cannot be performed promptly**.**
- In patients with HIV hospitalized for CAP, a Gram stain of expectorated sputum and two blood cultures are recommended, particularly in those with severe pneumonia, in those who are not on ART; or in those who are known to have a CD4 count <350 cells/mm^3 (and especially if <100 cells/mm^3) prior to hospitalization. Specimens should ideally be obtained before initiation of antibiotics, or within 12 hours to 18 hours of such initiation.
- Urinary antigen tests for *L. pneumophila* and *S. pneumoniae* are recommended in hospitalized patients, particularly those with severe CAP. In addition, lower respiratory tract secretions should be cultured for *Legionella* on selective media or undergo *Legionella* nucleic acid amplification testing in adults with severe CAP. Legionella testing should also be done in people with HIV with non-severe CAP when indicated by epidemiological factors, such as association with a *Legionella* outbreak or recent travel.
- Microbiologic diagnostic testing is indicated whenever epidemiologic, clinical, or radiologic clues prompt suspicion of specific pathogens that could alter standard empirical management decisions.
- If available, rapid MRSA nasal testing should be performed, particularly in patients with risk factors for MRSA or in a high prevalence setting, as results can direct empiric antibiotic therapy.[68]

Gram stain and culture of sputum is recommended in all hospitalized patients meeting the criteria stated above, and is optional in people with HIV with CAP not meeting these criteria. In general, Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained prior to—or not more than 12hours to 18 hours after—initiation of antibiotics, and

quality performance measures for collection, transport, and processing of samples can be met. Sputum cultures in people with HIV have been shown to identify a bacterial etiology in up to 30-40% of good quality specimens[55,69] although yield is less in other studies.[14,29] Correlation of sputum culture with Gram stain can help in interpretation of sputum culture data. For intubated patients, an endotracheal aspirate sample should be obtained promptly after intubation, or bronchoscopy may be indicated.

Blood cultures are more likely to be positive in people with HIV than in those without HIV. Patients with HIV, particularly those with lower CD4 counts, are at increased risk of invasive infection with *S. pneumoniae*. Given concerns for drug-resistant *S. pneumoniae*[70,71], as well as *S. aureus* and/or other drug-resistant pathogens, blood cultures are recommended for patients with HIV who meet the criteria as noted above, and are optional for those who do not meet the criteria listed.

Diagnostic thoracentesis should be performed in all patients with pleural effusion if concern exists for accompanying empyema, and pleural fluid should be sent for microbiologic studies. Therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion. Given the increased risk of invasive pneumococcal disease in patients with HIV, clinicians should be vigilant for evidence of extra-pulmonary complications of infection.

Preventing Exposure

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community. General precautions to maintain health, such as adhering to hand hygiene and cough etiquette and refraining from close contact with individuals who have respiratory infections, should be emphasized for patients with HIV as for other patient populations.

Preventing Disease

Pneumococcal Vaccine

Vaccination against *S. pneumoniae* is an important measure in preventing bacterial pneumonia. Some observational studies have reported benefits of pneumococcal polysaccharide vaccine (PPSV) use in people with HIV against IPD (e.g., bacteremia, meningitis)[49,72], and all-cause pneumonia;[73-75] however, results have been variable.[72,76-78] One randomized placebo-controlled trial of PPSV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia, and there was no evidence of reduced risk of IPD among vaccinated participants.[79] Follow-up of this cohort not only confirmed the increase in pneumonia in vaccinated participants, but also showed a decrease in all-cause mortality, although participants in this study were not treated with ART.[80] A recent study[81] evaluating the impact of the 13-valent pneumococcal conjugate vaccine (PCV13) vaccination on the rates of IPD in adults with HIV between 2008 and 2018 found that IPD rates remained high despite reductions with the introduction of PCV13. PCV20/non-PCV15 serotypes comprised 16.5% of cases of IPD, suggesting that the use of higher valent conjugate pneumococcal vaccines may reduce IPD.

In 2021, two PCVs, 15-valent (PCV15) and 20-valent (PCV20), were licensed by the FDA for use in U.S. adults.[82] PCV15 and PCV20 were licensed based on safety and immunogenicity data compared with the 13-valent PCV or 23-valent pneumococcal polysaccharide vaccine (PPSV23). Effectiveness data of these vaccine against pneumococcal disease in adults with HIV infection are currently not available. One phase 3 clinical trial of PCV15 followed by PPSV23 8 weeks later in people with HIV

demonstrated safety and immunogenicity of this approach.[83] No clinical data exist for the use of PCV20 in people with HIV. To date, one randomized, double-blind, placebo-controlled trial has assessed the efficacy of PCV against pneumococcal disease in adults with HIV. This was a trial on 7-valent PCV (PCV7) among adults with HIV in Malawi, which demonstrated 74% efficacy against vaccine-type IPD, with clear evidence of efficacy in those with CD4 counts <200 cells/mm^3.[84] However, study participants were those who had recovered from IPD, and received two doses of PCV7 four weeks apart. Therefore, findings may not be directly applicable to adults with HIV infection.

Patients with CD4 counts ≥200 cells/mm^3 should receive a dose of PPSV23 at least 8 weeks later **(AI).**[72-75,85-89] While individuals with HIV with CD4 counts <200 cells/mm^3 can also be offered PPSV23 at least 8 weeks after receiving PCV15 **(CIII)** (such as if there are concerns with retention in care), PPSV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm^3 while on ART **(BIII).** Clinical evidence supporting use of PPSV23 in persons with CD4 counts <200 cells/mm^3 appears strongest in patients who also have HIV RNA <100,000 copies/mL;[75,89] evidence also suggests benefit for those who start ART before receiving PPSV vaccination.[72,90]

People with HIV who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available. If PCV20 is used, their pneumococcal vaccinations are complete **(CIII).**

Influenza Vaccine

Influenza vaccination is pertinent to prevention of CAP from influenza or influenza-associated bacterial pneumonia, which can occur as a complication of influenza. Influenza and pneumococcal vaccines can be administered during the same visit. Use of high-dose inactivated influenza vaccine is associated with decreased incidence of influenza and greater antibody response in adults without HIV age ≥65 years compared with standard-dose inactivated vaccine.[91,92] One trial found greater immunogenicity in people with HIV age ≥18 years who were given high-dose influenza vaccine compared with standard-dose inactivated vaccine.[93] See the "Influenza Vaccine" section in the Immunization section of the Adult and Adolescent Opportunistic Infections Guidelines for a detailed evidence summary.

All people with HIV infection during influenza season **(AI)** should be immunized against influenza with inactivated, standard dose or recombinant influenza vaccine per recommendation of the season **(AI).** High-dose inactivated influenza vaccine may be given to individuals age >65 years **(AIII).** The inactivated influenza or recombinant vaccine can be administered at any time during pregnancy **(AI).**

Additional Vaccines

The incidence of *H. influenzae* type b infection in adults with HIV is low. Therefore, *H. influenzae* type vaccine is not usually recommended for adult use **(BIII)**[90] unless a patient also has anatomic or functional asplenia.

Recommendations for COVID-19 vaccination are provided in the Immunization section of the Adult and Adolescent Opportunistic Infections Guidelines.

Prophylaxis and Risk Reduction

Several factors are associated with a decreased risk of bacterial pneumonia in HIV, including use of ART and trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis.[55] In many studies, daily administration of TMP-SMX for PCP prophylaxis reduced the frequency of bacterial respiratory infections.[9,94,95] This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of TMP-SMX (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, in the United States, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(AIII).** Similarly, clarithromycin or azithromycin should not be prescribed solely for preventing bacterial respiratory infection **(AIII).**

A decreased absolute neutrophil count (e.g., <500 cells/mm^3) is associated with an increased risk of bacterial infections, including pneumonia, although this risk has been demonstrated primarily in persons with malignant neoplasms. To reduce the risk of such bacterial infections, clinicians should take steps to reverse neutropenia, such as by stopping myelosuppressive drugs **(CIII).** Studies of granulocyte-colony stimulating factor (G-CSF) in people with HIV have failed to document benefit.[96,97]

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes, using injection drugs, and consuming alcohol.[9,74,98-100] Clinicians should encourage cessation of these behaviors, refer patients to appropriate services, and/or prescribe medications to support quitting. Data demonstrate that smoking cessation can decrease the risk of bacterial pneumonia.[15]

Treating Disease

General Approach to Treatment

The basic principles of antibiotic treatment of CAP are the same for patients with HIV as for those who do not have HIV.[67] As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should preferably be collected before antibiotic therapy is initiated or within 12 hours to 18 hours of antibiotic initiation. However, antibiotic therapy should be administered promptly, without waiting for the results of diagnostic testing. Empiric therapy varies based on geographic region and common pathogens in these regions, and should take into account local resistance patterns, results of MRSA rapid swab testing if done, and individual patient risk factors, including severity of immunocompromise (recent CD4 cell count, HIV viral load) and use of ART.

In patients with HIV, providers must also consider the risk of opportunistic lung infections, such as PCP, that would alter empiric treatment. In settings where the prevalence of TB is high, initiation of empiric therapy for both bacterial pneumonia and TB may be appropriate for patients in whom both diagnoses are strong considerations and after diagnostic studies are undertaken. Because respiratory fluoroquinolones are also active against *M. tuberculosis*, they should be used with caution in patients with suspected TB who are not being treated with concurrent standard four-drug TB therapy. Thus, patients with TB who are treated with fluoroquinolones in the absence of standard four-drug TB therapy may have an initial, but misleading response, that could delay diagnosis of TB and initiation of appropriate multidrug TB therapy, increasing the risk of drug-resistant TB and TB transmission.

Assessing Severity of Disease and Treatment Location

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. In addition to considerations regarding ability to take oral medications, adherence, and other confounding factors (housing, comorbid diseases, etc.), severity of illness is a key factor that helps to guide decisions regarding treatment location for CAP—outpatient versus inpatient, including intensive care unit (ICU). Notably, no prospective randomized clinical trials have assessed the performance of the Pneumonia Severity Index (PSI) for CAP or other severity scores (e.g., the ATS/IDSA severity criteria[67] or CURB-65 Score for Pneumonia Severity, to guide decisions regarding inpatient or outpatient treatment location for people with HIV. However, the PSI, CURB-65, the ATS/IDSA severity criteria, and other scoring systems appear to be valid for predicting mortality in patients with HIV with CAP, especially when used in combination with CD4 count.[59,101,102]

Whether the performance of severity indices is improved by including HIV-related variables is uncertain. One study suggested that the site of care decision be dictated by considering the PSI score and CD4 count together.[101] Mortality was increased in patients with higher PSI risk class; however, even in those without an increased mortality risk by PSI, a CD4 count <200 cells/mm^3 was associated with an increased risk of death.[101] This led to the suggestion to hospitalize CAP patients with CD4 counts <200 cells/mm^3 and to use the PSI to help guide decision-making in those with higher CD4 counts.[103]

However, other studies have found the PSI was predictive of outcomes independent of CD4 count.[104] Furthermore, CD4 count or HIV RNA level are not clearly associated with short-term outcomes of CAP.[105] Other HIV-specific scoring systems such as the Veterans Aging Cohort Study (VACS) Index, although originally designed to predict overall mortality, may also be useful in predicting ICU admission and mortality. In a study of older patients with and without HIV with CAP, a higher VACS Index was associated with greater 30-day mortality, readmission, and length of stay.[106] Another possible tool is the SWAT-Bp tool developed in Malawi.[107] This tool measures male [S]ex, muscle [W]asting, non-[A]mbulatory, [T]emperature (>38°C or <35°C), and [B]lood [p]ressure (systolic<100 and/or diastolic<60)). In a retrospective study of 216 patients (84% with HIV), demonstrated moderate discriminatory power, while the CURB-65 was less accurate.

Thus in general, validated clinical prediction scores for prognosis can be used in patients with HIV in conjunction with clinical judgement to guide treatment location for CAP. Low risk patients for whom there are no other concerns regarding adherence or complicating factors can be treated as outpatients. Patients with severe CAP, including those presenting with shock or respiratory failure, usually require a higher level of care, typically ICU admission. Additionally, severe CAP criteria can include PSI risk class of III or IV or CURB-65 scores ≥3. Patients with ≥3 of the ATS/IDSA minor severity criteria for CAP[67] often require ICU or higher level of care, as well.

Empiric Antibiotic Therapy by Treatment Setting and Severity of Diseases

There is a general paucity of clinical trials evaluating different antibiotic regimens for treating CAP in populations with HIV and a lack of evidence that treatment response to antibiotics is different in individuals with HIV than in those without HIV. Therefore, treatment recommendations for CAP in individuals with HIV are generally consistent with the ATS/IDSA guidelines for people without HIV.[67]

Outpatient CAP Treatment

Individuals with HIV who are being treated as outpatients should receive an oral beta-lactam plus a macrolide **(AI),** or a respiratory fluoroquinolone **(AI).** Preferred beta-lactams are high-dose amoxicillin or amoxicillin-clavulanate; alternatives are cefpodoxime or cefuroxime. Preferred macrolides are azithromycin or clarithromycin. Preferred respiratory fluoroquinolones are moxifloxacin or levofloxacin. A respiratory fluoroquinolone (moxifloxacin or levofloxacin) should be used as an alternative to a beta lactam in patients who are allergic to penicillin. If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative **(BIII)** in addition to a beta-lactam.

Empirical monotherapy with a macrolide for outpatient CAP is not routinely recommended in patients with HIV for two reasons **(BIII).** First, increasing rates of pneumococcal resistance have been reported with erythromycin-resistant rates up to 30%,[108] prompting concerns for possible treatment failure. In this regard, local drug resistance patterns, if available, can help inform treatment decisions**.** Additionally, patients who are already receiving a macrolide for MAC prophylaxis may have resistance due to chronic exposure, and should also not receive macrolide monotherapy for empiric treatment of bacterial pneumonia. However, macrolides can be used as part of a combination CAP regimen.

Non-Severe CAP Inpatient Treatment

Individuals with HIV who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide **(AI)** or a respiratory fluoroquinolone **(AI).** Monotherapy with a macrolide is not recommended in the inpatient setting. The role for dual therapy with a macrolide is somewhat controversial based on prior observational studies and two prospective clinical trials in patients without HIV with CAP that evaluated outcomes in those treated with beta-lactam monotherapy and those treated with dual-therapy including a macrolide.[109,110] In one study, beta-lactam monotherapy was not found to be non-inferior to beta-lactam/macrolide combination therapy. Notably, in the monotherapy arm, patients who had more severe CAP, as indicated by a PSI ≥IV, or who had atypical pathogens were less likely to reach clinical stability. There were also more 30-day readmissions among the patients on monotherapy.[109] While there was a trend towards improved outcomes in those on dual therapy, the difference between arms was not statistically significant. In a pragmatic, cluster-randomized, cross-over trial of non-ICU hospitalized patients with CAP, beta-lactam monotherapy was found to be non-inferior to beta-lactam/macrolide combination therapy or fluoroquinolone monotherapy.[110] However in this study, the diagnosis of CAP did not require radiographic confirmation, illness was mild, and there were cross-overs between groups.

Only one study thus far has compared a cephalosporin (ceftriaxone) to dual therapy with a cephalosporin (ceftriaxone) plus macrolide in 225 people with HIV with CAP, finding no difference between in-hospital or 14-day mortality between the groups; most patients had lower severity of disease, with only 7% of the cohort having a CURB-65 score >2 and 17% with a PSI risk class >III.[111] Given the heterogeneity and limitations of recent studies and scarce data in patients with HIV, the recommendation for patients with HIV who are hospitalized with non-severe CAP remains that same as in people without HIV: to administer either beta-lactam/macrolide combination therapy, or a single drug regimen of a respiratory fluoroquinolone **(AI).**

Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Preferred macrolides are azithromycin and clarithromycin. Preferred respiratory fluoroquinolones are moxifloxacin or

levofloxacin. If a patient has contraindications to a macrolide or a fluoroquinolone, then doxycycline should be given as an alternative **(BIII)** in addition to a beta-lactam. Clinical and Laboratory Standards Institute and U. S. Food and Drug Administration (FDA) changes in the penicillin breakpoints for treatment of non-meningitis pneumococcal disease imply IV penicillin is an acceptable option for treatment of pneumococcal disease in patients with HIV **(BIII).**[112] In patients who are allergic to penicillin, a respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) alone should be used **(AI).** As noted, fluoroquinolone monotherapy should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy.

Severe CAP Treatment

Patients with severe CAP should not receive empiric monotherapy, even with a fluoroquinolone, because of the range of potential pathogens and the desirability of prompt and microbiologically active therapy (AI). In one study, the use of dual therapy (usually with a beta-lactam plus a macrolide) was associated with reduced mortality in patients with bacteremic pneumococcal pneumonia, including those admitted to the ICU.[113] Patients with severe pneumonia should be treated with an IV beta-lactam plus either azithromycin **(AI)** or a respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) **(AI).** Both have a strong recommendation. Weak observational data, in the absence of prospective randomized controlled data, suggest that beta-lactam plus macrolide may be associated with decreased mortality.[77,114,115] Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. In patients who are allergic to penicillin, aztreonam plus a respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(BIII).**

The majority of CAP pathogens can be treated adequately with recommended empiric regimens. The increased incidence of *P. aeruginosa* and *S. aureus* (including community-acquired MRSA) as causes of CAP are exceptions. Both of these pathogens occur in specific epidemiologic patterns with distinct clinical presentations for which empiric antibiotic coverage may be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empiric treatment if results are negative. In the most recent ATS/IDSA CAP guidelines, empiric therapy for *P. aeruginosa* or MRSA is recommended in those with severe CAP, who have had these organisms previously isolated from sputum cultures, with de-escalation if these organisms are not isolated from current cultures.[67]

The addition of corticosteroids for treating CAP has not been studied in people with HIV. Data from studies in people without HIV with CAP suggest that corticosteroids may decrease a composite outcome of mortality, time to clinical stability, and length of hospital stay.[116] Importantly, effects of corticosteroids appear variable according to etiology and severity of pneumonia, however, as corticosteroids may increase mortality in influenza pneumonia,[117] but decrease mortality in patients with COVID-19 who require higher levels of respiratory support.[118] The optimal regimen including dose, duration, and formulation of corticosteroid, and the patient population with bacterial non-viral related CAP most likely to benefit from the additional use of corticosteroids remain uncertain. Selecting HIV-uninfected patients with severe CAP and increased inflammation as defined by C-reactive protein levels >150 mg/mL is one strategy for treatment of CAP that has been shown to be beneficial.[119]

ATS/IDSA guidelines recommend not using corticosteroids routinely in non-severe **(AI)** or severe CAP **(BII)** but endorse use in CAP with refractory shock[67] Similarly, the use of corticosteroids in HIV-infected patients with severe CAP is not routinely recommended **(BII)** given the lack of data

specifically in HIV-infected population. If providers administer corticosteroids to HIV-infected patients with severe CAP, they must ensure that no other contraindications to steroids exist; in patients who have no contraindications and have persistent shock despite fluid resuscitation, Surviving Sepsis Guidelines[120] provide a weak recommendation for administering hydrocortisone 200 mg IV daily for 5 to 7 days or tapering once vasopressors are no longer needed**.**

Empiric Pseudomonas aeruginosa *Treatment*

If risk factors for *Pseudomonas* infection are present, an antipneumococcal, antipseudomonal beta-lactam plus either ciprofloxacin or levofloxacin (750-mg dose) should be used **(AI).** Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Alternative therapeutic agents that are recommended are an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin **(BII)** or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone **(BII).** In patients who are allergic to penicillin, aztreonam is recommended to be used in place of the beta-lactam **(BII).**

Empiric Staphylococcus aureus *Treatment*

A nasal swab for MRSA can help inform decision-making whether initial empiric coverage should include MRSA. In studies of patients without HIV, negative test results have a high negative predictive value for pneumonia due to MRSA. If the nasal swab is negative for MRSA and the pneumonia is not severe and no other risk factors or features suggestive of MRSA pneumonia are present, empiric coverage for MRSA may be withheld **(BII).**[68]

However, in patients who have risk factors for *S. aureus* infection, vancomycin or linezolid should be added to the antibiotic regimen **(AII).** Empiric coverage for MRSA should also be added if a rapid nasal swab is positive for MRSA, although the positive predictive value for pneumonia is only moderate, and therapy should be de-escalated if cultures are negative **(BIII).** Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) or the use of linezolid alone, is recommended by many experts if severe necrotizing pneumonia is present to minimize bacterial toxin production **(CII).**

Telavancin is an alternative agent that can be used for *S. aureus* pneumonia **(BIII);** it is currently FDA-approved for treatment of hospital-acquired and ventilator-associated (rather than community-acquired) pneumonia based on studies in people without HIV infection.[121] While ceftaroline has activity against MRSA, and data suggest it can be effective for MRSA pneumonia, it has been FDA approved for treatment of bacterial CAP based on two studies that did not include any MRSA isolates.[122] Neither telavancin or ceftaroline have been specifically studied in patients with HIV with bacterial pneumonia. Daptomycin should not be used to treat pneumonia as it is not active in the lung **(AI).**

Pathogen-Directed Therapy

When the etiology of the pneumonia has been identified based on reliable microbiological methods, antimicrobial therapy should be modified and directed at the identified pathogen **(BIII).**

Switch From Intravenous to Oral Therapy

A switch to oral therapy should be considered in patients with CAP on IV antibiotic therapy who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function.[67] A longer duration of IV and overall antibiotic therapy is often necessary in patients who have severe CAP or who have bacteremia, particularly if due to *S. pneumoniae* or *S. aureus* and complicated infection is present.

Special Considerations Regarding When to Start Antiretroviral Therapy

In patients with bacterial pneumonia who are not already on ART, ART should be initiated promptly (i.e., within 2 weeks of initiating therapy for the pneumonia) unless comorbidities make ART unwise **(AI)**.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

The clinical response to appropriate antimicrobial therapy for CAP is similar in patients with and without HIV.[43,58] A clinical response (i.e., reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) typically is observed within 48 to 72 hours after initiation of appropriate antimicrobial therapy. A review of patients with CAP found that advanced HIV infection and CD4 count <100 cells/mm^3 were predictors for longer time to clinical stability (i.e., >7 days) and that patients who received ART tended to become clinically stable sooner and had better outcomes.[103,106] The presence of bacteremia is a significant factor that impacts outcomes. Among those with pneumococcal pneumonia, longer time to clinical stability is more often seen in the setting of bacteremia. As in patients without HIV, radiographic improvement usually lags behind clinical improvement.

Immune reconstitution inflammatory syndrome (IRIS) has been rarely described in association with bacterial CAP and initiation of treatment with ART in patients with HIV. This could be secondary to a number of reasons: 1) patients with recurrent pneumonia have not been included in the study population; 2) IRIS among participants with bacterial pneumonia has not been specified or 3) this complication has truly not been observed.[2,123] Only case reports describe IRIS with pneumonia due to *Rhodococcus equii*. More commonly IRIS occurs with pneumonia due to *Pneumocystis* and mycobacterial infections.

Managing Treatment Failure

Patients who do not respond to appropriate antimicrobial therapy should undergo further evaluation to search for complications secondary to pneumonia (empyema, abscess formation, metastatic infection), other infectious process, the presence of a drug-resistant pathogen, and/or noninfectious causes of pulmonary dysfunction (pulmonary embolus, COPD).

Preventing Recurrence

Patients with HIV should receive pneumococcal **(AI)** and influenza vaccines **(AI)** as recommended**.** Antibiotic chemoprophylaxis generally is not recommended specifically to prevent recurrences of bacterial respiratory infections because of the potential for development of drug-resistant microorganisms and drug toxicity **(AI).** Smoking cessation reduces the risk of bacterial pneumonia (by approximately 27%),[124] and patients who smoke tobacco should be encouraged to quit and

provided with the appropriate tools and referrals whenever possible **(AI).** Likewise, patients with substance use disorders (alcohol, injection or non-injection drugs) should be referred for appropriate counseling and services **(AI).** However, likely the most important intervention for prevention of bacterial pneumonia (first episode or recurrence) is initiation and adherence to ART, which is beneficial even among those with high CD4 count at time of ART initiation.[4] Thus prompt initiation or re-initiation of ART is recommended for all patients with HIV with bacterial pneumonia **(AI).**

Special Considerations During Pregnancy

The diagnosis of bacterial respiratory tract infections in pregnant women is the same as in those who are not pregnant, with appropriate shielding of the abdomen during radiographic procedures. Bacterial respiratory tract infections should be managed in pregnant women as in women who are not pregnant, with certain exceptions. Among macrolides, clarithromycin is not recommended because of an increased risk of birth defects seen in some animal studies. Two studies, each involving at least 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk of spontaneous abortion was noted in one study.[125,126] Azithromycin did not produce birth defects in animal studies, but experience with human use in the first trimester is limited. Azithromycin is recommended when a macrolide is indicated in pregnancy **(BIII).** Arthropathy has been noted in immature animals with *in utero* exposure to quinolones. Studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[127,128] When indicated, quinolones can be used in pregnancy for serious respiratory infections only when a safer alternative is not available **(CIII).**[129]

Doxycycline is not recommended for use during pregnancy because of increased hepatotoxicity and staining of fetal teeth and bones. Beta-lactam antibiotics have not been associated with teratogenicity or increased toxicity in pregnancy. Clindamycin use in pregnancy has not been associated with an increased risk of birth defects or adverse outcomes.[130] Aminoglycosides can be used as needed. A theoretical risk of fetal renal or eighth nerve damage exists with aminoglycoside exposure during pregnancy, but this finding has not been documented in humans, except with streptomycin (10% risk) and kanamycin (2% risk). Animal reproductive toxicity studies in rats and rabbits were negative for vancomycin, but data on first trimester exposure in humans are limited.[131] A study of neonates after in utero exposure did not find evidence of renal or ototoxicity.[132] Reproductive toxicity studies of televancin in animals have shown increased rates of limb malformations in rats, rabbits, and mini pigs at doses similar to human exposure; no human data are available.[131] Use of telavancin should be avoided in the first trimester if alternate agents with more experience in use in pregnancy are available. Cases of exposure to telavancin in pregnancy should be reported to the Televancin Pregnancy Registry at 1-855-633-8479. Experience with linezolid in human pregnancy has been limited, but it was not teratogenic in mice, rats, and rabbits.

Pneumonia during pregnancy is associated with increased rates of preterm labor and delivery. Pregnant women with pneumonia after 20 weeks' gestation should be monitored for evidence of contractions **(BII).** Pneumococcal vaccine can be administered during pregnancy **(AIII).** A study comparing administration of PCV10, PPSV23, or control (1:1:1) among 347 women during weeks 13–34 of pregnancy found that PCV10 and PPSV23 were equally safe and immunogenic in pregnant women with HIV and conferred similar levels of seroprotection to their infants.[133] No adverse consequences have been reported among newborns whose mothers were vaccinated during pregnancy. Women who did not receive vaccines during pregnancy were vaccinated post-partum; these data demonstrated higher antibody responses compared to women vaccinated ante-partum, suggesting that postpartum booster doses may be beneficial and require further study.[134]

Inactivated influenza vaccine is recommended for all pregnant women during influenza season **(AI).** Live attenuated influenza vaccine should not be used in people with HIV **(AIII).** Because administration of vaccines can be associated with a transient rise in plasma HIV RNA levels, vaccination of pregnant women is recommended after ART has been initiated to minimize increases in plasma HIV RNA levels that might increase the risk of perinatal transmission of HIV.

Recommendations for Preventing and Treating Community-Acquired Pneumonia

Preventing *Streptococcus pneumoniae* Infections

Indications for Pneumococcal Vaccination

- All people with HIV regardless of CD4 count (AI)

Vaccination Recommendations

- For all people with HIV without history of pneumococcal vaccination or unknown vaccine history:
  - Administer either 15-valent pneumococcal conjugate vaccine (PCV15) or 20-valent pneumococcal conjugate vaccine (PCV20) (AII). If PCV20 is used, their pneumococcal vaccination is complete.
  - If PCV15 is used, a dose of PPSV23 should be administered at least 8 weeks later (AII).* No additional pneumococcal vaccine doses are recommended.
- For people with HIV who previously started or completed a pneumococcal vaccination series, there is no need to restart the series.**
  - People with HIV who received PCV13 and were 65 or older when they received a dose of PPSV23 do not require further doses of PPSV23; for those who received PPSV23 younger than age 65, additional doses of PPSV23 are recommended as indicated below (BIII).
    - People with HIV who have received PCV13 and PPSV23 at age <65 should receive a second dose of PPSV23 at least 5 years after the first dose. If they are age 65 or older at the time of their second dose, they do not require additional doses of PPSV23.
    - If they were <65 at the time of the second dose, they should receive a third and final dose at or after age 65, at least 5 years after the second PPSV23 dose.
  - People with HIV who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23 at any age (BIII).

Footnotes

* Patients with CD4 counts ≥200 cells/mm^3 should receive a dose of PPSV23 at least 8 weeks later (AI). While individuals with HIV with CD4 counts <200 cells/mm^3 can also be offered PPSV23 at least 8 weeks after receiving PCV15 (CIII) (such as if there are concerns with retention in care), PPSV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm^3 while on ART (BIII). Clinical evidence supporting use of PPSV23 in persons with CD4 counts <200 cells/mm^3 appears strongest in patients who also have HIV RNA <100,000 copies/mL; evidence also suggests benefit for those who start ART before receiving PPSV vaccination.

** People with HIV who have received PCV13 but have not completed their recommended pneumococcal vaccine series with PPSV23, one dose of PCV20 may be used if PPSV23 is not available. If PCV20 is used, their pneumococcal vaccinations are complete (CIII).

Preventing Influenza and Bacterial Pneumonia as a Complication of Influenza

Indication for Influenza Vaccination

- All people with HIV infection during influenza season (AI)

Vaccination

- Adults age ≥65 years are recommended to receive high-dose IIV (Fluzone® High-Dose) or adjuvanted IIV (FLUAD®) over standard-dose unadjuvanted vaccine (AII).
- People age ≥18 years also may use RIV (Flublok® Quadrivalent).

- For people with egg allergy, use IIV or RIV appropriate for age (if the allergic reaction is more severe than hives, give the vaccine in a medical setting appropriate to manage severe allergic reaction).
- The inactivated influenza or recombinant vaccine can be administered at any time during pregnancy (AI).
- Influenza vaccines are quadrivalent, with formulations that change from season to season.

Note: Live attenuated influenza vaccine is contraindicated in people with HIV (AIII).

Treating Community-Acquired Bacterial Pneumonia

Note: Empiric antimicrobial therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed below are suggested empiric therapy. The regimen should be modified as needed once microbiologic and drug susceptibility results are available. Providers must also consider the risk of opportunistic lung infections such as PCP or TB, which may alter the empiric therapy as needed.

Empiric Outpatient Therapy (Oral)

Preferred Therapy

- An oral beta-lactam + a macrolide (azithromycin or clarithromycin) (AI)
  - *Preferred beta-lactams*: high-dose amoxicillin or amoxicillin/clavulanate
  - *Alternative beta-lactams:* cefpodoxime or cefuroxime

or

- A respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] (AI), especially for patients with penicillin allergies.

Alternative Therapy

- A beta-lactam + doxycycline (BIII)

Empiric Therapy for Hospitalized Patients with Non-Severe CAP

Preferred Therapy

- An IV beta-lactam + a macrolide (azithromycin or clarithromycin) (AI)
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam

or

- A respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] (AI), especially for patients with penicillin allergies.

Alternative Therapy

- An IV beta-lactam + doxycycline (BIII)
- IV penicillin may be used for confirmed pneumococcal pneumonia (BIII)

Empiric Therapy for Patients with Severe CAP

Preferred Therapy

- An IV beta-lactam + azithromycin (AI), *or*
- An IV beta-lactam + a respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] (AI)
  - *Preferred beta-lactams*: ceftriaxone, cefotaxime, or ampicillin-sulbactam

Alternative Therapy

For Penicillin-Allergic Patients

- Aztreonam (IV) + a respiratory fluoroquinolone (moxifloxacin or levofloxacin)[a] (BIII)

Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia

Recommendations for Preventing and Treating Community-Acquired Pneumonia

Preferred Therapy

- An IV antipneumococcal, antipseudomonal beta-lactam + (ciprofloxacin IV or levofloxacin IV 750 mg/day) (AI)
  - *Preferred beta-lactams*: piperacillin-tazobactam, cefepime, imipenem, or meropenem

Alternative Therapy

- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + IV azithromycin (BII), *or*
- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + an antipneumococcal fluoroquinolone (moxifloxacin or levofloxacin) (BII)

For Penicillin-Allergic Patients

- Replace the beta-lactam with aztreonam (BII).

Empiric Therapy for Patients at Risk of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Pneumonia

Preferred Therapy

- A nasal swab for MRSA can help inform decision of initial coverage for MRSA (see text for discussion)
- Vancomycin IV or linezolid (IV or PO) should be added to the baseline regimen (AII).
- Although not routinely recommended, the addition of clindamycin to vancomycin (but not to linezolid) may be considered for severe necrotizing pneumonia to minimize bacterial toxin production (CII).

Duration of Therapy

- For most patients: 5–7 days. The patient should be afebrile for 48–72 hours, and should be clinically stable before discontinuation of therapy.
- Longer duration of antibiotics is often required if severe CAP or bacteremia is present, and particularly if due to *S. pneumoniae* or complicated *S. aureus* infection.

Switch from IV to PO Therapy

- A switch should be considered for patients who have improved clinically, can swallow and tolerate oral medications, and have intact gastrointestinal function (BIII).

Other Considerations

- Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance (up to 30%) (BIII), and patients receiving a macrolide for MAC prophylaxis may have resistance due to chronic exposure (BIII).
- Fluoroquinolones should be used with caution in patients in whom TB is suspected but who are not being treated with concurrent standard four-drug TB therapy (BIII).
- Once the pathogen has been identified by reliable microbiologic methods, antibiotic therapy should be modified to target the pathogen (BIII).
- If drug-resistant pathogens have not been identified by reliable microbiologic methods, antibiotic therapy can be de-escalated to cover routine causes of CAP (BIII).
- Antibiotics chemoprophylaxis is generally not recommended because of the potential for development of drug resistance microorganisms and drug toxicities (AI).

[a] Respiratory fluoroquinolones such as levofloxacin or moxifloxacin are also active against *Mycobacterium tuberculosis*. In patients with undiagnosed TB, fluoroquinolones may alter response to therapy, delay TB diagnosis, and increase the risk of drug resistance. These drugs should be used with caution in patients in whom TB is suspected but who are not receiving a standard 4-drug TB regimen.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IM = intramuscularly; IV = intravenously; MAC = *Mycobacterium avium* complex; MRSA = methicillin-resistant *Staphylococcus aureus;* PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; PO = orally; PPSV23 – 23-Valent Pneumococcal Polysaccharide Vaccine; TB = tuberculosis

References

1. Wallace JM, Hansen NI, Lavange L, et al. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 1997;155(1):72-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9001292.

2. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19440326.

3. Mussini C, Galli L, Lepri AC, et al. Incidence, timing, and determinants of bacterial pneumonia among HIV-infected patients: data from the ICONA Foundation cohort. *J Acquir Immune Defic Syndr*. 2013;63(3):339-345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23591636.

4. O'Connor J, Vjecha MJ, Phillips AN, et al. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per muL: secondary outcome results from a randomised controlled trial. *Lancet HIV*. 2017;4(3):e105-e112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28063815.

5. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992–1997. *MMWR CDC Surveill Summ*. 1999;48(2):1-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12412613.

6. Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med*. 2000;162(1):64-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10903221.

7. Serraino D, Puro V, Boumis E, et al. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993–2000. *AIDS*. 2003;17(14):2109-2116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14502014.

8. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000–2010. *J Infect Dis*. 2016;214(6):862-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27559122.

9. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. 1995;333(13):845-851. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7651475.

10. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis*. 2008;47(10):1345-1353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18834317.

11. Aston SJ, Ho A, Jary H, et al. Aetiology and risk factors for mortality in an adult community-acquired pneumonia cohort in Malawi. *Am J Respir Crit Care Med*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30625278.

12. Jambo KC, Banda DH, Kankwatira AM, et al. Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. *Mucosal Immunol*. 2014;7(5):1116-1126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24472847.

13. Charles TP, Shellito JE. Human immunodeficiency virus infection and host defense in the lungs. *Semin Respir Crit Care Med*. 2016;37(2):147-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26974294.

14. Gordin FM, Roediger MP, Girard PM, et al. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med*. 2008;178(6):630-636. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18617640.

15. Benard A, Mercie P, Alioum A, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. *PLoS One*. 2010;5(1):e8896. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20126646.

16. Lamas CC, Coelho LE, Grinsztejn BJ, Veloso VG. Community-acquired lower respiratory tract infections in HIV-infected patients on antiretroviral therapy: predictors in a contemporary cohort study. *Infection*. 2017;45(6):801-809. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28660356.

17. Edelman EJ, Gordon KS, Crothers K, et al. Association of prescribed opioids with increased risk of community-acquired pneumonia among patients with and without HIV. *JAMA Intern Med*. 2019;179(3):297-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30615036.

18. Attia EF, McGinnis KA, Feemster LC, et al. Association of COPD with risk for pulmonary infections requiring hospitalization in HIV-infected veterans. *J Acquir Immune Defic Syndr*. 2015;70(3):280-288. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26181820.

19. Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. 1986;104(1):38-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3484420.

20. Burack JH, Hahn JA, Saint-Maurice D, Jacobson MA. Microbiology of community-acquired bacterial pneumonia in persons with and at risk for human immunodeficiency virus type 1 infection. Implications for rational empiric antibiotic therapy. *Arch Intern Med*. 1994;154(22):2589-2596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7979856.

21. Miller RF, Foley NM, Kessel D, Jeffrey AA. Community acquired lobar pneumonia in patients with HIV infection and AIDS. *Thorax*. 1994;49(4):367-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8202910.

22. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. *Am J Respir Crit Care Med*. 1995;152(4 Pt 1):1309-1315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7551387.

23. Afessa B, Green B. Bacterial pneumonia in hospitalized patients with HIV infection: the Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. *Chest*. 2000;117(4):1017-1022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10767233.

24. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. *J Infect Dis*. 2001;184(3):268-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11443551.

25. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS*. 2002;16(1):85-95. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11741166.

26. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *Chest*. 2010;138(1):130-136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20173050.

27. Klein EY, Monteforte B, Gupta A, et al. The frequency of influenza and bacterial coinfection: a systematic review and meta-analysis. *Influenza Other Respir Viruses*. 2016;10(5):394-403. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27232677.

28. Tarp B, Jensen JS, Ostergaard L, Andersen PL. Search for agents causing atypical pneumonia in HIV-positive patients by inhibitor-controlled PCR assays. *Eur Respir J*. 1999;13(1):175-179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10836344.

29. Figueiredo-Mello C, Naucler P, Negra MD, Levin AS. Prospective etiological investigation of community-acquired pulmonary infections in hospitalized people living with HIV. *Medicine (Baltimore)*. 2017;96(4):e5778. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28121925.

30. Maartens G, Griesel R, Dube F, Nicol M, Mendelson M. Etiology of pulmonary infections in human immunodeficiency virus-infected inpatients using sputum multiplex real-time polymerase chain reaction. *Clin Infect Dis*. 2020;70(6):1147-1152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31286137.

31. Coleman BL, Fadel SA, Fitzpatrick T, Thomas SM. Risk factors for serious outcomes associated with influenza illness in high- versus low- and middle-income countries: systematic literature review and meta-analysis. *Influenza Other Respir Viruses*. 2018;12(1):22-29. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29197154.

32. Kenmoe S, Bigna JJ, Fatawou Modiyingi A, et al. Case fatality rate and viral aetiologies of acute respiratory tract infections in HIV positive and negative people in Africa: the VARIAFRICA-HIV systematic review and meta-analysis. *J Clin Virol*. 2019;117:96-102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31272038.

33. Collins JP, Campbell AP, Openo K, et al. Outcomes of immunocompromised adults hospitalized with laboratory-confirmed influenza in the United States, 2011–2015. *Clin Infect Dis*. 2020;70(10):2121-2130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31298691.

34. Mellor MM, Bast AC, Jones NR, et al. Risk of adverse coronavirus disease 2019 outcomes for people living with HIV. *AIDS*. 2021;35(4):F1-F10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33587448.

35. Danwang C, Noubiap JJ, Robert A, Yombi JC. Outcomes of patients with HIV and COVID-19 co-infection: a systematic review and meta-analysis. *AIDS Res Ther*. 2022;19(1):3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35031068.

36. Dong Y, Li Z, Ding S, et al. HIV infection and risk of COVID-19 mortality: a meta-analysis. *Medicine (Baltimore)*. 2021;100(26):e26573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34190201.

37. Levine SJ, White DA, Fels AO. The incidence and significance of *Staphylococcus aureus* in respiratory cultures from patients infected with the human immunodeficiency virus. *Am Rev Respir Dis*. 1990;141(1):89-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2297190.

38. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med*. 2008;168(20):2205-2210. Available at: http://archinte.jamanetwork.com/data/Journals/INTEMED/5723/ioi80120_2205_2210.pdf.

39. Everett CK, Subramanian A, Jarisberg LG, Fei M, Huang L. Characteristics of drug-susceptible and drug-resistant *Staphylococcus aureus* pneumonia in patients with HIV. *Epidemiology (Sunnyvale)*. 2013;3(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/25346868.

40. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. *Ann Intern Med*. 2008;148(4):249-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18283202.

41. Popovich KJ, Hota B, Aroutcheva A, et al. Community-associated methicillin-resistant *Staphylococcus aureus* colonization burden in HIV-infected patients. *Clin Infect Dis*. 2013;56(8):1067-1074. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23325428.

42. Zervou FN, Zacharioudakis IM, Ziakas PD, Rich JD, Mylonakis E. Prevalence of and risk factors for methicillin-resistant *Staphylococcus aureus* colonization in HIV infection: a meta-analysis. *Clin Infect Dis*. 2014;59(9):1302-1311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25031291.

43. Cilloniz C, Torres A, Manzardo C, et al. Community-acquired pneumococcal pneumonia in virologically suppressed HIV-infected adult patients: a matched case-control study. *Chest*. 2017;152(2):295-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28302496.

44. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of *Pneumocystis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. 1998;12(8):885-893. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9631142.

45. Bordon JM, Fernandez-Botran R, Wiemken TL, et al. Bacteremic pneumococcal pneumonia: clinical outcomes and preliminary results of inflammatory response. *Infection*. 2015;43(6):729-738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26424683.

46. Centers for Disease Control and Prevention. Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep*. 2012;61(40):816-819. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23051612.

47. Feikin DR, Jagero G, Aura B, et al. High rate of pneumococcal bacteremia in a prospective cohort of older children and adults in an area of high HIV prevalence in rural western Kenya. *BMC Infect Dis*. 2010;10:186. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20573224.

48. Heffernan RT, Barrett NL, Gallagher KM, et al. Declining incidence of invasive *Streptococcus pneumoniae* infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000. *J Infect Dis*. 2005;191(12):2038-2045. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15897989.

49. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med*. 2005;165(13):1533-1540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16009870.

50. Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med*. 2006;144(1):1-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16389249.

51. Cohen AL, Harrison LH, Farley MM, et al. Prevention of invasive pneumococcal disease among HIV-infected adults in the era of childhood pneumococcal immunization. *AIDS*. 2010;24(14):2253-2262. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20671543.

52. Burgos J, Penaranda M, Payeras A, et al. Invasive pneumococcal disease in HIV-infected adults: clinical changes after the introduction of the pneumococcal conjugate vaccine in children. *J Acquir Immune Defic Syndr*. 2012;59(1):31-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22156821.

53. Garcia Garrido HM, Mak AMR, Wit F, et al. Incidence and risk factors for invasive pneumococcal disease and community-acquired pneumonia in human immunodeficiency virus-infected individuals in a high-income setting. *Clin Infect Dis*. 2020;71(1):41-50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31634398.

54. Osmond DH, Chin DP, Glassroth J, et al. Impact of bacterial pneumonia and *Pneumocystis carinii* pneumonia on human immunodeficiency virus disease progression. Pulmonary Complications of HIV Study Group. *Clin Infect Dis*. 1999;29(3):536-543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10530443.

55. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. *Clin Infect Dis*. 2006;43(1):90-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16758423.

56. Malinis M, Myers J, Bordon J, et al. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. 2010;14(1):e22-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19586789.

57. Sanders KM, Marras TK, Chan CK. Pneumonia severity index in the immunocompromised. *Can Respir J*. 2006;13(2):89-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16550266.

58. Christensen D, Feldman C, Rossi P, et al. HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. *Clin Infect Dis*. 2005;41(4):554-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16028168.

59. Cordero E, Pachon J, Rivero A, et al. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. *Am J Respir Crit Care Med*. 2000;162(6):2063-2068. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11112115.

60. Sogaard OS, Lohse N, Gerstoft J, et al. Mortality after hospitalization for pneumonia among individuals with HIV, 1995–2008: a Danish cohort study. *PLoS One*. 2009;4(9):e7022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19750011.

61. Zifodya JS, Duncan MS, So-Armah KA, et al. Community-acquired pneumonia and risk of cardiovascular events in people living with HIV. *J Am Heart Assoc*. 2020;9(23):e017645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33222591.

62. Marcus JL, Leyden WA, Chao CR, et al. Immunodeficiency, AIDS-related pneumonia, and risk of lung cancer among HIV-infected individuals. *AIDS*. 2017;31(7):989-993. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28252529.

63. Sigel K, Wisnivesky J, Crothers K, et al. Immunological and infectious risk factors for lung cancer in US veterans with HIV: a longitudinal cohort study. *Lancet HIV*. 2017;4(2):e67-e73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27916584.

64. Morris AM, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med*. 2000;162(2 Pt 1):612-616. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10934095.

65. Evans SE, Jennerich AL, Azar MM, et al. Nucleic acid-based testing for noninfluenza viral pathogens in adults with suspected community-acquired pneumonia. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med*. 2021;203(9):1070-1087. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33929301.

66. Nyamande K, Lalloo UG. Serum procalcitonin distinguishes CAP due to bacteria, Mycobacterium tuberculosis and PJP. *Int J Tuberc Lung Dis*. 2006;10(5):510-515. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16704032.

67. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200(7):e45-e67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31573350.

68. Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The clinical utility of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal screening to rule out MRSA pneumonia: a diagnostic meta-analysis with antimicrobial stewardship implications. *Clin Infect Dis*. 2018;67(1):1-7. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29340593.

69. Cordero E, Pachon J, Rivero A, et al. Usefulness of sputum culture for diagnosis of bacterial pneumonia in HIV-infected patients. *Eur J Clin Microbiol Infect Dis*. 2002;21(5):362-367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12072920.

70. Jordano Q, Falco V, Almirante B, et al. Invasive pneumococcal disease in patients infected with HIV: still a threat in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2004;38(11):1623-1628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15156452.

71. Hamel MJ, Greene C, Chiller T, et al. Does cotrimoxazole prophylaxis for the prevention of HIV-associated opportunistic infections select for resistant pathogens in Kenyan adults? *Am J Trop Med Hyg*. 2008;79(3):320-330. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18784222.

72. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH, Chang SC. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. *Vaccine*. 2004;22(15-16):2006-2012. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15121313.

73. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS*. 1999;13(14):1971-1975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10513657.

74. Rodriguez-Barradas MC, Goulet J, Brown S, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. *Clin Infect Dis*. 2008;46(7):1093-1100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18444830.

75. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998–2003. *Vaccine*. 2008;26(46):5830-5834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18786586.

76. Barry PM, Zetola N, Keruly JC, Moore RD, Gebo KA, Lucas GM. Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990–2003. *AIDS*. 2006;20(3):437-444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16439878.

77. Veras MA, Enanoria WT, Castilho EA, Reingold AL. Effectiveness of the polysaccharide pneumococcal vaccine among HIV-infected persons in Brazil: a case control study. *BMC Infect Dis*. 2007;7:119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17956620.

78. Marcus JL, Baxter R, Leyden WA, et al. Invasive pneumococcal disease among HIV-infected and HIV-uninfected adults in a large integrated healthcare system. *AIDS Patient Care STDS*. 2016;30(10):463-470. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27749111.

79. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355(9221):2106-2111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10902624.

80. Watera C, Nakiyingi J, Miiro G, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS*. 2004;18(8):1210-1213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15166540.

81. Kobayashi M, Matanock A, Xing W, et al. Impact of 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease among adults with HIV—United States, 2008–2018. *J Acquir Immune Defic Syndr*. 2022;90(1):6-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35384920.

82. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the Advisory Committee on Immunization Practices—United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):109-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35085226.

83. Mohapi L, Pinedo Y, Osiyemi O, et al. Safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in adults living with HIV. *AIDS*. 2022;36(3):373-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34750291.

84. French N, Gordon SB, Mwalukomo T, et al. A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med*. 2010;362(9):812-822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20200385.

85. Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, October 2007–September 2008. *Ann Intern Med*. 2007;147(10):725-729. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17947396.

86. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. *J Infect Dis*. 1996;173(4):857-862. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8603963.

87. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med*. 2000;160(17):2633-2638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10999977.

88. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. *J Infect Dis*. 2001;183(9):1409-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11294675.

89. Penaranda M, Falco V, Payeras A, et al. Effectiveness of polysaccharide pneumococcal vaccine in HIV-infected patients: a case-control study. *Clin Infect Dis*. 2007;45(7):e82-87. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17806042.

90. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis*. 2014;58(3):309-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24421306.

91. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014;371(7):635-645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25119609.

92. Grohskopf LA. National Center for Immunization and Respiratory Diseases (U.S.) United States. Advisory Committee on Immunization Practices. Influenza Division. Influenza vaccines for older adults: GRADE summary. Presented at: ACIP meeting Influenza; 2022. Atlanta, GA. Available at: https://stacks.cdc.gov/view/cdc/114834.

93. McKittrick N, Frank I, Jacobson JM, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons: a single-center, parallel, randomized trial. *Ann Intern Med*. 2013;158(1):19-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23277897.

94. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. 1999;353(9163):1463-1468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10232311.

95. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. *N Engl J Med*. 1992;327(26):1842-1848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1448121.

96. Angel JB, High K, Rhame F, et al. Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. Leukine/HIV Study Group. *AIDS*. 2000;14(4):387-395. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10770541.

97. Keiser P, Rademacher S, Smith JW, Skiest D, Vadde V. Granulocyte colony-stimulating factor use is associated with decreased bacteremia and increased survival in neutropenic HIV-infected patients. *Am J Med*. 1998;104(1):48-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9528719.

98. Crothers K, Griffith TA, McGinnis KA, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *J Gen Intern Med*. 2005;20(12):1142-1145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16423106.

99. Navin TR, Rimland D, Lennox JL, et al. Risk factors for community-acquired pneumonia among persons infected with human immunodeficiency virus. *J Infect Dis*. 2000;181(1):158-164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10608762.

100. Justice AC, Lasky E, McGinnis KA, et al. Medical disease and alcohol use among veterans with human immunodeficiency infection: a comparison of disease measurement strategies. *Med Care*. 2006;44(8 Suppl 2):S52-60. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16849969.

101. Curran A, Falco V, Crespo M, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. *HIV Med*. 2008;9(8):609-615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18557951.

102. Almeida A, Almeida AR, Castelo Branco S, Vesza Z, Pereira R. CURB-65 and other markers of illness severity in community-acquired pneumonia among HIV-positive patients. *Int J STD AIDS*. 2016;27(11):998-1004. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26394997.

103. Madeddu G, Laura Fiori M, Stella Mura M. Bacterial community-acquired pneumonia in HIV-infected patients. *Curr Opin Pulm Med*. 2010;16(3):201-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20154625.

104. Chew KW, Yen IH, Li JZ, Winston LG. Predictors of pneumonia severity in HIV-infected adults admitted to an Urban public hospital. *AIDS Patient Care STDS*. 2011;25(5):273-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21488749.

105. Bordon J, Kapoor R, Martinez C, et al. CD4+ cell counts and HIV-RNA levels do not predict outcomes of community-acquired pneumonia in hospitalized HIV-infected patients. *Int J Infect Dis*. 2011;15(12):e822-827. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21885316.

106. Barakat LA, Juthani-Mehta M, Allore H, et al. Comparing clinical outcomes in HIV-infected and uninfected older men hospitalized with community-acquired pneumonia. *HIV Med*. 2015;16(7):421-430. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25959543.

107. Buss IM, Birkhamshaw E, Innes MA, Magadoro I, Waitt PI, Rylance J. Validating a novel index (SWAT-Bp) to predict mortality risk of community-acquired pneumonia in Malawi. *Malawi Med J*. 2018;30(4):230-235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31798800.

108. Centers for Disease Control and Prevention. *Streptococcus pneumoniae*, 2019. 2019. Available at: https://www.cdc.gov/abcs/downloads/SPN_Surveillance_Report_2019.pdf.

109. Garin N, Genne D, Carballo S, et al. beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med*. 2014;174(12):1894-1901. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25286173.

110. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med*. 2015;372(14):1312-1323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25830421.

111. Figueiredo-Mello C, Naucler P, Negra MD, Levin AS. Ceftriaxone versus ceftriaxone plus a macrolide for community-acquired pneumonia in hospitalized patients with HIV/AIDS: a randomized controlled trial. *Clin Microbiol Infect*. 2018;24(2):146-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28648859.

112. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus *Streptococcus pneumoniae*: coping with antimicrobial susceptibility in an era of resistance. *Clin Infect Dis*. 2009;48(11):1596-1600. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19400744.

113. Baddour LM, Yu VL, Klugman KP, et al. Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *Am J Respir Crit Care Med*. 2004;170(4):440-444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15184200.

114. Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2014;42(2):420-432. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24158175.

115. Vardakas KZ, Trigkidis KK, Falagas ME. Fluoroquinolones or macrolides in combination with beta-lactams in adult patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2017;23(4):234-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27965070.

116. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163(7):519-528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26258555.

117. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. 2019;23(1):99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30917856.

118. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32678530.

119. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA*. 2015;313(7):677-686. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25688779.

120. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34605781.

121. Rubinstein E, Lalani T, Corey GR, et al. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. *Clin Infect Dis*. 2011;52(1):31-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21148517.

122. File TM, Jr., Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis*. 2010;51(12):1395-1405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21067350.

123. Novak RM, Richardson JT, Buchacz K, et al. Immune reconstitution inflammatory syndrome: incidence and implications for mortality. *AIDS*. 2012;26(6):721-730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22233655.

124. De P, Farley A, Lindson N, Aveyard P. Systematic review and meta-analysis: influence of smoking cessation on incidence of pneumonia in HIV. *BMC Med*. 2013;11:15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23339513.

125. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *Am J Perinatol*. 1998;15(9):523-525. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9890248.

126. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiol Drug Saf*. 2000;9(7):549-556. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11338912.

127. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. 1996;69(2):83-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8902438.

128. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42(6):1336-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9624471.

129. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. 2006;107(5):1120-1138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648419.

130. McCormack WM, Rosner B, Lee YH, Munoz A, Charles D, Kass EH. Effect on birth weight of erythromycin treatment of pregnant women. *Obstet Gynecol*. 1987;69(2):202-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3543767.

131. Bookstaver PB, Bland CM, Griffin B, Stover KR, Eiland LS, McLaughlin M. A review of antibiotic use in pregnancy. *Pharmacotherapy*. 2015;35(11):1052-1062. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26598097.

132. Reyes MP, Ostrea EM, Jr., Cabinian AE, Schmitt C, Rintelmann W. Vancomycin during pregnancy: does it cause hearing loss or nephrotoxicity in the infant? *Am J Obstet Gynecol*. 1989;161(4):977-981. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2801848.

133. Weinberg A, Muresan P, Laimon L, et al. Safety, immunogenicity, and transplacental antibody transport of conjugated and polysaccharide pneumococcal vaccines administered to pregnant women with HIV: a multicentre randomised controlled trial. *Lancet HIV*. 2021;8(7):e408-e419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33915104.

134. Duarte G, Muresan P, Ward S, et al. Immunogenicity of conjugated and polysaccharide pneumococcal vaccines administered during pregnancy or postpartum to women with HIV. *J Infect Dis*. 2022;225(6):1021-1031. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34791324.

Cryptococcosis

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Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the cause. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the U.S. Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of people with advanced HIV in some high-resourced countries had disseminated cryptococcosis.[1] In a surveillance study in the late 1990s, people with HIV who developed cryptococcosis were severely immunosuppressed and had barriers to accessing routine HIV medical care.[2] Estimates indicate that every year, approximately 280,000 cases of cryptococcal infection in people with AIDS occur worldwide, and the disease accounts for 15% of AIDS-related deaths.[3] Overall, 90% of cryptococcal cases in people with HIV are observed in those who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3. The incidence of the disease has declined substantially among people treated effectively with ART.[4]

Clinical Manifestations

In people with HIV, cryptococcosis commonly presents as subacute meningitis or meningoencephalitis with fever, malaise, and headache slowly developing over many weeks, with a median duration of 2 weeks.[1] Classic meningeal symptoms and signs—such as neck stiffness and photophobia—occur in only one-quarter to one-third of people. Some individuals experience encephalopathic symptoms—such as lethargy, altered mentation, personality changes, and memory loss—that are usually a result of increased intracranial pressure (ICP).[5] Among people presenting with cryptococcal meningitis shortly after initiating ART, the symptom onset can be more acute, likely related to an unmasking immune reconstitution inflammatory syndrome (IRIS).[6]

Despite manifesting principally as a central nervous system (CNS) disease, cryptococcosis may involve any bodily organ. In fact, despite widespread disseminated disease, people with HIV may manifest few symptoms. Skin lesions may show different manifestations, including umbilicated skin lesions that mimic those seen with molluscum contagiosum. Isolated pulmonary infection is also possible; symptoms and signs include cough and dyspnea in association with an abnormal chest radiograph, which typically demonstrates lobar consolidation, although nodular infiltrates have been reported. Pulmonary cryptococcosis may present as acute respiratory distress syndrome and even mimic *Pneumocystis* pneumonia.

Diagnosis

In people with HIV, cryptococcosis is usually disseminated at the time of diagnosis and most commonly presents as subacute meningoencephalitis. Analysis of cerebrospinal fluid (CSF) in initial cases generally demonstrates mildly elevated protein levels, low-to-normal glucose concentrations, and a variable presence of pleocytosis consisting mostly of lymphocytes. Some people with advanced HIV may have very few CSF inflammatory cells. A Gram stain or an India ink preparation, if available, may reveal numerous yeast forms. In patients with HIV and cryptococcal meningitis, the

opening pressure for the CSF may be elevated, with pressures ≥25 cm CSF in 60% to 80% of patients.[7,8]

Cryptococcal disease can be diagnosed by culture, CSF microscopy, cryptococcal antigen (CrAg) detection, or CSF polymerase chain reaction (PCR). In HIV-related cryptococcal meningitis, most blood cultures and CSF cultures will be positive (47% to 70% and 90% to 94%, respectively).[5] Visible *Cryptococcus* colonies on a fungal Sabouraud dextrose agar plate, or even a standard aerobic bacterial culture, generally can be detected within 7 days. *Cryptococcus* may be identified occasionally on a routine Gram stain preparation of CSF as poorly staining Gram-positive yeasts. India ink staining of CSF demonstrates encapsulated yeasts in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. India ink is relatively insensitive early in disease when <1,000 *Cryptococcus* colony-forming units (CFU)/mL are present.[9] In tissue or fluids, yeasts will stain with Grocott methenamine silver stain, and the capsule will stain with mucicarmine or alcian blue stains. Positive cultures are required to prove yeast viability because strains can be stain positive with nonviable yeasts.

Cryptococcus can infect any part of the body, but brain and lungs are frequently target organs. Cultures and/or histopathology are essential for precise diagnosis. However, in many patients with advanced HIV, the presentation is more commonly a meningeal syndrome rather than a pulmonary syndrome.

CSF CrAg is usually positive in people with cryptococcal meningoencephalitis; however, early meningitis can present with negative CSF studies and a positive CrAg in blood only.[10] Thus, serum CrAg testing always should be performed in an immunocompromised individual with an unknown CNS disorder.[10] Serum CrAg is positive in both meningeal and non-meningeal cryptococcal infections and may be present weeks to months before symptom onset.[11] All positive CrAg tests in patients with HIV require consideration for therapy.

Three methods exist for antigen detection: latex agglutination, enzyme immunoassay (EIA), and lateral flow assay (LFA). The IMMY CrAg LFA (IMMY, Norman, Oklahoma) is the only LFA test for CrAg approved by the U.S. Food and Drug Administration (FDA). It is a useful initial screening tool for diagnosing cryptococcosis in people with HIV when applied to serum or plasma,[9,12] and it also can be used with whole blood or CSF. CrAg testing of serum or plasma may be particularly useful when a lumbar puncture is delayed or refused. In a person with HIV, when serum CrAg LFA titers are ≥1:160, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are ≥1:640, or when there is high clinical suspicion, disseminated and/or CNS involvement should be assumed, regardless of CSF antigen titer results.[13,14] Antigen titers by the LFA are approximately fourfold higher than those with latex agglutination or EIA testing; thus, a titer of 1:640 by LFA is approximately equal to a titer of 1:160 by EIA or latex agglutination. A prozone effect needs to be checked when CrAg with latex agglutination and LFA testing is negative despite observing yeasts in tissues or fluids.

In 2016, the BioFire FilmArray Meningitis/Encephalitis Panel PCR assay (BioFire Diagnostics, Salt Lake City, Utah) was approved by the FDA. This multiplex PCR tests for 14 targets, including *C. neoformans* and *C. gattii,* and performs well in infections with a moderate-to-high fungal burden.[15-17] False negative results have been noted to occur when there is a low burden of yeasts; in one study, when there were <100 CFU/mL, the sensitivity of the PCR test fell to 50%.[15] In one well-described case, a woman who had two negative results with this PCR assay later had a positive result on a CrAg test done by IMMY LFA.[18] Thus, a negative CSF PCR does not completely exclude

cryptococcal meningitis, and CrAg testing of CSF and blood should always be performed simultaneously. The PCR assay appears to have diagnostic utility when a second episode of cryptococcal meningitis is suspected; the test has been noted to differentiate a relapse (PCR positive) from IRIS (PCR negative).[15]

Preventing Exposure

Cryptococcus is ubiquitous in the environment, and people with HIV cannot completely avoid exposure to *C. neoformans* or *C. gattii.* Limited epidemiological evidence suggests that exposure to dried bird droppings, including those from chickens and pet birds, may increase the risk of infection and should be avoided. It is likely that many patients are infected with mixed strains of *Cryptococcus* over a lifetime, and clinical implications remain uncertain.[19,20]

Preventing Disease

The incidence of cryptococcal disease is low among people with HIV in the United States. However, one report indicates that among study participants with HIV in the United States with peripheral blood CD4 counts ≤100 cells/mm^3, the prevalence of cryptococcal antigenemia—a harbinger of disease—was 2.9%, and for those with CD4 counts ≤50 cells/mm^3, the prevalence was 4.3%.[21] Routine surveillance testing for serum CrAg in people with newly diagnosed HIV who have no overt clinical signs of meningitis is recommended for patients whose CD4 counts are ≤200 cells/mm^3 and particularly in those with CD4 counts ≤50 cells/mm^3 **(AII).**[22] All positive tests generally should prompt CSF evaluation for CNS infection, particularly when the serum LFA titer is ≥1:160 **(AII).**[23] See section on Treatment of Asymptomatic Antigenemia.

Prospective controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in people with HIV who have CD4 counts <100 cells/mm.[24,25] However, in the United States, primary prophylaxis in the absence of a positive serum CrAg test is not recommended because of the relative infrequency of cryptococcal disease, lack of clear survival benefit associated with prophylaxis,[26] possibility of drug–drug interactions, potential development of antifungal drug resistance, and cost **(BII).**

Treating Disease

Recommendations for Treating Cryptococcosis
Treating CNS and/or Disseminated Disease
Treatment consists of three phases: induction, consolidation, and maintenance therapy. Induction Therapy (Duration: 2 Weeks, Followed by Consolidation Therapy) • Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days (AII). LP should be performed at Day 7 and Day 14 to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily LP should be performed until the pressure is decreased into the normal range and symptoms have abated (AII). *Preferred Regimens* • In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and IV fluid is possible: o Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (AII)

- In resource-limited health care systems, as recommended by the World Health Organization:
  - Liposomal amphotericin B 10 mg/kg IV as a single dose on Day 1, followed by flucytosine 25 mg/kg PO four times a day plus fluconazole 1,200 mg PO daily for 2 weeks (AI)

Alternative Regimens

- Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (BII), *or*
- Amphotericin B deoxycholate 1 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 1 week, followed by fluconazole 1,200 mg PO daily for an additional week (BI)

Note: The flucytosine dose should be adjusted in renal impairment and ideally use TDM (see Table 6).

Additional Studied Regimens (Duration of Therapy: 2 Weeks)

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day (BI)
- Liposomal amphotericin B 3–4 mg/kg IV once daily plus fluconazole 800–1,200 mg PO once daily (BIII)
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus fluconazole 800–1,200 mg PO once daily (BI)
- Fluconazole 1,200 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day (BII)

If the patient has not improved clinically or remains clinically unstable, continue or start (liposomal amphotericin B or amphotericin B deoxycholate) plus flucytosine induction therapy until the CSF culture is confirmed to be negative (BIII).

Additional Considerations

- CSF opening pressure should always be measured when an LP is performed. Repeated therapeutic LPs are essential to manage symptomatic increased ICP and have a survival benefit (AII).
- Corticosteroids should not be used routinely during induction therapy unless used for management of IRIS (AI).
- Corticosteroids, acetazolamide, and mannitol are ineffective in reducing ICP and are not recommended (AIII).

Consolidation Therapy (Duration of Therapy: ≥8 Weeks, Followed by Maintenance Therapy)

Perform LP after 1 week and/or 2 weeks of induction therapy to document the culture is negative (AII). After 2 weeks of induction therapy, people who are clinically stable may be switched to consolidation therapy while awaiting culture results. Duration of consolidation therapy should be for at least 8 weeks after receiving CSF culture at 2 weeks is negative (AII).

Preferred Regimen

- Fluconazole 800 mg PO daily (AI)
- For clinically stable patients, continue fluconazole 800 mg until CSF cultures are known to be sterile and ART has been initiated; dose then can be reduced to 400 mg PO daily (AII).
- If CSF remains positive in a clinically stable patient after 2 weeks of induction therapy, use one of the following two options for an additional 2 weeks before reducing the dose to fluconazole 800 mg PO daily:
  - Fluconazole 1,200 mg PO daily plus flucytosine 25 mg/kg PO four times a day for an additional 2 weeks (BIII), or
  - Fluconazole 1,200 mg PO daily for an additional 2 weeks (BIII)

Alternative Regimen

- Itraconazole 200 mg PO twice a day, if fluconazole is not available or not tolerated (CI)

Maintenance Therapy

Preferred Regimen

- Fluconazole 200 mg PO once daily for ≥1 year from initiation of antifungal therapy (AI)

Alternative Regimen

- Itraconazole 200 mg PO twice a day, if fluconazole is not available or not tolerated (CI)
- If susceptibility studies have been performed and the fluconazole MIC is ≥16 μg/mL, the fluconazole dose may be increased to 400 mg daily (BIII).

Criteria for Stopping Maintenance Therapy (BII)

- At least 1 year from initiation of antifungal therapy, *and*
- Patient remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥100 cells/mm^3 and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy

- If CD4 count declines to <100 cells/mm^3 (AIII)

Treating Non-CNS Extrapulmonary Disease, Diffuse Pulmonary Disease, or Non-CNS Symptoms With Normal CSF and Serum CrAg Titer **≥1:640** by LFA **(or ≥1:160 by EIA or** Latex Agglutination)

Administer the same treatment as for patients with cryptococcal meningitis to people with the following conditions:

- Non-CNS extrapulmonary disease (BIII)
- Diffuse pulmonary disease (BIII)
- Non-CNS symptoms, normal CSF, and serum CrAg titer ≥1:640 by LFA (or ≥1:160 by EIA or latex agglutination) (BII)

Note: All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease.

Treating Non-CNS Focal Pulmonary Infiltrates (With Mild Symptoms) and Negative Serum CrAg

- Fluconazole 400 mg daily for 6 to 12 months (duration guided by symptom resolution) (BIII)

Treating Isolated Asymptomatic Cryptococcal Antigenemia (Serum CrAg Titer of LFA <**1:640** [or **<1:160 by** EIA or Latex Agglutination])

- Fluconazole 800–1,200 mg PO daily for 2 weeks, followed by fluconazole 400–800 mg PO daily for 10 weeks, then fluconazole 200 mg PO daily for a total of 6 months plus effective ART (BIII)

Note: Those with lower risk and serum CrAg titer <1:80 by LFA (<1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture (AI). All others should undergo CSF sampling to rule out CNS disease.

Treatment in Pregnancy

Preferred Therapy During First Trimester

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII), *or*
- Lipid formulation amphotericin B 3–4 mg/kg IV daily (AIII)
- Addition of flucytosine should be considered only when the benefits outweigh the risks, with delay until after the first trimester when feasible (AIII).

Notes: Optimal dosing of liposomal amphotericin B in pregnancy is unknown. Use of ideal body weight rather than total body weight may minimize risk of adverse effects to the fetus while maintaining efficacy (BII). In general, azole antifungal agents should be avoided in the first trimester of pregnancy because of potential teratogenic effect, unless benefit is felt to outweigh risk (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system; CrAg = cryptococcal antigen; CSF = cerebrospinal fluid; EIA = enzyme immunoassay; ICP = intracranial pressure; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LFA = lateral flow assay; LP = lumbar puncture; MIC = minimum inhibitory concentration; PO = orally; TDM = therapeutic drug monitoring

Treatment of Central Nervous System and/or Disseminated Disease

Treatment of CNS and disseminated disease consists of three phases: induction, consolidation, and maintenance.

Induction Therapy

For induction treatment of cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously (IV), in combination with oral flucytosine, is recommended for 2 weeks in a resource-available health care system **(AII),** and in resource-limited health care systems, a single dose of liposomal amphotericin B (10 mg/kg) is recommended, followed by 2 weeks of flucytosine and fluconazole **(AI).** Historically, amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily had been the preferred formulation of the drug.[27] In resource-available health care systems, however, lipid formulations of amphotericin B have become the standard polyene formulations because they are effective for cryptococcosis and have lower toxicity. A study that compared amphotericin B deoxycholate (0.7 mg/kg daily) and liposomal amphotericin B (AmBisome) at two doses (3 mg/kg daily and 6 mg/kg daily) showed similar outcomes for all three regimens; however, lower nephrotoxicity was observed among those receiving the 3 mg/kg daily liposomal amphotericin B regimen.[28] The noncomparative CLEAR study demonstrated a 58% response rate in people with HIV and cryptococcosis who were treated with amphotericin B lipid complex (Abelcet) at a mean dose of 4.4 mg/kg daily.[29]

Several large clinical trials that used shorter courses of amphotericin B have been reported from Africa.[30,31] A multicenter clinical trial that evaluated two different induction regimens in 721 African adults with HIV found that an initial regimen of 1 week of amphotericin B deoxycholate at 1 mg/kg/day and flucytosine 25 mg/kg four times daily, followed by 1 week of oral fluconazole 1,200 mg/day was non-inferior (95% confidence interval [CI], -12.5 to 5.35 at 10 weeks) to the standard regimen of 2 weeks of amphotericin B deoxycholate 1 mg/kg/day and flucytosine 25 mg/kg four times daily when outcomes at 10 weeks were studied.[30] At 1 year, follow-up of 236 participants from this treatment trial continued to show noninferiority of the 1-week amphotericin B deoxycholate regimen compared with the 2-week regimen.[32]

A phase 3 open-label, randomized, controlled noninferiority trial of single-dose liposomal amphotericin B was conducted at five sites in Africa in 814 patients.[33] Results of this study showed that outcomes of people receiving a single dose of liposomal amphotericin B, 10 mg/kg, combined with 14 days of oral flucytosine, 25 mg/kg four times daily, and oral fluconazole, 1,200 mg/day, were not inferior to a control group that received therapy with amphotericin B deoxycholate, 1 mg/kg/day, and flucytosine, 25 mg/kg four times daily for 7 days, followed by oral fluconazole, 1,200 mg/day for another 7 days.[33] At 10 weeks, deaths were reported in 101 participants (24.8%; 95% CI, 20.7–29.3) in the liposomal amphotericin B group and 117 participants (28.7%; 95% CI, 24.4–33.4) in the control group (difference, −3.9 percentage points); the upper boundary of the one-sided

95% CI was 1.2 percentage points (within the noninferiority margin; P <0.001 for noninferiority). Grade 3 or 4 toxicity was reduced in the single-dose liposomal amphotericin B group compared with the amphotericin B deoxycholate group (50% vs. 62.3%, P <0.001).[33] It is important to note that patients in both groups were monitored closely in a hospital for a minimum of 7 days. Lumbar punctures were performed on Day 7 and Day 14 and daily if ICP was >25 cm of CSF or if the patient demonstrated symptoms and signs consistent with elevated ICP.

Currently, several different treatment regimens for **induction therapy** of cryptococcal meningitis are recommended:

- Irrespective of which regimen is used, patients must be followed carefully in the hospital for at least 7 days and ideally 14 days **(AII).** Lumbar puncture should be performed on Day 7 and Day 14 of treatment to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily lumbar punctures should be performed until the pressure and symptoms are decreased to the normal range **(AII).**

Preferred Regimens

In the United States and other settings where daily monitoring of electrolytes and kidney function and administration of electrolytes and intravenous fluids is possible:

- Liposomal amphotericin B (IV 3–4 mg/kg daily) plus flucytosine (25 mg/kg orally [PO] four times daily) for 2 weeks is the regimen preferred and recommended by the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections Adults and Adolescent With HIV (the Panel) **(AII).**[28,34]

In resource-limited health care settings:

- A single dose of liposomal amphotericin B (IV 10 mg/kg on Day 1) combined with oral flucytosine (25 mg/kg four times daily) and fluconazole (1,200 mg/day) for 2 weeks is the preferred regimen recommended by the World Health Organization **(AI).**[33]

Alternative Regimens

- If amphotericin B lipid complex is the only available lipid amphotericin B formulation available, a dosage of 5 mg/kg IV daily combined with flucytosine 25 mg/kg PO four times daily should be administered for 2 weeks **(BII).** However, there is much less experience with amphotericin B lipid complex than with the liposomal amphotericin B formulation.
- If amphotericin B deoxycholate is the only available formulation of amphotericin B, this can be used at a dosage of 1 mg/kg IV daily combined with flucytosine 25 mg/kg PO four times daily for 1 week, followed by fluconazole 1,200 mg/day PO for an additional week **(BI).**[30]

When using flucytosine, therapeutic drug monitoring should be performed, if available, particularly in patients who have renal impairment. Serum peak concentrations of flucytosine should be obtained 2 hours post dose after three to five doses have been administered. Peak serum concentrations should be between 25 mg/L and 100 mg/L.[17] Renal function should be monitored closely and the flucytosine dose adjusted accordingly for those with renal impairment (see Table 6). For those without access to timely flucytosine concentrations, which is a common occurrence, frequent blood counts and renal functions are needed to detect bone marrow toxicity, especially when renal impairment is present.

The addition of flucytosine to the amphotericin B regimen during acute treatment is associated with more rapid sterilization of CSF and survival benefit.[34-36] For instance, a randomized clinical trial of 299 patients showed that the combination of amphotericin B deoxycholate at a dose of 1 mg/kg daily plus flucytosine was associated with improved survival compared to the same dose of amphotericin B without adjunctive flucytosine.[37] Adjunctive fluconazole 800 to 1,200 mg per day plus amphotericin B has been used in the absence of flucytosine, but flucytosine has a survival advantage over fluconazole and is preferred **(BI).**[30] Amphotericin B deoxycholate with flucytosine **(BI)** or with fluconazole at a dose of 800 to 1,200 mg per day **(BI)** or liposomal amphotericin B with fluconazole at a dose of 800 to 1,200 mg per day **(BIII)** may be reasonable alternatives in some circumstances.

Fluconazole, administered at 1,200 mg daily **(CIII)** or with flucytosine **(BII),** is a potential all-oral alternative to amphotericin B regimens.[30,38] Based on studies assessing early fungicidal activity, fluconazole alone (1,200 mg/day) is inferior to amphotericin B for induction therapy.[39,40] Therefore, fluconazole is preferably used with flucytosine. Fluconazole alone is recommended only for patients who cannot tolerate other agents or who do not respond to standard treatment, or when other antifungals are not available.

Consolidation Therapy

A lumbar puncture and repeat CSF culture should be performed after 1 week and/or 2 weeks of induction therapy in all patients **(AII).** After 2 weeks of induction therapy, clinically stable patients may be switched to consolidation therapy while awaiting CSF culture results. Successful induction therapy is defined as substantial clinical improvement and a negative CSF culture from the end-of-induction lumbar puncture. India ink and CSF CrAg may remain positive at Week 2 of therapy and are not indicative of failure. Monitoring serum or CSF CrAg titers is of no value in determining initial response to therapy and **is not recommended (AII).**[41,42] If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of lumbar opening pressure and CSF culture, should be performed.

Consolidation therapy should be initiated with fluconazole 800 mg daily for at least 8 weeks after receiving a clinically successful 2 weeks of induction therapy **(AII).** The recommendation to use 800 mg rather than 400 mg fluconazole for consolidation therapy is based on several findings. Early clinical trials that used 400 mg fluconazole for consolidation noted breakthrough infection during consolidation.[27] Fluconazole 400 mg per day provides concentrations in the CSF that are only fungistatic, and other studies showed that the early antifungal activity of fluconazole in CSF of people with cryptococcal meningitis increases linearly with increasing doses of the drug.[37,39] A phase 2 trial of treatment with either 400 mg or 800 mg fluconazole found that relapses were more frequent in people receiving 400 mg fluconazole.[43] In clinically stable people, the dose of fluconazole for consolidation therapy should be 800 mg per day until CSF cultures are known to be sterile and ART is initiated, at which point the dose can be decreased to 400 mg per day **(AII).**[44]

For people who have completed first-line recommended or other regimen(s) as 2-week induction therapy but have not improved clinically or remain clinically unstable, continuation or starting of amphotericin B plus flucytosine is recommended until the CSF fungal cultures are confirmed to be negative **(BIII).** For outpatients who are not ill enough to be hospitalized but still have positive CSF cultures after completing 2 weeks of induction therapy, flucytosine can continue to be administered for an additional 2 weeks with fluconazole at a dose of 1,200 mg daily or fluconazole monotherapy can be administered at 1,200 mg daily **(BIII).** A lumbar puncture should be performed after 4 weeks of induction therapy to confirm that the cultures have become negative; if still positive, another 2-

week liposomal amphotericin B plus flucytosine induction course may be considered. For all people with CSF cultures positive at Week 2, the duration of consolidation therapy should be for 8 weeks from the time the CSF cultures are confirmed as negative.[27,35,45]

Itraconazole 200 mg twice per day can be used as an alternative therapy for consolidation if fluconazole is not available or is not tolerated by an individual patient **(CI),** but it is clearly inferior to fluconazole.[45] Limited data are available for use of the newer triazoles—voriconazole, posaconazole, and isavuconazole—for either consolidation or maintenance therapy for patients with cryptococcosis. Most of the reported data have been on the use of these extended-spectrum triazole antifungals for treatment of refractory cases, with success rates of approximately 50%.[46-48] Currently, the role of posaconazole, voriconazole, and isavuconazole in the initial management of cryptococcosis has not been established, and these agents **are not initially recommended** for consolidation or maintenance therapy **(AIII).** Echinocandins have no clinical activity against *Cryptococcus* spp. and **are not recommended** for the clinical management of cryptococcosis **(AII).**

Maintenance Therapy

Fluconazole 200 mg per day is used for maintenance treatment and continued until at least 1 year from initiation of antifungal therapy and assuming there is some immune reconstitution on ART and the patient is asymptomatic at the end of 1 year **(AI)** (see the Preventing Recurrence section below).[49]

Treatment of Non–Central Nervous System Cryptococcosis and Asymptomatic Antigenemia

Non-CNS extrapulmonary cryptococcosis and diffuse pulmonary disease should be treated the same as CNS disease **(BIII).** For those with mild symptoms and only focal pulmonary infiltrates with negative serum CrAg, treatment with fluconazole 400 mg per day for 6 to 12 months combined with effective ART is recommended **(BIII).** Duration of therapy should be guided by symptom resolution.[22]

All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease.[13,23,50] If the CSF is normal but the serum CrAg titer is ≥1:640 by LFA (or ≥1:160 by EIA or latex agglutination), even in the absence of meningitis, the risk for mortality and/or progression to meningitis increases with fluconazole monotherapy alone, and these patients should be treated the same as patients with cryptococcal meningitis **(BII).**[23]

Whether to sample the CSF to rule out CNS disease in people with isolated, fully asymptomatic cryptococcal antigenemia is dependent on underlying risk, such as advanced immunosuppression and absence of antiretroviral therapy, and the serum CrAg LFA titer. Those at lower risk and with serum CrAg titer <1:80 by LFA (or <1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture, as empiric treatment for meningitis does not improve outcomes **(AI).**[51] All others should undergo CSF sampling to rule out CNS disease. Those with normal CSF, fully asymptomatic cryptococcal antigenemia, and serum CrAg titers <1:640 by LFA (or <1:160 by EIA or latex agglutination) should be treated with fluconazole 800 to 1,200 mg per day for 2 weeks, followed by 400 to 800 mg per day for 10 weeks, followed by 200 mg daily, for a total of 6 months combined with effective ART **(BIII).**[22]

Special Considerations Regarding ART Initiation

Unlike with other opportunistic infections (OIs), ART initiation generally is deferred for 4 to 6 weeks after antifungal agents are started for treatment of CNS cryptococcosis **(AI).** A randomized clinical trial conducted at three sites in Africa compared patients with cryptococcal meningitis who started ART within 1 to 2 weeks (median 9 days) after the diagnosis of meningitis with patients for whom ART was delayed for 4 to 6 weeks (median 36 days) after diagnosis.[52] This clinical trial used amphotericin B deoxycholate 0.7 to 1.0 mg/kg once daily plus fluconazole 800 mg once daily during the induction phase of antifungal treatment. A significantly greater increase in 6-month mortality occurred in the early ART group than in the delayed ART group (45% vs. 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of the study ($P = 0.007$). The difference in mortality between the early ART group and the delayed ART group was even greater among individuals with CSF white cell count <5 cells/μL ($P = 0.008$). The excess deaths in the early ART group may have been attributable to paradoxical IRIS, although the timing and incidence of IRIS reportedly did not differ between the two groups.[53] In a trial conducted in China, 102 participants with cryptococcal meningitis were randomized to start ART within either 2 to 5 weeks or >5 weeks after starting antifungal therapy; the majority received amphotericin with flucytosine induction therapy. The primary analysis did not demonstrate a statistically significant difference in mortality; however, a smaller secondary analysis of 78 patients demonstrated excess risk of death in the early ART group compared with the deferred group within the window of 5 to 10 weeks after initiation of antifungal treatment.[54] It is not clear that the secondary analysis had adequate statistical power for the comparison, making the overall interpretation of this study complicated. In a recently published retrospective observational cohort study of participants enrolled from high-resourced health care systems in Europe and North America, investigators used marginal structural modeling with category censoring, inverse proportional weighting, and adjustment for bias to simulate a randomized trial of earlier versus later initiation of ART.[53] A total of 630 people with HIV were identified with cryptococcal meningitis from more than 30 cohorts between 1994 and 2012. Participants were eligible for the analyses if at meningitis diagnosis they were older than 16 years and had a CD4 count, a viral load measurement and follow-up laboratory test results, study visits, and outcomes data. Among these, 432 (69%) were considered ineligible due to insufficient outcome data (256; 41%) or missing baseline CD4 or HIV viral load (176; 28%). Among the 190 eligible patients, 145 started ART during treatment for cryptococcal meningitis.[55] The primary analysis for the simulated trial compared initiation of ART within 14 days of cryptococcal meningitis diagnosis versus starting ART within 14 to 56 days of diagnosis. There were 13 deaths in the early ART group and 20 deaths in the delayed ART group, with an adjusted hazard ratio (aHR) of 1.40 (0.66–2.95) for early versus later initiation of ART. The authors concluded that there was little evidence that earlier ART was associated with higher mortality. The incidence of IRIS was not reported.[55,56]

The issue of when to start ART in the setting of cryptococcal meningitis remains controversial. The randomized trials, most of which are more than a decade old, were largely done in low- and middle-income countries where access to currently recommended antifungal treatment, monitoring, and support may have been less optimal, and they demonstrated overall mortality rates substantially higher than had been reported in higher resourced settings. While the observational cohort study in higher resourced settings is limited by its observational, retrospective nature and cannot fully address unrecognized biases, it is unlikely that a suitably powered prospective randomized trial can be done in high-resourced settings now, given the precipitous decline in incidence of cryptococcal meningitis in people with HIV treated with more effective antifungal therapy and more effective and better tolerated ART regimens than were available in some of the earlier trials. Therefore, most experts aim to start ART within 4 weeks of antifungal therapy; however, individual patient factors may allow for

earlier or later initiation of ART. In general, ensuring that the patient's CSF cultures are sterile before starting ART will reduce the risk of IRIS.[57] If ART must be started sooner, the patient should be monitored closely for paradoxical IRIS with a low threshold to intervene (see "Monitoring of Response to Therapy and Adverse Events," below).[55] For non-CNS cryptococcosis, for which the risk of symptomatic IRIS appears to be lower, the optimal time to begin ART after antifungal therapy is less clear. However, in patients with non-CNS cryptococcosis, it is prudent to delay initiation of ART for 2 weeks after starting antifungal therapy **(BIII).**

All of the triazole antifungals have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. These interactions and recommendations for dosage adjustments, where feasible, are listed in the Drug–Drug Interaction tables in the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV.

Monitoring and Management of Response to Therapy and Adverse Events

Elevation of ICP can cause clinical deterioration despite a microbiologic response; complications are more likely to occur if the CSF lumbar opening pressure is ≥25 cm CSF in the lateral decubitus position.[7,27] In a large clinical trial in people with AIDS and cryptococcal meningitis, increased ICP was associated with 92% of deaths during the first 2 weeks of antifungal therapy and 71% of deaths during Weeks 3 to 10.[7] In another clinical trial, people with HIV who received at least one therapeutic lumbar puncture within 7 days after diagnosis (median time of 3 days) had a 69% relative reduction in the risk of death through 11 days, regardless of initial opening pressure.[58] Although it is uncertain which patients with high lumbar opening pressures will experience clinical deterioration, those with symptoms and signs of increased ICP require immediate clinical intervention to reduce ICP.

Control of elevated ICP is critical to reducing acute mortality. Lumbar opening pressure should be measured in all people with cryptococcal meningitis at the time of diagnosis. However, in routine practice, CSF opening pressure frequently is not measured. Among people in whom CSF opening pressure was not measured initially, a repeat lumbar puncture should be performed with measurement of opening pressure. For people with ongoing headaches, a repeat lumbar puncture should be performed with urgency, and among those without headaches, a repeat lumber puncture should be considered strongly within 48 hours of the initial procedure.[58] Measures to decrease ICP should be used for all people with cryptococcal meningitis who have confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs indicative of increased ICP. Drainage of CSF via lumbar puncture is recommended for initial management **(AII).** One approach is to remove a volume of CSF that reduces the opening pressure by at least 50% or normalizes the pressure to <20 cm CSF.[58,59] In the absence of a manometer, removal of 20 to 25 mL of CSF is recommended **(AIII).** Among patients with ongoing symptoms, therapeutic lumbar punctures should be repeated at least daily until symptoms and signs consistently improve and opening pressure normalizes to <20 cm CSF **(AII).** Because a survival benefit is associated with therapeutic lumbar puncture regardless of baseline CSF opening pressure, strong consideration should be given to repeating a therapeutic lumbar puncture within 72 hours of the initial procedure in those who are relatively asymptomatic or who had a baseline CSF opening pressure of <25 cm CSF, because ICP can be a dynamic process that changes over time **(BII).**[58] If the initial opening pressure was not measured, a second lumbar puncture is recommended **(AII).**

CSF shunting through a lumbar drain or ventriculostomy should be considered for people who cannot tolerate repeated lumbar punctures or for those in whom signs and symptoms of increased ICP persist

after multiple lumbar punctures **(BIII).** Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended (AIII).** Acetazolamide **should not be used** as therapy for increased ICP management because it may exacerbate hyperchloremic acidosis from amphotericin B and does not result in a meaningful decrease in ICP **(AI).**[60] A randomized study that compared a 6-week course of a tapering dose of dexamethasone with placebo among 451 Asian and African patients with cryptococcal meningitis found that dexamethasone did not improve survival through 10 weeks, was noted to not be as effective at killing of *Cryptococcus,* and was associated with more adverse events.[61] These data support the recommendation that **corticosteroids should not be used** during induction therapy for ICP control for HIV-associated cryptococcal meningitis unless they are being used for treatment of IRIS **(AI).**

People treated with amphotericin B formulations should be monitored for nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1,000 mL of normal saline reduces the risk of nephrotoxicity during amphotericin B treatment. For people with severe infusion-related adverse reactions, acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered 30 minutes before the infusion to reduce the severity of amphotericin B infusion reactions **(CIII);** meperidine (25–50 mg titrated during infusion) is effective for treating amphotericin B–associated rigors and should be given before each dose daily and after the first incidence of rigors to prevent future rigors **(BII).** Routine use of potassium chloride (40 mEq per day) and magnesium (8 mEq per day) supplementation should be considered because the risk of hypokalemia and hypomagnesemia becomes near universal after 1 week of therapy, regardless of the amphotericin B formulation used **(AII).**[62]

Flucytosine is associated with concentration-dependent bone marrow toxicity. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities. In people receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine concentrations. Peak serum flucytosine concentrations should be obtained 2 hours after an oral dose; the therapeutic range is between 25 and 100 mg/L. If therapeutic drug monitoring is not possible or kidney dysfunction is not present, frequent complete blood counts with differential (i.e., at least biweekly) can be used to detect cytopenias **(BII).**[30]

Common side effects of higher dose fluconazole therapy can include dry skin (17% of patients) and alopecia (16% of patients).[63] Increased liver transaminases or alkaline phosphatase are relatively rare in fluconazole dosages of 400 to 800 mg, with only 1 to 2% of patients having values >5 times the upper limit of normal.[52] For people who have difficulty tolerating higher fluconazole doses, the consolidation therapy fluconazole dose can be reduced to 400 mg per day after ART initiation. **(BII).**[44]

Immune Reconstitution Inflammatory Syndrome

An estimated 10 to 30% of people with HIV who have cryptococcal meningitis experience IRIS after initiation or reinitiation of effective ART and both unmasking (before start of antifungal therapy) or paradoxical (after start of antifungal therapy) IRIS may occur.[64,65] People with HIV who have cryptococcal IRIS are more likely to be ART naive and those whose CSF has less inflammation on presentation seem to be at higher risk of cryptococcal IRIS.[66] The risk of IRIS can be minimized by achieving CSF culture sterility before starting ART, using fluconazole 800 mg per day as consolidation therapy, and deferring ART initiation for 4 to 6 weeks from the start of antifungal therapy **(AII).**[52,67] Distinguishing paradoxical IRIS from treatment failure with culture-positive relapse is difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite

microbiological evidence of effective antifungal therapy with sterile CSF cultures,[66,68] whereas treatment failure is associated with continued positive cultures. The primary microbiological criterion for treatment failure is a CSF culture that yields *Cryptococcus*, not the visual appearance of yeasts during treatment; the culture may take days to weeks to become positive. A negative PCR test (e.g., BioFire FilmArray Meningitis/Encephalitis Panel) has a high predictive value for sterile CSF cultures and can be diagnostically useful for distinguishing paradoxical IRIS with a negative CSF PCR from culture-positive relapse with a positive CSF PCR.[15]

The appropriate management strategy for IRIS **is to continue both ART and antifungal therapy** and reduce elevated ICP if present **(AII).** While diagnostic tests are pending, escalating antifungal therapy (i.e., restarting amphotericin B therapy or increasing the fluconazole dose to 1,200 mg per day) is recommended **(BIII).** In people with severe symptoms of IRIS, some experts recommend a brief course of tapering doses of corticosteroids. Dosages have varied but commonly start at 1.0 mg/kg per day of prednisone; precise data-driven management strategies have not been developed. Serum C–reactive protein (CRP) is generally elevated at the time IRIS develops;[69] CRP will decrease with corticosteroid therapy if IRIS is present and can be used to empirically monitor IRIS resolution. Once clinical improvement is evident, it is recommended that fluconazole at consolidation therapy doses should be continued or restarted upon hospital discharge **(BIII).**

The risk of IRIS appears to be much lower and the syndrome seems to be less severe with other forms of cryptococcosis—such as lymphadenitis, cutaneous abscesses, and bony lesions—than with cryptococcal meningitis.[70] Management of IRIS with other forms of cryptococcosis is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy **(AIII),** and only considering the use of corticosteroids if clinical symptoms are severe **(CIII).**

Managing Treatment Failure

Treatment failure is defined as (1) a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy that has included management of increased ICP, or (2) relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Primary fluconazole resistance in *Cryptococcus* isolates has been reported in the United States but is uncommon.[71] Therefore, susceptibility testing is not recommended routinely for initial management of cryptococcosis. However, if treatment failure or relapse occurs, *Cryptococcus* isolates should undergo antifungal susceptibility testing. Robust clinical data are lacking, but strains of *Cryptococcus* with fluconazole minimum inhibitory concentrations (MIC) ≥16 µg/mL are considered not fully susceptible.[72,73]

Optimal therapy for patients with treatment failure has not been established. If treatment failure occurs after induction with alternative regimens, preferred regimens should be started. Furthermore, those initially treated with an amphotericin B formulation should remain on this agent until clinical response occurs. In this setting, liposomal amphotericin B (3–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is better tolerated and has greater efficacy than the deoxycholate formulation[28,74,75] and should be considered when initial treatment with other regimens fails **(AII).**

In the setting of treatment failure or relapse, verifying CSF culture sterility at the completion of re-induction therapy is critical **(AIII).** After CSF sterility is achieved, outpatient consolidation therapy should consist of fluconazole at a higher dose of 1,200 mg per day and optimization of ART. For *Cryptococcus* with decreased azole-susceptibility (i.e., ≥16 µg/mL MIC for fluconazole), adjunctive

weekly amphotericin B administration during consolidation therapy may be considered **(BIII).**[73] Higher doses of fluconazole (i.e., 1,200 mg per day) in combination with flucytosine 25 mg/kg four times per day also may be considered **(BI).** The newer triazoles—posaconazole, voriconazole, and isavuconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy,[46-48] but they offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates only high-level fluconazole resistance. Most clinical failures are not due to antifungal drug resistance but rather result from inadequate induction therapy, nonadherence, drug-drug interactions that decrease the serum concentrations of fluconazole (e.g., with rifampin), or the development of paradoxical IRIS. Failures also may occur with high fungal burden disease and/or severe immunosuppression of host.

Preventing Recurrence

When to Start Maintenance Therapy

People who have completed 10 weeks of induction and consolidation therapy for cryptococcal meningitis or disseminated cryptococcosis should be treated with chronic maintenance or suppressive therapy with fluconazole 200 mg per day for at least 1 year **(AI).** Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease and should generally not be considered **(CI).**[45 73] For people in whom susceptibility studies have been performed and the fluconazole MIC is ≥16 µg/mL, the fluconazole dose may be increased to 400 mg per day **(BIII).** Failure to administer this secondary prophylaxis for an entire year is the most common reason for subsequent relapse of cryptococcal disease.[76]

When to Stop Maintenance Therapy

Data evaluating relapse after successful antifungal therapy for cryptococcosis and discontinuation of maintenance therapy while on ART are limited. In a European study, recurrences of cryptococcosis were not found among 39 participants on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 count was 297 cells/mm^3, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[77] A prospective randomized study of 60 people in Thailand documented no recurrences of cryptococcosis during 48 weeks of follow-up among 22 patients whose antifungal therapy was discontinued after reaching a CD4 count >100 cells/mm^3 with a sustained undetectable HIV RNA level for 3 months on potent ART.[78] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated OIs, it is reasonable to discontinue maintenance therapy after at least 1 year from initiation of antifungal therapy in people whose CD4 counts are ≥100 cells/mm^3 with undetectable viral loads on ART **(BII).**[79] Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/mm^3 **(AIII).**

Special Considerations During Pregnancy

During pregnancy, the diagnosis of cryptococcal infections is the same as for other people with HIV. Treatment should be initiated promptly after a diagnosis is confirmed, with attention to management of increased ICP. During the postpartum period, anti-inflammatory responses in pregnancy (enhancement of Th2 and suppression of Th1 cytokines) are reversed and may lead to overt clinical manifestations of a previously asymptomatic cryptococcal infection resembling IRIS.[80-82] Close collaboration between obstetric and infectious disease experts is recommended. For most patients with cryptococcal infection, experts recommend deferring ART initiation for 4 to 6 weeks after

antifungal agents are started to reduce the risk of IRIS; in pregnancy, however, starting ART as expeditiously as possible is associated with lower risk of perinatal transmission of HIV. For CNS cryptococcal infection during pregnancy, decisions about the timing of ART initiation should be made in consultation with the patient, the infectious diseases consultant, and the obstetrician. If ART is started sooner than generally recommended, close monitoring for IRIS should be implemented with a low threshold for treatment for IRIS. During pregnancy, the risk of IRIS associated with non-CNS cryptococcosis appears to be lower, and a delay in ART initiation of no longer than 2 weeks after starting antifungal therapy is recommended.

Extensive clinical experience with amphotericin B deoxycholate has not been associated with teratogenicity, and this remains a preferred therapy for cryptococcosis in the first trimester of pregnancy **(AIII).** Although there is less experience in pregnancy with lipid formulations of amphotericin B, these products have been associated with less nephrotoxicity and electrolyte abnormalities than amphotericin B deoxycholate and are an alternative as a preferred therapy for the initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis during pregnancy **(AIII).** Optimal dosing of liposomal amphotericin B in pregnancy is unknown. A recent review of dosing strategies in pregnancy recommended use of ideal body weight rather than total body weight to minimize risk of adverse effects to the fetus while maintaining efficacy **(BII).**[83] Neonates born to women on chronic amphotericin B at delivery may be at increased risk for renal toxicity and electrolyte abnormalities and should be appropriately evaluated as newborns.[84]

During pregnancy, flucytosine use should be considered only when the benefits outweigh the risks to the mother and fetus and should be delayed until after the first trimester when feasible **(AIII).** In animal studies, flucytosine is teratogenic and may be associated with cleft palate and other bone abnormalities. Flucytosine use in pregnancy is limited to case reports and small series, although normal outcomes have been described.[85-87]

In general, azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit outweighs the risk **(BIII).** Fluconazole has teratogenic potential in the first trimester. Congenital malformations similar to those observed in animals exposed to the drug—including craniofacial and limb abnormalities—have been reported in infants born to mothers who received fluconazole at doses of ≥400 mg per day throughout or beyond the first trimester of pregnancy.[88] Furthermore, animal data suggest that moderate alcohol consumption during pregnancy may increase the potency of fluconazole, resulting in increased risk of craniofacial defects.[89]

Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short-term exposure. A recent meta-analysis describing birth defects in infants exposed to fluconazole during the first trimester evaluated nine cohort, case-control or randomized controlled studies, including 53,407 pregnancies with fluconazole exposure and 3,319,353 without fluconazole exposure.[90] Maternal exposure to fluconazole was correlated with an increased prevalence of heart defects in infants for both low dose (≤150 mg) (odds ratio [OR] 1.95; 95% CI, 1.18–3.21; $P = 0.01$) or any dose (OR 1.79; 95% CI, 1.18–2.71; $P = 0.01$). No association was found between either low- or high-dose fluconazole exposure and orofacial, CNS, genitourinary, musculoskeletal, or gastrointestinal defects.[91] One registry-based cohort study[92] of 7,352 women reported a threefold increase in incidence of Tetralogy of Fallot, and a large population-based case-control study[93] specifically noted an increase in transposition of the great arteries (OR 7.56, 95% CI, 1.22–35.45). The latter study also suggested an increase in cleft lip with cleft palate (OR 5.53; 95% CI, 1.68–18.24). In three nested case-control studies using data from the Quebec Prescription Drug

Insurance database, there was an increased prevalence of cardiac septal closure anomalies for maternal fluconazole doses greater than 150 mg during pregnancy (OR 1.81; 95% CI, 1.04–3.14).[94] A recent population-based cohort study (included in the meta-analysis) of 1,969,954 pregnancies, including 37,650 pregnancies exposed to fluconazole, found an increased risk of musculoskeletal malformations following exposure to fluconazole during the first trimester of pregnancy (risk of 52.1 per 10,000 pregnancies exposed to fluconazole versus 37.3 per 10,000 pregnancies exposed to topical azoles).[95]

A nationwide cohort study in Denmark[96] found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies (n = 16,561, HR, 1.48; 95% CI, 1.23–1.77) or those with topical azole exposure only (n = 5,646, HR 1.62; 95% CI, 1.26–2.07). Similarly, the nested case-control studies in Canada (n = 320, 868 pregnancies) found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies, and that risk was greater with higher dose of fluconazole exposure (adjusted odds ratio [aOR] with ≤150 mg 2.23, 95% CI, 1.96–2.54; aOR with >150 mg 3.20; 95% CI, 2.73–3.75).[94] However, a cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use during pregnancy and risk of stillbirth or neonatal death.[97] The meta-analysis noted above also found no association between fluconazole exposure and risk of abortion or stillbirth.[90] Most of the studies regarding effects of fluconazole during pregnancy have involved low doses of the drug and short-term exposure.

On the basis of reported birth defects, the use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks **(CIII).** Amphotericin B should be continued throughout the first trimester if possible **(AIII).** After the first trimester, switching to oral fluconazole may be considered if appropriate clinically for consolidation or maintenance therapy **(CIII).**

Although there have been case reports of birth defects in infants exposed to itraconazole, a recent systematic review and meta-analysis of four cohort studies involving 971,450 pregnant women with 1,311 exposures, found no significant difference in the overall risk of birth defects between those with maternal exposure to itraconazole and those not exposed.[98] While limb and congenital heart defects were the most common defects seen, they were within the rates of the defects published by EUROCAT (the European network of population-based registries for epidemiological surveillance of congenital anomalies). However, the rate of eye defects was higher than that published by EUROCAT. There was no difference in the rates of spontaneous abortion or stillbirth from itraconazole exposure.

Voriconazole (at doses lower than recommended human doses), posaconazole, and isavuconazole are teratogenic and embryotoxic in animals; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans. Voriconazole, posaconazole, and isavuconazole **are not recommended** for use during pregnancy, especially in the first trimester **(CIII).**

References

1. Aberg J, WG. P. Cryptococcosis. In: AIDS Therapy. M. H. Dolin R, Saag MS, ed. New York, NY: Churchill Livingstone; 2002:498-510.

2. Mirza SA, Phelan M, Rimland D, et al. The changing epidemiology of cryptococcosis: an update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. *Clin Infect Dis*. 2003;36(6):789-794. Available at: https://pubmed.ncbi.nlm.nih.gov/12627365.

3. Rajasingham R, Govender NP, Jordan A, et al. The global burden of HIV-associated cryptococcal infection in adults in 2020: a modelling analysis. *Lancet Infect Dis*. 2022;22(12):1748-1755. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36049486.

4. Pyrgos V, Seitz AE, Steiner CA, Prevots DR, Williamson PR. Epidemiology of cryptococcal meningitis in the US: 1997–2009. *PLoS One*. 2013;8(2):e56269. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23457543.

5. Maziarz EK, Perfect JR. Cryptococcosis. *Infect Dis Clin North Am*. 2016;30(1):179-206. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26897067.

6. Rhein J, Hullsiek KH, Evans EE, et al. Detrimental outcomes of unmasking cryptococcal meningitis with recent ART initiation. *Open Forum Infect Dis*. 2018;5(8):ofy122. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30094292.

7. Graybill JR, Sobel J, Saag M, et al. Diagnosis and management of increased intracranial pressure in patients with AIDS and cryptococcal meningitis. The NIAID Mycoses Study Group and AIDS Cooperative Treatment Groups. *Clin Infect Dis*. 2000;30(1):47-54. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10619732.

8. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS*. 2009;23(6):701-706. Available at: https://pubmed.ncbi.nlm.nih.gov/19279443.

9. Boulware DR, Rolfes MA, Rajasingham R, et al. Multisite validation of cryptococcal antigen lateral flow assay and quantification by laser thermal contrast. *Emerg Infect Dis*. 2014;20(1):45-53. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24378231.

10. Ssebambulidde K, Bangdiwala AS, Kwizera R, et al. Symptomatic cryptococcal antigenemia presenting as early cryptococcal meningitis with negative cerebral spinal fluid analysis. *Clin Infect Dis*. 2019;68(12):2094-2098. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30256903.

11. French N, Gray K, Watera C, et al. Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. *AIDS*. 2002;16(7):1031-1038. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11953469.

12. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal

meningitis. *Clin Infect Dis*. 1994;18(5):789-792. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8075272.

13. Beyene T, Zewde AG, Balcha A, et al. Inadequacy of high-dose fluconazole monotherapy among cerebrospinal fluid cryptococcal antigen (CrAg)-positive human immunodeficiency virus-infected persons in an Ethiopian CrAg screening program. *Clin Infect Dis*. 2017;65(12):2126-2129. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29020172.

14. Wake RM, Britz E, Sriruttan C, et al. High cryptococcal antigen titers in blood are predictive of subclinical cryptococcal meningitis among human immunodeficiency virus-infected patients. *Clin Infect Dis*. 2018;66(5):686-692. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29028998.

15. Rhein J, Bahr NC, Hemmert AC, et al. Diagnostic performance of a multiplex PCR assay for meningitis in an HIV-infected population in Uganda. *Diagn Microbiol Infect Dis*. 2016;84(3):268-273. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26711635.

16. Hanson KE, Slechta ES, Killpack JA, et al. Preclinical assessment of a fully automated multiplex PCR panel for detection of central nervous system pathogens. *J Clin Microbiol*. 2016;54(3):785-787. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26719436.

17. Leber AL, Everhart K, Balada-Llasat JM, et al. Multicenter evaluation of BioFire FilmArray Meningitis/Encephalitis Panel for detection of bacteria, viruses, and yeast in cerebrospinal fluid specimens. *J Clin Microbiol*. 2016;54(9):2251-2261. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27335149.

18. O'Halloran JA, Franklin A, Lainhart W, Burnham CA, Powderly W, Dubberke E. Pitfalls associated with the use of molecular diagnostic panels in the diagnosis of cryptococcal meningitis. *Open Forum Infect Dis*. 2017;4(4):ofx242. Available at: https://pubmed.ncbi.nlm.nih.gov/29255738.

19. Kassi FK, Drakulovski P, Bellet V, et al. Cryptococcus genetic diversity and mixed infections in Ivorian HIV patients: a follow up study. *PLoS Negl Trop Dis*. 2019;13(11):e0007812. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31738768.

20. Desnos-Ollivier M, Patel S, Spaulding AR, et al. Mixed infections and in vivo evolution in the human fungal pathogen Cryptococcus neoformans. *mBio*. 2010;1(1). Available at: https://www.pubmed.ncbi.nlm.nih.gov/20689742.

21. McKenney J, Bauman S, Neary B, et al. Prevalence, correlates, and outcomes of cryptococcal antigen positivity among patients with AIDS, United States, 1986–2012. *Clin Infect Dis*. 2015;60(6):959-965. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25422390.

22. Chang CC, Harrison TS, Bicanic TA, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. *Lancet Infect Dis*. 2024;24(8):e495-e512. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38346436.

23. Rajasingham R, Wake RM, Beyene T, Katende A, Letang E, Boulware DR. Cryptococcal meningitis diagnostics and screening in the era of point-of-care laboratory testing. *J Clin*

Microbiol. 2019;57(1):*In Press.* doi: 10.1128/JCM.01238-01218. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30257903.

24. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. 1999;28(5):1049-1056. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10452633.

25. Powderly WG, Finkelstein D, Feinberg J, et al. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):700-705. Available at: https://pubmed.ncbi.nlm.nih.gov/7854376.

26. Awotiwon AA, Johnson S, Rutherford GW, Meintjes G, Eshun-Wilson I. Primary antifungal prophylaxis for cryptococcal disease in HIV-positive people. *Cochrane Database Syst Rev*. 2018;8(8):CD004773. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30156270.

27. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med*. 1997;337(1):15-21. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9203426.

28. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis*. 2010;51(2):225-232. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20536366.

29. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. *Clin Infect Dis*. 2005;40 Suppl 6:S409-413. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15809927.

30. Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal combinations for treatment of cryptococcal meningitis in Africa. *N Engl J Med*. 2018;378(11):1004-1017. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29539274.

31. Jarvis JN, Leeme TB, Molefi M, et al. Short-course high-dose liposomal amphotericin B for human immunodeficiency virus-associated cryptococcal meningitis: a phase 2 randomized controlled trial. *Clin Infect Dis*. 2019;68(3):393-401. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29945252.

32. Kanyama C, Molloy SF, Chan AK, et al. One-year mortality outcomes from the Advancing Cryptococcal Meningitis Treatment for Africa trial of cryptococcal meningitis treatment in Malawi. *Clin Infect Dis*. 2020;70(3):521-524. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31155650.

33. Jarvis JN, Lawrence DS, Meya DB, et al. Single-dose liposomal amphotericin B treatment for cryptococcal meningitis. *N Engl J Med*. 2022;386(12):1109-1120. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35320642.

34. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O, French Cryptococcosis Study Group. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med*. 2007;4(2):e21. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17284154.

35. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis*. 2000;30(4):710-718. Available at: https://pubmed.ncbi.nlm.nih.gov/10770733.

36. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O, French Cryptococcosis Study Group. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One*. 2008;3(8):e2870. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18682846.

37. Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. *N Engl J Med*. 2013;368(14):1291-1302. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23550668.

38. Larsen RA, Bozzette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis*. 1994;19(4):741-745. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7803641.

39. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naive or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis*. 2007;45(1):76-80. Available at: https://pubmed.ncbi.nlm.nih.gov/17554704.

40. Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. *Clin Infect Dis*. 2008;47(12):1556-1561. Available at: https://pubmed.ncbi.nlm.nih.gov/18990067.

41. Kabanda T, Siedner MJ, Klausner JD, Muzoora C, Boulware DR. Point-of-care diagnosis and prognostication of cryptococcal meningitis with the cryptococcal antigen lateral flow assay on cerebrospinal fluid. *Clin Infect Dis*. 2014;58(1):113-116. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24065327.

42. Aberg JA, Watson J, Segal M, Chang LW. Clinical utility of monitoring serum cryptococcal antigen (sCRAG) titers in patients with AIDS-related cryptococcal disease. *HIV Clin Trials*. 2000;1(1):1-6. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11590483.

43. Pappas PG, Chetchotisakd P, Larsen RA, et al. A phase II randomized trial of amphotericin B alone or combined with fluconazole in the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis*. 2009;48(12):1775-1783. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19441980.

44. Rolfes MA, Rhein J, Schutz C, et al. Cerebrospinal fluid culture positivity and clinical outcomes after amphotericin-based induction therapy for cryptococcal meningitis. *Open Forum Infect Dis*. 2015;2(4):ofv157. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26716103.

45. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. 1999;28(2):291-296. Available at: https://pubmed.ncbi.nlm.nih.gov/10064246.

46. Perfect JR, Marr KA, Walsh TJ, et al. Voriconazole treatment for less-common, emerging, or refractory fungal infections. *Clin Infect Dis*. 2003;36(9):1122-1131. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12715306.

47. Pitisuttithum P, Negroni R, Graybill JR, et al. Activity of posaconazole in the treatment of central nervous system fungal infections. *J Antimicrob Chemother*. 2005;56(4):745-755. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16135526.

48. Thompson GR, 3rd, Rendon A, Ribeiro Dos Santos R, et al. Isavuconazole treatment of cryptococcosis and dimorphic mycoses. *Clin Infect Dis*. 2016;63(3):356-362. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27169478.

49. Powderly WG, Saag MS, Cloud GA, et al. A controlled trial of fluconazole or amphotericin B to prevent relapse of cryptococcal meningitis in patients with the acquired immunodeficiency syndrome. The NIAID AIDS Clinical Trials Group and Mycoses Study Group. *N Engl J Med*. 1992;326(12):793-798. Available at: https://pubmed.ncbi.nlm.nih.gov/1538722.

50. Faini D, Kalinjuma AV, Katende A, et al. Laboratory-reflex cryptococcal antigen screening is associated with a survival benefit in Tanzania. *J Acquir Immune Defic Syndr*. 2019;80(2):205-213. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30422904.

51. Meya DB, Williamson PR. Cryptococcal disease in diverse hosts. *N Engl J Med*. 2024;390(17):1597-1610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38692293.

52. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. 2014;370(26):2487-2498. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24963568.

53. Scriven JE, Rhein J, Hullsiek KH, et al. Early ART after cryptococcal meningitis is associated with cerebrospinal fluid pleocytosis and macrophage activation in a multisite randomized trial. *J Infect Dis*. 2015;212(5):769-778. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25651842.

54. Zhao H, Zhou M, Zheng Q, et al. Clinical features and outcomes of cryptococcemia patients with and without HIV infection. *Mycoses*. 2021;64(6):656-667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33609302.

55. Ingle SM, Miro JM, May MT, et al. Early antiretroviral therapy not associated with higher cryptococcal meningitis mortality in people with human immunodeficiency virus in high-income countries: an international collaborative cohort study. *Clin Infect Dis*. 2023;77(1):64-73. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36883578.

56. Boulware DR, Jarvis JN. Timing of antiretroviral therapy in cryptococcal meningitis: what we can (and cannot) learn from observational data. *Clin Infect Dis*. 2023;77(1):74-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36883585.

57. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated Immune reconstitution inflammatory syndrome (C-IRIS). *AIDS*. 2013. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23525034.

58. Rolfes MA, Hullsiek KH, Rhein J, et al. The effect of therapeutic lumbar punctures on acute mortality from cryptococcal meningitis. *Clin Infect Dis*. 2014;59(11):1607-1614. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25057102.

59. Fessler RD, Sobel J, Guyot L, et al. Management of elevated intracranial pressure in patients with cryptococcal meningitis. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17(2):137-142. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9473014.

60. Newton PN, Thai le H, Tip NQ, et al. A randomized, double-blind, placebo-controlled trial of acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis. *Clin Infect Dis*. 2002;35(6):769-772. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12203177.

61. Beardsley J, Wolbers M, Kibengo FM, et al. Adjunctive dexamethasone in HIV-associated cryptococcal meningitis. *N Engl J Med*. 2016;374(6):542-554. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26863355.

62. Bahr NC, Rolfes MA, Musubire A, et al. Standardized electrolyte supplementation and fluid management improves survival during amphotericin therapy for cryptococcal meningitis in resource-limited settings. *Open Forum Infect Dis*. 2014;1(2):ofu070. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25734140.

63. Davis MR, Nguyen MH, Donnelley MA, Thompson GR, III. Tolerability of long-term fluconazole therapy. *J Antimicrob Chemother*. 2019;74(3):768-771. Available at: https://pubmed.ncbi.nlm.nih.gov/30535104.

64. Shelburne SA, 3rd, Darcourt J, White AC, Jr., et al. The role of immune reconstitution inflammatory syndrome in AIDS-related Cryptococcus neoformans disease in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2005;40(7):1049-1052. Available at: https://pubmed.ncbi.nlm.nih.gov/15825000.

65. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(4):251-261. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20334848.

66. Boulware DR, Bonham SC, Meya DB, et al. Paucity of initial cerebrospinal fluid inflammation in cryptococcal meningitis is associated with subsequent immune reconstitution inflammatory syndrome. *J Infect Dis*. 2010;202(6):962-970. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20677939.

67. Chang CC, Dorasamy AA, Gosnell BI, et al. Clinical and mycological predictors of cryptococcosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2013;27(13):2089-2099. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23525034.

68. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *Lancet Infect Dis*. 2010;10(11):791-802. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21029993.

69. Boulware DR, Meya DB, Bergemann TL, et al. Clinical features and serum biomarkers in HIV immune reconstitution inflammatory syndrome after cryptococcal meningitis: a prospective cohort study. *PLoS Med*. 2010;7(12):e1000384. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21253011.

70. Kuttiatt V, Sreenivasa P, Garg I, Shet A. Cryptococcal lymphadenitis and immune reconstitution inflammatory syndrome: current considerations. *Scand J Infect Dis*. 2011;43(8):664-668. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21534892.

71. Brandt ME, Pfaller MA, Hajjeh RA, et al. Trends in antifungal drug susceptibility of Cryptococcus neoformans isolates in the United States: 1992 to 1994 and 1996 to 1998. *Antimicrob Agents Chemother*. 2001;45(11):3065-3069. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11600357.

72. Witt MD, Lewis RJ, Larsen RA, et al. Identification of patients with acute AIDS-associated cryptococcal meningitis who can be effectively treated with fluconazole: the role of antifungal susceptibility testing. *Clin Infect Dis*. 1996;22(2):322-328. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8838190.

73. Chesdachai S, Rajasingham R, Nicol MR, et al. Minimum inhibitory concentration distribution of fluconazole against Cryptococcus species and the Fluconazole Exposure Prediction Model. *Open Forum Infect Dis*. 2019;6(10). Available at: https://www.pubmed.ncbi.nlm.nih.gov/31420668.

74. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS*. 1997;11(12):1463-1471. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9342068.

75. Chen SC, Australasian Society for Infectious Diseases Mycoses Iterest G. Cryptococcosis in Australasia and the treatment of cryptococcal and other fungal infections with liposomal amphotericin B. *J Antimicrob Chemother*. 2002;49 Suppl 1(Suppl 1):57-61. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11801583.

76. Jarvis JN, Meintjes G, Williams Z, Rebe K, Harrison TS. Symptomatic relapse of HIV-associated cryptococcal meningitis in South Africa: the role of inadequate secondary prophylaxis. *S Afr Med J*. 2010;100(6):378-382. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20526411.

77. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent

antiretroviral therapy. *Ann Intern Med*. 2002;137(4):239-250. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12186514.

78. Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in human immunodeficiency virus-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. *Clin Infect Dis*. 2003;36(10):1329-1331. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12746781.

79. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. *Clin Infect Dis*. 2004;38(4):565-571. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14765351.

80. Pastick KA, Nalintya E, Tugume L, et al. Cryptococcosis in pregnancy and the postpartum period: case series and systematic review with recommendations for management. *Med Mycol*. 2020;58(3):282-292. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31689712.

81. Miyoshi S, Oda N, Gion Y, et al. Exacerbation of pulmonary cryptococcosis associated with enhancement of Th2 response in the postpartum period. *J Infect Chemother*. 2021;27(8):1248-1250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33840597.

82. Singh N, Perfect JR. Immune reconstitution syndrome and exacerbation of infections after pregnancy. *Clin Infect Dis*. 2007;45(9):1192-1199. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17918082.

83. O'Grady N, McManus D, Briggs N, Azar MM, Topal J, Davis MW. Dosing implications for liposomal amphotericin B in pregnancy. *Pharmacotherapy*. 2023;43(5):452-462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36862037.

84. AmBisome® (amphotericin B) liposome for injection [package insert]. U.S. Food and Drug Administration. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/050740Orig1s033lbl.pdf.

85. Curole DN. Cryptococcal meningitis in pregnancy. *J Reprod Med*. 1981;26(6):317-319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7252951.

86. Schonebeck J, Segerbrand E. Candida albicans septicaemia during first half of pregnancy successfully treated with 5-fluorocytosine. *Br Med J*. 1973;4(5888):337-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4202261.

87. Philpot CR, Lo D. Cryptococcal meningitis in pregnancy. *Med J Aust*. 1972;2(18):1005-1007. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4578877.

88. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22(2):336-340. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8838193.

89. Metruccio F, Battistoni M, Di Renzo F, Moretto A, Menegola E. Moderate alcohol consumption during pregnancy increases potency of two different drugs (the antifungal

fluconazole and the antiepileptic valproate) in inducing craniofacial defects: prediction by the in vitro rat whole embryo culture. *Arch Toxicol*. 2023;97(2):619-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36385218.

90. Budani MC, Fensore S, Di Marzio M, Tiboni GM. Maternal use of fluconazole and congenital malformations in the progeny: a meta-analysis of the literature. *Reprod Toxicol*. 2021;100:42-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33383164.

91. Zhang Z, Zhang X, Zhou YY, Jiang CM, Jiang HY. The safety of oral fluconazole during the first trimester of pregnancy: a systematic review and meta-analysis. *BJOG*. 2019;126(13):1546-1552. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31446677.

92. Molgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369(9):830-839. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23984730.

93. Howley MM, Carter TC, Browne ML, Romitti PA, Cunniff CM, Druschel CM. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2016;214(5):657 e651-659. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26640069.

94. Berard A, Sheehy O, Zhao JP, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ*. 2019;191(7):E179-E187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30782643.

95. Zhu Y, Bateman BT, Gray KJ, et al. Oral fluconazole use in the first trimester and risk of congenital malformations: population based cohort study. *BMJ*. 2020;369:m1494. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32434758.

96. Mølgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58-67. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26746458.

97. Pasternak B, Wintzell V, Furu K, Engeland A, Neovius M, Stephansson O. Oral fluconazole in pregnancy and risk of stillbirth and neonatal death. *JAMA*. 2018;319(22):2333-2335. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29896619.

98. Liu D, Zhang C, Wu L, Zhang L, Zhang L. Fetal outcomes after maternal exposure to oral antifungal agents during pregnancy: a systematic review and meta-analysis. *Int J Gynaecol Obstet*. 2020;148(1):6-13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31691277.

Cryptosporidiosis

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Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infects the small bowel mucosa, and, if symptomatic, the infection typically causes diarrhea. *Cryptosporidium* can also infect other gastrointestinal and extraintestinal sites, especially in individuals whose immune systems are suppressed. Advanced immunosuppression—typically CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis.[1] The three species that most commonly infect humans are *C. hominis*, *C. parvum*, and *C. meleagridis*. Infections are usually caused by one species, but a mixed infection is possible.[2,3]

Cryptosporidiosis remains a common cause of chronic diarrhea in people with HIV and AIDS in low- and middle-income countries.[4] In high-income countries with low rates of environmental contamination and widespread availability of potent antiretroviral therapy (ART), the incidence of cryptosporidiosis in people with HIV has decreased. In the United States, the incidence of cryptosporidiosis in people with HIV is now <1 case per 1,000 person-years.[5]

Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with humans or animals infected with *Cryptosporidium*, particularly those with diarrhea. *Cryptosporidium* oocysts can contaminate public water supplies and recreational water sources—such as swimming pools and lakes—and may persist despite standard chlorination. Person-to-person transmission of *Cryptosporidium* is common, especially among sexually active men who have sex with men.

Clinical Manifestations

Patients with cryptosporidiosis most commonly present with acute or subacute onset of watery diarrhea, which may be accompanied by nausea, vomiting, and lower abdominal cramping. Disease severity can range from asymptomatic to profuse, watery, voluminous diarrhea.[6] More severe symptoms tend to occur in immunosuppressed people, whereas transient diarrhea alone is typical in people with competent immune systems. Fever is present in approximately one-third of patients, and malabsorption is common. The epithelium of the biliary tract and the pancreatic duct can be infected with *Cryptosporidium*, leading to sclerosing cholangitis and to pancreatitis secondary to papillary stenosis, particularly among people with prolonged disease and low CD4 counts.[7] Pulmonary *Cryptosporidium* infections also have been reported and may be under-recognized.[8,9]

Diagnosis

Diagnosis of cryptosporidiosis was traditionally made by microscopic identification of the oocysts in stool with acid-fast staining or direct immunofluorescence, which offers higher sensitivity.[10] Concentration methods (e.g., formalin-ethyl acetate) may facilitate diagnosis of cryptosporidiosis. However, these methods are insensitive, and other diagnostic methods are being increasingly used. Antigen detection by enzyme-linked immunosorbent assay or immunochromatographic tests also is

useful; depending on the specific test, sensitivities reportedly range from 66% to 100%. However, some immunochromatographic tests produce frequent false-positive results.[11] Polymerase chain reaction and multiplex molecular methods are increasingly used for diagnosis and can identify a greater number of cases than microscopic methods.[10,12] Cryptosporidial enteritis also can be diagnosed from small sections of tissue from intestinal biopsy.

A single stool specimen is usually adequate to diagnose cryptosporidiosis in individuals with profuse diarrheal illness, whereas repeat stool sampling is recommended for those with milder disease.

Preventing Exposure

People with HIV should be educated and counseled about how *Cryptosporidium* can be transmitted **(BIII).** Modes of transmission include direct contact with animals and people, including diapered children, infected with *Cryptosporidium*; swallowing contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Scrupulous handwashing can reduce the risk of diarrhea, including diarrhea caused by *Cryptosporidium*, in individuals with HIV.[13] People with HIV should be advised to wash their hands after potential contact with human feces (including after diapering small children). Handwashing also should be recommended in association with the following activities: after handling pets or other animals, after gardening or any other contact with soil, before preparing food or eating, and before and after sex **(BIII).** Individuals with HIV should avoid unprotected sex, especially practices that could lead to direct (e.g., oral-anal sex) or indirect (e.g., penile-anal sex) contact with feces. They should be advised to use prophylactic barrier methods—such as condoms and dental dams—during sex to reduce such exposures **(BIII).**

People with HIV—particularly those with CD4 counts <200 cells/mm^3—should avoid direct contact with diarrhea or stool from pets **(BIII).** They should wear gloves when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII).** People with HIV should also limit or avoid direct exposure to calves and lambs **(BII).** Paying attention to hygiene and avoiding direct contact with stool are important when visiting farms or petting zoos or other premises where animals are housed or exhibited.

People with HIV should not drink water directly from lakes or rivers **(AIII).** Waterborne infection also can result from swallowing water during recreational activities. Individuals with HIV should be cautioned that lakes, rivers, saltwater beaches, some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium*. *Cryptosporidium* oocysts are extremely chlorine resistant and thus may persist even in chlorinated recreational water.[14,15] They should avoid swimming in water that is likely contaminated and should avoid swallowing water while swimming or playing in recreational water **(BIII).**

Outbreaks of cryptosporidiosis have been linked to drinking water from municipal water supplies. During outbreaks or in other situations in which a community boil water advisory is issued, boiling water for at least 1 minute will eliminate the risk for cryptosporidiosis **(AIII).** Using submicron personal-use water filters (home or office types) or bottled water also may reduce the risk of infection from water from a municipal source or a well **(BII).**

For people with low CD4 counts, the magnitude of the risk of acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain but is likely small. Available data are inadequate to recommend that all people with HIV boil water or avoid drinking tap water in non-outbreak settings. However, people with HIV may consider drinking only filtered water **(CIII),** despite the complexities involved in selecting appropriate water filters, the lack of enforceable standards for removal of *Cryptosporidium* oocysts, the costs of the products, and the difficulty of using the products consistently. Note that ice made from contaminated tap water also can be a source of infection.

People with HIV with low CD4 counts should be cautious about eating raw oysters because cryptosporidial oocysts can survive in oysters for >2 months and have been found in oysters harvested from certain commercial oyster beds **(CIII).** In the hospital setting, standard precautions for use of gloves and for handwashing after removal of gloves should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible individual with HIV **(BIII).** Because of the potential for fomite transmission, some specialists recommend that people with HIV, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII).**

People with HIV who travel to low- and middle-income countries should be warned to avoid drinking tap water or using tap water to brush their teeth **(BIII).** They should also avoid using ice that is not made from bottled water and consuming raw fruits or vegetables that may have been washed in tap water **(BIII).**

People with HIV also should avoid other sources of *Cryptosporidium* oocysts as much as possible **(BIII).** This includes avoiding directly working with people with diarrhea; with farm animals, such as cattle and sheep; and with domestic pets that are very young or have diarrhea. If exposure is unavoidable, gloves should be worn and good hand hygiene observed.

Preventing Disease

Recommendations for Preventing Cryptosporidiosis
Preventing Chronic Cryptosporidiosis • Because chronic cryptosporidiosis occurs primarily in people with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease (AII).

Key: ART = antiretroviral therapy

Because chronic cryptosporidiosis occurs primarily in people with HIV with advanced immunodeficiency, initiation of ART before they become severely immunosuppressed should prevent the disease **(AII).** Rifabutin and possibly clarithromycin taken for *Mycobacterium avium* complex prophylaxis have been found to protect against cryptosporidiosis.[16,17] Rifaximin, which is used for prevention of traveler's diarrhea, also has been used to treat cryptosporidial diarrhea. However, it is unclear whether rifaximin can protect against cryptosporidiosis.[18] Data are insufficient, however, to warrant a recommendation to use rifaximin, rifabutin, or clarithromycin as chemoprophylaxis for cryptosporidiosis.

Treating Disease

Recommendations for Treating Cryptosporidiosis
Managing Cryptosporidiosis • Preferred Management Strategies o Aggressive oral and/or IV rehydration and replacement of electrolyte loss (AIII), *and* o Symptomatic treatment of diarrhea with antimotility agents (AIII); tincture of opium may be more effective than loperamide (CIII). o People with HIV not taking ART should initiate ART to achieve immune restoration to CD4 count >100 cells/mm^3 (AII). • General Considerations o Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for at least 14 days (CIII) plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or* o Paromomycin 500 mg PO four times a day for at least 14 days to 21 days (CIII) plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement *Pregnancy Considerations* • During pregnancy, rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis (AII). • Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium is not recommended in late pregnancy (AIII). • Loperamide is the preferred antimotility agent in late pregnancy (CIII). Loperamide should be avoided in the first trimester unless benefits are felt to outweigh potential risks (CIII). • Nitazoxanide (CIII) and paromomycin (CIII) can be used in pregnancy after the first trimester.
Other Considerations
• Because diarrhea can cause lactase deficiency, people with cryptosporidiosis should avoid milk products (CIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; IV = intravenous; PO = orally

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/mm^3 usually leads to resolution of clinical cryptosporidiosis[19-22] and is the mainstay of treatment. People with HIV not already taking antiretrovirals who develop cryptosporidiosis should be started on ART as part of the initial management of cryptosporidiosis **(AII).** Management should also include symptomatic treatment of diarrhea with antimotility agents **(AIII).** Tincture of opium may be more effective than loperamide **(CIII).** Octreotide, a synthetic octapeptide analog of naturally occurring somatostatin that is approved to treat secreting tumor–induced diarrhea, is no more effective than other oral antidiarrheal agents and **is usually not recommended (CII).**[23] Because diarrhea can cause lactase deficiency, people with HIV and cryptosporidiosis should avoid milk products **(CIII).**

Rehydration and repletion of electrolyte losses by either oral or intravenous route are important. Stool volume in patients with HIV and AIDS with severe diarrhea can exceed 10 L/day; managing the diarrhea often requires intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions **(AIII).** Most patients can be treated with enteral nutrition; total parenteral nutrition is rarely indicated **(CIII).**

Patients with biliary tract involvement may require endoscopic retrograde cholangiopancreatography for diagnosis. They may also benefit from sphincterotomy, stenting, or both.[7,24]

Several agents—including nitazoxanide, paromomycin, clofazimine, and spiramycin—have been investigated in small, randomized controlled clinical trials of adults with HIV.[25] No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[26]

Nitazoxanide is an orally administered nitrothiazole benzamide with *in vivo* activity against a broad range of helminths, bacteria, and protozoa. Nitazoxanide is approved by the U.S. Food and Drug Administration for treatment of cryptosporidiosis in children over 1 year of age and adults. Nitazoxanide 500 mg administered twice daily for 3 days to adults without HIV but with cryptosporidiosis resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.[27,28] In one study, adults with HIV with cryptosporidiosis and CD4 counts >50 cells/mm^3 were treated with nitazoxanide 500 mg to 1,000 mg twice daily for 14 days; the nitazoxanide treatment group had substantially higher rates of parasitological cure and resolution of diarrhea than the placebo group.[29] Efficacy of nitazoxanide for the treatment of cryptosporidial diarrhea in children with HIV, however, was not confirmed in two randomized trials in children.[30,31] Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts <50 cells/mm^3, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment.[32] Adverse events associated with nitazoxanide are typically mild, and no important drug–drug interactions have been reported. Because of the clinical significance of cryptosporidiosis, many experts will institute a trial of nitazoxanide or paromomycin in conjunction with ART but never instead of ART **(CIII).**

Paromomycin is a nonabsorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. Paromomycin in high doses is effective for the treatment of cryptosporidiosis in animal models. A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, there were few cures, relapses were common, and long-term success rates were only 33%.[24] Two randomized trials comparing paromomycin with placebo demonstrated limited effectiveness of the drug among patients with AIDS and cryptosporidiosis.[33,34] One case series suggested a better response rate in patients receiving paromomycin along with ART.[35] Paromomycin may be used instead of nitazoxanide in conjunction with ART but never instead of ART **(CIII).**

Special Considerations with Regard to Starting ART

As noted above, patients with cryptosporidiosis should be offered ART as part of the initial management of cryptosporidiosis **(AII).** In animal and *in vitro* models, HIV protease inhibitors (PI) can inhibit *Cryptosporidium*, but there is no clinical evidence that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII).**[36,37]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients should be monitored closely for signs and symptoms of volume depletion, electrolyte imbalance, weight loss, and malnutrition. Immune reconstitution inflammatory syndrome (IRIS) has been described in association with three cases of extraintestinal cryptosporidiosis.[38]

Managing Treatment Failure

Supportive treatment and optimization of ART to achieve full virologic suppression are the main approaches to managing treatment failure **(AIII).** The clinical response rather than results of stool tests should be used to guide the response to therapy. Some authorities advocate adding antiparasitic drugs **(CIII),** such as nitazoxanide or paromomycin alone or in combination with azithromycin, as well as optimizing ART in patients with treatment failure and cryptosporidiosis.[39,40]

Preventing Recurrence

No pharmacologic interventions are known to be effective in preventing the recurrence of cryptosporidiosis.

Special Considerations During Pregnancy

During pregnancy, rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis **(AII).** Pregnancy should not preclude the use of ART and, in fact, is always an indication for ART. Nitazoxanide is not teratogenic in animals, but no data on use in human pregnancy are available. Nitazoxanide can be used in pregnancy after the first trimester in people with severe symptoms **(CIII).** Limited information is available about the teratogenic potential of paromomycin, but oral administration is associated with minimal systemic absorption, which may minimize potential risk. Paromomycin can be used in pregnancy after the first trimester in people with severe symptoms **(CIII).** Loperamide is poorly absorbed and has not been associated with birth defects in animal studies. However, one study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.[41] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII).** Loperamide is the preferred antimotility agent in late pregnancy **(CIII).** Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium **is not recommended** in late pregnancy **(AIII).**[42]

References

1. Flanigan T, Whalen C, Turner J, et al. Cryptosporidium infection and CD4 counts. *Ann Intern Med*. 1992;116(10):840-842. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1348918.

2. Cama VA, Ross JM, Crawford S, et al. Differences in clinical manifestations among Cryptosporidium species and subtypes in HIV-infected persons. *J Infect Dis*. 2007;196(5):684-691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17674309.

3. Wanyiri JW, Kanyi H, Maina S, et al. Cryptosporidiosis in HIV/AIDS patients in Kenya: clinical features, epidemiology, molecular characterization and antibody responses. *Am J Trop Med Hyg*. 2014;91(2):319-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24865675.

4. Wang RJ, Li JQ, Chen YC, Zhang LX, Xiao LH. Widespread occurrence of Cryptosporidium infections in patients with HIV/AIDS: Epidemiology, clinical feature, diagnosis, and therapy. *Acta Trop*. 2018;187:257-263. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30118699.

5. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000–2010. *J Infect Dis*. 2016;214(6):862-872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27559122.

6. Checkley W, White AC, Jr., Jaganath D, et al. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for cryptosporidium. *Lancet Infect Dis*. 2015;15(1):85-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25278220.

7. Naseer M, Dailey FE, Juboori AA, Samiullah S, Tahan V. Epidemiology, determinants, and management of AIDS cholangiopathy: A review. *World J Gastroenterol*. 2018;24(7):767-774. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29467548.

8. Sponseller JK, Griffiths JK, Tzipori S. The evolution of respiratory Cryptosporidiosis: evidence for transmission by inhalation. *Clin Microbiol Rev*. 2014;27(3):575-586. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24982322.

9. Mor SM, Ascolillo LR, Nakato R, et al. Expectoration of Cryptosporidium Parasites in Sputum of Human Immunodeficiency Virus-Positive and -Negative Adults. *Am J Trop Med Hyg*. 2018;98(4):1086-1090. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29405104.

10. Garcia LS, Arrowood M, Kokoskin E, et al. Practical guidance for clinical microbiology laboratories: laboratory diagnosis of parasites from the gastrointestinal tract. *Clin Microbiol Rev*. 2018;31(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/29142079.

11. Roellig DM, Yoder JS, Madison-Antenucci S, et al. Community laboratory testing for Cryptosporidium: multicenter study retesting public health surveillance stool samples positive for Cryptosporidium by rapid cartridge assay with direct fluorescent antibody testing. *PLoS One*. 2017;12(1):e0169915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28085927.

12. Ryan U, Paparini A, Oskam C. New technologies for detection of enteric parasites. *Trends Parasitol*. 2017;33(7):532-546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28385423.

13. Huang DB, Zhou J. Effect of intensive handwashing in the prevention of diarrhoeal illness among patients with AIDS: a randomized controlled study. *J Med Microbiol*. 2007;56(Pt 5):659-663. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17446290.

14. King BJ, Monis PT. Critical processes affecting Cryptosporidium oocyst survival in the environment. *Parasitology*. 2007;134(Pt 3):309-323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17096874.

15. Gharpure R, Perez A, Miller AD, Wikswo ME, Silver R, Hlavsa MC. Cryptosporidiosis outbreaks—United States, 2009–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(25):568-572. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31246941.

16. Holmberg SD, Moorman AC, Von Bargen JC, et al. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. HIV Outpatient Study (HOPS) Investigators. *JAMA*. 1998;279(5):384-386. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9459473.

17. Fichtenbaum CJ, Zackin R, Feinberg J, Benson C, Griffiths JK, AIDS Clinical Trials Group New Works Concept Sheet Team 064. Rifabutin but not clarithromycin prevents cryptosporidiosis in persons with advanced HIV infection. *AIDS*. 2000;14(18):2889-2893. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11153670.

18. Gathe JC, Jr., Mayberry C, Clemmons J, Nemecek J. Resolution of severe cryptosporidial diarrhea with rifaximin in patients with AIDS. *J Acquir Immune Defic Syndr*. 2008;48(3):363-364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18580340.

19. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. 2000;19(3):213-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10795595.

20. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2000;25(2):124-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11103042.

21. Schmidt W, Wahnschaffe U, Schafer M, et al. Rapid increase of mucosal CD4 T cells followed by clearance of intestinal cryptosporidiosis in an AIDS patient receiving highly

active antiretroviral therapy. *Gastroenterology*. 2001;120(4):984-987. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11231952.

22. Dillingham RA, Pinkerton R, Leger P, et al. High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study. *Am J Trop Med Hyg*. 2009;80(6):1060-1064. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19478276.

23. Simon DM, Cello JP, Valenzuela J, et al. Multicenter trial of octreotide in patients with refractory acquired immunodeficiency syndrome-associated diarrhea. *Gastroenterology*. 1995;108(6):1753-1760. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7768380.

24. Hashmey R, Smith NH, Cron S, Graviss EA, Chappell CL, White AC, Jr. Cryptosporidiosis in Houston, Texas. A report of 95 cases. *Medicine (Baltimore)*. 1997;76(2):118-139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9100739.

25. Diptyanusa A, Sari IP. Treatment of human intestinal cryptosporidiosis: a review of published clinical trials. *Int J Parasitol Drugs Drug Resist*. 2021;17:128-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34562754.

26. White AC, Jr. Cryptosporidiosis (*Cryptosporidium* Species). In: Secondary White AC, Jr., ed^eds. Subsidiary White AC, Jr., trans. Secondary Cryptosporidiosis (*Cryptosporidium* Species). Vol. 9th ed. Philadelphia: Elsevier Saunders; 2020:3410-3420.

27. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by Cryptosporidium parvum: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis*. 2001;184(1):103-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11398117.

28. Rossignol JF, Kabil SM, el-Gohary Y, Younis AM. Effect of nitazoxanide in diarrhea and enteritis caused by Cryptosporidium species. *Clin Gastroenterol Hepatol*. 2006;4(3):320-324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16527695.

29. Rossignol JF, Hidalgo H, Feregrino M, et al. A double-'blind' placebo-controlled study of nitazoxanide in the treatment of cryptosporidial diarrhoea in AIDS patients in Mexico. *Trans R Soc Trop Med Hyg*. 1998;92(6):663-666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10326116.

30. Amadi B, Mwiya M, Sianongo S, et al. High dose prolonged treatment with nitazoxanide is not effective for cryptosporidiosis in HIV positive Zambian children: a randomised controlled trial. *BMC Infect Dis*. 2009;9:195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19954529.

31. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet*. 2002;360(9343):1375-1380. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12423984.

32. Rossignol JF. Nitazoxanide in the treatment of acquired immune deficiency syndrome-related cryptosporidiosis: results of the United States compassionate use program in 365 patients. *Aliment Pharmacol Ther*. 2006;24(5):887-894. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16918894.

33. White AC, Jr., Chappell CL, Hayat CS, Kimball KT, Flanigan TP, Goodgame RW. Paromomycin for cryptosporidiosis in AIDS: a prospective, double-blind trial. *J Infect Dis*. 1994;170(2):419-424. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8035029.

34. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: no more effective than placebo for treatment of cryptosporidiosis in patients with advanced human immunodeficiency virus infection. AIDS Clinical Trial Group. *Clin Infect Dis*. 2000;31(4):1084-1092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11049793.

35. Maggi P, Larocca AM, Ladisa N, et al. Opportunistic parasitic infections of the intestinal tract in the era of highly active antiretroviral therapy: is the CD4(+) count so important? *Clin Infect Dis*. 2001;33(9):1609-1611. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11588705.

36. Hommer V, Eichholz J, Petry F. Effect of antiretroviral protease inhibitors alone, and in combination with paromomycin, on the excystation, invasion and in vitro development of Cryptosporidium parvum. *J Antimicrob Chemother*. 2003;52(3):359-364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12888587.

37. Mele R, Gomez Morales MA, Tosini F, Pozio E. Indinavir reduces Cryptosporidium parvum infection in both in vitro and in vivo models. *Int J Parasitol*. 2003;33(7):757-764. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12814654.

38. Sullivan T, Reese L, Huprikar S, Lee M. Pulmonary cryptosporidiosis and immune reconstitution inflammatory syndrome: a case report and review. *Int J STD AIDS*. 2013;24(4):333-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23970667.

39. Smith NH, Cron S, Valdez LM, Chappell CL, White AC, Jr. Combination drug therapy for cryptosporidiosis in AIDS. *J Infect Dis*. 1998;178(3):900-903. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9728569.

40. Tomczak E, McDougal AN, White AC, Jr. Resolution of cryptosporidiosis in transplant recipients: review of the literature and presentation of a renal transplant patient treated with nitazoxanide, azithromycin, and rifaximin. *Open Forum Infect Dis*. 2022;9(1):ofab610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34993260.

41. Kallen B, Nilsson E, Otterblad Olausson P. Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatr*. 2008;97(5):541-545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18394096.

42. Esposito DB, Huybrechts KF, Werler MM, et al. Characteristics of prescription opioid analgesics in pregnancy and risk of neonatal opioid withdrawal syndrome in newborns.

JAMA Netw Open. 2022;5(8):e2228588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36001312.

Cystoisosporiasis (Formerly Isosporiasis)

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Epidemiology

Cystoisosporiasis, also known as Isosporiasis, is a protozoan gastrointestinal infection that occurs worldwide but is more common in tropical and subtropical regions. Immunocompromised people, including those who have HIV, are at increased risk for chronic, debilitating illness.[1-7] Infection results from ingestion of sporulated oocysts, such as from contaminated food or water. After ingestion, the parasite invades enterocytes in the small intestine. Ultimately, immature oocysts are produced and shed in stool.[8] Although *Cystoisospora (Isospora) belli* completes its life cycle in humans, oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective when ingested. Available data suggest that the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.[2] For complete lifecycle, see the Centers for Disease Control and Prevention Cystoisosporiasis webpage.

C. belli is frequently found in tropical and subtropical regions including the Caribbean, Central and South America, Africa, India, and Southeast Asia.[9] However, cases of *C. belli* can also occur in resource-rich countries like the United States due to travel and immigration, especially when individuals are exposed to contaminated food or water sources.[10] This parasitic infection is more commonly observed in people with HIV (especially, but not exclusively in those with low CD4 T lymphocyte [CD4] cell counts), and outbreaks among institutionalized groups have also been reported.[11-13]

Clinical Manifestations

The most common manifestation of cystoisosporiasis is watery, non-bloody diarrhea, which may be associated with abdominal pain, cramping, anorexia, nausea, vomiting, and low-grade fever. The diarrhea can be profuse and prolonged, lasting several weeks or more, particularly in people with HIV or other immunocompromising conditions. This kind of diarrhea often results in severe dehydration, electrolyte abnormalities (e.g., hypokalemia), weight loss, and malabsorption.[6,7,14-18] Extraintestinal infection—such as in the biliary tract, lymph nodes, spleen, and liver—has been documented in postmortem examinations of people with HIV.[2,19-21] Acalculous cholecystitis/cholangiopathy[2,22-24] and reactive arthritis[25] also have been reported.

Diagnosis

Typically, infection is diagnosed by detecting *Cystoisospora (Isospora)* oocysts (dimensions, 23–36 μm by 12–17 μm) in fecal specimens.[2] Oocysts may be shed intermittently and at low levels, even by individuals with profuse diarrhea. Diagnosis can be facilitated by repeated stool examinations with sensitive methods, such as modified acid-fast techniques, on which oocysts stain bright red, and ultraviolet fluorescence microscopy, under which there is autofluorescence.[2,26] The microbiology/parasitology laboratory should be notified of the patient's immunodeficiency status to ensure appropriate testing is done. Infection can also be diagnosed by detecting oocysts in duodenal

aspirates or mucus, or by identifying developmental stages of the parasite in intestinal biopsy specimens or using the string test (Entero-Test).[2,16]

Polymerase chain reaction (PCR) methods are increasingly used to detect *C. belli* for diagnosis, as supported by existing literature.[10] These molecular quantitative PCR or qPCR techniques offer such advantages as faster detection and the ability to detect multiple parasites simultaneously, making them more efficient than traditional microscopy.[27] PCR methods have demonstrated a sensitivity ranging from 87% to 100% and a specificity ranging from 88% to 100% for detecting *C. belli*.[27] However, it is important to note that the availability of PCR may be limited in certain settings.

A distinguishing feature of *C. belli* is eosinophilia.[28] However, other helminths, certain fungi (e.g., coccidioidomycosis, histoplasmosis, cryptococcosis), and certain protozoan parasites (e.g., *Dientamoeba fragilis*, *Sarcocycstis*) should be part of the differential diagnosis as these can also cause eosinophilia in the blood.

Preventing Exposure

C. belli is acquired by ingesting contaminated water or food. Hand washing with soap, avoiding potentially contaminated food (e.g., salads) or water in cystoisosporiasis-endemic areas, and proper food preparation (peeling fruits and cooking vegetables) can help prevent infection.

Water filtration using certified filters is effective (absolute one micron or less, National Sanitation Foundation/American National Standards Institute [ANSI] Standard 53 or Standard 58 for cyst removal or cyst reduction by an ANSI-accredited certification organization).[29] Filters that may **not** be designed to safely remove *C. belli* and other protozoans include those with a nominal pore size of one micron or smaller, filters labeled as "Effective against Giardia" or "Effective against parasites," carbon filters, active carbon filters, chlorinated filters, ultraviolet light filters, water purifiers, and filters labeled as "U.S. Environmental Protection Agency (EPA) approved" or "EPA registered" (note: the EPA does not test, certify, or register filters based on their ability to remove *Cystoisospora* and other protozoans).

Preventing Disease

Recommendations for Preventing First Episode of *Cystoisospora belli* Infection (Primary Prophylaxis)
Indication
• Individuals with CD4 count <200 cells/mm^3 living in or traveling to regions endemic for *Cystoisospora belli* (CII).
Preferred Therapy
• TMP-SMX (160 mg/800 mg) PO three times weekly (AI), *or*
• TMP-SMX (160 mg/800 mg) PO daily (AI)
Criteria for Discontinuation of Primary Prophylaxis
• Sustained increase in CD4 count to ≥200 cells/mm^3 for >6 months in response to ART (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally; TMP-SMX = trimethoprim-sulfamethoxazole

Several studies have found that chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is associated with a lower incidence or prevalence of cystoisosporiasis.[1,3,4,30] In a randomized,

placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against cystoisosporiasis in people with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).[1] In an observational study,[3] the incidence of cystoisosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in individuals with CD4 counts <50 cells/mm^3. In that study, multivariable analysis found the relative hazard for *C. belli* infection was 6.2 in individuals with CD4 counts between 50 and 199 cells/mm^3 and 15.9 for individuals with CD4 counts <50 cells/mm^3. After adjustment for the CD4 count, the risk of cystoisosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine (unspecified regimens). In analyses of data from a Los Angeles County AIDS surveillance registry during the pre-ART era, the prevalence of cystoisosporiasis was lower in people with a history of *Pneumocystis* pneumonia (PCP) compared to those without PCP; indirect evidence of a protective effect from the use of TMP-SMX for PCP treatment and secondary prevention.[4] Given the substantially increased risk of infection in individuals with low CD4 counts, we recommend ensuring that individuals with CD4 counts <200 cells/mm^3 are started and maintained on TMP-SMX if they are living in or traveling to regions endemic for *C. belli* **(CII)**. Primary prophylaxis can be discontinued for people with a sustained increase in CD4 count to ≥200 cells/mm^3 for >6 months in response to ART **(BIII).** Data on alternative medications for primary prophylaxis for people with sulfa intolerance are limited. The primary approach to prevention of cystoisosporiasis is to reduce the risk of acquisition by avoiding potentially contaminated food or water in cystoisosporiasis-endemic areas via regular hand washing, proper food preparation (peeling fruits, cooking vegetables), and use of certified water filters of 1 micron or less.

Treating Disease

Recommendations for Treating *Cystoisospora belli* Infection
General Management Considerations
• Fluid and electrolyte support in patients with dehydration (AIII)
• Nutritional supplementation for people who are malnourished (AIII)
Preferred Therapy for Acute Infection
• TMP-SMX (160 mg/800 mg) PO (or IV) four times daily for 10 days (AII), *or*
• TMP-SMX (160 mg/800 mg) PO (or IV) twice daily for 7 days (BI), *or*
o In patients with persistent or worsening symptoms while on TMP-SMX (160 mg/800 mg) twice daily, consider increasing the daily dose and/or extending the duration to 3–4 weeks (BIII).
Note: IV TMP-SMX may be used for patients with potential or documented malabsorption.
Alternative Therapy for Acute Infection (For Patients With Sulfa Intolerance [AIII])
• Pyrimethamine 50–75 mg PO daily plus leucovorin 10–25 mg PO daily for 4 weeks (BIII), *or*
• Ciprofloxacin 500 mg PO or 400 mg IV (for those who cannot tolerate PO) twice daily for 7 days (CI)
Chronic Maintenance Therapy (or Secondary Prophylaxis) (In People With HIV and CD4 Count <200 cells/mm^3)
Preferred Therapy
• TMP-SMX (160 mg/800 mg) PO three times weekly (AI), *or*
• TMP-SMX (160 mg/800 mg) PO daily (AIII)

Alternative Therapy

- TMP-SMX (320 mg/1,600 mg) PO three times weekly (BIII), *or*
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (BIII), *or*
- Ciprofloxacin 500 mg PO three times weekly (CI) as a second-line alternative

Criteria for Discontinuation of Chronic Maintenance Therapy

- Sustained increase in CD4 count ≥200 cells/mm^3 for >6 months in response to ART and without evidence of active *C. belli* infection (BIII)

Other Considerations

- TMP-SMX double-strength tablets are (160 mg/800 mg).
- Ciprofloxacin can increase QTc and has been associated with tendon rupture and aortic aneurysms.
- Due to concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection (CIII), unless it is needed for PCP prophylaxis. Clinicians should consider giving supplemental folic acid 4 mg/day to women of childbearing potential on TMP-SMX prior to pregnancy or as soon as possible in their first trimester (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IV = intravenously; PCP = *Pneumocystis* pneumonia; PO = orally; QTc = QT corrected for heart rate; TMP-SMX = trimethoprim-sulfamethoxazole

Clinical management includes fluid and electrolyte support for people with dehydration **(AIII)** and nutritional supplementation for people who are malnourished **(AIII).** TMP-SMX is the antimicrobial agent of choice for treatment of cystoisosporiasis **(AII).** It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for people with documented sulfa intolerance **(AIII)** or in whom treatment fails **(BIII).**

Three studies in people with HIV in Haiti have demonstrated the effectiveness of various TMP-SMX treatment regimens.[6,7,31] Participants in these studies were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not reported. Based on the initial studies,[6,7] the traditional treatment regimen has been a 10-day course of TMP-SMX (160/800 mg) administered orally four times daily **(AII).**[7,32] In another study, TMP-SMX (160/800 mg) administered twice daily for seven days was also effective **(BI).**[31] Although published experience using twice-daily TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but increase the daily dose and/or the duration of therapy (up to 3 to 4 weeks)[6,16] if symptoms worsen or persist **(BIII).** Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption or for those who cannot tolerate oral medications.

Some data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.[2,15,16,33,34] However, the combination of pyrimethamine plus sulfadoxine **is not typically recommended (CIII),** due to associations with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,[35] and slow clearance from the body after therapy is discontinued. In addition, sulfadoxine is not commercially available in the United States.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of cystoisosporiasis.[3,36,37] Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) for 4 weeks may be an effective treatment alternative option for sulfa-intolerant patients **(BIII).** The leucovorin is given to prevent myelosuppression from pyrimethamine.

Ciprofloxacin is a second-line agent that can be used for individuals with sulfa allergy and an inability to obtain pyrimethamine **(CI).** In a randomized, controlled trial in Haiti, ciprofloxacin 500 mg orally (PO) twice daily for 7 days was less effective than PO TMP-SMX but may have modest activity against *C. belli*.[31]

Special Considerations With Regard to Starting ART

There are limited data on the effectiveness of ART for *C. belli* infection in the setting of HIV coinfection.[3,23,30] Immune reconstitution with ART may result in fewer relapses of cystoisosporiasis, and immune reconstitution inflammatory syndrome (IRIS) has not been reported. Therefore, for people with HIV and cystoisosporiasis, TMP-SMX therapy and ART should both be started as soon as possible, and ART initiation should not be deferred **(AIII).**

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

People treated for cystoisosporiasis should be monitored for clinical response and adverse events. In people with HIV, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, elevated transaminase levels, and hyperkalemia. For ciprofloxacin, side effects beyond gastrointestinal issues include prolong QT intervals and tendonitis and tendon rupture. For pyrimethamine, side effects include bone marrow suppression. As noted earlier, IRIS has not been described in this population.

Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of nonadherence, malabsorption, and concurrent other gastrointestinal infections or enteropathies should be considered and the TMP-SMX regimen (daily dose, duration, and mode of administration) should be reevaluated **(AIII).**[38] For people with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered **(BIII).**

The effectiveness of albendazole,[37,39,40] nitazoxanide,[41,42] doxycycline,[43] and the macrolides roxithromycin and spiramycin,[33,44,45] have not been substantiated. Metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone appear to be ineffective.[14,33,34,36,44]

Preventing Recurrence

People with HIV with CD4 counts <200 cells/mm^3 should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX **(AI),** which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections. Based on observational studies in Haiti, approximately 50% of patients who did not receive secondary prophylaxis had symptomatic recurrences approximately 2 months after completing a course of TMP-SMX therapy. These relapses rapidly responded to retreatment and secondary prophylaxis decreased the risk of another relapse.[6,7,31] In a randomized, placebo-controlled trial in Haiti, no symptomatic recurrences were noted in people who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) **(AI).**[7] Daily TMP-SMX (160/800 mg) **(AIII)** and thrice-weekly TMP-SMX (320/1600 mg) have been effective **(BIII)**[5,16]; however, clinical and parasitological relapses despite maintenance TMP-SMX therapy and ART have been reported.[23] Many of these studies were conducted in the pre-ART era. It is unclear if recurrent *Cystoisospora* infections are due to relapse or reinfection.

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used **(BIII).**[36] Based on limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative, although some data question whether it is efficacious at all **(CI).**[31]

When To Stop Secondary Prophylaxis

The issue of discontinuing prophylaxis has not been evaluated in a clinical trial. Chemoprophylaxis probably can be safely discontinued in individuals without evidence of active *C. belli* infection who have a sustained increase in the CD4 count to levels ≥200 cells/mm^3 for >6 months after initiation of ART **(BIII).**

Special Considerations During Pregnancy

TMP-SMX is the agent of choice for treatment as well as primary and secondary prophylaxis during pregnancy. Although first-trimester exposure to TMP has been associated with a small increase in the risk of birth defects,[46-49] TMP-SMX therapy should be provided in the setting of maternal symptomatic *C. belli* infection. Due to concerns about possible teratogenicity associated with first-trimester drug exposure, clinicians may withhold secondary prophylaxis during the first trimester and treat only symptomatic infection, unless TMP-SMX is needed for PCP prophylaxis **(CIII).** Most members of the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV recommend that clinicians give supplemental folic acid 4 mg/day to women who are on TMP-SMX if they are capable of becoming pregnant, or as soon as possible in their first trimester **(BIII).**[48-50] Additional details regarding the use of TMP-SMX during pregnancy are provided at *Pneumocystis* Pneumonia. Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.[51] Long-term therapy with pyrimethamine should be used only if the potential benefit outweighs the potential risk. Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities, but efficacy against *C. belli* has been questioned.[52] Both TMP-SMX and ciprofloxacin are category C for pregnancy.

References

1. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. 1999;353(9163):1463-1468. Available at: https://pubmed.ncbi.nlm.nih.gov/10232311.

2. Lindsay DS, Dubey JP, Blagburn BL. Biology of Isospora spp. from humans, nonhuman primates, and domestic animals. *Clin Microbiol Rev*. 1997;10(1):19-34. Available at: https://pubmed.ncbi.nlm.nih.gov/8993857.

3. Guiguet M, Furco A, Tattevin P, Costagliola D, Molina JM, French Hospital Database on HIVCEG. HIV-associated Isospora belli infection: incidence and risk factors in the French Hospital Database on HIV. *HIV Med*. 2007;8(2):124-130. Available at: https://pubmed.ncbi.nlm.nih.gov/17352769.

4. Sorvillo FJ, Lieb LE, Seidel J, Kerndt P, Turner J, Ash LR. Epidemiology of isosporiasis among persons with acquired immunodeficiency syndrome in Los Angeles County. *Am J Trop Med Hyg*. 1995;53(6):656-659. Available at: https://pubmed.ncbi.nlm.nih.gov/8561272.

5. Certad G, Arenas-Pinto A, Pocaterra L, et al. Isosporiasis in Venezuelan adults infected with human immunodeficiency virus: clinical characterization. *Am J Trop Med Hyg*. 2003;69(2):217-222. Available at: https://pubmed.ncbi.nlm.nih.gov/13677379.

6. DeHovitz JA, Pape JW, Boncy M, Johnson WD, Jr. Clinical manifestations and therapy of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1986;315(2):87-90. Available at: https://pubmed.ncbi.nlm.nih.gov/3487730.

7. Pape JW, Verdier RI, Johnson WD, Jr. Treatment and prophylaxis of Isospora belli infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1989;320(16):1044-1047. Available at: https://pubmed.ncbi.nlm.nih.gov/2927483.

8. Centers for Disease Control and Prevention. Cystoisosporiasis. 2024. Available at: https://www.cdc.gov/dpdx/cystoisosporiasis/index.html.

9. Hechenbleikner EM, McQuade JA. Parasitic colitis. *Clin Colon Rectal Surg*. 2015;28(2):79-86. Available at: https://pubmed.ncbi.nlm.nih.gov/26034403.

10. Legua P, Seas C. Cystoisospora and cyclospora. *Curr Opin Infect Dis*. 2013;26(5):479-483. Available at: https://pubmed.ncbi.nlm.nih.gov/23982239.

11. Johnstone SL, Erasmus L, Thomas J, et al. Epidemiology and aetiology of moderate to severe diarrhoea in hospitalised patients >/=5 years old living with HIV in South Africa, 2018–2021: a case-control analysis. *PLOS Glob Public Health*. 2023;3(9):e0001718. Available at: https://pubmed.ncbi.nlm.nih.gov/37682831.

12. Nsagha DS, Njunda AL, Assob NJC, et al. Intestinal parasitic infections in relation to CD4(+) T cell counts and diarrhea in HIV/AIDS patients with or without antiretroviral therapy in Cameroon. *BMC Infect Dis*. 2016;16:9. Available at: https://pubmed.ncbi.nlm.nih.gov/26754404.

13. Assefa S, Erko B, Medhin G, Assefa Z, Shimelis T. Intestinal parasitic infections in relation to HIV/AIDS status, diarrhea and CD4 T-cell count. *BMC Infect Dis.* 2009;9:155. Available at: https://pubmed.ncbi.nlm.nih.gov/19765310.

14. Forthal DN, Guest SS. Isospora belli enteritis in three homosexual men. *Am J Trop Med Hyg*. 1984;33(6):1060-1064. Available at: https://pubmed.ncbi.nlm.nih.gov/6507724.

15. Modigliani R, Bories C, Le Charpentier Y, et al. Diarrhoea and malabsorption in acquired immune deficiency syndrome: a study of four cases with special emphasis on opportunistic protozoan infestations. *Gut*. 1985;26(2):179-187. Available at: https://pubmed.ncbi.nlm.nih.gov/4038492.

16. Whiteside ME, Barkin JS, May RG, Weiss SD, Fischl MA, MacLeod CL. Enteric coccidiosis among patients with the acquired immunodeficiency syndrome. *Am J Trop Med Hyg*. 1984;33(6):1065-1072. Available at: https://pubmed.ncbi.nlm.nih.gov/6334448.

17. Bialek R, Overkamp D, Rettig I, Knobloch J. Case report: nitazoxanide treatment failure in chronic isosporiasis. *Am J Trop Med Hyg*. 2001;65(2):94-95. Available at: https://pubmed.ncbi.nlm.nih.gov/11508398.

18. Williams DT, Smith RS, Mallon WK. Severe hypokalemia, paralysis, and AIDS-associated isospora belli diarrhea. *J Emerg Med*. 2011;41(6):e129-132. Available at: https://pubmed.ncbi.nlm.nih.gov/18993015.

19. Frenkel JK, Silva MB, Saldanha J, et al. Isospora belli infection: observation of unicellular cysts in mesenteric lymphoid tissues of a Brazilian patient with AIDS and animal inoculation. *J Eukaryot Microbiol*. 2003;50 Suppl:682-684. Available at: https://pubmed.ncbi.nlm.nih.gov/14736218.

20. Restrepo C, Macher AM, Radany EH. Disseminated extraintestinal isosporiasis in a patient with acquired immune deficiency syndrome. *Am J Clin Pathol*. 1987;87(4):536-542. Available at: https://pubmed.ncbi.nlm.nih.gov/3826017.

21. Bernard E, Delgiudice P, Carles M, et al. Disseminated isosporiasis in an AIDS patient. *Eur J Clin Microbiol Infect Dis.* 1997;16(9):699-701. Available at: https://pubmed.ncbi.nlm.nih.gov/9352268.

22. Benator DA, French AL, Beaudet LM, Levy CS, Orenstein JM. Isospora belli infection associated with acalculous cholecystitis in a patient with AIDS. *Ann Intern Med*. 1994;121(9):663-664. Available at: https://pubmed.ncbi.nlm.nih.gov/7944075.

23. Lagrange-Xelot M, Porcher R, Sarfati C, et al. Isosporiasis in patients with HIV infection in the highly active antiretroviral therapy era in France. *HIV Med*. 2008;9(2):126-130. Available at: https://pubmed.ncbi.nlm.nih.gov/18257775.

24. Walther Z, Topazian MD. Isospora cholangiopathy: case study with histologic characterization and molecular confirmation. *Hum Pathol*. 2009;40(9):1342-1346. Available at: https://pubmed.ncbi.nlm.nih.gov/19447468.

25. Gonzalez-Dominguez J, Roldan R, Villanueva JL, Kindelan JM, Jurado R, Torre-Cisneros J. Isospora belli reactive arthritis in a patient with AIDS. *Ann Rheum Dis.* 1994;53(9):618-619. Available at: https://pubmed.ncbi.nlm.nih.gov/7979603.

26. Bialek R, Binder N, Dietz K, Knobloch J, Zelck UE. Comparison of autofluorescence and iodine staining for detection of Isospora belli in feces. *Am J Trop Med Hyg*. 2002;67(3):304-305. Available at: https://pubmed.ncbi.nlm.nih.gov/12408672.

27. Taniuchi M, Verweij JJ, Sethabutr O, et al. Multiplex polymerase chain reaction method to detect Cyclospora, Cystoisospora, and Microsporidia in stool samples. *Diagn Microbiol Infect Dis.* 2011;71(4):386-390. Available at: https://pubmed.ncbi.nlm.nih.gov/21982218.

28. Dubey JP, Almeria S. Cystoisospora belli infections in humans: the past 100 years. *Parasitology*. 2019;146(12):1490-1527. Available at: https://pubmed.ncbi.nlm.nih.gov/31303182.

29. Centers for Disease Control and Prevention. About choosing home water filters. 2024. Available at: https://www.cdc.gov/drinking-water/prevention/about-choosing-home-water-filters.html.

30. Dillingham RA, Pinkerton R, Leger P, et al. High early mortality in patients with chronic acquired immunodeficiency syndrome diarrhea initiating antiretroviral therapy in Haiti: a case-control study. *Am J Trop Med Hyg*. 2009;80(6):1060-1064. Available at: https://pubmed.ncbi.nlm.nih.gov/19478276.

31. Verdier RI, Fitzgerald DW, Johnson WD, Jr., Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of Isospora belli and Cyclospora cayetanensis infection in HIV-infected patients. A randomized, controlled trial. *Ann Intern Med*. 2000;132(11):885-888. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10836915.

32. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis.* 2017;65(12):e45-e80. Available at: https://pubmed.ncbi.nlm.nih.gov/29053792.

33. Ebrahimzadeh A, Bottone EJ. Persistent diarrhea caused by Isospora belli: therapeutic response to pyrimethamine and sulfadiazine. *Diagn Microbiol Infect Dis.* 1996;26(2):87-89. Available at: https://pubmed.ncbi.nlm.nih.gov/8985661.

34. Trier JS, Moxey PC, Schimmel EM, Robles E. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. *Gastroenterology*. 1974;66(5):923-935. Available at: https://pubmed.ncbi.nlm.nih.gov/4826994.

35. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for Pneumocystis carinii infections in AIDS. *Lancet*. 1985;1(8441):1332. Available at: https://pubmed.ncbi.nlm.nih.gov/2860516.

36. Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. Isospora belli infection: treatment with pyrimethamine. *Ann Intern Med*. 1988;109(6):474-475. Available at: https://pubmed.ncbi.nlm.nih.gov/3261956.

37. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. *Scand J Infect Dis.* 2002;34(11):859-862. Available at: https://pubmed.ncbi.nlm.nih.gov/12578164.

38. Iordanov RB, Leining LM, Wu M, Chan G, DiNardo AR, Mejia R. Case report: molecular diagnosis of Cystoisospora belli in a severely immunocompromised patient with HIV and Kaposi sarcoma. *Am J Trop Med Hyg*. 2021;106(2):678-680. Available at: https://pubmed.ncbi.nlm.nih.gov/34844211.

39. Dionisio D, Sterrantino G, Meli M, Leoncini F, Orsi A, Nicoletti P. Treatment of isosporiasis with combined albendazole and ornidazole in patients with AIDS. *AIDS*. 1996;10(11):1301-1302. Available at: https://pubmed.ncbi.nlm.nih.gov/8883600.

40. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia--clinical, parasitological and mucosal responses. *Aliment Pharmacol Ther*. 2002; 16(3):595-601. Available at: https://pubmed.ncbi.nlm.nih.gov/11876715.

41. Romero Cabello R, Guerrero LR, Munoz Garcia MR, Geyne Cruz A. Nitazoxanide for the treatment of intestinal protozoan and helminthic infections in Mexico. *Trans R Soc Trop Med Hyg*. 1997;91(6):701-703. Available at: https://pubmed.ncbi.nlm.nih.gov/9580117.

42. Doumbo O, Rossignol JF, Pichard E, et al. Nitazoxanide in the treatment of cryptosporidial diarrhea and other intestinal parasitic infections associated with acquired immunodeficiency syndrome in tropical Africa. *Am J Trop Med Hyg*. 1997;56(6):637-639. Available at: https://pubmed.ncbi.nlm.nih.gov/9230795.

43. Meyohas MC, Capella F, Poirot JL, et al. [Treatment with doxycycline and nifuroxazide of Isospora belli infection in AIDS]. *Pathol Biol (Paris)*. 1990;38(5 (Pt 2)):589-591. Available at: https://pubmed.ncbi.nlm.nih.gov/2385457.

44. Gaska JA, Tietze KJ, Cosgrove EM. Unsuccessful treatment of enteritis due to Isospora belli with spiramycin: a case report. *J Infect Dis.* 1985;152(6):1336-1338. Available at: https://pubmed.ncbi.nlm.nih.gov/4067332.

45. Musey KL, Chidiac C, Beaucaire G, Houriez S, Fourrier A. Effectiveness of roxithromycin for treating Isospora belli infection. *J Infect Dis.* 1988;158(3):646. Available at: https://pubmed.ncbi.nlm.nih.gov/3411149.

46. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001;153(10):961-968. Available at: https://pubmed.ncbi.nlm.nih.gov/11384952.

47. Jungmann EM, Mercey D, DeRuiter A, et al. Is first trimester exposure to the combination of antiretroviral therapy and folate antagonists a risk factor for congenital abnormalities? *Sex Transm Infect*. 2001;77(6):441-443. Available at: https://pubmed.ncbi.nlm.nih.gov/11714944.

48. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. 2001;15(6):637-646. Available at: https://pubmed.ncbi.nlm.nih.gov/11738517.

49. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 2000;343(22):1608-1614. Available at: https://pubmed.ncbi.nlm.nih.gov/11096168.

50. Bortolus R, Filippini F, Cipriani S, et al. Efficacy of 4.0 mg versus 0.4 mg folic acid supplementation on the reproductive outcomes: a randomized controlled trial. *Nutrients.* 2021;13(12). Available at: https://pubmed.ncbi.nlm.nih.gov/34959975.

51. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. 2001;95(4):424-428. Available at: https://pubmed.ncbi.nlm.nih.gov/11579889.

52. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. 2006;107(5):1120-1138. Available at: https://pubmed.ncbi.nlm.nih.gov/16648419.

Cytomegalovirus Disease

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Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpesvirus family that can cause disseminated or localized end-organ disease in people with HIV. CMV infection is common in the general population, but CMV prevalence differs by geography, socioeconomic status, and race or ethnicity.[1] In the U.S. National Health and Nutrition Examination Survey 1999–2004, overall CMV seroprevalence for individuals aged 6 to 49 years in the United States was 50.4%. Higher CMV seropositivity was associated with older age; being female; foreign birthplace; and markers of lower socioeconomic status, such as low household income, low education, and high household crowding.[1] CMV seroprevalence is generally higher among developing countries, with seroprevalence between 40% to 70% of adults in most high-income countries,[2] compared with 80% to 100% in several low-income countries.[2-4] Few studies have evaluated CMV seroprevalence among people with HIV, but data reported from Africa suggests CMV seroprevalence is similar or slightly higher among adults with HIV versus adults without HIV.[3,5,6]

CMV is acquired through contact with CMV-infected body fluids. CMV can be transmitted in several ways, including through breastfeeding, perinatally, sexually, viral shedding in bodily fluids (saliva, urine, or tears), and through blood products (transfusions, transplantation).[7,8] After primary infection, CMV establishes a lifelong latent infection that can reactivate and cause clinical disease, particularly in persons with compromised immune systems.[9] End-organ disease caused by CMV occurs in people with HIV— especially those with advanced disease and typically among those with CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3—who are not receiving, adherent to, or responding to antiretroviral therapy (ART).[10-12] Among those treated with ART who have achieved virologic suppression, a new diagnosis of CMV end-organ disease is exceedingly rare.

Before potent ART, an estimated 30% of people with advanced HIV experienced CMV retinitis, the most common CMV end-organ disease in people with HIV.[10-12] The incidence of new cases of CMV end-organ disease has declined by ≥95% with the advent of potent ART.[13,14] The incidence rate of CMV retinitis in individuals with HIV since the introduction of effective ART has been reported to be 0.36 per 100 person-years, with those with a CD4 count below 50 cells/mm^3 accounting for the majority of cases.[15] For people with established CMV retinitis, recurrence of active lesions occurs at a rate substantially lower than that seen in the era before potent ART. Nevertheless, even for those with retinitis whose immune recovery is sufficient to warrant discontinuation of anti-CMV therapy (i.e., CD4 counts ≥100 cells/mm^3), relapse at a rate of 0.03 per person-year has been documented.[16] CMV is the most common cause of vision loss in people with HIV, even in the era of effective ART; therefore, regular ophthalmologic follow-up is needed regardless of whether anti-CMV therapy is continued.[15] See CMV Retinitis Monitoring below for more information.

Clinical Manifestations

CMV Retinitis

Retinitis is the most common clinical manifestation of CMV end-organ disease in people with HIV. It presents as unilateral disease in two-thirds of cases, but ultimately progresses to bilateral in most affected people in the absence of therapy or immune recovery.[16]

Peripheral retinitis (i.e., outside the major vascular arcades, not involving the macula or optic disc) may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Posterior retinal lesions, especially those impinging on the macula or optic disc, are associated with decreased visual acuity or central visual field defects.

CMV retinitis is a full-thickness necrotizing retinal infection that typically produces fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage.[17,18] The most typical feature is the lesion border, which has tiny, dry-appearing, granular, dot-like "satellites" at the interface between infected and normal retina. Vitreous humor inflammation is unlikely unless immune recovery with ART occurs.[10] Blood vessels near the lesions may appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, may have only a granular appearance throughout the lesion.

In the absence of effective ART or specific anti-CMV therapy, retinitis lesions invariably enlarge. Untreated lesions in severely immunodeficient individuals will involve the entire retina within 6 months. Movement of lesion borders occurs at variable rates in different directions,[19] causing a characteristic "brushfire" pattern, with the granular, leading edges advancing before an atrophic gliotic scar.[20]

CMV Colitis and Esophagitis

Colitis occurs in 5% to 10% of people with advanced HIV.[11] The most frequent clinical manifestations are weight loss, fever, anorexia, abdominal pain, diarrhea (often bloody), and malaise. In the colon, and especially in the cecum, CMV can cause perforation and present as an acute abdomen. Computed tomography (CT) may show colonic thickening or a colonic mass that may be mistaken for malignancy or other opportunistic infections (OIs). Hemorrhage and perforation can be life-threatening complications.

Esophagitis and occasional oral ulcers occur in a small percentage of people with advanced HIV, leading to odynophagia, nausea, mid-epigastric or retrosternal discomfort, and fever.

CMV Pneumonia

In contrast to other severely immunosuppressing conditions, CMV pneumonitis is uncommon in people with advanced HIV. CMV is detected frequently in the bronchoalveolar lavage (BAL) using DNA–specific polymerase chain reaction (PCR), but it is usually a bystander and should trigger a search for a more likely causative pathogen.

CMV of the Central Nervous System

CMV neurologic disease includes dementia, ventriculoencephalitis, central nervous system vasculitis, and polyradiculomyelopathies.[21] People with dementia caused by CMV encephalitis

typically are lethargic or confused, with or without fever. People with ventriculoencephalitis have a more acute course, with focal neurologic signs, often including cranial nerve palsies or nystagmus, and rapid progression to death. Periventricular enhancement on imaging (CT or magnetic resonance) highly suggests CMV ventriculoencephalitis rather than HIV-associated neurocognitive disorder. CMV polyradiculomyelopathy and transverse myelitis cause a Guillain-Barré–like syndrome characterized by radicular back pain, urinary retention, and progressive bilateral weakness in the lower extremities. Clinical symptoms usually progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia. Additionally, spastic myelopathy and sacral paresthesia may occur.

Diagnosis

The diagnosis of CMV end-organ disease is typically based on the clinical presentation and, when possible, evidence of the virus in tissue. CMV is often present in end-organ disease and can be detected by PCR, antigen assays, or culture. Detection of CMV in blood has limited utility in diagnosing CMV end-organ disease in people with HIV. A negative serum or plasma PCR assay does not rule out CMV end-organ disease, and CMV viremia may be present in the absence of end-organ disease, particularly in those with low CD4 cell counts.[21-26]

The presence of CMV serum antibodies does not establish the presence of CMV disease, because a large proportion of the general population has been exposed to CMV and is seropositive. However, a negative immunoglobulin G antibody level indicates that CMV is unlikely to be the cause of the disease process.

CMV Retinitis

CMV retinitis is usually diagnosed based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Nearly all cases can be diagnosed clinically. In rare cases, the diagnosis may be unclear, and PCR of aqueous or vitreous humor specimens for CMV and other pathogens—especially herpes simplex virus, varicella-zoster virus, and *Toxoplasma gondii*—can be useful for establishing the diagnosis. Detection of CMV DNA in cerebrospinal fluid (CSF) or vitreous or aqueous humor specimens is highly suggestive that CMV is the cause of ocular disease. In one study, CMV DNA was detected in 82% of vitreous specimens collected at diagnosis of CMV retinitis, 77% of relapsed retinitis, and 23% of quiescent retinitis.[27] Therefore, failure to detect CMV DNA in vitreous specimens does not rule out the presence of CMV retinitis. A response to empiric anti-CMV therapy also can be an important diagnostic indicator.

CMV Colitis and Esophagitis

CMV colitis is usually diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions on hematoxylin and eosin stains.[11,28] Similarly, CMV esophagitis is diagnosed by the presence of ulcers of the distal esophagus together with biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.[11] The number of inclusion bodies in specimens can vary widely and may be rare. Immunohistochemistry can also be used to detect CMV in tissue. In the absence of histopathologic changes, culturing CMV and detection of CMV DNA by PCR from a biopsy or cells brushed from the colon or the esophagus are insufficient to diagnose of CMV colitis or esophagitis, because a

substantial number of patients with low CD4 cell counts may shed CMV in in the gastrointestinal tract in the absence of clinical disease.[26]

CMV Pneumonia

The diagnosis of CMV pneumonitis, a rare entity in people with HIV, requires consistent clinical and radiological findings (e.g., diffuse pulmonary interstitial infiltrates, fever, and cough or dyspnea), identification of multiple CMV inclusion bodies in lung tissue or cytology, and the absence of any other pathogens that are more commonly associated with pneumonitis.[24,29,30] CMV PCR from the BAL has not been shown to have diagnostic value in people with HIV. Detection of CMV in the lungs in the absence of these criteria typically represents viral shedding, rather than clinical disease.

CMV of the Central Nervous System

CMV neurologic disease is diagnosed based on a compatible clinical syndrome and the presence of CMV in CSF or brain tissue, most often evaluated with PCR.[12,22,25] The CSF in CMV encephalitis typically demonstrates lymphocytic pleocytosis, low-to-normal glucose levels, and normal-to-elevated protein levels, although normal CSF findings do not rule out the diagnosis of CMV encephalitis. The CSF in CMV polyradiculopathy usually demonstrates neutrophilic pleocytosis (usually 100–200 neutrophils/µL and some erythrocytes) accompanied by low glucose levels and elevated protein levels.

Preventing Exposure

CMV infection is common in the general U.S. population, with higher seroprevalence among older individuals, women, people born outside of the United States, and people with lower socioeconomic status.[1] However, in people with HIV, CMV seropositivity cannot be assumed. Limited options exist to prevent exposure to CMV among adults with HIV, but condoms may reduce sexual transmission of CMV.[31,32]

Preventing Disease

Recommendations for Preventing CMV Disease
• To prevent CMV end-organ disease, administer ART to maintain the CD4 count ≥100 cells/mm^3 (AI).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus

CMV end-organ disease is best prevented using ART to maintain a CD4 count ≥100 cells/mm^3 **(AI).** A randomized, placebo-controlled trial failed to show benefit for the use of valganciclovir prophylaxis (the current standard oral agent for treatment of CMV disease) combined with ART as preventive therapy for CMV end-organ disease in people at high risk (CD4 count <100 cells/mm^3 and CMV viremia detected by plasma CMV DNA PCR assay).[33] Therefore, valganciclovir primary prophylaxis **is not recommended** to prevent CMV end-organ disease in people with HIV, even among patients who have CMV viremia **(AI),** and monitoring of CMV viremia **is not recommended**.

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. People who have a low CD4 cell count (<100 cells/mm^3) and are not on ART should be made aware of how to recognize floaters in the eye and their

implication. Development of floaters or changes in visual acuity should prompt an urgent referral to ophthalmology **(AIII).** The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) recommends a baseline ophthalmologic examination for people with HIV and CD4 counts <100 cells/mm^3, with counseling about the potential symptoms of CMV retinitis **(CIII).** In the premodern ART era, it was common for follow-up ophthalmologic examinations to be performed every 3 to 4 months for persons with CD4 counts <50 cells/mm^3 (the range associated with most cases of CMV retinitis), because early CMV retinitis may be asymptomatic. The same follow-up schedule is appropriate in the era of effective ART if CD4 counts fall below 50 cells/mm^3 for any reason, including treatment failure **(CIII).** Individuals with CMV retinitis and ART failure are more likely to be asymptomatic than were individuals in the premodern ART era.[18]

Treating Disease

Recommendations for Treating Cytomegalovirus Infections

Treating CMV Retinitis

General Considerations

- CMV retinitis should be treated with the active participation of an ophthalmologist who is familiar with CMV retinitis diagnosis and management.
- See CMV Retinitis Monitoring below for ophthalmic monitoring recommendations for people on treatment for CMV retinitis and after discontinuation of maintenance therapy.

Induction Therapy Followed by Maintenance Therapy

Preferred Therapy

- Valganciclovir[a] 900 mg PO every 12 hours for 14–21 days, then maintenance therapy with valganciclovir 900 mg PO once daily (AI), *or*
- Ganciclovir[a] 5 mg/kg IV every 12 hours for 14–21 days, then maintenance therapy with valganciclovir 900 mg PO once daily (AI), *or*
- Ganciclovir[a] 5 mg/kg IV every 12 hours for 14–21 days, then maintenance therapy with ganciclovir 5 mg/kg IV daily (AI)

Notes

- Many clinicians prefer the IV formulation when retinitis is more central and sight-threatening or when adequate GI absorption is a concern; transition to oral valganciclovir can be considered when there is evidence of clinical response.
- PO valganciclovir is the preferred maintenance regimen as it is the easiest and least toxic to administer to an outpatient population, provided that GI absorption is adequate.

Alternative Therapy

- Foscarnet[a] 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 14–21 days, then maintenance therapy with foscarnet 90 mg/kg or 120 mg/kg IV every 24 hours (BI) *or*
- Cidofovir[a,b] 5 mg/kg IV every week for 2 weeks, then maintenance therapy with cidofovir 5 mg/kg IV every other week. Administer 1 L of normal saline before and, if additional fluid load can be tolerated, administer another 1 L of normal saline after each cidofovir infusion. Administer probenecid 2 g PO 3 hours before each cidofovir dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) (CI).
  - Note: Cidofovir should be avoided in patients with sulfonamide allergy because of cross-hypersensitivity with probenecid.

If Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea or optic disc)

- Add intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection), repeated weekly during the induction period until lesion inactivity is achieved (BIII), then systemic treatment alone is considered to be adequate for maintenance therapy.
  - Note: Intravitreal administration of cidofovir is contraindicated, as it has been associated with uveitis and marked hypotony of the injected eye (AIII).

Peripheral Lesions

- Valganciclovir[a] 900 mg PO every 12 hours for 14–21 days, then maintenance therapy with valganciclovir 900 mg PO once daily (AI)

Duration of Induction Therapy for CMV Retinitis

- Minimum 14–21 days; duration determined by clinical response based on retinal examination
- Note: Many clinicians continue induction-level treatment until retinal lesion opacity is resolved or markedly reduced, indicating virus inactivity (BIII).

Starting Maintenance Therapy for CMV Retinitis

- Maintenance therapy is started after induction has achieved control of retinitis. Regimens are as detailed above.

Immune Recovery Uveitis

- The Panel favors the use of both corticosteroids and anti-CMV therapy for active intraocular inflammation at the onset of IRU and the use of corticosteroids for cystoid macular edemas, a late complication of IRU (CIII).
- Corticosteroids can be administered by oral, periocular, or intravitreal routes.
  - Prednisone 1 mg/kg PO daily (maximum dose of 60–80 mg/day) until clinical response, but for no longer than 1 month, followed by tapering and discontinuation over 2 to 3 months (BIII)
  - Periocular or intravitreal corticosteroid injections can be repeated after the expected duration of effect if there is evidence of incomplete clinical response and no treatment complications (BIII).

Stopping Maintenance Therapy for CMV Retinitis

- CMV treatment for at least 3 months, and lesions are inactive, and CD4 count ≥100 cells/mm^3 for at least 3 months in response to ART (AII)
  - Note: In all people for whom anti-CMV maintenance therapy has been discontinued, ophthalmologic monitoring for early detection of CMV relapse and IRU should be performed at least every 3 months and then yearly after immune reconstitution (AIII). Monitoring CMV viral load in blood has poor positive predictive value for relapse of retinitis and, therefore, is not recommended for people with HIV (AII).

Restarting Maintenance Therapy for CMV Retinitis

- CD4 count <100 cells/mm^3 (AIII)

Treating CMV Colitis or Esophagitis

Preferred Therapy

- Ganciclovir[a] 5 mg/kg IV every 12 hours (AI); may switch to valganciclovir 900 mg PO every 12 hours once the patient can absorb and tolerate PO therapy (AIII)
- Valganciclovir[a] 900 mg PO every 12 hours can be used in patients with mild disease (AIII).

Alternative Therapy

- Foscarnet[a] 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours (BIII)—for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance; *or*
- Cidofovir[a,b] 5 mg/kg/week IV for 2 weeks, then 5 mg/kg IV every other week. Administer 1 L of normal saline before and, if additional fluid load can be tolerated, administer another 1 L of normal saline after cidofovir infusion. Administer probenecid 2 g PO 3 hours before each cidofovir dose followed by 1 g PO 2 hours after the dose and 1 g PO 8 hours after the dose (total of 4 g) (CI).
  - Note: Cidofovir should be avoided in patients with sulfonamide allergy because of cross-hypersensitivity with probenecid.

Duration of Anti-CMV Therapy

- 21–42 days or until signs and symptoms have resolved (AIII)

Note: After resolution of acute disease, maintenance therapy is not routinely recommended for CMV GI disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially.

Treating CMV Pneumonia

Preferred Therapy

- Ganciclovir[a] 5 mg/kg IV every 12 hours (BIII)

Alternative Therapy

- Foscarnet[a] 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours (BIII)

Note: Transition to valganciclovir 900 mg PO twice daily can be considered if CMV pneumonia is not life-threatening and oral medications can be absorbed (BIII).

Duration of Anti-CMV Therapy

- ≥21 days or until signs and symptoms have resolved (CII)

Note: After resolution of acute disease, maintenance therapy is not routinely recommended for CMV pneumonia unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially.

Treating CMV Neurological Disease

Preferred Therapy

- Ganciclovir[a] 5 mg/kg IV every 12 hours plus foscarnet[a] (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours) (BIII)
- The role of oral valganciclovir has not been established.

Duration of Anti-CMV Therapy

- ≥21 days based on clinical response (AIII)

Note: After resolution of acute disease, maintenance therapy is not routinely recommended for CMV CNS disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially.

Pregnancy Considerations

- During pregnancy, indications for treatment of CMV infection are the same as for other people with HIV (AIII).
- Valganciclovir is the preferred treatment for maternal CMV disease during pregnancy (BIII).
- Foscarnet and cidofovir are not recommended in the absence of resistance or toxicity with ganciclovir/valganciclovir (AIII); use of foscarnet and cidofovir should only be done in consultation with a maternal–fetal medicine specialist, and additional fetal surveillance may be recommended in the setting of maternal renal insufficiency (BIII).

- In pregnant women diagnosed with primary CMV infection, the fetus should be monitored by periodic ultrasound after 20 weeks gestation (CIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; CNS = central nervous system; GI = gastrointestinal; IRU = immune recovery uveitis; IV = intravenously; the Panel = the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV; PO = orally

[a] Renal dose adjustment required in patients with chronic renal insufficiency and/or acute renal failure

[b] Contraindicated for serum creatinine >1.5 mg/dL or creatinine clearance <55 mL/min

CMV Retinitis

The therapeutic approach to CMV retinitis should be individualized based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and the location of lesions. CMV retinitis should be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of this retinal disease.

The Panel recommends the following as first-line therapies for treating CMV retinitis: oral valganciclovir **(AI),** intravenous (IV) ganciclovir **(AI),** or IV ganciclovir induction followed by oral valganciclovir maintenance **(AI);** other effective treatments, such as IV foscarnet **(BI)** and IV cidofovir **(CI),** are not routinely recommended due to substantial toxicities, including nephrotoxicity.[20,34-41] Systemic therapy has been documented to reduce CMV involvement in the contralateral eye,[34] reduce CMV visceral disease, and improve survival.[35,42] Given the evident benefits of systemic anti-CMV therapy, treatment regimens for CMV retinitis should include a systemic component as recommended in the table above. Few trials have compared regimen efficacy during the past 15 years. None of the listed regimens have been proven in clinical trials to be more effective in protecting vision.[36-40]

The Panel recommends IV ganciclovir **(AI)** or oral valganciclovir **(AI)** for an induction period lasting at least 14 to 21 days, with the duration determined by clinical response based on retinal examination. Many clinicians continue induction-level treatment until retinal lesion opacity is resolved or markedly reduced, indicating virus inactivity **(BIII).**[20] Many clinicians prefer the IV formulation for induction when retinitis is more central and sight-threatening or when adequate gastrointestinal (GI) absorption is a concern. In such cases, transition to oral valganciclovir can be considered when there is evidence of clinical response. In cases where toxicity of ganciclovir and valganciclovir (e.g., severe cytopenias) is a concern or there is concern for ganciclovir-resistant CMV, IV foscarnet should be used **(BI).** If both ganciclovir and foscarnet should be avoided or cannot be used, IV cidofovir should be used **(CI).** Cidofovir administration is complicated by the need to coadminister IV saline hydration and probenecid with each dose to counter the nephrotoxicity of the drug. In addition, IV cidofovir is associated with an increased risk of intraocular inflammation, hypotony, and neutropenia.[43-46]

In the presence of immediately sight-threatening retinal lesions (those within 1,500 microns of the fovea or optic disc) at presentation, the Panel recommends supplementing systemic therapy with intravitreal injections of ganciclovir or foscarnet, at least initially, to provide immediate, high intraocular levels of the drug and presumably faster control of the retinitis **(BIII).** Injections are continued on a weekly basis during induction therapy until lesion inactivity is achieved, at which time systemic treatment alone is adequate for maintenance therapy. The recommendation to supplement systemic therapy with intravitreal injections is based both on the experience of ophthalmologists who saw considerable disease early in the HIV epidemic, and pharmacokinetic

considerations, but the clinical benefit of such supplementation has not been confirmed in clinical trials. Although intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are being achieved over time with systemically delivered medications,[34] such injections can be complicated by bacterial or fungal infections, hemorrhage, or retinal detachment.

Intravitreal cidofovir is associated with hypotony and uveitis—and a substantially increased risk of immune recovery uveitis—and **is not recommended (AIII).**[39,47] The ganciclovir implant, a reservoir device for the slow release of drug into the eye, previously used for local therapy, is no longer manufactured. Intravitreal drug injections are not necessary for people with peripheral retinal lesions; oral valganciclovir alone will be adequate **(AI).**

After completing induction therapy, patients should be transitioned to a maintenance regimen. See When to Start Maintenance Therapy below.

CMV Disease Other Than Retinitis

CMV Colitis and Esophagitis

For patients who have colitis or esophagitis, anti-CMV therapy for 21 to 42 days is recommended until resolution of signs and symptoms **(AIII),** based on data that CMV persists with only 14 days of treatment for CMV colitis in people with HIV.[48] IV ganciclovir is the therapy of choice **(AI)** and can be switched to oral valganciclovir once the person can tolerate and absorb oral medications, extrapolated from randomized, clinical trial data showing non-inferiority of oral valganciclovir for treatment of CMV disease in people receiving a solid organ transplant (SOT) **(AIII).**[49] Oral valganciclovir can be used in patients with mild disease **(AIII).** Foscarnet with IV hydration should be used as an alternative if ganciclovir-related toxicity is treatment-limiting or in cases of ganciclovir-resistant virus **(BIII).** Cidofovir, administered with saline hydration before and after therapy, can be used as an alternative **(CI).**

CMV Pneumonia

Experience treating well-documented CMV pneumonia in people with HIV is limited and anecdotal. Treatment with IV ganciclovir or, alternatively, with foscarnet, is recommended **(BIII).** The optimal duration of therapy is a minimum of 21 days (extrapolated from SOT data) **(CII).** The role of oral valganciclovir has not been established, but based on clinical experience with SOT, transition to oral valganciclovir can be considered if CMV pneumonia is not life-threatening and oral medications can be absorbed **(BIII).**

CMV of the Central Nervous System

Therapy for neurologic disease has not been extensively studied. Given the poor outcomes in many patients with CMV-related neurologic disease, the Panel recommends initiating therapy with both IV ganciclovir and IV foscarnet, despite the substantial toxicities associated with such an approach **(BIII).**[50] The role of oral valganciclovir has not been established. The optimal duration of therapy has not been established, but a minimum duration of 21 days is recommended, with extension based on clinical response **(AIII).**

After resolution of acute disease, chronic maintenance therapy is not routinely recommended for CMV GI disease, pneumonia, or central nervous system disease. See When to Start Maintenance Therapy for exceptions.

Special Considerations Regarding IRIS and Antiretroviral Therapy Initiation

Immune recovery uveitis (IRU) is an ocular form of immune reconstitution inflammatory syndrome (IRIS) characterized by inflammation in the anterior chamber or vitreous body. It is presumed to be prompted by immune recovery with ART. IRU can occur both in the context of active CMV retinitis and in persons who have previously had CMV retinitis. IRU is usually observed in patients with a substantial rise in CD4 cell count in the first 4 to 12 weeks after ART initiation.[51-55] The estimated incidence of IRU is 0.02 per person-year after immune recovery.[56] Ocular complications of IRU include macular edema and the development of epiretinal membranes, which can cause loss of vision. Although the inflammatory reactions seen at the onset of IRU can be transient as immune reconstitution occurs, the complications may persist, permanently compromising vision.

Treatment of IRU usually consists of corticosteroid therapy, but the benefit of anti-CMV therapy is unclear.[51,57] The Panel favors the use of both corticosteroids and anti-CMV therapy for active intraocular inflammation at the onset of IRU and the use of corticosteroids for cystoid macular edemas, a late complication of IRU **(CIII).** Data are insufficient upon which to base a recommendation regarding the preferred route of corticosteroid administration; periocular, intravitreal, and oral administration all have been reported to be potentially successful.[52,58-61] Although specific oral corticosteroid regimens for the treatment of CMV as a complication of IRU have not been studied in prospective clinical trials, it is reasonable to follow guidelines for use of oral prednisone in other inflammatory eye diseases.[62] In general, prednisone 1 mg/kg/day, with a maximum adult oral dose of 60 mg/day to 80 mg/day, should be administered until there is a clinical response, but for no longer than 1 month, followed by a tapering regimen and discontinuation over 2 to 3 months **(BIII).** Periocular or intravitreal corticosteroid injections can be repeated after the injection's expected duration of effect if there has been an incomplete clinical response and there have been no treatment complications **(BIII).**

One study demonstrated a substantial increase in IRU associated with immediate, as opposed to deferred initiation, of ART (71% vs. 31%).[63] However, in the current era, the rate of clinically significant IRU following initiation of ART appears to be low (approximately 0.02 per person-year).[56] Delaying ART until retinitis is controlled may reduce the likelihood or severity of IRU; however, this strategy must be weighed against the potential for a worsened immunocompromised state and the occurrence of other OIs.

As CMV replication usually declines within 1 to 2 weeks after anti-CMV therapy is initiated, ART should be initiated no later than 1 to 2 weeks after starting anti-CMV therapy for retinitis, esophagitis, colitis, or other end-organ diseases caused by CMV **(BIII).** IRIS is a particular concern with any neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis. In these cases, however, the Panel recommends initiating ART within 2 weeks, although clinical judgment based on the individual case is needed **(BIII).**

Monitoring of Response to Therapy and Adverse Events

CMV Retinitis Monitoring

Indirect ophthalmoscopy of both eyes through dilated pupils should be performed at the time of diagnosis of CMV retinitis, 2 weeks after initiating therapy, and monthly thereafter while the patient is on anti-CMV treatment **(BIII).** The purpose of such examinations is to evaluate treatment efficacy, identify second eye involvement in cases of unilateral disease, and detect IRU or complications such as retinal detachment. Monthly fundus photographs, using a standardized technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early lesion reactivation.

For people who have experienced immune recovery (CD4 count ≥100 cells/mm^3 for ≥3 months), the frequency of ophthalmologic follow-up can be decreased to every 3 months. Individuals should be examined at least yearly when CD4 counts stabilize and remain above 100 cells/mm^3, HIV RNA blood levels remain undetectable, and existing CMV retinitis lesions have remained clinically inactive for an extended period; however, examinations should be repeated if laboratory values suggest loss of immune reconstitution (CD4 count <100 cells/mm^3) **(AIII).** Clinicians should be aware that lesion reactivation and retinal complications still occasionally occur in patients with immune reconstitution, and regular ophthalmologic follow-up as noted above is needed whether anti-CMV therapy is continued.[15]

Monitoring CMV viral load in blood has poor positive predictive value for detecting relapse of retinitis and **is not recommended** for people with HIV **(AII).**[64]

People with CD4 counts below 100 cells/mm^3 who have no visual changes or evident CMV-related retinal pathology remain at risk for CMV retinitis prior to immune reconstitution after initiation of ART.[65,66] Development of CMV retinitis in the setting of recent ART initiation is not IRIS and should be treated with systemic anti-CMV therapy, similar to any person with CMV retinitis, and the ART regimen should be continued **(AII).** Corticosteroids are not recommended in people with initial CMV retinitis after initiating effective ART **(AIII).**

In addition, in the absence of IRU, corticosteroids should not be used in people undergoing treatment for CMV retinitis who have worsening retinitis upon ART initiation; however, anti-CMV therapy and ART regimens should be continued **(AIII).** IRU can occur months or years after successful treatment of CMV retinitis in a person with a history of CMV retinitis whose immune function is deteriorating and who subsequently starts taking ART or has such therapy optimized.

Drug Adverse Effects

Adverse effects of ganciclovir/valganciclovir include anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Ganciclovir-related neutropenia can often be reversed with granulocyte colony-stimulating factor.[67,68] In people receiving ganciclovir or valganciclovir, complete blood counts (CBC) and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy, or more frequently if indicated **(AIII).**

Adverse effects of foscarnet include nephrotoxicity and electrolyte abnormalities, seizures that occur characteristically in the context of renal insufficiency, and anemia. Foscarnet should be administered with intravenous hydration. Genital ulcers also can occur during foscarnet administration in people

with urinary incontinence due to the toxic effects of excreted drug on exposed skin. Foscarnet is typically given in the inpatient setting because of the intensity of monitoring and need for hydration. Serum electrolytes (including potassium, magnesium, calcium, and phosphorus), renal function tests and CBC should be closely monitored **(AIII).** In people who receive foscarnet as maintenance therapy in the outpatient setting, serum electrolytes, renal function tests, and CBC should be performed at least weekly, if stable **(AIII).** Foscarnet treatment should be stopped if the treating physician determines that there has been a substantial worsening of renal function or there is a severe electrolyte imbalance when compared to pre-treatment values **(AIII);** no definitive laboratory profile exists to prompt treatment discontinuation.

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and hypotony (low intraocular pressure). The risk of severe renal injury from IV cidofovir can be reduced by pre- and post-hydration and oral probenecid before cidofovir administration. Serum creatinine, urinalysis, and CBC should be analyzed within 48 hours of each IV cidofovir infusion. Drug administration is contraindicated if renal dysfunction or substantial proteinuria is detected (see Table 6 for renal dosing information). Particular attention is needed for patients receiving other potentially nephrotoxic medications, including tenofovir disoproxil fumarate. Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony, even when CMV disease does not include retinitis.

Managing Treatment Failure

Failure of therapy for CMV retinitis or reactivation of lesions is most likely in patients who do not experience substantial immune reconstitution after initiation or optimization of ART.[18] Treatment failure may also result from inadequate anti-CMV intraocular drug levels, CMV drug resistance, or nonadherence to CMV treatment or ART. Many experts believe that early progression of disease (enlargement of lesions or new lesions) is most often caused by the limited intraocular penetration of systemically administered drugs.[57,69,70] Data are limited on treatment failure for CMV disease other than retinitis, but the potential mechanisms and management strategies for treatment failure are likely similar to those seen in the setting of retinitis.

When lesions reactivate in patients receiving maintenance therapy, a round of treatment induction with the current maintenance therapy is recommended, followed by reinstitution of maintenance therapy **(BIII).**[71] Ganciclovir and foscarnet in combination appear to provide superior efficacy than either agent alone, and their combination is recommended for people whose disease does not respond to single-drug therapy or if there is continued progression or multiple reactivations of retinitis **(CIII).**[71] Notably, this drug combination is associated with substantial toxicity.

Drug resistance can occur in patients receiving long-term anti-CMV therapy.[72-75] Drug resistance developed at a rate of approximately 25% per person-year in the pre-ART era[72,76,77] for ganciclovir, foscarnet, and cidofovir.[72,73] In the ART era, the 1-year incidence of resistance appears to be lower (approximately 5% per person-year).[78] Low-level resistance to ganciclovir occurs through mutations in the CMV UL97 (phosphotransferase) gene, and high-level resistance to ganciclovir typically occurs because of mutations in both the CMV UL97 and UL54 (DNA polymerase) genes.[74,79-83] Resistance to foscarnet or cidofovir occurs because of mutations in the CMV UL54 gene. High-level resistance to ganciclovir often is associated with cross-resistance to cidofovir[81] and occasionally to foscarnet.[82] Although early progression of CMV disease (within 2 months) in patients who recently started anti-CMV drug treatment is typically not a result of drug resistance, late CMV reactivation after many months of treatment may be due to resistance.[40] By themselves, peripheral blood CMV

viral load measurements have poor positive predictive value for treatment failure.[64] Maribavir has recently been approved by the U.S. Food and Drug Administration for treatment of posttransplant refractory CMV but has not been studied extensively in people with HIV.

Ganciclovir resistance in patients who fail therapy can be detected by CMV DNA PCR of blood specimens followed by detection of UL97 mutations by DNA sequencing or by a point mutation assay.[84,85–86] Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in less than 48 hours and correlates well with conventional drug susceptibility testing and clinical outcomes.[86] A comparison of circulating CMV in blood and vitreous fluid showed identical UL97 sequences in more than 90% of cases;[27] therefore, evaluating the blood for resistance is reasonable, and detection of resistance in the blood or urine correlates with the clinical behavior of retinitis in most cases.[87] Viral culture and susceptibility testing and viral DNA sequencing often are not available in clinical laboratories because they are too time-consuming or costly. UL97 mutants usually respond to foscarnet, as do some UL54 mutants.[88] The Panel recommends treating ganciclovir-resistant CMV with a series of intravitreal injections of foscarnet and/or IV foscarnet or IV cidofovir **(CIII).** Intravitreal administration of cidofovir **is not recommended,** as it has been associated with uveitis and marked hypotony of the injected eye **(AIII).**[55,89]

Preventing Recurrence

When to Start Maintenance Therapy

After induction therapy for CMV retinitis is completed, chronic maintenance therapy should be started **(AI).**[21,25,34,37,90] Maintenance therapy is started after induction has achieved control of retinitis, as evidenced by resolved or markedly reduced retinal lesion opacity. Oral valganciclovir is the preferred regimen as it is the easiest and least toxic to administer to an outpatient population, provided that GI absorption is adequate. Alternative regimens for chronic suppression include parenteral ganciclovir, parenteral foscarnet, and parenteral cidofovir. Systemic therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred. Repeated intravitreal injections of ganciclovir or foscarnet alone have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series,[91] but this strategy should be reserved for those individuals who cannot be treated with systemic therapy.

The choice of regimen—including drug type and administration route—should be made in consultation with an ophthalmologist. Considerations should include the anatomic location of the retinal lesion, vision in the contralateral eye, and the individual's immunologic and virologic status, comorbidities, concomitant medications, and response to ART. Ocular complications, such as IRU and retinal detachment, are related to lesion size; therefore, the retinitis should be controlled with anti-CMV therapy to minimize lesion size until immune recovery is sufficient. Furthermore, evidence from both the pre-ART and ART eras demonstrates that specific anti-CMV therapy decreases mortality among immune-compromised patients with CMV retinitis.[26,35,41,92]

After resolution of the acute non-ocular CMV disease and initiation of effective ART, chronic maintenance therapy is not routinely recommended for CMV GI disease, pneumonia, and central nervous system disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially.

When to Stop Maintenance Therapy

Based on the experience of multiple investigators and following guidelines published by the U.S Public Health Service and the Infectious Diseases Society of America, the Panel recommends treatment with systemic anti-CMV therapy for at least 3 months, maintaining a sustained (at least 3 months) increase in CD4 count ≥100 cells/mm^3 while on ART, and ensuring CMV retinitis lesions are inactive before stopping maintenance therapy **(AII).**[13,93-101] Such decisions should be made in consultation with an ophthalmologist.

Retinitis relapse[102,103] occurs at a rate of 0.03/person-years in people with CD4 counts ≥100 cells/mm^3 and has been documented in people with CD4 counts >750 cells/mm^3. Therefore, in all people for whom anti-CMV maintenance therapy has been discontinued, ophthalmologic monitoring for early detection of CMV relapse and IRU should be performed at least every 3 months and then yearly after immune reconstitution **(AIII).** Monitoring CMV viral load in blood has poor positive predictive value for relapse of retinitis and, therefore, **is not recommended** for people with HIV **(AII).**[64]

Reactivation of CMV retinitis occurs frequently in people whose CD4 cell counts have decreased to <50 cells/mm^3 and whose anti-CMV maintenance therapies have been discontinued.[104] Therefore, for people with CMV retinitis, reinstitution of maintenance therapy should occur if the CD4 cell count has decreased to <100 cells/mm^3 after prior successful immune reconstitution **(AIII).**

Special Considerations During Pregnancy

During pregnancy, diagnostic considerations and indications for treatment are the same as for other people with HIV **(AIII).** Active CMV retinitis or other end-organ CMV disease during pregnancy is uncommon in the ART era. Suspected or confirmed fetal CMV infection is not an indication for the treatment of the mother in the absence of maternal disease (see below).[105] If anti-CMV treatment is required during pregnancy because of active maternal CMV disease, ART should be given as soon as possible and no longer than 2 weeks after initiating anti-CMV therapy to prevent transmission to the fetus and to limit other complications of immune compromise, balancing concerns about the possible development of IRIS. Duration of anti-CMV therapy should follow guidance for nonpregnant adults.

Based on limited data (case reports only), toxicity reports, and ease of use of the various drugs, valganciclovir is considered the best choice of treatment for maternal CMV disease requiring treatment during pregnancy **(BIII).** Ganciclovir is embryotoxic among rabbits and mice and teratogenic (e.g., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.[106-108] As a prodrug with conversion to ganciclovir for activity, valganciclovir is expected to have similar reproductive toxicity. However, safe use of valganciclovir in all trimesters of human pregnancy after organ transplantation and in other patient populations has been reported.[106,107,109,110] Valganciclovir use during pregnancy may result in fetal anemia. Additional fetal surveillance may be considered if maternal CMV treatment is required.

For retinal disease in pregnancy, the use of intravitreal ganciclovir injections as local therapy that is not systemically absorbed should pose no risk to the fetus.[111] People with inactive retinal disease who achieved immune reconstitution before pregnancy do not require treatment with an anti-CMV agent.

Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits.[112,113] No experience with use early in human pregnancy has been reported. A single case report of use in the

third trimester described a normal infant outcome.[114] Cidofovir is embryotoxic and teratogenic (e.g., meningomyelocele and skeletal abnormalities) in rats and rabbits.[115] No experience with use of cidofovir in human pregnancy has been reported. Based on these concerns, foscarnet or cidofovir use in pregnancy **is not recommended** in the absence of resistance or toxicity with ganciclovir/valganciclovir **(AIII);** if either agent is used, this should be done in consultation with a maternal–fetal medicine specialist. Use of either drug may result in maternal renal toxicity and/or insufficiency. Additional fetal surveillance may be recommended in the setting of maternal renal insufficiency **(BIII).**[105,116-120]

Suspected or Confirmed Fetal CMV

Primary infection, reactivation, or reinfection with CMV during pregnancy (non-primary infection)[121] can lead to *in-utero* transmission and congenital CMV disease. Maternal CMV infection and fetal congenital CMV infection have been associated with an increased risk of perinatal HIV transmission among pregnant women who have not received ART.[122] Maternal ART to prevent perinatal HIV has been associated with decreased rates of perinatal/early postnatal CMV and decreased CMV-related clinical symptoms among infants exposed to or infected with HIV.[123] Studies indicate the prevalence of congenital CMV disease among infants in the United States who are exposed to HIV is 1.2% to 1.3%.[124] Risk factors for congenital CMV include mothers with CD4 <200 cells/mm^3, mothers with urinary CMV shedding,[125] and perinatal HIV infection.[90]

In women diagnosed with primary CMV infection in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation **(CIII).**[126] In studies in populations without HIV, about 5% to 25% of newborns infected with CMV had ultrasound evidence of congenital infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel).[126] Any ultrasound findings suspicious of congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis.[118] Referral to a maternal–fetal medicine specialist for evaluation, counseling, and potential further testing is recommended. Potential noninvasive biomarkers for predicting congenital CMV infection are under study.[127]

If fetal CMV infection is confirmed, there is no standard maternal or fetal therapy that can prevent congenital CMV.[105,126] Although several observational studies reported the possible effectiveness and safety of hyperimmune globulin (HIG) in pregnancy for the treatment of congenital CMV,[128-131] two large, randomized, placebo-controlled trials demonstrated that HIG is not effective at decreasing the risk of congenital CMV in the setting of maternal primary infection.[132-134] Thus, HIG administration **is not recommended** during pregnancy **(AI).** Limited recent data exist for use of oral valacyclovir in the setting of maternal primary CMV infection that occurs close to the time of conception or in the first trimester of pregnancy to reduce neonatal CMV infection.[135-139] Additional studies are needed to validate this strategy and it has not been endorsed by the Society of Maternal-Fetal Medicine nor the American College of Obstetricians and Gynecologists.

References

1. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus Seroprevalence in the United States: The National Health and Nutrition Examination Surveys, 1988–2004. *Clinical Infectious Diseases*. 2010;50(11):1439-1447. Available at: https://doi.org/10.1086/652438.

2. Fowler K, Mucha J, Neumann M, et al. A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment, screening, and vaccine development. *BMC Public Health*. 2022;22(1):1659. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36050659.

3. Bates M, Brantsaeter AB. Human cytomegalovirus (CMV) in Africa: a neglected but important pathogen. *J Virus Erad*. 2016;2(3):136-142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27482452.

4. Zuhair M, Smit GSA, Wallis G, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: A systematic review and meta-analysis. *Rev Med Virol*. 2019;29(3):e2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30706584.

5. Mhandire D, Duri K, Kaba M, et al. Seroprevalence of Cytomegalovirus infection Among HIV-infected and HIV-uninfected pregnant women attending antenatal clinic in Harare, Zimbabwe. *Viral Immunol*. 2019;32(7):289-295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31347990.

6. Hoehl S, Berger A, Ciesek S, Rabenau HF. Thirty years of CMV seroprevalence-a longitudinal analysis in a German university hospital. *Eur J Clin Microbiol Infect Dis*. 2020;39(6):1095-1102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31989374.

7. Centers for Disease Control and Prevention. Clinical overview of CMV and congenital CMV. 2024. Available at: https://www.cdc.gov/cytomegalovirus/hcp/clinical-overview/index.html

8. Gupta M, Shorman M. Cytomegalovirus infections. StatPearls. Treasure Island (FL). StatPearls Publishing. 2025. Accessed: July 2,2025. https://pubmed.ncbi.nlm.nih.gov/29083720/.

9. Griffiths P, Baraniak I, Reeves M. The pathogenesis of human cytomegalovirus. *J Pathol*. 2015;235(2):288-297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25205255.

10. Jabs DA, Van Natta ML, Kempen JH, et al. Characteristics of patients with cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol*. 2002;133(1):48-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11755839.

11. Dieterich DT, Rahmin M. Cytomegalovirus colitis in AIDS: presentation in 44 patients and a review of the literature. *J Acquir Immune Defic Syndr*. 1991;4 Suppl 1:S29-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1848619.

12. Arribas JR, Storch GA, Clifford DB, Tselis AC. Cytomegalovirus encephalitis. *Ann Intern Med*. 1996;125(7):577-587. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8815757.

13. Jabs DA, Van Natta ML, Holbrook JT, et al. Longitudinal study of the ocular complications of AIDS: 1. Ocular diagnoses at enrollment. *Ophthalmology*. 2007;114(4):780-786. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17258320.

14. Schwarcz L, Chen MJ, Vittinghoff E, Hsu L, Schwarcz S. Declining incidence of AIDS-defining opportunistic illnesses: results from 16 years of population-based AIDS surveillance. *AIDS*. 2013;27(4):597-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23079812.

15. Sugar EA, Jabs DA, Ahuja A, et al. Incidence of cytomegalovirus retinitis in the era of highly active antiretroviral therapy. *Am J Ophthalmol*. 2012;153(6):1016-1024 e1015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22310076.

16. Jabs DA, Van Natta ML, Thorne JE, et al. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: 2. Second eye involvement and retinal detachment. *Ophthalmology*. 2004;111(12):2232-2239. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15582079.

17. Holland GN, Vaudaux JD, Jeng SM, et al. Characteristics of untreated AIDS-related cytomegalovirus retinitis. I. Findings before the era of highly active antiretroviral therapy (1988 to 1994). *Am J Ophthalmol*. 2008;145(1):5-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18154750.

18. Holland GN, Vaudaux JD, Shiramizu KM, et al. Characteristics of untreated AIDS-related cytomegalovirus retinitis. II. Findings in the era of highly active antiretroviral therapy (1997 to 2000). *Am J Ophthalmol*. 2008;145(1):12-22. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18154751.

19. Holland GN, Shuler JD. Progression rates of cytomegalovirus retinopathy in ganciclovir-treated and untreated patients. *Arch Ophthalmol*. 1992;110(10):1435-1442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1329703.

20. Holland GN. AIDS and ophthalmology: the first quarter century. *Am J Ophthalmol*. 2008;145(3):397-408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18282490.

21. Arribas JR, Clifford DB, Fichtenbaum CJ, Commins DL, Powderly WG, Storch GA. Level of cytomegalovirus (CMV) DNA in cerebrospinal fluid of subjects with AIDS and CMV infection of the central nervous system. *J Infect Dis*. 1995;172(2):527-531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7622897.

22. Dodt KK, Jacobsen PH, Hofmann B, et al. Development of cytomegalovirus (CMV) disease may be predicted in HIV-infected patients by CMV polymerase chain reaction and the antigenemia test. *AIDS*. 1997;11(3):F21-28. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9147416.

23. Zurlo JJ, O'Neill D, Polis MA, et al. Lack of clinical utility of cytomegalovirus blood and urine cultures in patients with HIV infection. *Ann Intern Med*. 1993;118(1):12-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8093214.

24. Rodriguez-Barradas MC, Stool E, Musher DM, et al. Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS. *Clin Infect Dis*. 1996;23(1):76-81. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8816133.

25. Wolf DG, Spector SA. Diagnosis of human cytomegalovirus central nervous system disease in AIDS patients by DNA amplification from cerebrospinal fluid. *J Infect Dis*. 1992;166(6):1412-1415. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1331254.

26. Deayton JR, Prof Sabin CA, Johnson MA, Emery VC, Wilson P, Griffiths PD. Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy. *Lancet*. 2004;363(9427):2116-2121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15220032.

27. Hu H, Jabs DA, Forman MS, et al. Comparison of cytomegalovirus (CMV) UL97 gene sequences in the blood and vitreous of patients with acquired immunodeficiency syndrome and CMV retinitis. *J Infect Dis*. 2002;185(7):861-867. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11920309.

28. Laine L, Bonacini M, Sattler F, Young T, Sherrod A. Cytomegalovirus and Candida esophagitis in patients with AIDS. *J Acquir Immune Defic Syndr*. 1992;5(6):605-609. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1316961.

29. Poh KC, Zheng S. A rare case of CMV pneumonia in HIV-infection. *Respir Med Case Rep*. 2019;28:100945. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31709138.

30. Jabbehdari S, Marjani M, Moniri A, et al. Cytomegalovirus pneumonia in HIV-infected patients: case series from Iran. *HIV & AIDS Review*. 2022;21(4):327-331. Available at: https://hivaids.termedia.pl/Cytomegalovirus-pneumonia-in-HIV-infected-patients-case-series-from-Iran,146650,0,2.html.

31. Drew LW. Condoms and the transmission of cytomegalovirus. *Sexually Transmitted Diseases*. 1998;25(9):481-482. Available at: https://journals.lww.com/stdjournal/fulltext/1998/10000/condoms_and_the_transmission_of_cytomegalovirus.7.aspx.

32. Katznelson S, Drew WL, Mintz L. Efficacy of the condom as a barrier to the transmission of cytomegalovirus. *J Infect Dis*. 1984;150(1):155-157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6086770.

33. Wohl DA, Kendall MA, Andersen J, et al. Low rate of CMV end-organ disease in HIV-infected patients despite low CD4+ cell counts and CMV viremia: results of ACTG protocol A5030. *HIV Clin Trials*. 2009;10(3):143-152. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632953.

34. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. Roche Ganciclovir Study Group. *N Engl J Med*. 1999;340(14):1063-1070. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10194235.

35. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia J. Mortality risk for patients with cytomegalovirus retinitis and acquired immune deficiency syndrome. *Clin Infect Dis*. 2003;37(10):1365-1373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14583871.

36. Studies of Ocular Complications of ARGTACTG. The ganciclovir implant plus oral ganciclovir versus parenteral cidofovir for the treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome: The Ganciclovir Cidofovir Cytomegalovirus Retinitis Trial. *Am J Ophthalmol*. 2001;131(4):457-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11292409.

37. Musch DC, Martin DF, Gordon JF, Davis MD, Kuppermann BD. Treatment of cytomegalovirus retinitis with a sustained-release ganciclovir implant. The Ganciclovir Implant Study Group. *N Engl J Med*. 1997;337(2):83-90. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9211677.

38. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med*. 2002;346(15):1119-1126. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11948271.

39. Kempen JH, Jabs DA, Wilson LA, Dunn JP, West SK, Tonascia JA. Risk of vision loss in patients with cytomegalovirus retinitis and the acquired immunodeficiency syndrome. *Arch Ophthalmol*. 2003;121(4):466-476. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12695243.

40. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial. 4. Visual outcomes. Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *Ophthalmology*. 1994;101(7):1250-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8035989.

41. Bowen EF, Wilson P, Cope A, et al. Cytomegalovirus retinitis in AIDS patients: influence of cytomegaloviral load on response to ganciclovir, time to recurrence and survival. *AIDS*. 1996;10(13):1515-1520. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8931786.

42. Jabs DA, Ahuja A, Van Natta M, Dunn JP, Yeh S, Studies of the Ocular Complications of ARG. Comparison of treatment regimens for cytomegalovirus retinitis in patients with AIDS in the era of highly active antiretroviral therapy. *Ophthalmology*. 2013;120(6):1262-1270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23419804.

43. Davis JL, Taskintuna I, Freeman WR, Weinberg DV, Feuer WJ, Leonard RE. Iritis and hypotony after treatment with intravenous cidofovir for cytomegalovirus retinitis. *Arch Ophthalmol*. 1997;115(6):733-737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9194724.

44. Long-term follow-up of patients with AIDS treated with parenteral cidofovir for cytomegalovirus retinitis: the HPMPC Peripheral Cytomegalovirus Retinitis Trial. The Studies of Ocular Complications of AIDS Research Group in collaboration with the AIDS Clinical Trials Group. *AIDS*. 2000;14(11):1571-1581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10983644.

45. Labetoulle M, Goujard C, Frau E, Offret H, Delfraissy JF, Gasnault J. Cidofovir ocular toxicity is related to previous ocular history. *AIDS*. 2000;14(5):622-623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10780729.

46. Lampinen TM, Critchlow CW, Kuypers JM, et al. Association of antiretroviral therapy with detection of HIV-1 RNA and DNA in the anorectal mucosa of homosexual men. *AIDS*. 2000;14(5):F69-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10780708.

47. Taskintuna I, Rahhal FM, Rao NA, et al. Adverse events and autopsy findings after intravitreous cidofovir (HPMPC) therapy in patients with acquired immune deficiency syndrome (AIDS). *Ophthalmology*. 1997;104(11):1827-1836; discussion 1836-1827. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9373113.

48. Dieterich DT, Kotler DP, Busch DF, et al. Ganciclovir treatment of cytomegalovirus colitis in AIDS: a randomized, double-blind, placebo-controlled multicenter study. *J Infect Dis*. 1993;167(2):278-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8380610.

49. Asberg A, Humar A, Rollag H, et al. Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients. *Am J Transplant*. 2007;7(9):2106-2113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17640310.

50. Anduze-Faris BM, Fillet AM, Gozlan J, et al. Induction and maintenance therapy of cytomegalovirus central nervous system infection in HIV-infected patients. *AIDS*. 2000;14(5):517-524. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10780714.

51. Nguyen QD, Kempen JH, Bolton SG, Dunn JP, Jabs DA. Immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis after highly active antiretroviral therapy. *Am J Ophthalmol*. 2000;129(5):634-639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10844056.

52. Karavellas MP, Plummer DJ, Macdonald JC, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful highly active antiretroviral therapy. *J Infect Dis*. 1999;179(3):697-700. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9952380.

53. Robinson MR, Reed G, Csaky KG, Polis MA, Whitcup SM. Immune-recovery uveitis in patients with cytomegalovirus retinitis taking highly active antiretroviral therapy. *Am J Ophthalmol*. 2000;130(1):49-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11004259.

54. Karavellas MP, Song M, Macdonald JC, Freeman WR. Long-term posterior and anterior segment complications of immune recovery uveitis associated with cytomegalovirus retinitis. *Am J Ophthalmol*. 2000;130(1):57-64. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11004260.

55. Kempen JH, Min YI, Freeman WR, et al. Risk of immune recovery uveitis in patients with AIDS and cytomegalovirus retinitis. *Ophthalmology*. 2006;113(4):684-694. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16581429.

56. Jabs DA, Ahuja A, Van Natta ML, et al. Long-term outcomes of cytomegalovirus retinitis in the era of modern antiretroviral therapy: results from a United States cohort. *Ophthalmology*. 2015;122(7):1452-1463. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25892019.

57. Jabs DA, Wingard JR, de Bustros S, de Miranda P, Saral R, Santos GW. BW B759U for cytomegalovirus retinitis: intraocular drug penetration. *Arch Ophthalmol*. 1986;104(10):1436-1437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3021090.

58. Rodrigues Alves N, Barao C, Mota C, Costa L, Proenca RP. Immune recovery uveitis: a focus review. *Graefes Arch Clin Exp Ophthalmol*. 2024;262(8):2703-2712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38381160.

59. El-Bradey MH, Cheng L, Song MK, Torriani FJ, Freeman WR. Long-term results of treatment of macular complications in eyes with immune recovery uveitis using a graded treatment approach. *Retina*. 2004;24(3):376-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15187659.

60. Kuppermann BD, Holland GN. Immune recovery uveitis. *Am J Ophthalmol*. 2000;130(1):103-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11004267.

61. Holland GN. Immune recovery uveitis. *Ocul Immunol Inflamm*. 1999;7(3-4):215-221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10611730.

62. Jabs DA, Rosenbaum JT, Foster CS, et al. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol*. 2000;130(4):492-513. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11024423.

63. Ortega-Larrocea G, Espinosa E, Reyes-Teran G. Lower incidence and severity of cytomegalovirus-associated immune recovery uveitis in HIV-infected patients with delayed highly active antiretroviral therapy. *AIDS*. 2005;19(7):735-738. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15821403.

64. Jabs DA, Martin BK, Forman MS, Ricks MO. Cytomegalovirus (CMV) blood DNA load, CMV retinitis progression, and occurrence of resistant CMV in patients with CMV retinitis. *The Journal of Infectious Diseases*. 2005;192(4):640-649. Available at: https://doi.org/10.1086/432012.

65. Ruiz-Cruz M, Alvarado-de la Barrera C, Ablanedo-Terrazas Y, Reyes-Teran G. Proposed clinical case definition for cytomegalovirus-immune recovery retinitis. *Clin Infect Dis*. 2014;59(2):298-303. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24771331.

66. Jabs DA, Van Natta ML, Holland GN, Danis R, Studies of the Ocular Complications of ARG. Cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome after initiating antiretroviral therapy. *Am J Ophthalmol*. 2017;174:23-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27984023.

67. Dubreuil-Lemaire ML, Gori A, Vittecoq D, et al. Lenograstim for the treatment of neutropenia in patients receiving ganciclovir for cytomegalovirus infection: a randomised, placebo-controlled trial in AIDS patients. *Eur J Haematol*. 2000;65(5):337-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11092465.

68. Kuritzkes DR, Parenti D, Ward DJ, et al. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. G-CSF 930101 Study Group. *AIDS*. 1998;12(1):65-74. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9456256.

69. Kuppermann BD, Quiceno JI, Flores-Aguilar M, et al. Intravitreal ganciclovir concentration after intravenous administration in AIDS patients with cytomegalovirus retinitis: implications for therapy. *J Infect Dis*. 1993;168(6):1506-1509. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8245536.

70. Arevalo JF, Gonzalez C, Capparelli EV, et al. Intravitreous and plasma concentrations of ganciclovir and foscarnet after intravenous therapy in patients with AIDS and cytomegalovirus retinitis. *J Infect Dis*. 1995;172(4):951-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7561215.

71. Combination foscarnet and ganciclovir therapy vs monotherapy for the treatment of relapsed cytomegalovirus retinitis in patients with AIDS. The Cytomegalovirus Retreatment Trial. The Studies of Ocular Complications of AIDS Research Group in Collaboration with the AIDS Clinical Trials Group. *Arch Ophthalmol*. 1996;114(1):23-33. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8540847.

72. Jabs DA, Enger C, Dunn JP, Forman M. Cytomegalovirus retinitis and viral resistance: ganciclovir resistance. CMV Retinitis and Viral Resistance Study Group. *J Infect Dis*. 1998;177(3):770-773. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9498461.

73. Jabs DA, Enger C, Forman M, Dunn JP. Incidence of foscarnet resistance and cidofovir resistance in patients treated for cytomegalovirus retinitis. The Cytomegalovirus Retinitis and Viral Resistance Study Group. *Antimicrob Agents Chemother*. 1998;42(9):2240-2244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9736542.

74. Jabs DA, Martin BK, Forman MS, et al. Mutations conferring ganciclovir resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis*. 2001;183(2):333-337. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11120934.

75. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. *Proc Natl Acad Sci U S A*. 2000;97(14):8039-8044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10859361.

76. Jabs DA, Enger C, Dunn JP, Forman M, Hubbard L. Cytomegalovirus retinitis and viral resistance: 3. Culture results. CMV Retinitis and Viral Resistance Study Group. *Am J Ophthalmol*. 1998;126(4):543-549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9780099.

77. Weinberg A, Jabs DA, Chou S, et al. Mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis*. 2003;187(5):777-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12599051.

78. Martin BK, Ricks MO, Forman MS, Jabs DA, Cytomegalovirus Ra, Group VRS. Change over time in incidence of ganciclovir resistance in patients with cytomegalovirus retinitis. *Clin Infect Dis*. 2007;44(7):1001-1008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17342657.

79. Chou S, Erice A, Jordan MC, et al. Analysis of the UL97 phosphotransferase coding sequence in clinical cytomegalovirus isolates and identification of mutations conferring ganciclovir resistance. *J Infect Dis*. 1995;171(3):576-583. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7876604.

80. Chou S, Guentzel S, Michels KR, Miner RC, Drew WL. Frequency of UL97 phosphotransferase mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. *J Infect Dis*. 1995;172(1):239-242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7797920.

81. Smith IL, Cherrington JM, Jiles RE, Fuller MD, Freeman WR, Spector SA. High-level resistance of cytomegalovirus to ganciclovir is associated with alterations in both the UL97 and DNA polymerase genes. *J Infect Dis*. 1997;176(1):69-77. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9207351.

82. Chou S, Lurain NS, Thompson KD, Miner RC, Drew WL. Viral DNA polymerase mutations associated with drug resistance in human cytomegalovirus. *J Infect Dis*. 2003;188(1):32-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12825168.

83. Chou S, Van Wechel LC, Lichy HM, Marousek GI. Phenotyping of cytomegalovirus drug resistance mutations by using recombinant viruses incorporating a reporter gene. *Antimicrob Agents Chemother*. 2005;49(7):2710-2715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15980340.

84. Wolf DG, Smith IL, Lee DJ, Freeman WR, Flores-Aguilar M, Spector SA. Mutations in human cytomegalovirus UL97 gene confer clinical resistance to ganciclovir and can be detected directly in patient plasma. *J Clin Invest*. 1995;95(1):257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7814623.

85. Vitravene Study G. Randomized dose-comparison studies of intravitreous fomivirsen for treatment of cytomegalovirus retinitis that has reactivated or is persistently active despite other therapies in patients with AIDS. *Am J Ophthalmol*. 2002;133(4):475-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11931781.

86. Jabs DA, Martin BK, Ricks MO, Forman MS, Cytomegalovirus Ra, Group VRS. Detection of ganciclovir resistance in patients with AIDS and cytomegalovirus retinitis: correlation of genotypic methods with viral phenotype and clinical outcome. *J Infect Dis*. 2006;193(12):1728-1737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16703517.

87. Jabs DA, Martin BK, Forman MS, et al. Cytomegalovirus resistance to ganciclovir and clinical outcomes of patients with cytomegalovirus retinitis. *Am J Ophthalmol*. 2003;135(1):26-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12504693.

88. Jabs DA, Martin BK, Forman MS, Cytomegalovirus Ra, Group VRR. Mortality associated with resistant cytomegalovirus among patients with cytomegalovirus retinitis and AIDS. *Ophthalmology*. 2010;117(1):128-132 e122. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19818505.

89. Banker AS, Arevalo JF, Munguia D, et al. Intraocular pressure and aqueous humor dynamics in patients with AIDS treated with intravitreal cidofovir (HPMPC) for cytomegalovirus retinitis. *Am J Ophthalmol*. 1997;124(2):168-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9262540.

90. (ACTG) ACTG. Studies of ocular complications of AIDS Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 1. Rationale, design, and methods. AIDS Clinical Trials Group (ACTG). *Control Clin Trials*. 1992;13(1):22-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1315661.

91. Young S, Morlet N, Besen G, et al. High-dose (2000-microgram) intravitreous ganciclovir in the treatment of cytomegalovirus retinitis. *Ophthalmology*. 1998;105(8):1404-1410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9709750.

92. Spector SA, Wong R, Hsia K, Pilcher M, Stempien MJ. Plasma cytomegalovirus (CMV) DNA load predicts CMV disease and survival in AIDS patients. *J Clin Invest*. 1998;101(2):497-502. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9435323.

93. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;177(4):1080-1083. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9534987.

94. Vrabec TR, Baldassano VF, Whitcup SM. Discontinuation of maintenance therapy in patients with quiescent cytomegalovirus retinitis and elevated CD4+ counts. *Ophthalmology*. 1998;105(7):1259-1264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9663231.

95. Macdonald JC, Torriani FJ, Morse LS, Karavellas MP, Reed JB, Freeman WR. Lack of reactivation of cytomegalovirus (CMV) retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4 T cells in response to highly active antiretroviral therapy. *J Infect Dis*. 1998;177(5):1182-1187. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9593001.

96. Whitcup SM, Fortin E, Lindblad AS, et al. Discontinuation of anticytomegalovirus therapy in patients with HIV infection and cytomegalovirus retinitis. *JAMA*. 1999;282(17):1633-1637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10553789.

97. Jabs DA, Bolton SG, Dunn JP, Palestine AG. Discontinuing anticytomegalovirus therapy in patients with immune reconstitution after combination antiretroviral therapy. *Am J Ophthalmol*. 1998;126(6):817-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9860006.

98. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2001;15(1):23-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11192865.

99. Walmsley SL, Raboud J, Angel JB, et al. Long-term follow-up of a cohort of HIV-infected patients who discontinued maintenance therapy for cytomegalovirus retinitis. *HIV Clin Trials*. 2006;7(1):1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16632459.

100. Holbrook JT, Colvin R, van Natta ML, et al. Evaluation of the United States Public Health Service guidelines for discontinuation of anticytomegalovirus therapy after immune recovery in patients with cytomegalovirus retinitis. *Am J Ophthalmol*. 2011;152(4):628-637 e621. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21742304.

101. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *MMWR Recomm Rep*. 1999;48(RR-10):1-59, 61-56. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10499670.

102. Jabs DA, Ahuja A, Van Natta M, Lyon A, Srivastava S, Gangaputra S. Course of cytomegalovirus retinitis in the era of highly active antiretroviral therapy: five-year outcomes. *Ophthalmology*. 2010;117(11):2152-2161.e2151-2152. Available at: https://pubmed.ncbi.nlm.nih.gov/20673591/.

103. Komanduri KV, Feinberg J, Hutchins RK, et al. Loss of cytomegalovirus-specific CD4+ T cell responses in human immunodeficiency virus type 1-infected patients with high CD4+ T cell counts and recurrent retinitis. *J Infect Dis*. 2001;183(8):1285-1289. Available at: https://pubmed.ncbi.nlm.nih.gov/11262214/.

104. Torriani FJ, Freeman WR, Macdonald JC, et al. CMV retinitis recurs after stopping treatment in virological and immunological failures of potent antiretroviral therapy. *AIDS*. 2000;14(2):173-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10708288.

105. Practice bulletin no. 151: Cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. *Obstet Gynecol*. 2015;125(6):1510-1525. Available at: https://pubmed.ncbi.nlm.nih.gov/26000539.

106. Faqi AS, Klug A, Merker HJ, Chahoud I. Ganciclovir induces reproductive hazards in male rats after short-term exposure. *Hum Exp Toxicol*. 1997;16(9):505-511. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9306137.

107. Miller BW, Howard TK, Goss JA, Mostello DJ, Holcomb WL, Jr., Brennan DC. Renal transplantation one week after conception. *Transplantation*. 1995;60(11):1353-1354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8525535.

108. Pescovitz MD. Absence of teratogenicity of oral ganciclovir used during early pregnancy in a liver transplant recipient. *Transplantation*. 1999;67(5):758-759. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10096536.

109. Adler SP, Nigro G, Pereira L. Recent advances in the prevention and treatment of congenital cytomegalovirus infections. *Semin Perinatol*. 2007;31(1):10-18. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17317422.

110. Seidel V, Feiterna-Sperling C, Siedentopf JP, et al. Intrauterine therapy of cytomegalovirus infection with valganciclovir: review of the literature. *Med Microbiol Immunol*. 2017;206(5):347-354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28733760.

111. Henry K, Cantrill H, Fletcher C, Chinnock BJ, Balfour HH, Jr. Use of intravitreal ganciclovir (dihydroxy propoxymethyl guanine) for cytomegalovirus retinitis in a patient with AIDS. *Am J Ophthalmol*. 1987;103(1):17-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3026186.

112. FOSCAVIR ® (foscarnet sodium) injection 2011.

113. Mathias CV, Simões MJ, Amed AM, et al. Foscarnet effects on the rat pregnancy outcome. *Int J Morphol*. 2005;23(2):137-140. Available at: https://www.scielo.cl/pdf/ijmorphol/v23n2/art08.pdf.

114. Alvarez-McLeod A, Havlik J, Drew KE. Foscarnet treatment of genital infection due to acyclovir-resistant herpes simplex virus type 2 in a pregnant patient with AIDS: case report. *Clin Infect Dis*. 1999;29(4):937-938. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10589917.

115. De Clercq E. Therapeutic potential of Cidofovir (HPMPC, Vistide) for the treatment of DNA virus (i.e. herpes-, papova-, pox- and adenovirus) infections. *Verh K Acad Geneeskd Belg*. 1996;58(1):19-47; discussion 47-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8701600.

116. Indications for Outpatient Antenatal Fetal Surveillance: ACOG Committee Opinion, Number 828. *Obstet Gynecol*. 2021;137(6):e177-e197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34011892.

117. Khalil A, Sotiriadis A, Chaoui R, et al. ISUOG Practice Guidelines: role of ultrasound in congenital infection. *Ultrasound Obstet Gynecol*. 2020;56(1):128-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32400006.

118. Enders M, Daiminger A, Exler S, Ertan K, Enders G, Bald R. Prenatal diagnosis of congenital cytomegalovirus infection in 115 cases: a 5 years' single center experience. *Prenat Diagn*. 2017;37(4):389-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28207161.

119. Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. *Am J Obstet Gynecol*. 2016;214(6):B5-b11. Available at: https://pubmed.ncbi.nlm.nih.gov/26902990/.

120. Boppana SB, Hui L. Cytomegalovirus infection in pregnancy. 2024. Available at: https://www.uptodate.com/contents/cytomegalovirus-infection-in-pregnancy

121. Yamamoto AY, Mussi-Pinhata MM, Boppana SB, et al. Human cytomegalovirus reinfection is associated with intrauterine transmission in a highly cytomegalovirus-immune maternal population. *Am J Obstet Gynecol*. 2010;202(3):297 e291-298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20060091.

122. Adachi K, Xu J, Ank B, et al. Congenital cytomegalovirus and HIV perinatal transmission. *Pediatr Infect Dis J*. 2018;37(10):1016-1021. Available at: https://pubmed.ncbi.nlm.nih.gov/30216294/.

123. Frederick T, Homans J, Spencer L, et al. The effect of prenatal highly active antiretroviral therapy on the transmission of congenital and perinatal/early postnatal cytomegalovirus among HIV-infected and HIV-exposed infants. *Clin Infect Dis*. 2012;55(6):877-884. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22675157.

124. Purswani MU, Russell JS, Dietrich M, et al. Birth prevalence of congenital cytomegalovirus nfection in HIV-exposed uninfected children in the era of combination antiretroviral therapy. *The Journal of Pediatrics*. 2020;216:82-87.e82. Available at: https://www.sciencedirect.com/science/article/pii/S0022347619311618?via%3Dihub.

125. Adachi K, Xu J, Ank B, et al. Cytomegalovirus urinary shedding in HIV-infected pregnant women and congenital cytomegalovirus infection. *Clin Infect Dis*. 2017;65(3):405-413. Available at: https://pubmed.ncbi.nlm.nih.gov/28369278/.

126. Society-for-Maternal-Fetal-Medicine, Hughes BL, Gyamfi-Bannerman C. Diagnosis and antenatal management of congenital cytomegalovirus infection. *Am J Obstet Gynecol*. 2016;214(6):B5-B11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26902990.

127. Tanimura K, Yamada H. Potential biomarkers for predicting congenital cytomegalovirus infection. *Int J Mol Sci*. 2018;19(12):3760. Available at: https://www.mdpi.com/1422-0067/19/12/3760/htm#.

128. Kagan KO, Enders M, Schampera MS, et al. Prevention of maternal-fetal transmission of cytomegalovirus after primary maternal infection in the first trimester by biweekly hyperimmunoglobulin administration. *Ultrasound Obstet Gynecol*. 2019;53(3):383-389. Available at: https://pubmed.ncbi.nlm.nih.gov/29947159/.

129. Nigro G, Adler SP, La Torre R, Best AM, Congenital-Cytomegalovirus-Collaborating-Group. Passive immunization during pregnancy for congenital cytomegalovirus infection. *N Engl J Med*. 2005;353(13):1350-1362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16192480.

130. Nigro G, Torre RL, Pentimalli H, et al. Regression of fetal cerebral abnormalities by primary cytomegalovirus infection following hyperimmunoglobulin therapy. *Prenat Diagn*. 2008;28(6):512-517. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18509871.

131. Nigro G, Adler SP, Congenital-Cytomegalic-Disease-Collaborating-Group. High-dose cytomegalovirus (CMV) hyperimmune globulin and maternal CMV DNAemia independently predict infant outcome in pregnant women with a primary CMV infection. *Clin Infect Dis*. 2020;71(6):1491-1498. Available at: https://pubmed.ncbi.nlm.nih.gov/31628849/.

132. Hughes B. LB17. Randomized trial to prevent congenital cytomegalovirus (CMV). *Open Forum Infectious Diseases* 2019;6:S1000-S1001. Available at: https://academic.oup.com/ofid/article/6/Supplement_2/S1000/5603805.

133. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. *N Engl J Med*. 2014;370(14):1316-1326. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24693891.

134. Hughes BL, Clifton RG, Rouse DJ, et al. A trial of hyperimmune globulin to prevent congenital cytomegalovirus infection. *N Engl J Med*. 2021;385(5):436-444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34320288.

135. Egloff C, Sibiude J, Vauloup-Fellous C, et al. New data on efficacy of valacyclovir in secondary prevention of maternal-fetal transmission of cytomegalovirus. *Ultrasound Obstet Gynecol*. 2023;61(1):59-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35900718.

136. Shahar-Nissan K, Pardo J, Peled O, et al. Valaciclovir to prevent vertical transmission of cytomegalovirus after maternal primary infection during pregnancy: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;396(10253):779-785. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32919517.

137. Chatzakis C, Sotiriadis A, Dinas K, Ville Y. Neonatal and long-term outcomes of infants with congenital cytomegalovirus infection and negative amniocentesis: systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2023;61(2):158-167. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36412976.

138. Faure-Bardon V, Fourgeaud J, Stirnemann J, Leruez-Ville M, Ville Y. Secondary prevention of congenital cytomegalovirus infection with valacyclovir following maternal primary infection in early pregnancy. *Ultrasound Obstet Gynecol*. 2021;58(4):576-581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33998084.

139. Zammarchi L, Tomasoni LR, Liuzzi G, et al. Treatment with valacyclovir during pregnancy for prevention of congenital cytomegalovirus infection: a real-life multicenter Italian observational study. *Am J Obstet Gynecol*. 2023;5(10):1-10. Available at: https://www.ajogmfm.org/article/S2589-9333(23)00243-4/fulltext.

Hepatitis B Virus Infection

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Epidemiology

After acquiring hepatitis B virus (HBV) infection, many adults spontaneously recover and develop protective hepatitis B surface antibodies (anti-HBs). However, some progress to chronic hepatitis B, which is a leading cause of chronic liver disease worldwide.[1-6] Globally and in North America, approximately 8% of people with HIV have evidence of chronic HBV infection, but this varies by region of the world.[7]

Transmission routes vary geographically, with perinatal and early-childhood exposures responsible for most HBV transmission in higher-prevalence regions.[8] In low-prevalence regions—such as Europe and North America—a large proportion of transmission is through sexual contact and injection drug use, but perinatal transmission also occurs.[9] Although the general modes of transmission are similar to those of HIV, HBV is transmitted more efficiently than HIV.[4,6] People with HIV are at increased risk for developing chronic HBV infection.[10] Ten genotypes of HBV (A–J) have been identified, and their geographic distributions differ,[11] with genotype A being most common in North America and Western Europe, genotypes B and C in Asia, and genotypes A, D, and E in sub-Saharan Africa in people with HBV infection.[12,13]

Approximately 5% of people with chronic HBV infection are coinfected with hepatitis D virus (HDV), which requires HBV for its propagation since it uses the hepatitis B surface antigen as its envelope.[14] Thus, prevalence of HDV mirrors that of chronic HBV infection.

Clinical Manifestations

HBV has an average incubation period of 90 days (range 60–150 days) from exposure to onset of symptoms.[15] Acute HBV infection is asymptomatic in approximately 70% and <1% develop fulminant hepatic failure.[1,16] When symptoms manifest, they may include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice. Most people with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue. Between 15% and 40% of people with chronic HBV infection will eventually develop cirrhosis, hepatocellular carcinoma (HCC), or liver failure, and up to 25% of people will die prematurely from complications of chronic HBV infection.[17]

Diagnosis

Centers for Disease Control and Prevention (CDC) recommends testing all people over the age of 18, including those with HIV, for chronic HBV infection.[18] Initial testing should include a triple screening panel of serologic testing for HBV surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and anti-HBs.[18] In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure, and anti-HBc immunoglobulin M (IgM) is usually detectable at the onset of symptoms. See CDC's Clinical Testing and Diagnosis for Hepatitis B for information on how to interpret laboratory results.

Chronic HBV infection is defined as persistent HBsAg detected on two occasions at least 6 months apart.[1] People with chronic HBV infection should be tested further for HBV e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. "Active" disease, which can be HBeAg negative or HBeAg positive, can be distinguished from inactive disease by the presence of both serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevations, defined as ≥2 times the upper limit of normal (≥70 U/L for males and ≥50 U/L for females).[1] Because people with chronic HBV infection are at risk for coinfection with HDV, anti-HDV should be checked once chronic HBV infection is diagnosed. If positive, then HDV RNA should be obtained to look for chronic infection.

In a low-prevalence country—such as the United States—isolated anti-HBc also may represent a false-positive result. However, the presence of an isolated positive anti-HBc test result can signify infection with HBV in the past with subsequent loss of anti-HBs. Isolated anti-HBc occurs in 7% to 19% of people with HIV.[19-22] Frequency of HBV viremia among people with HIV and isolated anti-HBc typically ranges from 1% to 10%.[19,20,23,24] Because most people with HIV with isolated anti-HBc are HBV DNA negative,[25] routinely checking HBV DNA is not recommended. The clinical significance of isolated anti-HBc is unknown,[19,22,26-28] but in people with HIV, it may indicate chronic or, more likely, resolved HBV infection.[29] People with HIV—particularly those with underlying hepatitis C virus (HCV) coinfection—have a higher frequency of isolated anti-HBc.[21,25,30,31]

People whose past infection has resolved are HBsAg negative with positive anti-HBs and anti-HBc.[1,32]

Diagnosing HBV Disease Progression and the Role of Assessing Liver Fibrosis

Compared with people with HBV mono-infection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[33] People with HIV/HBV are also more likely to have detectable HBeAg,[33,34] lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.[35-37]

Chronic HBV infection is a dynamic disease with a number of phases (see the American Association for the Study of Liver Diseases' 2018 Hepatitis B Guidance). In HIV/HBV coinfection, monitoring and treatment are focused on the simultaneous and immediate treatment of both viruses regardless of HBV phase.

People with HIV and chronic HBV should be linked to care and have a complete history and physical examination for signs of cirrhosis or HCC. HBV serologic and quantitative nucleic acid testing (HBeAg/anti-HBe and HBV DNA) and other laboratory testing—complete blood count, ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, international normalized ratio (INR), hepatitis A virus (HAV) immunoglobulin G (IgG) (to determine the need for vaccination), HCV IgG (if positive, HCV viral load), antibodies to hepatitis D virus IgG (if positive, HDV RNA), abdominal ultrasound, and liver fibrosis assessments (transient elastography or serum markers e.g. Fibrosure)—should be performed at the initial visit.[1] The decision to perform a liver biopsy should be individualized, but the procedure is rarely necessary.[1] People with chronic HBV infection are at increased risk of HCC; therefore, HCC surveillance every 6 months (ultrasound with or without alfa fetoprotein) is required for people who have cirrhosis and for people in the following groups who are at increased risk of disease progression: Asian males older than age 40, Asian females older than age 50, and males older than age 20 who are from sub-Saharan Africa.[1] People with HIV/HBV coinfection are at increased risk of HCC,[38,39] and some experts recommend ongoing

semi-annual HCC surveillance for all people aged 40 years and older with HIV/HBV coinfection **(BIII).**

Preventing Disease

See the Hepatitis B Virus row of the Recommended Adult Immunization Schedule by Medical Condition and Other Indications table in the Immunizations for Preventable Diseases in Adults and Adolescents With HIV chapter for a summary of HBV vaccination recommendations. The evidence summary in this section will be moved to the Immunizations chapter in the next update.

All family members and sexual contacts of people with chronic HBV infection should be tested, and all susceptible household and sexual contacts should receive hepatitis B (HepB) vaccine regardless of whether they have HIV **(AII).** All people with HIV who are not immune to HBV infection (anti-HBc and anti-HBs negative) and do not have chronic HBV, as well as those who have failed a prior HBV vaccine series, should receive HepB vaccination with one of the available vaccines **(AII).**

Available adult single-antigen HepB vaccines in the United States that have been studied in people with HIV include two recombinant HBsAg vaccines (Engerix-B and Recombivax HB) and a recombinant HBsAg vaccine conjugated to a cytosine phosphoguanine oligonucleotide adjuvant (HepBCpG), which is a toll-like receptor 9 agonist (Heplisav-B).

The preferred vaccine in previously unvaccinated patients is Heplisav-B given at 0 and 4 weeks **(AII).** A single-arm study in 68 people with HIV, who were naive to HepB vaccine, and received Heplisav-B at 0, 4, and 24 weeks demonstrated a seropositivity rate (anti-HBs >10 mIU/mL) at 4 weeks and 20 weeks after the second dose of 87% and 98.5%, respectively.[40] The seropositivity rate 4 weeks after the third dose was 100%.

A two-dose Heplisav-B is appropriate only when both doses are Heplisav-B. In other situations, three total doses of vaccine should be given **(AI).** If Heplisav-B is not available, then vaccinate either with double-dose vaccine Engerix-B or double-dose Recombivax HB as the primary three-dose series **(AII),** or combined HepA and HepB (i.e., Twinrix) as a three-dose series **(AII).** A meta-analysis of 10 studies of people with HIV demonstrated that compared to a single dose, a double dose of Engerix-B or Recombivax HB had better response rates at 4 to 6 weeks (odds ratio [OR] 1.76; 95% confidence interval [CI], 1.36–2.29) and at >12 months (OR 2.28; 95% CI, 1.73–3.01) after vaccine completion.[41] A double dose of Engerix-B is 40 mcg (two injections of the 20-mcg dose). A double dose of Recombivax HB is 20 mcg (two injections of the 10-mcg dose).

The magnitude and duration of immunogenicity to HepB vaccination with the two recombinant vaccines (Engerix-B, Recombivax HB) in adults with HIV are significantly lower than in healthy adults who are HIV seronegative.[42-44] Factors associated with poor response to these two recombinant vaccines include low CD4 T lymphocyte (CD4) cell counts,[42,45-50] presence of detectable HIV RNA,[46,50,51] coinfection with HCV, occult HBV infection, and the general health status of the host.[20,25,52-56] Although vaccine response to the two recombinant vaccines is better when CD4 counts are >350 cells/mm^3, vaccination should not be deferred until CD4 counts increase to >350 cells/mm^3 in those at high risk for HBV infection because some people with HIV with CD4 counts ≤350 cells/mm^3 do respond to vaccination **(AII).**

Response to HepB vaccination, defined as anti-HBs ≥10 mIU/mL, should be documented 4 weeks after the last dose of vaccine **(AII).** In an observational study of 409 people with HIV who received

the HepB vaccine, those with anti-HBs ≥10 mIU/mL were less likely to develop breakthrough HBV infection compared to those who did not achieve that level.[57] In addition, among those with a breakthrough HBV infection, 0% of those with anti-HBs ≥10 mIU/mL developed chronic infection compared to 35% of those with anti-HBs <10 mIU/mL ($P = 0.02$).

In those who failed a prior vaccine series with Engerix-B or Recombivax HB, Heplisav-B at 0 and 4 weeks is recommended **(AI)**, and a third dose at 24 weeks can be considered since three doses results in higher anti-HBs titers **(BIII).** In a study of 561 people with HIV and prior nonresponse to Engerix-B or Recombivax HB, they were randomized to either Heplisav-B at 0 and 4 weeks, Heplisav-B at 0, 4, and 24 weeks, or Engerix-B at 0, 4, 24 weeks. Participants had CD4 counts >100 cells/mm^3 (median 635 cells/mm^3) and HIV RNA <1,000 copies/mL (94% <40 copies/mL). Four weeks after the last dose, the proportion with anti-HBs >10 mIU/mL (positive) was 93.1%, 99.4%, and 80.6% in two-dose Heplisav-B, three-dose Heplisav-B, and three-dose Engerix-B, respectively ($P < 0.05$). Of note, 96% of those who received the three-dose Heplisav-B had anti-HBs titers >100 IU/mL compared to 70% of those who received the two-dose Heplisav-B and 63% who received Engerix-B.[58] These data suggest that a third dose may be beneficial to provide more durable immunity but further follow-up is needed.

Because of waning immunity, some experts would check anti-HBs annually and give a booster dose if levels fall below 10 mIU/mL, particularly if a person has ongoing risk factors for acquiring HBV and is not receiving tenofovir **(CIII).**[59] Waning immunity is typically seen in people with low CD4 cell counts (<350 cells/mm^3) and may be a consequence of the height of the initial antibody response after immunization. In a study of people with HIV who had antibody titers assessed 4 weeks after completing the three-dose hepatitis B vaccine series, those who had a titer <100 mIU/mL were significantly more likely to have waning immunity over the next 5 years compared with individuals who had higher titers after vaccination.[60]

People with isolated anti-HBc should be vaccinated with one standard dose of HepB vaccine (one dose of Heplisav-B, or Engerix-B, or Recombivax HB), and anti-HBs titers should be checked 1 to 2 months after vaccination **(BII).** If the anti-HBs titer is ≥100 mIU/mL, no further vaccination is needed, but if the titer is <100 mIU/mL, a complete series of the same HepB vaccine should be completed and followed by anti-HBs testing **(BII).**[61] The cutoff of 100 mIU/mL is used in this situation because one study demonstrated that 100% of people with isolated anti-HBc who achieved a titer of 100 mIU/mL after a booster dose maintained an anti-HBs response for >18 months compared with only 23% of those who achieved a titer of 10 to 100 mIU/mL.[61] If anti-HBs quantitative titers are not available, then the complete series of HepB vaccine should be completed followed by qualitative anti-HBs testing **(BII).**

HBV-active ART (includes tenofovir with lamivudine [3TC] or emtricitabine [FTC]) decreases the risk for acute HBV infection, but it does not eliminate the risk, so taking ART alone is not a recommended strategy to prevent HBV infection. Therefore, HepB vaccine is recommended even if receiving an HBV-active ART regimen **(AIII).** In a study that evaluated HBV incidence in 591 males who have sex with men (MSM) with HIV, the HBV incidence rate for men not on HBV-active ART was 23.8 per 1,000 person-years (PYs) compared to 2.6 per 1,000 PYs for men on HBV-active ART with HIV RNA <400 copies/mL.[62] The protective effect against incident HBV was similar in those taking lamivudine- or tenofovir-containing ART regimens. In another report of 354 people with HIV and without prior HBV, the risk of new HBV infection was substantially reduced in those receiving HBV-active ART (hazard ratio 0.11, 95% CI 0.03–0.39); those receiving HBV-active ART who acquired HBV were taking lamivudine, and some acquired lamivudine-resistant virus.[63] The potential

benefit of a tenofovir- versus lamivudine-containing regimen in preventing HBV infection was examined in a study of 381 males with HIV and found HBV incidence rates to be 2.85, 1.36, and 0.14 cases per 100 PYs among those taking ART without hepatitis B virus antibody (anti-HBV) activity, lamivudine without tenofovir, and tenofovir, respectively.[64] In another study of 786 MSM on pre-exposure prophylaxis (PrEP), there were fewer incident HBV infections in persons who took tenofovir-based PrEP compared to those who did not take PrEP (3.8% vs. 0.8%, $P = 0.02$).[65]

Preventing Other Liver Diseases

Hepatitis A vaccination is recommended for all people with HIV, including during pregnancy, who are HAV total (IgG plus IgM) antibody negative **(AIII).** Among people with HIV with CD4 counts <200 cells/mm^3, responses to the hepatitis A vaccine are reduced.[66,67] Antibody response should be assessed at least 1 month after vaccination is complete. If total HAV antibody (anti-HAV) immunoglobulin (IgG and IgM) is negative, people should be revaccinated when their CD4 count is >200 cells/mm^3 **(BIII).**

People with chronic HBV infection should be advised to avoid alcohol consumption **(AIII).**

Treating Hepatitis B Virus Infection

Recommendations for Treating Chronic Hepatitis B Virus Infection

Indication for Therapy

- All people with HIV/HBV coinfection (HBsAg positive) regardless of CD4 count and HBV DNA level (AII), should be treated with an ART regimen that includes drugs active against both HIV and HBV infections (AII).
- Some experts recommend that people with isolated anti-HBc positivity receive an ART regimen that includes drugs active against HBV and HIV (CIII). However, an ART regimen without HBV activity can be considered, provided HBV DNA is undetectable and the benefits outweigh the risks of potential HBV reactivation (CIII). Please also see recommendations below in the Special Considerations When Initiating Nucleos(t)ide-Sparing Regimens section.

Preferred Therapy (CrCl ≥60 mL/min)

- The ART regimen should include two drugs active against HBV, preferably with—
  - TAF (10 or 25 mg)[a] plus FTC 200 mg or TAF 25 mg plus 3TC 300 mg PO once daily (AII), *or*
  - TDF 300 mg plus (FTC 200 mg or 3TC 300 mg) once daily (AII)

Preferred Therapy (CrCl 30–59 mL/min)

- The ART regimen should include two drugs active against HBV, preferably with—
  - TAF (10 or 25 mg)[a] plus FTC 200 mg PO once daily (AII)

Preferred Therapy (CrCl <30 mL/min, Not Receiving HD)

- Renally dosed entecavir (in place of TDF/[FTC or 3TC] or TAF/FTC) (AIII), with a fully suppressive ARV regimen), *or*
- ART with renally dose-adjusted TDF and (FTC or 3TC) (AIII) when recovery of renal function is unlikely.
- If CrCl ≥ 15 to 29 mL/min, then ART with TAF (10 or 25 mg) once daily plus renally dose-adjusted FTC or 3TC is an option (AIII).
  - Some clinicians may choose to continue full-dose FTC or 3TC to allow for people with CrCl 15–29 mL/min to remain on fixed-dose TAF/FTC products.

Preferred Therapy (Receiving HD)

- ART with renally dose-adjusted TDF plus [FTC 200 mg or 3TC 300 mg once daily] (AII) *or*
- ART with TAF [10 or 25 mg][a] plus FTC 200 mg PO once daily (given after HD on dialysis days) (AII). TAF and FTC do not require renal dose adjustment in people receiving HD; therefore, fixed-dose TAF/FTC products may be continued.

Note: See Table 6 for dosing recommendation for TDF, TAF, FTC, and 3TC for people with renal impairment.

Duration of Therapy/**Monitoring** During Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely (AIII).
- HBV DNA should be monitored at 6-month intervals (AII).
- HBsAg should be monitored yearly (AIII).

Special Considerations When Initiating Nucleos(t)ide-Sparing Regimens

- *In people without a history of chronic HBV infection*: Prior to initiating or switching to a nucleos(t)ide-sparing ARV regimen, HBsAg, anti-HBs, and anti-HBc should be checked to evaluate for unrecognized chronic HBV infection unless evaluated within the last 3 months (AIII).
- *In people with chronic HBV infection (HBsAg positive):*
  - Anti-HBV therapy (TDF, TAF, or entecavir) must be given if there is a switch to a nucleos(t)ide-sparing ARV regimen (AIII).
  - Switching to the one-pill regimen of DTG/3TC without additional anti-HBV therapy (TDF, TAF, or entecavir) should be avoided because 3TC is then the only active drug against HBV (AIII).
  - Switching to DTG/RPV or long-acting CAB/RPV without addition of an anti-HBV drug (TAF, TDF, or entecavir) should be avoided (AIII).
- *In people with isolated anti-HBc positivity*: Some experts recommend against switching to DTG/3TC or a nucleos(t)ide-sparing ARV regimen without additional anti-HBV therapy, but this could be considered if the benefits outweigh the risk of potential HBV reactivation (CIII).
- *In people with anti-HBc and anti-HBs positivity*: Switch to a nucleos(t)ide-sparing ARV regimen without additional anti-HBV therapy is possible (AIII).

Other Considerations

- Because people with HBV/HCV/HIV coinfection appear to have accelerated liver fibrosis progression, high risk of HCC, and increased mortality, treatment for both HBV and HCV infection should be initiated, if feasible (AII).
- Because HBV reactivation can occur during treatment for HCV with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation (AIII).
- When changing ART regimens, it is crucial to continue agents with anti-HBV activity due to risk of HBV reactivation with hepatic flare after stopping anti-HBV treatment (AIII).
- If anti-HBV therapy must be discontinued, serum transaminase and HBV DNA levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter (AIII).
- If a hepatic flare occurs after drug discontinuation, HBV therapy should be reinstituted because it can be potentially lifesaving (AIII).
- If immunosuppressive therapy is given, HBV reactivation can occur.
  - People who are HBsAg positive should be administered treatment for HBV infection regardless of HBV DNA level (AII).

- For people who are HBsAg-negative/anti-HBc-positive, it is prudent to include TDF or TAF/FTC or 3TC as part of the ART regimen prior to immunosuppression to prevent reactivation (BIII).
- For people who are HBsAg-negative/anti-HBc positive, if TDF or TAF cannot be given, then they can either be monitored or be given prophylaxis with entecavir to prevent reactivation depending on the degree of immunosuppression and whether HBV DNA is detectable (BIII) (see Special Considerations During Immunosuppressive Therapy section below). If anti-CD20 is given, then treatment with entecavir is recommended regardless of HBV DNA (AII).
- Treatment should be continued for 6 months after immunosuppressive therapy is complete or for 12 months after anti-CD20 therapy is complete (BIII).

Pregnancy Considerations

- During pregnancy, TAF or TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone in the context of chronic HBV infection (AIII).
- Infants born to women who are HBsAg positive should receive HBIG and HepB vaccine (first dose of three) within 12 hours of delivery (AI). The second and third doses of vaccine should be administered at 1–2 months and 6 months of age, respectively (AI).

[a] TAF 10 mg dose is in the fixed-dose combination tablets of elvitegravir/cobicistat/TAF/FTC and darunavir/cobicistat/TAF/FTC; when TAF is used with other antiretrovirals, the dose is 25 mg.

Key: 3TC = lamivudine; anti-HBc = HBV core antibody; anti-HBs = HBV surface antibody; anti-HBV = hepatitis A virus antibody; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CrCl = creatinine clearance; CAB = cabotegravir; DTG = dolutegravir; FTC = emtricitabine; HBsAg = HBV surface antigen; HBV = hepatitis B virus; HBIG = hepatitis B immune globulin G; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HD = hemodialysis; HepB = hepatitis B; NRTI = nucleoside reverse transcriptase inhibitor; PO = orally; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

Preferred Regimens

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV mono-infection: to prevent disease progression and to reduce HBV-related morbidity and mortality. All people with HIV/HBV coinfection (HBsAg positive) regardless of CD4 count and HBV DNA level **(AII),** should be treated with an antiretroviral (ART) regimen that includes drugs active against both HIV and HBV infections **(AII).**

The Adult and Adolescent Antiretroviral Guidelines recommend the fixed-dose coformulations of tenofovir disoproxil fumarate (TDF)/(FTC or 3TC), TAF/FTC, abacavir/3TC, or 3TC alone (with dolutegravir) as nucleoside reverse transcriptase inhibitor (NRTI) regimen backbones for ART-naive people regardless of CD4 count.[68] Because both components of the tenofovir combinations (tenofovir and either FTC or 3TC) have anti-HBV activity, they are also the treatment of choice for people with HIV/HBV coinfection **(AII)** regardless of CD4 count **(AI)** and HBV DNA level **(AII)** (see Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines). TDF and TAF are both active against wild-type and 3TC-resistant HBV strains. Studies among people with HIV/HBV coinfection (most of them carrying 3TC-resistant HBV) have shown, on average, 4 $\log_{10}$ declines in HBV DNA levels.[69-74] TDF and TAF have a high genetic barrier for development of resistance mutations.[1,75] For people with isolated anti-HBc positivity, some experts recommend tenofovir-based ART because of the potential risk for HBV reactivation, but the precise risk is unknown (see the Nucleos(t)ide-Sparing Regimens section below) **(CIII).** However, a regimen without TDF or TAF can be considered if the HBV DNA is undetectable and the benefits outweigh the risk of HBV reactivation **(CIII).**

The decision to use TAF/FTC versus TDF/FTC should be based upon creatinine clearance (CrCl) and an assessment of risk for nephrotoxicity and risk for acceleration of bone loss.

- Among people with CrCl ≥60 mL/min, either TAF/(FTC or 3TC) or TDF/(FTC or 3TC) can be considered.
- Among people with a CrCl 30 to 59 mL/min, a TAF/FTC regimen is preferred.
- Currently approved fixed-dose combination TAF/FTC-containing regimens for the treatment of HIV are not recommended for use among people with CrCl <30 mL/min who are not on hemodialysis. For these people, renally dosed entecavir with a fully suppressive ART regimen is recommended since entecavir without suppressive ART can lead to emergence of the HIV M184V mutation **(AIII).** Renally dosed TDF and FTC or 3TC also can be used if recovery of renal function is unlikely **(AIII).** If renally dosed TDF is used, then the CrCl needs to be monitored carefully. In people with CrCl ≥15 to 29 mL/min, ART with TAF (as a single agent) and renally dosed FTC or 3TC may be used **(AIII).** Of note, some clinicians may choose to continue full-dose FTC to allow for people with CrCl 15 to 29 mL/min to remain on fixed-dose TAF/FTC products.
- In people receiving hemodialysis, ART with either renally dosed TDF plus (FTC or 3TC) **(AII)** or TAF/FTC (**AII**) may be used. TAF and FTC do not require dose adjustment in patients receiving hemodialysis; co-formulated full-dose products may be continued and given after dialysis on the day of hemodialysis. Refer to What to Start: Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Therapy and Appendix B, Table 12. Antiretroviral Dosing Recommendations in Adults With Renal or Hepatic Insufficiency in the Adult and Adolescent Antiretroviral Guidelines for more information.

Among people with HIV/HBV coinfection, switching from a primarily TDF-based ART regimen to single-tablet TAF/FTC/elvitegravir/cobicistat maintained or achieved HBV suppression, with improved estimated glomerular filtration rate (eGFR) and bone turnover markers.[76] Among people with HBV mono-infection, TAF 25 mg was non-inferior to TDF 300 mg based on the percentage of people with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = 0.47$). People on TAF also experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than people receiving TDF ($P < 0.0001$). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ($P = 0.004$).[77,78] In a randomized placebo-controlled study of HIV/HBV coinfected people (mainly Asians), TAF/FTC/bictegravir (BIC) was superior to TDF/FTC/DTG in achieving HBV DNA <29 IU/ml (63% vs. 43%, respectively; $P = 0.002$) at 48 weeks but was similar at 96 weeks (75% vs 70%, respectively; $P = 0.64$).[79] Those receiving TAF/FTC/BIC had higher HBeAg seroconversion at 96 weeks (32% vs. 15%; $P = 0.008$) and HBsAg loss was not statistically different (23% vs. 14%; $P = 0.07$). Although the data are intriguing, whether these responses are related to ethnicity, HBV genotype, or other HIV-related factors still needs to be determined.

Chronic administration of 3TC or FTC as the only active drug against HBV **is not recommended** because of the high rate of selection of HBV drug-resistance mutations **(AI).**

People receiving ART should continue HBV therapy indefinitely **(AIII)** because relapses after response can occur, particularly in those with lower CD4 counts.[1] Additionally, discontinuation of nucleos(t)ide analog therapy is associated with an HBV reactivation in approximately 30% of cases,[80,81] as well as possible decompensation of liver disease and even death.[42,82-84] If anti-HBV therapy and ART must be discontinued for people with chronic HBV, serum transaminase levels and

HBV DNA should be monitored every 6 weeks for 3 months and every 3 months thereafter while off anti-HBV agents **(AIII).** If a flare occurs, anti-HBV therapy and ART should be reinstituted and can be potentially lifesaving **(AIII).**

Some people with HIV/HBV coinfection also have chronic HCV infection. Scant information is available on the treatment of HBV/HCV/HIV coinfection. Because people with HBV/HCV/HIV coinfection appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,[85-87] attempts should be made to treat both hepatitis viruses, if feasible. Because HBV reactivation can occur during treatment for HCV infection with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation **(AIII).**[88-91] See the Hepatitis C Virus chapter for more information.

Considerations When Using Nucleos(t)ide-Sparing Regimens

With increasing use of nucleos(t)ide-sparing regimens, HBV status must be considered before such a switch. We recommend checking HBsAg, anti-HBc, and anti-HBs prior to changing to a nucleos(t)ide-sparing regimen to avoid reactivation of an unrecognized chronic HBV infection unless evaluated within the last 3 months **(AIII).** In people with a chronic HBV infection, switching to the one-pill regimen of dolutegravir (DTG)/3TC should be avoided because 3TC is then the only active drug against HBV **(AIII).** Further, switching to long-acting cabotegravir/rilpivirine (RPV) or DTG/RPV without addition of an anti-HBV drug (TAF, TDF, or entecavir) should be avoided **(AIII).**

In people with isolated anti-HBc positivity, some experts would recommend not switching to DTG/3TC or a nucleos(t)ide-sparing regimen because there is a small risk of reactivation, but this could be considered if the benefits outweigh the risk **(CIII).**[92] In a study using data from the Veterans Aging Cohort Study, HBV reactivation occurred in 1.6% of individuals who were anti-HBc positive and HBsAg negative after switching to a nucleos(t)ide-sparing regimen.[92] The risk was 20.2% in people with a remote positive HBsAg compared to 1.0% in those without a prior positive HBsAg. In people with recovery from a past HBV infection (anti-HBc positive, anti-HBs positive), DTG/3TC or a nucleos(t)ide-sparing regimen is an option provided they maintain undetectable HIV RNA levels **(AIII).**[92] In people with prior receipt of the HBV vaccine, anti-HBs should be rechecked prior to switching to a nucleos(t)ide-sparing regimen because incident infections have been reported in such situations **(AIII).**[93]

Alternative Treatment of HBV Infection Among People With HIV Who Are Not Receiving HBV-Active ART

All people with HIV should receive ART. Among people with HIV/HBV coinfection, co-treatment is essential and recommended.[68] Pegylated interferon (IFN)-α-2a (or 2b) monotherapy is approved for HBV treatment, but it should only be used in rare cases with consultation of an expert.

Regimens That Are Not Recommended

Tenofovir (TDF and TAF), entecavir, 3TC, and FTC **should not be used alone** in the absence of a fully HIV-suppressive ART regimen because of the potential for development of HIV drug-resistance mutations **(AI).**[94,95] Other anti-HBV treatment regimens include adefovir in combination with 3TC or FTC in addition to a fully suppressive ART regimen[74,96,97]; however, data on this regimen among people with HIV/HBV coinfection are limited. In addition, compared with TDF or

TAF or entecavir, adefovir is associated with higher incidence of toxicity, including renal disease, as well as higher rates of HBV treatment failure. Therefore, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) **does not recommend** an adefovir-containing regimen for people with HIV/HBV coinfection **(AI).**

Monitoring of Response to Therapy and Adverse Events

To evaluate response, HBV DNA should be monitored at 6-month intervals **(AII).** Treatment responses are slower than responses to HIV therapy and are defined as the following for nucleos(t)ide analog therapy:

- Virologic response: undetectable HBV DNA (<10 IU/mL) by real-time polymerase chain reaction[98]
- Partial virologic response: HBV DNA ≥1 $\log_{10}$ decline, but still detectable HBV DNA at 12 months[98]
- Primary nonresponse: HBV DNA <1 $\log_{10}$ decline after 3 months[99]

See the Managing Treatment Failure section below for information on managing partial virologic response.

For people who are HBeAg positive, loss of HBeAg is also a measure of virologic response. Other markers that indicate treatment success include improvement in liver histology based on biopsy, transient elastography or other noninvasive tests; normalization of serum aminotransferases; and, in those with loss of HBeAg, the development of anti-HBe. Sustained loss of HBsAg is considered by some to be a complete response or functional cure; however, this desirable serologic response is uncommon (<1% of HBsAg-positive people without HIV per year).[1] Interestingly, after ART initiation, in some studies people coinfected with HIV and HBV have up to 20% chance of loss of HBsAg especially in the first 1 to 2 years.[100,101] For this reason, HBsAg should be checked yearly after ART initiation **(AIII)**. If HBsAg loss occurs and there is a desire to switch to a nucleos(t)ide-sparing regimen, this option may be considered as long as HIV RNA suppression is maintained.

Adverse Events

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both increased serum creatinine and renal tubular dysfunction are more frequent among people with HIV who have underlying renal insufficiency, are older, or have been treated with TDF for prolonged periods.[102] These biochemical changes are usually reversible when TDF is discontinued or changed to TAF.[103]

Electrolytes and serum creatinine levels should be evaluated at baseline and every 6 months. Because renal toxicity may be reversible, alternative anti-HBV therapy should be used if renal toxicity occurs **(AI).** If TDF is used among people with baseline renal insufficiency, either a dose adjustment as noted in the package insert or a change to TAF with appropriate dose adjustment is required.[103] See Table 6. Dosing Recommendations in People With Renal Insufficiency for more information.

TDF has been associated with a decrease in bone mineral density (BMD). TAF is associated with less of a decrease in BMD than TDF in studies of hepatitis B treatment.[104] TAF also has been associated

with early weight gain among people with HIV although the long-term consequences of this are unclear.[105]

See Considerations for Antiretroviral Use in Patients With Coinfection: Hepatitis B Virus/HIV Coinfection in the Adult and Adolescent Antiretroviral Guidelines for more information on adverse events related to TAF and TDF.

Entecavir-associated lactic acidosis is uncommon but has been reported among people with HBV mono-infection with advanced cirrhosis.[106-108]

Immune Reconstitution Inflammatory Syndrome

Return of immune competence after ART (or after steroid withdrawal or chemotherapy) can lead to reactivation of HBV-associated liver disease. Any immune reconstitution can lead to a rise in serum aminotransferases, so-called "hepatitis flare,"[109] which constitutes immune reconstitution inflammatory syndrome (IRIS) among people with HIV/HBV coinfection. IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 counts rise within the first 6 to 12 weeks after ART is started, with signs and symptoms characteristic of acute hepatitis and without another cause for the flare.[110,111] After introduction of ART, serum ALT levels should be monitored closely; some experts recommend ALT testing at 6 and 12 weeks, then every 3 to 6 months thereafter. Any association between abnormal aminotransferases and clinical jaundice or synthetic dysfunction (elevated INR and low serum albumin) should prompt consultation with a hepatologist **(CI).**[103]

Flares are worse among people with more severe liver disease, especially those with cirrhosis.[112] Distinguishing between drug-induced liver injury, HBV drug resistance, HBeAg seroconversion, or other causes of hepatitis (i.e., acute hepatitis caused by HAV, HCV, HDV, hepatitis E virus, Epstein-Barr virus, herpes simplex virus, or cytomegalovirus infection) and IRIS may be difficult. ART-associated hepatotoxicity may be dose dependent or idiosyncratic. Among people with HIV, the risk of ART-associated hepatotoxicity has been associated consistently with elevated pre-ART aminotransferases (ALT, AST) and the presence of HBV or HCV coinfection. In HIV/HBV coinfection, baseline elevated HBV DNA levels are predictive of hepatotoxicity.[113-116] Despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (90%) people with HIV/HBV coinfection do not have ART-associated hepatotoxicity,[117] and clinically significant hepatotoxicity (elevated direct bilirubin and INR) is rare. Aminotransferase levels return to baseline in most cases, even if the offending medication is continued.[118,119] Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless the following symptoms are observed: hypersensitivity (e.g., fever, lymphadenopathy, rash), symptomatic hepatitis (i.e., nausea, vomiting, abdominal pain, or jaundice), or elevations in serum aminotransferase levels >10 times the upper limit of normal **(AIII).**[120] Liver histology also may help to differentiate drug toxicity (e.g., increased eosinophils) from viral hepatitis (e.g., portal inflammation). If aminotransferases increase >2 times the baseline level, the Panel recommends monitoring aminotransferases weekly and also obtaining bilirubin and INR until the aminotransferases begin declining **(AIII).**

Other noninfectious causes of abnormal liver tests that should be considered include use of drugs or alcohol and steatotic liver disease.[121]

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogs is defined as primary nonresponse (HBV DNA <1 $\log_{10}$ decline) after 3 months of therapy among people who consistently adhere to HBV therapy or an increase in HBV DNA levels >1 $\log_{10}$ above nadir. In either situation, treatment failure generally is due to either drug-resistant HBV if the person is on 3TC/FTC monotherapy or to nonadherence to therapy.[1] If drug-resistant HBV is present, a change in treatment is needed **(AII).** Distinct resistance patterns exist with the different groups of anti-HBV drugs: the L-nucleosides (telbivudine, 3TC/FTC); acyclic phosphonates/nucleotides (adefovir and tenofovir); and D-cyclopentane (entecavir), which shares some resistance mutations with the L-nucleosides. Many experts will obtain HBV-resistance testing because it has value in distinguishing between nonadherence and drug resistance, evaluating people with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.[122] However, TDF is associated infrequently with clinical resistance, although slow response has been noted, as discussed above. Addition of entecavir has led to suppression of HBV DNA among people whose response to TDF is slow.[123]

With 3TC monotherapy for HBV, the rate of developing 3TC-resistance is approximately 20% per year among people with HIV/HBV coinfection.[124] If 3TC resistance is suspected or documented, TDF or TAF should be added to the ART regimen **(AIII).**[125-127] Because people with 3TC-resistant HBV will have cross-resistance to the other L-nucleosides (FTC), and partial resistance to entecavir, those agents **should not be used** among people found to have 3TC-resistant HBV **(AI).**[128] All nucleoside analogs must be dose-adjusted for renal insufficiency per package insert guidelines and Table 6. Dosing Recommendations in People With Renal Insufficiency.

If treatment failure occurs on entecavir, TDF or TAF (with or without FTC) is recommended because of the cross-resistance that occurs with L-nucleosides (3TC, FTC) **(AI).**

People whose HBV infection initially failed to respond to pegylated IFN-α can be given nucleos(t)ide analog therapy following the recommendations previously described **(CIII).**

If treatment failure with TDF or TAF occurs, particularly in 3TC- or FTC-experienced people, entecavir may be an active alternative, especially if higher doses of entecavir can be used **(CIII).**

Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly among people who are receiving an HBV drug with high potency and a high genetic barrier to resistance—such as tenofovir—but HBV DNA levels may still be detectable for some years.[1] Thus, in a person who is adherent to therapy with a partial virologic response to tenofovir, the drug should be continued with monitoring of HBV DNA levels **(BII).** Improved virologic response has been reported with the addition of entecavir to TDF; however, whether such "intensification therapy" is required is unclear.[129]

Special Considerations for Treating End-Stage Liver Disease

People with HIV/HBV coinfection who have end-stage liver disease (cirrhosis) should be managed as a person with HBV mono-infection with end-stage liver disease, including referral to a hepatologist **(AIII).** Among people with HIV/HBV coinfection in end-stage liver disease, IFN-α is **contraindicated (AI),** but nucleos(t)ide analogs are safe and efficacious **(AI).**[124,130,131] All people with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).[132,133]

Management of ascites includes sodium restriction (<2 g/day) and the recommended diuretic regimen is spironolactone combined with furosemide (ratio of 40 mg furosemide:100 mg spironolactone) **(AI).** All people who have had SBP and those with ascites total protein <1 g/dL should receive prophylaxis against SBP with administration of oral antibiotics, such as ciprofloxacin (500 mg/day), or trimethoprim-sulfamethoxazole (one double-strength tablet/day) **(AI).**[134]

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all people with cirrhosis at the time of diagnosis and then every 1 year to 2 years to identify substantial gastroesophageal varices (see the American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Guidance). People with varices require nonselective beta blockers—such as nadolol or propranolol—that are the mainstay of both primary and secondary prevention of variceal hemorrhage. Esophageal variceal banding is another preventive option, particularly for those who cannot tolerate beta blockers. Hepatic encephalopathy is treated with a 40-g protein diet and the use of nonabsorbable disaccharides—such as lactulose—and/or nonabsorbable antibiotics, such as rifaximin.[1]

Because people with HBV-related cirrhosis are at increased risk of HCC,[135] imaging studies with alpha fetoprotein should be performed every 6 months, as recommended in HBV mono-infection **(AI).**[1] Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center. Usually, ultrasound is the initial preferred imaging modality.[1]

People with HIV/HBV coinfection with decompensated liver disease and/or early HCC are candidates for liver transplantation. HIV infection is not a contraindication to organ transplantation among people on suppressive ART.[136] Because transplantation does not cure HBV infection, post-transplant hepatitis B immune globulin (HBIG) and HBV treatment is required **(AII).** People with HIV who are potential candidates for liver transplantation should be referred to a liver specialist for further evaluation.

Preventing Recurrence

As previously indicated, most people should continue HBV therapy with nucleos(t)ide analogs indefinitely **(AIII)** because relapses after response can occur, particularly in those with lower CD4 counts, and because reports of hepatitis flares after discontinuation of 3TC in those who have not reached treatment endpoints can be extrapolated to other HBV-active drugs.[82-84]

Special Considerations During Immunosuppressive Therapy

With immunosuppressive therapy, both in the context of malignancy and rheumatologic/autoimmune diseases, reactivation of HBV infection can occur. HBV reactivation in people without HIV with HBsAg-positive/anti-HBc-positive disease receiving immunomodulatory therapy is well described, especially with anti-CD20 antibodies.[137-139] Even among people with HBsAg-negative/anti-HBc-positive disease, HBV reactivation occurs in up to 18% of people receiving anti-cancer drugs[140] and 1.7% of people receiving rheumatologic disease drugs.[141]

If not already performed, people with HIV undergoing immunosuppressive therapy should have HBsAg, anti-HBc, and anti-HBs testing. People who are HBsAg positive should receive treatment with TDF or TAF plus 3TC or an FTC-based ART regimen (see Preferred Regimens above) **(AII).** The optimal approach for those people with HBsAg-negative/anti-HBc positive disease is unknown.

However, because TDF or TAF plus FTC or 3TC is a preferred backbone for ART, it is prudent to start or modify ART to include these drugs before initiating immunosuppressive, cytotoxic, or immunomodulatory therapy among people with HBsAg-negative/anti-HBc-positive disease **(BIII).** If TDF or TAF/FTC or 3TC cannot be used as part of their HIV regimen, these people either could receive entecavir for anti-HBV prophylaxis or could be monitored and given entecavir if signs of HBV reactivation occur (increase in HBV DNA or HBsAg seroreversion) **(BIII).** The option to give pre-emptive entecavir prophylaxis (in the presence of a fully suppressive ARV regimen) is preferred if HBV DNA is detectable or if immunosuppression is more severe, such as with anti-CD20 antibodies **(AII).**[139] No studies have been performed on the appropriate length of therapy, but the Panel agrees with the AASLD 2018 Hepatitis B Guidance recommendation to continue treatment for 6 months after cessation of immunosuppressive therapy and for 12 months in the setting of anti-CD20 antibodies **(BIII).**[1]

Special Considerations During Pregnancy

Screening for HBV during pregnancy is established during pregnancy , which may be first diagnosed at this time **(AI).**[59] In the interest of completing adult HBV screening, prenatal visits are an opportunity to offer the triple panel and link the patient to care or vaccinate as needed. People with HIV should be tested for HBsAg during each pregnancy, preferably in the first trimester, even if vaccinated or tested previously.[18,59] If a history of appropriately timed triple panel screening is elicited without subsequent risk for exposure to HBV (i.e., no new HBV exposures since triple panel screening), then only HBsAg screening is needed. Such testing enables documentation of the HBsAg test result during pregnancies with maternal chronic infection or maternal immunity to ensure timely prophylaxis for exposed infants (see below). Those who are both HBsAg negative and anti-HBs negative should be offered vaccination against HBV **(AII)**. In the context of chronic HBV infection during pregnancy, if the HepA vaccine series has not been previously administered, then screen for immunity to HAV infection. Those who screen negative for total anti-HAV should receive the HepA vaccine series **(AIII).**[142] Treatment of symptomatic acute HBV infection during pregnancy is supportive, with special attention given to maintaining blood glucose levels and normal clotting status. High maternal HBV DNA levels correlate strongly with perinatal HBV transmission, including failures of HBV passive-active immunoprophylaxis.[143-146] See Hepatitis B Virus/HIV Coinfection in the Recommendations for the Use of Antiretroviral Drugs During Pregnancy and Interventions to Reduce Perinatal HIV Transmission in the United States.

As for all people with HIV/HBV coinfection, during pregnancy ART that includes drugs active against both HIV and HBV should be used **(AII).** TAF or TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone **(AIII).**[142] Entecavir has not been well evaluated in pregnancy, with too few exposures to assess overall risk; thus, it is **currently not recommended** during pregnancies affected by HBV/HIV coinfection **(AIII).**[142]

Cases of adverse events during pregnancy related to any of the antiretroviral or anti-HBV drugs listed should be reported to the Antiretroviral Pregnancy Registry (800-258-4263 or SM_APR@APRegistry.com). As of June 2024, 5,684 cases of pregnancy outcomes after first-trimester exposures to 3TC have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure (see *The Antiretroviral Pregnancy Registry Interim Report*). 3TC use during pregnancy has been well tolerated and is a recommended NRTI for use in pregnancy **(AII).**[147] Similarly, no increase in birth defects has been noted in 5,030 cases of first-trimester exposure to FTC. FTC is a recommended NRTI and is used commonly in pregnancy **(BII).**[148] A total of 5,014 cases of first-trimester exposure to TDF and 1,242 cases of

first-trimester exposure to TAF have been reported to the Antiretroviral Pregnancy Registry with no increase in birth defects noted.[148]

Several large studies have been conducted to evaluate the effect of tenofovir use in pregnancy. No evidence exists that the use of TDF increases the risk of birth defects. Overall, the available evidence does not indicate a link between maternal TDF use and infants who are low birth weight or small for gestational age. Some concern remains regarding a link between maternal TDF use and preterm birth,[149] but the evidence is mixed; the role of concomitant medications and other cofactors and/or confounders requires further investigation.[147]

Infants born to women who are HBsAg positive should receive HBIG and HepB vaccine (first dose of three) within 12 hours of delivery **(AI).** The second and third doses of vaccine should be administered at 1 to 2 months and 6 months of age, respectively **(AI).** Infants who weigh <2,000 g at birth should receive HBIG and four doses of HepB vaccine; administer one dose of HepB vaccine within 12 hours of delivery and initiate the three-dose HepB vaccine series beginning at age 1 month (four doses total: birth, 1 month, 2–3 months, and 6 months).

References

1. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology*. 2018;67(4):1560-1599. Available at: https://pubmed.ncbi.nlm.nih.gov/29405329.

2. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet*. 2015;386(10003):1546-1555. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26231459.

3. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204-1222. Available at: https://www.sciencedirect.com/science/article/pii/S0140673620309259?via%3Dihub.

4. Jeng WJ, Papatheodoridis G, Lok ASF. Hepatitis B. *Lancet*. 2023;401(10381):1039-1052. Available at: https://www.sciencedirect.com/science/article/pii/S0140673622014684?via%3Dihub.

5. Huang DQ, Terrault NA, Tacke F, et al. Global epidemiology of cirrhosis - aetiology, trends and predictions. *Nat Rev Gastroenterol Hepatol*. 2023;20(6):388-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36977794.

6. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol*. 2023;79(2):516-537. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36990226.

7. Leumi S, Bigna JJ, Amougou MA, Ngouo A, Nyaga UF, Noubiap JJ. Global burden of hepatitis B infection in people living with human immunodeficiency virus: a systematic review and meta-analysis. *Clin Infect Dis*. 2020;71(11):2799-2806. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31813969.

8. Gomes C, Wong RJ, Gish RG. Global perspective on hepatitis B virus infections in the era of effective vaccines. *Clin Liver Dis*. 2019;23(3):383-399. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31266615.

9. Ghany MG, Perrillo R, Li R, et al. Characteristics of adults in the hepatitis B research network in North America reflect their country of origin and hepatitis B virus genotype. *Clin Gastroenterol Hepatol*. 2015;13(1):183-192. Available at: https://pubmed.ncbi.nlm.nih.gov/25010003.

10. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis*. 1995;20(4):992-1000. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7795104.

11. Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. *World J Gastroenterol*. 2014;20(18):5427-5434. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24833873.

12. Liu CJ, Kao JH. Global perspective on the natural history of chronic hepatitis B: role of hepatitis B virus genotypes A to J. *Semin Liver Dis*. 2013;33(2):97-102. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23749665.

13. Kafeero HM, Ndagire D, Ocama P, et al. Mapping hepatitis B virus genotypes on the African continent from 1997 to 2021: a systematic review with meta-analysis. *Sci Rep*. 2023;13(1):5723. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37029173.

14. Stockdale AJ, Kreuels B, Henrion MYR, et al. The global prevalence of hepatitis D virus infection: systematic review and meta-analysis. *J Hepatol*. 2020;73(3):523-532. Available at: https://pubmed.ncbi.nlm.nih.gov/32335166.

15. Centers for Disease Control and Prevention. Clinical overview of hepatitis B. 2024. Available at: https://www.cdc.gov/hepatitis-b/hcp/clinical-overview/index.html.

16. Wright TL, Mamish D, Combs C, et al. Hepatitis B virus and apparent fulminant non-A, non-B hepatitis. *Lancet*. 1992;339(8799):952-955. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1348798.

17. McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology*. 2009;49(5 Suppl):S45-55. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19399792.

18. Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. *MMWR Recomm Rep*. 2023;72(1):1-25. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36893044.

19. Palacios R, Mata R, Hidalgo A, et al. Very low prevalence and no clinical significance of occult hepatitis B in a cohort of HIV-infected patients with isolated anti-HBc seropositivity: the BHOI study. *HIV Clin Trials*. 2008;9(5):337-340. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18977722.

20. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004;36(3):869-875. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15213572.

21. Witt MD, Seaberg EC, Darilay A, et al. Incident hepatitis C virus infection in men who have sex with men: a prospective cohort analysis, 1984–2011. *Clin Infect Dis*. 2013;57(1):77-84. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23532480.

22. Bhattacharya D, Tseng CH, Tate JP, et al. Isolated hepatitis B core antibody is associated with advanced hepatic fibrosis in HIV/HCV infection but not in HIV infection alone. *J Acquir Immune Defic Syndr*. 2016;72(1):e14-17. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26829660.

23. French AL, Operskalski E, Peters M, et al. Isolated hepatitis B core antibody is associated with HIV and ongoing but not resolved hepatitis C virus infection in a cohort of U.S. women. *J Infect Dis*. 2007;195(10):1437-1442. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17436223.

24. Neau D, Winnock M, Jouvencel AC, et al. Occult hepatitis B virus infection in HIV-infected patients with isolated antibodies to hepatitis B core antigen: Aquitaine cohort, 2002–2003. *Clin Infect Dis*. 2005;40(5):750-753. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15714424.

25. Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. *J Acquir Immune Defic Syndr*. 2003;34(4):439-441. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14615664.

26. Lo Re V, 3rd, Wertheimer B, Localio AR, et al. Incidence of transaminitis among HIV-infected patients with occult hepatitis B. *J Clin Virol*. 2008;43(1):32-36. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18486540.

27. Tsui JI, French AL, Seaberg EC, et al. Prevalence and long-term effects of occult hepatitis B virus infection in HIV-infected women. *Clin Infect Dis*. 2007;45(6):736-740. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17712758.

28. Filippini P, Coppola N, Pisapia R, et al. Impact of occult hepatitis B virus infection in HIV patients naive for antiretroviral therapy. *AIDS*. 2006;20(9):1253-1260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16816553.

29. Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the Multicenter AIDS Cohort Study. *Clin Infect Dis*. 2013;56(4):606-612. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23090927.

30. Gandhi RT, Wurcel A, Lee H, et al. Response to hepatitis B vaccine in HIV-1-positive subjects who test positive for isolated antibody to hepatitis B core antigen: implications for hepatitis B vaccine strategies. *J Infect Dis*. 2005;191(9):1435-1441. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15809901.

31. Spradling PR, Xing J, Harris AM, Ly KN. Estimated prevalence and number of persons with isolated antibody to hepatitis B core antigen and associated occult hepatitis B, United States, 2001–2018. *J Infect Dis*. 2022;225(3):465-469. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34252183.

32. Block TM, Locarnini S, McMahon BJ, Rehermann B, Peters MG. Use of current and new endpoints in the evaluation of experimental hepatitis B therapeutics. *Clin Infect Dis*. 2017;64(9):1283-1288. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28200098.

33. Colin JF, Cazals-Hatem D, Loriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology*. 1999;29(4):1306-1310. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10094979.

34. Gilson RJ, Hawkins AE, Beecham MR, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS*. 1997;11(5):597-606. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9108941.

35. Thio CL, Seaberg EC, Skolasky R, Jr., et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002;360(9349):1921-1926. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12493258.

36. Brau N, Fox RK, Xiao P, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol*. 2007;47(4):527-537. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17692986.

37. Rajbhandari R, Jun T, Khalili H, Chung RT, Ananthakrishnan AN. HBV/HIV coinfection is associated with poorer outcomes in hospitalized patients with HBV or HIV. *J Viral Hepat*. 2016;23(10):820-829. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27291562.

38. Wandeler G, Mauron E, Atkinson A, et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: relevance for screening strategies. *J Hepatol*. 2019;71(2):274-280. Available at: https://www.sciencedirect.com/science/article/pii/S0168827819302260?via%3Dihub.

39. Kim HN, Newcomb CW, Carbonari DM, et al. Risk of HCC with hepatitis B viremia among HIV/HBV-coinfected persons in North America. *Hepatology*. 2021;74(3):1190-1202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33780007.

40. Marks KM, Kang M, Umbleja T, et al. Immunogenicity and safety of hepatitis B virus (HBV) vaccine with a toll-like receptor 9 agonist adjuvant in HBV vaccine-naive people with human immunodeficiency virus. *Clin Infect Dis*. 2023;77(3):414-418. Available at: https://www.pubmed.ncbi.nlm.nih.gov/37017075.

41. Lee JH, Hong S, Im JH, Lee JS, Baek H, Kwon HY. Systematic review and *meta*-analysis of immune response of double dose of hepatitis B vaccination in HIV-infected patients. *Vaccine*. 2020;38(24):3995-4000. Available at: https://www.sciencedirect.com/science/article/pii/S0264410X20304928?via%3Dihub.

42. Rey D, Krantz V, Partisani M, et al. Increasing the number of hepatitis B vaccine injections augments anti-HBs response rate in HIV-infected patients. Effects on HIV-1 viral load. *Vaccine*. 2000;18(13):1161-1165. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10649616.

43. Loke RH, Murray-Lyon IM, Coleman JC, Evans BA, Zuckerman AJ. Diminished response to recombinant hepatitis B vaccine in homosexual men with HIV antibody: an indicator of poor prognosis. *J Med Virol*. 1990;31(2):109-111. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2143776.

44. Tayal SC, Sankar KN. Impaired response to recombinant hepatitis B vaccine in asymptomatic HIV-infected individuals. *AIDS*. 1994;8(4):558-559. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7912087.

45. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine*. 2005;23(22):2902-2908. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15780739.

46. Veiga AP, Casseb J, Duarte AJ. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naive) and CD45RO+ (memory) subsets in HIV-1-infected subjects. *Vaccine*. 2006;24(49-50):7124-7128. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16884833.

47. Bruguera M, Cremades M, Salinas R, Costa J, Grau M, Sans J. Impaired response to recombinant hepatitis B vaccine in HIV-infected persons. *J Clin Gastroenterol*. 1992;14(1):27-30. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1532609.

48. Keet IP, van Doornum G, Safary A, Coutinho RA. Insufficient response to hepatitis B vaccination in HIV-positive homosexual men. *AIDS*. 1992;6(5):509-510. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1535502.

49. Ristola MA, Vuola JM, Valle M, von Reyn CF. Antibody responses to intradermal recombinant hepatitis B immunization among HIV-positive subjects. *Vaccine*. 2004;23(2):205-209. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15531038.

50. Tedaldi EM, Baker RK, Moorman AC, et al. Hepatitis A and B vaccination practices for ambulatory patients infected with HIV. *Clin Infect Dis*. 2004;38(10):1478-1484. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15156488.

51. Overton ET, Sungkanuparph S, Powderly WG, Seyfried W, Groger RK, Aberg JA. Undetectable plasma HIV RNA load predicts success after hepatitis B vaccination in HIV-infected persons. *Clin Infect Dis*. 2005;41(7):1045-1048. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16142673.

52. Lee SD, Chan CY, Yu MI, Lu RH, Chang FY, Lo KJ. Hepatitis B vaccination in patients with chronic hepatitis C. *J Med Virol*. 1999;59(4):463-468. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10534727.

53. Wiedmann M, Liebert UG, Oesen U, et al. Decreased immunogenicity of recombinant hepatitis B vaccine in chronic hepatitis C. *Hepatology*. 2000;31(1):230-234. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10613751.

54. Anthony DD, Yonkers NL, Post AB, et al. Selective impairments in dendritic cell-associated function distinguish hepatitis C virus and HIV infection. *J Immunol*. 2004;172(8):4907-4916. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15067070.

55. Sarobe P, Lasarte JJ, Casares N, et al. Abnormal priming of CD4(+) T cells by dendritic cells expressing hepatitis C virus core and E1 proteins. *J Virol*. 2002;76(10):5062-5070. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11967322.

56. Auffermann-Gretzinger S, Keeffe EB, Levy S. Impaired dendritic cell maturation in patients with chronic, but not resolved, hepatitis C virus infection. *Blood*. 2001;97(10):3171-3176. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11342445.

57. Landrum ML, Hullsiek KH, Ganesan A, et al. Hepatitis B vaccination and risk of hepatitis B infection in HIV-infected individuals. *AIDS*. 2010;24(4):545-555. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19487908.

58. Marks KM, Kang M, Umbleja T, et al. HepB-CpG vs HepB-Alum vaccine in people with HIV and prior vaccine nonresponse: the BEe-HIVe randomized clinical trial. *JAMA*. 2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39616603.

59. Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep*. 2018;67(1):1-31. Available at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm.

60. Lopes VB, Hassing RJ, de Vries-Sluijs TE, et al. Long-term response rates of successful hepatitis B vaccination in HIV-infected patients. *Vaccine*. 2013;31(7):1040-1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23273969.

61. Piroth L, Launay O, Michel ML, et al. Vaccination against hepatitis B virus (HBV) in HIV-1-infected patients with isolated anti-HBV core antibody: the ANRS HB EP03 CISOVAC Prospective Study. *J Infect Dis*. 2016. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26768256.

62. Falade-Nwulia O, Seaberg EC, Snider AE, et al. Incident hepatitis B virus infection in HIV-infected and HIV-uninfected men who have sex with men from pre-HAART to HAART periods: a cohort study. *Ann Intern Med*. 2015;163(9):673-680. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26457744.

63. Gatanaga H, Hayashida T, Tanuma J, Oka S. Prophylactic effect of antiretroviral therapy on hepatitis B virus infection. *Clin Infect Dis*. 2013;56(12):1812-1819. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23487374.

64. Heuft MM, Houba SM, van den Berk GE, et al. Protective effect of hepatitis B virus-active antiretroviral therapy against primary hepatitis B virus infection. *AIDS*. 2014;28(7):999-1005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24685742.

65. Mizushima D, Takano M, Aoki T, et al. Effect of tenofovir-based HIV pre-exposure prophylaxis against HBV infection in men who have sex with men. *Hepatology*. 2023;77(6):2084-2092. Available at: https://pubmed.ncbi.nlm.nih.gov/36960800.

66. Weinberg A, Huang S, Fenton T, et al. Virologic and immunologic correlates with the magnitude of antibody responses to the hepatitis A vaccine in HIV-infected children on highly active antiretroviral treatment. *J Acquir Immune Defic Syndr*. 2009;52(1):17-24. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19617848.

67. Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. *Am J Med*. 2005;118 Suppl 10A:75S-83S. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16271546.

68. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. 2024. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines.

69. van Bommel F, Wunsche T, Schurmann D, Berg T. Tenofovir treatment in patients with lamivudine-resistant hepatitis B mutants strongly affects viral replication. *Hepatology*. 2002;36(2):507-508. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12143063.

70. Nunez M, Perez-Olmeda M, Diaz B, Rios P, Gonzalez-Lahoz J, Soriano V. Activity of tenofovir on hepatitis B virus replication in HIV-co-infected patients failing or partially responding to lamivudine. *AIDS*. 2002;16(17):2352-2354. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12441815.

71. Ristig MB, Crippin J, Aberg JA, et al. Tenofovir disoproxil fumarate therapy for chronic hepatitis B in human immunodeficiency virus/hepatitis B virus-coinfected individuals for whom interferon-alpha and lamivudine therapy have failed. *J Infect Dis*. 2002;186(12):1844-1847. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12447773.

72. Nelson M, Portsmouth S, Stebbing J, et al. An open-label study of tenofovir in HIV-1 and hepatitis B virus co-infected individuals. *AIDS*. 2003;17(1):F7-10. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12478090.

73. Benhamou Y, Tubiana R, Thibault V. Tenofovir disoproxil fumarate in patients with HIV and lamivudine-resistant hepatitis B virus. *N Engl J Med*. 2003;348(2):177-178. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12519935.

74. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. 2006;44(5):1110-1116. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17058225.

75. Huhn GD, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. *J Acquir Immune Defic Syndr*. 2017;74(2):193-200. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27753684.

76. Gallant J, Brunetta J, Crofoot G, et al. Brief report: efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-1/hepatitis B-coinfected adults. *J Acquir Immune Defic Syndr*. 2016;73(3):294-298. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27171740.

77. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1(3):196-206. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28404092.

78. Chan HL, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*. 2016;1(3):185-195. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28404091.

79. Avihingsanon A, Lu HZ, Leong CL, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 and hepatitis B coinfection (ALLIANCE): a double-blind, multicentre, randomised controlled, phase 3 non-inferiority trial. *Lancet Hiv*. 2023;10(10):E640-E652. Available at: https://pubmed.ncbi.nlm.nih.gov/37494942.

80. Dore GJ, Soriano V, Rockstroh J, et al. Frequent hepatitis B virus rebound among HIV-hepatitis B virus-coinfected patients following antiretroviral therapy interruption. *AIDS*. 2010;24(6):857-865. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20216301.

81. Bellini C, Keiser O, Chave JP, et al. Liver enzyme elevation after lamivudine withdrawal in HIV-hepatitis B virus co-infected patients: the Swiss HIV Cohort Study. *HIV Med*. 2009;10(1):12-18. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18795964.

82. Bessesen M, Ives D, Condreay L, Lawrence S, Sherman KE. Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis*. 1999;28(5):1032-1035. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10452630.

83. Proia LA, Ngui SL, Kaur S, Kessler HA, Trenholme GM. Reactivation of hepatitis B in patients with human immunodeficiency virus infection treated with combination antiretroviral therapy. *Am J Med*. 2000;108(3):249-251. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10723980.

84. Neau D, Schvoerer E, Robert D, et al. Hepatitis B exacerbation with a precore mutant virus following withdrawal of lamivudine in a human immunodeficiency virus-infected patient. *J Infect*. 2000;41(2):192-194. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11023772.

85. Puoti M, Spinetti A, Ghezzi A, et al. Mortality for liver disease in patients with HIV infection: a cohort study. *J Acquir Immune Defic Syndr*. 2000;24(3):211-217. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10969344.

86. Bonacini M, Louie S, Bzowej N, Wohl AR. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. *AIDS*. 2004;18(15):2039-2045. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15577625.

87. Donato F, Boffetta P, Puoti M. A meta-analysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. *Int J Cancer*. 1998;75(3):347-354. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9455792.

88. Collins JM, Raphael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. *Clin Infect Dis*. 2015;61(8):1304-1306. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26082511.

89. Takayama H, Sato T, Ikeda F, Fujiki S. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. *Hepatol Res*. 2015. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26297529.

90. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. *J Clin Virol*. 2016;78:27-30. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26967675.

91. Ende AR, Kim NH, Yeh MM, Harper J, Landis CS. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. *J Med Case Rep*. 2015;9:164. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26215390.

92. Denyer RV, Tate JP, Benator DA, Kim JK, Weintrob AC. 1026. Hepatitis B reactivation in persons with HIV with positive hepatitis B core antibody after switching to antiretroviral therapy without hepatitis B activity. *Open Forum Infect Dis*. 2023;10:1-2. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10679264.

93. Vasishta S, Dieterich D, Mullen M, Aberg J. Brief report: hepatitis B infection or reactivation after switch to 2-drug antiretroviral therapy: a case series, literature review, and management discussion. *J Acquir Immune Defic Syndr*. 2023;94(2):160-164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37345994.

94. McMahon MA, Jilek BL, Brennan TP, et al. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med*. 2007;356(25):2614-2621. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17582071.

95. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med*. 2007;356(14):1445-1454. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17409326.

96. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet*. 2001;358(9283):718-723. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11551579.

97. Ingiliz P, Valantin MA, Thibault V, et al. Efficacy and safety of adefovir dipivoxil plus pegylated interferon-alpha2a for the treatment of lamivudine-resistant hepatitis B virus infection in HIV-infected patients. *Antivir Ther*. 2008;13(7):895-900. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19043923.

98. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22436845.

99. Zoulim F, Locarnini S. Management of treatment failure in chronic hepatitis B. *J Hepatol*. 2012;56 Suppl 1:S112-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22300461.

100. Matthews GV, Ali RJ, Avihingsanon A, et al. Quantitative HBsAg and HBeAg predict hepatitis B seroconversion after initiation of HAART in HIV-HBV coinfected individuals. *PLoS One*. 2013;8(4):e61297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23593455.

101. Chihota BV, Wandeler G, Chilengi R, et al. High rates of hepatitis B virus (HBV) functional cure among human immunodeficiency virus-HBV coinfected patients on antiretroviral therapy in Zambia. *J Infect Dis*. 2020;221(2):218-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31613956.

102. Nishijima T, Kawasaki Y, Tanaka N, et al. Long-term exposure to tenofovir continuously decrease renal function in HIV-1-infected patients with low body weight: results from 10 years of follow-up. *AIDS*. 2014;28(13):1903-1910. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25259702.

103. Pozniak A, Arribas JR, Gathe J, et al. Switching to tenofovir alafenamide, coformulated with elvitegravir, cobicistat, and emtricitabine, in HIV-infected patients with renal impairment: 48-week results from a single-arm, multicenter, open-label phase 3 study. *J Acquir Immune Defic Syndr*. 2016;71(5):530-537. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26627107.

104. Agarwal K, Brunetto M, Seto WK, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol*. 2018;68(4):672-681. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29756595.

105. Mallon PW, Brunet L, Hsu RK, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. *J Int AIDS Soc*. 2021;24(4):e25702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33838004.

106. Lange CM, Bojunga J, Hofmann WP, et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology*. 2009;50(6):2001-2006. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19937695.

107. Marzano A, Marengo A, Marietti M, Rizzetto M. Lactic acidosis during entecavir treatment in decompensated hepatitis B virus-related cirrhosis. *Dig Liver Dis*. 2011;43(12):1027-1028. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21782535.

108. Mao H, Kang T. Lactic acidosis during entecavir antiviral treatment in a patient with hepatitis B virus-related decompensated cirrhosis. *West Indian Med J*. 2015;64(2):165-166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26360694.

109. Lau GK. Does treatment with interferon-based therapy improve the natural history of chronic hepatitis B infection? *J Hepatol*. 2007;46(1):6-8. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17112628.

110. Drake A, Mijch A, Sasadeusz J. Immune reconstitution hepatitis in HIV and hepatitis B coinfection, despite lamivudine therapy as part of HAART. *Clin Infect Dis*. 2004;39(1):129-132. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15206064.

111. Shelburne SA, 3rd, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)*. 2002;81(3):213-227. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11997718.

112. Crane M, Oliver B, Matthews G, et al. Immunopathogenesis of hepatic flare in HIV/hepatitis B virus (HBV)-coinfected individuals after the initiation of HBV-active antiretroviral therapy. *J Infect Dis*. 2009;199(7):974-981. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19231993.

113. Pineda JA, Santos J, Rivero A, et al. Liver toxicity of antiretroviral combinations including atazanavir/ritonavir in patients co-infected with HIV and hepatitis viruses: impact of pre-existing liver fibrosis. *J Antimicrob Chemother*. 2008;61(4):925-932. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18276600.

114. Neukam K, Mira JA, Collado A, et al. Liver toxicity of current antiretroviral regimens in HIV-infected patients with chronic viral hepatitis in a real-life setting: the HEPAVIR SEG-HEP Cohort. *PLoS One*. 2016;11(2):e0148104. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26848975.

115. Hoffmann CJ, Charalambous S, Martin DJ, et al. Hepatitis B virus infection and response to antiretroviral therapy (ART) in a South African ART program. *Clin Infect Dis*. 2008;47(11):1479-1485. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18937580.

116. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283(1):74-80. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10632283.

117. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS*. 2004;18(17):2277-2284. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15577540.

118. Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr*. 2003;34 Suppl 1:S21-33. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14562855.

119. Sherman KE, Shire NJ, Cernohous P, et al. Liver injury and changes in hepatitis C virus (HCV) RNA load associated with protease inhibitor-based antiretroviral therapy for treatment-naive HCV-HIV-coinfected patients: lopinavir-ritonavir versus nelfinavir. *Clin Infect Dis*. 2005;41(8):1186-1195. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16163639.

120. Reuben A. Hy's law. *Hepatology*. 2004;39(2):574-578. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14768020.

121. Spradling PR, Bulkow L, Teshale EH, et al. Prevalence and causes of elevated serum aminotransferase levels in a population-based cohort of persons with chronic hepatitis B virus infection. *J Hepatol*. 2014;61(4):785-791. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24911461.

122. Lok AS, Zoulim F, Locarnini S, et al. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology*. 2007;46(1):254-265. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17596850.

123. Park ES, Lee AR, Kim DH, et al. Identification of a quadruple mutation that confers tenofovir resistance in chronic hepatitis B patients. *J Hepatol*. 2019;70(6):1093-1102. Available at: https://pubmed.ncbi.nlm.nih.gov/30794889.

124. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology*. 1999;30(5):1302-1306. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10534354.

125. Matthews GV, Seaberg E, Dore GJ, et al. Combination HBV therapy is linked to greater HBV DNA suppression in a cohort of lamivudine-experienced HIV/HBV coinfected individuals. *AIDS*. 2009;23(13):1707-1715. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19584701.

126. Vassiliadis TG, Giouleme O, Koumerkeridis G, et al. Adefovir plus lamivudine are more effective than adefovir alone in lamivudine-resistant HBeAg- chronic hepatitis B patients: a 4-year study. *J Gastroenterol Hepatol*. 2010;25(1):54-60. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19780875.

127. Lampertico P, Vigano M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology*. 2007;133(5):1445-1451. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17983801.

128. Ze E, Baek EK, Lee JJ, et al. Long-term outcomes of two rescue therapies in lamivudine-refractory patients with chronic hepatitis B: combined lamivudine and adefovir, and 1-mg entecavir. *Clin Mol Hepatol*. 2014;20(3):267-273. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25320730.

129. Luetkemeyer AF, Charlebois ED, Hare CB, et al. Resistance patterns and response to entecavir intensification among HIV-HBV-coinfected adults with persistent HBV viremia. *J Acquir Immune Defic Syndr*. 2011;58(3):e96-99. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22005002.

130. Lai CL, Chien RN, Leung NW, et al. A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. *N Engl J Med*. 1998;339(2):61-68. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9654535.

131. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med*. 1999;341(17):1256-1263. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10528035.

132. Runyon BA, American Association for the Study of Liver Diseases. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*. 2013;57(4):1651-1653. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23463403.

133. Runyon BA, Practice Guidelines Committee of the American Association for the Study of Liver Diseases. Management of adult patients with ascites due to cirrhosis. *Hepatology*. 2004;39(3):841-856. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14999706.

134. Singh N, Gayowski T, Yu VL, Wagener MM. Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. *Ann Intern Med*. 1995;122(8):595-598. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7887554.

135. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology*. 1997;26(3 Suppl 1):34S-38S. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9305661.

136. Miro JM, Laguno M, Moreno A, Rimola A, Hospital Clinic OLT in HIV Working Group. Management of end stage liver disease (ESLD): what is the current role of orthotopic liver transplantation (OLT)? *J Hepatol*. 2006;44(1 Suppl):S140-145. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16352366.

137. Lau GK, Yiu HH, Fong DY, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology*. 2003;125(6):1742-1749. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14724827.

138. Lee YH, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis*. 2013;16(5):527-531. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24164839.

139. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology*. 2015;148(1):215-219; quiz e216-217. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25447850.

140. Huang YH, Hsiao LT, Hong YC, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol*. 2013;31(22):2765-2772. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23775967.

141. Mori S, Fujiyama S. Hepatitis B virus reactivation associated with antirheumatic therapy: risk and prophylaxis recommendations. *World J Gastroenterol*. 2015;21(36):10274-10289. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26420955.

142. Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Hepatitis B virus/HIV coinfection. 2023. Available at: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/hepatitis-b-virushiv-coinfection?view=full.

143. del Canho R, Grosheide PM, Schalm SW, de Vries RR, Heijtink RA. Failure of neonatal hepatitis B vaccination: the role of HBV-DNA levels in hepatitis B carrier mothers and HLA antigens in neonates. *J Hepatol*. 1994;20(4):483-486. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8051386.

144. Ngui SL, Andrews NJ, Underhill GS, Heptonstall J, Teo CG. Failed postnatal immunoprophylaxis for hepatitis B: characteristics of maternal hepatitis B virus as risk factors. *Clin Infect Dis*. 1998;27(1):100-106. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9675462.

145. Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust*. 2009;190(9):489-492. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19413519.

146. Kubo A, Shlager L, Marks AR, et al. Prevention of vertical transmission of hepatitis B: an observational study. *Ann Intern Med*. 2014;160(12):828-835. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24862434.

147. Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States. 2023. Available at: https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines.

148. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989–31 January 2024. Morrisville, NC: Registry Coordinating Center. 2024. Available at: https://www.apregistry.com.

149. Kiweewa FM, Tierney C, Butler K, et al. Brief report: impact of antiretroviral regimen on pregnancy and infant outcomes in women with HIV/HBV coinfection. *J Acquir Immune Defic Syndr*. 2022;91(1):79-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35621877.

Hepatitis C Virus Infection

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Epidemiology

Prevalence and Incidence Estimates

Hepatitis C virus (HCV) is an enveloped, single-stranded RNA virus of the Flaviviridae family with seven known genotypes and 84 subtypes, with genotypes 1 and 3 being most common worldwide.[1-3] It is the most commonly reported bloodborne infection in the United States and is a leading cause of liver-related morbidity and mortality, particularly among people with HIV. In 2019, the estimated global prevalence of chronic HCV infection was 58 million (0.8% of general population), a decline from previous estimates of 71 million in 2015.[4] In the United States, updated estimates for 2013 to 2016 are that approximately 4.1 million people were HCV antibody positive (past or current infection; 1.7% of all adults); 2.4 million were HCV RNA positive (current infection; 1% of all adults).[5] Comparable data from 2003 to 2010 showed that 4.6 million people were antibody positive and 3.5 million were living with current HCV infection.[6] These updated lower prevalence estimates reflect interval trends, including increased cures with new treatment options and increasing death rates due to aging. However, these may be offset by increases in incident cases due to the opioid crisis in vulnerable counties.[7,8] Despite variable state-level surveillance practices,[9] Centers for Disease Control and Prevention (CDC) surveillance data from 2019 show regional differences in incidence and prevalence, increasing rates in rural areas, ongoing racial/ethnic disparities, and changing demographics, including a bimodal distribution of infections with peaks at 29 years and at 59 years of age.[10] Attributable mortality is highly variable among states and counties.[11]

Given the shared transmission routes between HIV and HCV, estimates of the burden of HCV infection in people with HIV (HIV/HCV coinfection) have been highly variable depending on the comprehensiveness of databases analyzed. A global systematic review and meta-analysis of studies published between 2002 and 2015 estimated that there were 2.3 million cases of coinfection worldwide, with 1.3 million (58%) attributed to persons who inject drugs; this translates to HCV coinfection prevalence of 6.2% among people with HIV.[12] Compared with people without HIV, the odds of HCV infection in people with HIV are six times higher. The prevalence of HCV infection among people with HIV is distributed in the following subgroups: people who inject drugs (82.4%), men who have sex with men (MSM, 6.4%), and those who are pregnant or heterosexually exposed (2.4%).[12] Estimates of HCV coinfection in the United States[10] have been cited as 21% but have ranged from 6% to 30% with high variability based on the distribution of HIV transmission risk factors.[13,14] In the United States, it is estimated that 62% to 80% of people who inject drugs who have HIV also have HCV infection.[10]

The availability of highly effective treatments for HCV infection has led to national and global initiatives aimed at HCV elimination in general and in high-risk persons, such as those with HIV coinfection. The World Health Organization has developed targets for countries to achieve HCV elimination by 2030: diagnosing 90% of those with chronic infection and curing 80% of those diagnosed.[4] The CDC *Division of Viral Hepatitis 2025 Strategic Plan* aims to increase HCV cure to >85% by 2030.[15] The use of an HCV cascade of care has shown that there are ongoing gaps to attaining cure encompassing screening, initiating and completing treatment, and preventing

reinfection.[16,17] Worldwide, 15.2 million (26.2%) out of an estimated 58 million people knew their HCV status by the end of 2019.[18] With progress in direct antiviral treatments, 9.4 million people received HCV treatment, with the vast majority cured, between 2015 and 2019.[18] Micro-elimination efforts to scale-up treatment as prevention among people with HIV have successfully demonstrated that such efforts can decrease hepatitis C incidence.[19-24]

Transmission Routes

Both HIV and HCV can be transmitted by percutaneous exposure to blood or blood products, sexual intercourse, and perinatal transmission; however, the relative efficiency of transmission by these routes varies substantially.[25] HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes.[26,27] Transmission via injection drug use remains the most common mode of acquisition in the United States, while transmission through contaminated blood products is now rare. Health care–associated transmission of HCV also can occur because of improper reuse of parenteral medications and equipment.[28] Other factors that have been associated with HCV infection include accidental occupation-related needlestick injuries, intranasal cocaine use, chronic hemodialysis, and tattoo placement.

Multiple outbreaks of acute HCV infection in MSM demonstrate that sexual transmission is an important mode of acquisition in this population. Risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted infections (STIs).[29-32] Evidence for increasing HCV incidence and prevalence in HIV-negative men seen in HIV pre-exposure prophylaxis (PrEP) clinics has led to current recommendations to monitor for acute HCV infection and routinely test for HCV as part of PrEP care.[33-35] Heterosexual transmission of HCV is uncommon but more likely in those whose partners have HIV/HCV coinfection.[16,36-38]

Perinatal transmission of HCV infection occurs in approximately 7% and 12% of infants born to HCV-seropositive and RNA-positive mothers without and with HIV infection,[39-41] respectively, with possible decreased transmission risk for women with HIV receiving antiretroviral treatment.[42]

Clinical Manifestations

Both acute and chronic HCV infections are usually minimally symptomatic or asymptomatic. Fewer than 20% of patients with acute infection have characteristic symptoms, including low-grade fever, mild right-upper-quadrant pain, nausea, vomiting, anorexia, dark urine, and jaundice. Unexplained elevations in serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels may be the only laboratory finding during acute and chronic infection. Recognition of acute HCV infection in patients with new-onset liver enzyme elevations is clinically important; early initiation of HCV treatment can lower the likelihood of poorer outcomes and prevent transmission to others (treatment as prevention).[43-45]

Cirrhosis develops in 20 to 40% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable.[46-48] Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use.[47,49] HIV coinfection adversely affects the course of HCV infection, resulting in significantly accelerated progression of liver disease to cirrhosis, particularly in those with advanced immunodeficiency[50,51] (CD4 T lymphocyte [CD4] count <200 cells/mm^3). Further, coinfected patients with cirrhosis progress more rapidly to life-limiting outcomes—such as end-stage liver

disease and hepatocellular carcinoma (HCC)—than those who are HCV mono-infected,[52,53] even if they are virally suppressed.[54] Because of its high prevalence and accelerated progression, HCV infection was a leading non-AIDS cause of death in people with HIV before the advent of highly effective direct-acting antivirals.[55-57] In addition to liver disease, HCV may be associated with symptomatic vasculitis due to cryoglobulinemia (largely affecting the skin or joints), renal disease (membranoproliferative glomerulonephritis), and porphyria cutanea tarda.

Diagnosis

On entry into HIV care, all patients should undergo routine HCV screening **(AII).** Initial testing for HCV should be performed using a U.S. Food and Drug Administration (FDA)-approved immunoassay licensed for detection of antibody to HCV (anti-HCV) in blood.[58,59] For at-risk HCV-seronegative individuals, specifically MSM or persons who inject drugs, HCV antibody testing, using an FDA-approved immunoassay, is recommended annually or as indicated by clinical presentation, risk activities, or exposure **(AII).** Concordantly, both the American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) HCV guidance and CDC PrEP guidelines also recommend HCV serologic testing at baseline and every 12 months for MSM, transgender women, and people who inject drugs.[59,60] Nucleic acid testing for HCV RNA is recommended in settings where acute infection is suspected or in persons with known prior infection cleared spontaneously or after treatment **(AIII).**

False-negative anti-HCV antibody results are possible among people with HIV but uncommon (2% to 4%), and more likely to be seen in patients with advanced immunosuppression[61] (CD4 cell count <200 cells/ mm^3). HCV RNA testing should be performed in those patients with risk factors or unexplained ALT elevation. In addition, negative anti-HCV antibody results can occur during acute infection. Following acute HCV infection, the duration of the window period prior to seroconversion is highly variable, ranging from 2 weeks to more than 24 weeks,[62,63] with antibody response in most persons detectable at 8 to 12 weeks. Serum ALT levels are frequently elevated early in the course of HCV infection, and high ALT levels should prompt testing for HCV RNA if serologic test results are negative or indeterminate in individuals at risk of HCV infection.[64]

Individuals who test positive for HCV antibody should undergo additional diagnostic testing by using a sensitive quantitative assay to measure plasma HCV RNA level and confirm current infection **(AI).** This should preferentially be done as an automatic reflex to HCV RNA testing of the leftover serum from the blood draw for antibody testing to facilitate diagnosis.[65] Reinfection can occur in both seropositive individuals who spontaneously clear their infection or those who achieve a sustained virologic response to treatment. Diagnosing a new active infection will require HCV RNA testing in such individuals **(AII).**

Preventing Exposure

The primary route of HCV transmission is blood-to-blood contact, most commonly from sharing drug-injection equipment or paraphernalia (i.e., “cookers,” filters, or water) previously used by an infected person with HCV. Prevention approaches for persons who inject drugs include harm-reduction encompassing opioid agonist therapy and syringe services programs to avoid the reuse or sharing of syringes, needles, water, cotton, and other drug preparation equipment.[66,67] Both needle and syringe exchange programs and opioid substitution therapy have been shown to reduce the risk of HCV acquisition in people who inject drugs.[67,68] HCV also can be transmitted sexually, especially among MSM with HIV.[69] Risk factors for sexual HCV acquisition include unprotected anal receptive

intercourse, fisting, sharing of sex toys, ulcerative STIs, and use of methamphetamine or other sex-enhancing drugs (injection or otherwise).[70,71]

Patients should be counseled regarding the risk of sexual HCV acquisition **(AII).** Those with multiple sex partners or STIs should be advised to use barrier protection to reduce their risk of STIs including hepatitis C infection **(AII).**

Preventing Disease

There is no available vaccine or recommended post-exposure prophylaxis to prevent HCV infection.[72,73] Following acute HCV infection, chronic infection can be prevented within the first 6 to 12 months after infection through antiviral treatment; high rates of viral clearance have been observed with HCV treatment during the acute phase of infection.[74,75]

Because most patients with acute HCV infection may transmit to others and are at risk for loss to follow-up, immediate treatment with the same regimens recommended for chronic HCV should be offered **(AIII).**[44,76] Specific treatment regimens in acute infection are the same as those recommended for chronic HCV infection and are detailed in the Treating HCV section.

People with HCV infection should be tested for previous or concurrent hepatitis B virus (HBV) infection because coinfection with HBV is associated with increased morbidity **(AII).** Those without evidence of immunity to HBV infection should be vaccinated (see the Hepatitis B Virus Infection section) **(AII).** Likewise, because acute hepatitis A virus (HAV) infection is more likely to be fulminant in persons with HCV infection,[77] these patients should be screened for immunity (HAV immunoglobulin G or antibody total) and non-immune persons should be vaccinated **(AII).**

People with HCV infection should be counseled about methods to prevent liver damage by avoiding any alcohol consumption (because alcohol accelerates progression of liver disease), limiting ingestion of potentially hepatotoxic medications (e.g., acetaminophen should be limited to <2 g/day for those with acute infection or bridging fibrosis/cirrhosis), and avoiding iron supplementation in the absence of documented iron deficiency.[78]

People with HIV/HCV coinfection with cirrhosis are at risk of life-threatening complications and should be managed in consultation with a gastroenterologist or hepatologist. In particular, individuals with cirrhosis should undergo serial screening for HCC; current guidelines recommend performing ultrasonography at 6-month intervals, although the optimal screening strategy is unknown **(AIII).**[79] Because of its relatively poor specificity and sensitivity, serum alfa-fetoprotein is an adjunct to ultrasonography but should not be the sole screening method.[79] HIV infection is not a contraindication to liver transplantation; accordingly, coinfected patients with decompensated liver disease and/or early HCC may be considered for transplantation at specialized transplant centers.

Although earlier studies focused on the potential for antiretroviral (ARV)-associated liver injury with certain agents, more recent studies have found that effective HIV treatment is associated with reduced risk of liver disease progression, though not to levels of persons with HCV infection without HIV.[54,80] Coinfected patients should be treated in accordance with the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV.

Treating HCV Infection

Introduction

Direct-acting antiviral (DAA) regimens for HCV infection have become standardized with one of two pangenotypic, highly efficacious and well-tolerated antiviral treatment regimens, which are the preferred therapy for HCV infection for almost all persons with HIV and HCV. Clinicians can refer to the most recent AASLD/IDSA HCV treatment guidance.

The goals of therapy, treatment regimen, and monitoring parameters for patients with HIV/HCV coinfection are similar to those recommended for patients with HCV mono-infection. However, people with HIV were historically considered a "special population" with regard to HCV treatment. This designation was rooted in inferior responses to interferon-based treatment for those with HIV.[81,82] The arrival of initial DAA regimens narrowed the gap in response to treatment but continued to present significant drug–drug interaction considerations and, in some circumstances, warrant extended treatment durations.

Simplified approaches to HCV treatment have emerged as a means to facilitate treatment by non-specialist providers and increase treatment uptake for the majority of persons with HCV infection. In general, simplified approaches to HCV treatment apply to treatment-naive persons without cirrhosis and encompass minimal baseline testing (with omission of genotype), standardized treatment approaches using pangenotypic regimens, no on-treatment testing or in-person follow-up, and limited follow-up to confirm sustained virologic response (SVR).

Several factors now allow people with HIV to access simplified HCV treatment recommendations. The emergence of unboosted integrase strand transfer inhibitor (INSTI)-based ARV regimens has eliminated clinically significant drug interactions with current first-line DAA regimens. Additionally, the improved safety profile of tenofovir alafenamide (TAF) combined with safety data in the setting of boosted ARV regimens during coadministration with DAAs obviate the need for enhanced toxicity monitoring for people with HIV in most instances. Finally, accumulation of clinical efficacy data and the necessity of expanding treatment access support the use of simpler standardized treatment approaches initially validated in HCV mono-infected populations for those with HIV. Based on these developments and the emergence of pangenotypic DAA regimens, treatment of HCV can be approached using simplified protocols for the majority of people with HIV.

Published clinical trial data directly support a simplified approach to HCV treatment, including for people with HIV. The AIDS Clinical Trial Groups (ACTG) A5360 study (MINMON) evaluated an approach consisting of limited baseline testing and supply of the entire 84-tablet (12-week) sofosbuvir/velpatasvir treatment regimen in 399 participants, including 166 with HIV.[83] All participants were HCV treatment-naive, compensated cirrhosis was allowed, and no pre-treatment HCV genotyping was performed. No on-study laboratory monitoring or in-person follow-up was conducted. The SVR after 12 weeks post-treatment (SVR12) was 95% overall (95% CI, 92.4% to 96.7%) and 95% in the subset of people with HIV (157/166).

The SMART-C study randomized participants to either a standard 8-week treatment with glecaprevir/pibrentasvir (n = 127), which included in-person follow-up at weeks 4 and 8 with medication refill required at week 4, or to a simplified approach (n = 253) that omitted the on-treatment visits with all medication dispensed at initiation.[84] Persons with previous HCV treatment or cirrhosis were excluded and only a small number of people with HIV (n = 27) were included. A

modified intention-to-treat analysis (excluding lost to follow-up and missing SVR12 results) established non-inferiority of the simplified approach with SVR12 of 97% (233/241) compared with 98% (121/123) in the standard-approach arm. No difference in response was seen by HIV status.

Staging and Monitoring

While a pre-HCV treatment assessment of patient readiness for therapy should be completed, with an indication that reasonable adherence can be expected, HCV DAA therapy should not be withheld solely due to perceived lack of adherence with HIV therapy or untreated HIV infection **(BIII).** Evidence suggests the level of adherence needed for HCV cure is more modest than that required to maintain HIV viral suppression.[85-87] In addition, despite a lack of HIV control, patients may be uniquely motivated by the potential for HCV cure, thereby increasing the likelihood of successful treatment.

Additional fibrosis stage assessment may be indicated in people with HIV with an indeterminate FIB-4 (1.45–3.25) score, particularly if cirrhosis is suspected **(BIII).** Additional blood- or serum-based assays for fibrosis staging **are not recommended** because they provide little benefit over FIB-4 **(BII).**[88,89]

Non-invasive ultrasound-based (e.g., shear wave elastography or vibration controlled transient elastography) or imaging-based (e.g., magnetic resonance elastography) modalities are recommended if available **(BII).** Liver biopsy **is no longer recommended** for liver fibrosis staging related to HCV infection unless there is another indication to obtain one **(AII).** Treatment should not be withheld if access to additional staging modalities is not readily available **(AIII).**

Simplified Approach to HCV Treatment

The current AASLD/IDSA HCV guidance for simplified HCV treatment of treatment-naive adults (without cirrhosis or with compensated cirrhosis) excludes persons with HIV. The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommends an approach that allows most people with HIV to qualify for simplified HCV treatment. This simplified approach is appropriate except in certain people with HIV with conditions noted in **Box 1.** Such exclusions highlight the importance of particular ARV regimens with significant drug–drug interactions with ARVs (see below).

Box 1. Characteristics of People with HIV for Whom Simplified Hepatitis C Virus Treatment Is Not Recommended[a]

1. Prior HCV treatment (Reinfection after prior successful therapy is not an exclusion.)
2. Decompensated cirrhosis[b]
3. TDF-containing regimen with an eGFR <60mL/min
4. On efavirenz, etravirine, nevirapine, or boosted HIV-1 protease inhibitors[c]
5. Untreated chronic HBV infection
6. Pregnancy

[a] People with HIV and HCV infection who meet these exclusion criteria should be treated for HCV following standard approaches (see the AASLD/IDSA HCV Guidance).

[b] Including, but not limited to, current or prior variceal bleeding, ascites, or hepatic encephalopathy

[c] People with HIV on boosted protease inhibitors are not eligible for treatment with glecaprevir/pibrentasvir and may require on-treatment monitoring.

Key: eGFR = estimated glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; TDF = tenofovir disoproxil fumarate

A limited pre-treatment assessment for people with HIV is essentially the same as for people without HIV who qualify for a simplified approach **(Box 2) (AIII).** Key components are documentation of active HCV infection and initial assessment of liver fibrosis stage. Determination of HCV genotype prior to treatment is not necessary in treatment-naive patients, with the exception of persons with compensated cirrhosis who are planned for treatment with sofosbuvir/velpatasvir. In this case, if genotype 3 HCV infection is identified, additional testing for resistance-associated substitution (RASs) is required before treatment with sofosbuvir/velpatasvir. Notably, HIV parameters (i.e., HIV RNA or CD4 count) are not required to determine eligibility for a simplified approach. The efficacy of HCV DAA treatment for people does not appear to be compromised at lower CD4 counts.[90-92]

Box 2. Pre-treatment Assessment Under Simplified Approach

1. Creatinine, liver function tests, and complete blood count
2. HCV RNA
3. Hepatitis B surface antigen
4. Initial fibrosis staging with FIB-4 (FIB-4 calculator)[a]
5. Medication and drug interaction review
6. HCV genotype required if cirrhosis is present

[a] Additional testing may be required if results are indeterminate (see text).

Key: HCV = hepatitis C virus

Drug–Drug Interactions

Drug interactions with ARVs pose less of a constraint on DAA use to treat HCV infection in people with HIV given the prominence of unboosted INSTI and TAF among first-line ARV regimens.[93] A comprehensive review of drug interactions between ARVs and antivirals for hepatitis C can be found within the Hepatitis C Virus/HIV Coinfection section of the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Interactions of clinical significance pertaining to the recommended DAA regimens are highlighted here and in **Table 4.**

Efavirenz coadministration results in a significant decrease in glecaprevir, pibrentasvir, and velpatasvir exposures.[94,95] People with HIV on an efavirenz-containing regimen are not eligible for simplified DAA treatment approaches **(Box 1)** and generally require an ARV switch prior to DAA treatment **(AII).**

Given similar pharmacologic profiles, including cytochrome P450 (CYP) enzyme induction, nevirapine and etravirine are also not recommended for coadministration with HCV DAAs, including glecaprevir/pibrentasvir and sofosbuvir/velpatasvir **(AII).**

Ritonavir- or cobicistat-boosted protease inhibitors significantly increase glecaprevir and pibrentasvir exposure[94]; people with HIV on boosted protease inhibitor (PI)–based ARV regimens were not included in registrational trials of glecaprevir/pibrentasvir and coadministration is not

recommended **(BII).**[96] Boosted protease inhibitors also increase velpatasvir exposure, which in turn increases tenofovir plasma exposure particularly when administered as TDF.[95] People with HIV on boosted ARV regimens were included in sofosbuvir/velpatasvir registrational trials, and the combination was not associated with increased adverse events.[97]

Given these considerations, sofosbuvir/velpatasvir can be co-administered with boosted ARV regimens **(AII);** TAF-based regimens are preferred. People on TDF-containing boosted ARV regimens are not eligible for simplified HCV treatment if their estimated glomerular filtration rate is <60 mL/min because monitoring on treatment is recommended **(AII).**

Summary of Major Drug Interactions Between HIV and HCV Antivirals

HIV Antivirals	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir
EFV, ETR, NVP, and other strong CYP 3A4 and P-gp inducers	Significant decrease in glecaprevir and pibrentasvir concentrations (avoid)	Significant decrease in velpatasvir concentrations (avoid)
PI/r, PI/c, unboosted ATV	Significant increase in glecaprevir and pibrentasvir concentrations (avoid)	Boosted PIs may increase velpatasvir concentrations, but no significant adverse events in clinical trial Coadministration allowed
TDF, TAF	Coadministration allowed	TAF preferred If TDF is used with boosted PIs if GFR <60 mL/min, monitoring is recommended.
RPV, DOR, EVG/c, RAL, BIC, DTG, ABC, FTC, 3TC, MVC	Coadministration allowed	Coadministration allowed

Key: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; BIC = bictegravir; CYP = cytochrome P450; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; GFR = glomerular filtration rate; FTC = emtricitabine; MVC = maraviroc; NVP = nevirapine; PI = protease inhibitor; PI/c = protease inhibitor/cobicistat; PI/r = protease inhibitor/ritonavir; P-gp = p-glycoprotein; RAL = raltegravir; RPV = rilpivirine; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

HCV Treatment Regimens

In HCV treatment-naive persons **without cirrhosis,** the recommended DAA regimens are either—

- Glecaprevir/pibrentasvir fixed dose combination (FDC) (100-mg/40-mg tablet), three tablets daily for 8 weeks **(AI)**

OR

- Sofosbuvir/velpatasvir FDC (400-mg/100-mg tablet), one tablet daily for 12 weeks **(AI)**

As noted in **Box 1,** these recommendations do not apply to HCV treatment–experienced patients because some of these individuals may require other DAA combinations and/or consultation with an expert. Persons meeting other criteria listed in **Box 1** should be treated according to standard approaches. Clinicians can refer to the most recent HCV treatment guidance for recommendations.

Primary data supporting the efficacy and safety of the two recommended treatment regimens in people with HIV come from registrational trials. In the ASTRAL-5 study, 12 weeks of sofosbuvir/velpatasvir without ribavirin was given to 106 people with HIV, including 19 with cirrhosis.[97] The SVR12 was 95% by intention-to-treat analysis with only two of five failures due to confirmed viral relapse. All participants with cirrhosis were cured. The EXPEDITION-2 study evaluated glecaprevir/pibrentasvir 300 mg/120 mg in 153 people with HIV with duration determined by cirrhosis status, with 137 non-cirrhotic participants treated for 8 weeks and 16 with cirrhosis treated for 12 weeks.[96] By intention-to-treat analysis, SVR12 was 98%, including 135 out of 137 participants without cirrhosis and 15 out of 16 participants with cirrhosis. The only confirmed virologic failure was virologic breakthrough at week 8 in a participant with genotype 3 and cirrhosis. Both regimens were well tolerated with low rates of discontinuation and no severe treatment-associated adverse events.

If compensated cirrhosis is present and sofosbuvir/velpatasvir is the planned regimen, then pre-treatment HCV genotyping is recommended **(AII).** If HCV genotype 3 is identified, NS5A resistance testing and modification of the sofosbuvir/velpatasvir regimen or selection of an alternative therapy may be necessary (for a full discussion, see the HCV treatment guidance). For all other genotypes or if glecaprevir/pibrentasvir is being used (regardless of genotype), no modification to the treatment regimen is required in the setting of compensated cirrhosis **(AIII).** The lower-strength recommendation for use of 8 weeks of glecaprevir/pibrentasvir in the setting of cirrhosis stems from a lack of prospective trials evaluating this duration in people with HIV and cirrhosis; 12 weeks of glecaprevir/pibrentasvir may be used in this setting **(CI).** The EXPEDITION-8 trial evaluated 8 weeks of glecaprevir/pibrentasvir in 343 participants with compensated cirrhosis and without HIV infection.[98] The intention-to-treat SVR12 was 98% and >99% in a per protocol analysis. The lone virologic failure was in genotype 3 infection yielding a per protocol SVR12 in this group of 98% (60/61). Data from real-world experience of use of 8 weeks of glecaprevir/pibrentasvir in the setting of cirrhosis were recently presented and included a small number of people with HIV.[99] Of the 20 people with HIV treated for 8 weeks, 19 out of 20 achieved SVR with no confirmed virologic failures.

Specific Treatment Situations

Acute HCV Infection Treatment

People with HIV are at risk for acute HCV infection. Given the public health implications in reducing onward transmission, in addition to benefit for the individual, HCV treatment should be started as soon as possible in this population **(AIII).**[21,44,100] The simplified treatment regimens outlined above are recommended in acute HCV infection **(AII);** shorter durations of therapy are currently being investigated. Patients who achieve viral clearance either spontaneously or after treatment should be counseled about the potential for reinfection.

Prior DAA Failure Retreatment

Despite the high cure rates associated with current DAA regimens, the large number of DAA treatments will inevitably result in an appreciable number of DAA failures. Persons with HIV were not included in the registrational trial of sofosbuvir/velpatasvir/voxilaprevir for retreatment of HCV infection[101]; nor were they included in initial prospective trials of either glecaprevir/pibrentasvir or sofosbuvir plus glecaprevir/pibrentasvir for HCV treatment of prior NS5A inhibitor containing DAA failures.[102,103] A follow-up prospective study comparing 12 weeks versus 16 weeks of

glecaprevir/pibrentasvir for genotype 1 sofosbuvir plus NS5A inhibitor failures did include a small number of people with HIV (~5%).[104] Similarly, published real-world experiences with retreatment of prior DAA failures are underrepresented with respect to people with HIV (all <5% except one with 15%).[105-108]

Drawing on the experience with initial DAA therapy of HCV infection, where people with HIV have nearly identical outcomes to persons with HCV infection alone, treatment approaches for DAA failures should be the same as those for persons with HCV mono-infection **(AIII).** Clinicians should refer to the most recent HCV treatment guidance for up-to-date recommendations.

Laboratory Monitoring and Post-Treatment Follow-Up

Laboratory monitoring while on treatment is not required for patients qualifying for the simplified treatment approach. However, documentation of HCV RNA levels at week 4 of therapy may be required by some payors prior to providing additional refills needed to complete therapy.

Effort should be made to document SVR (HCV RNA less than lower limits of quantification) at least 12 weeks after completion of therapy **(AI).** Patients without cirrhosis who achieve SVR do not require continued liver disease monitoring.

Periodic assessment for HCV reinfection should be done via HCV RNA testing on an at least yearly basis for those with ongoing risk behaviors or more frequently as dictated by clinical circumstances (e.g., new STI diagnosis or elevated liver enzymes) **(AII).**

In the setting of cirrhosis, hepatocellular carcinoma screening with liver ultrasound every 6 months should continue indefinitely **(BII).**

Special Considerations During Pregnancy

Testing for HCV infection should be performed during pregnancy to allow appropriate management for HCV-affected mothers during their pregnancy and after delivery and also to ensure their infants are identified as at risk for transmission and monitored **(AIII).**[109]

The rate of perinatal transmission has been reported at approximately 7% for infants born to mothers without HIV and 12% for infants born to mothers with HIV.[35,39,110] Due in large part to the opioid epidemic, more infants are born today with HCV infection than ever before[111,112]; thus, universal screening during each pregnancy, regardless of HIV status, is now the standard of care.[113] For the care of the infant, knowledge of exposure risk allows for screening for perinatal transmission.[114] During pregnancy, harm-reduction counseling and linkage to HCV care and treatment are important.[115]

Assessments for liver disease stage can be delayed until pregnancy related and postpartum changes have resolved. Individuals with known cirrhosis are at higher risks of complications during pregnancy, both for the individual and their infant. Hepatitis A and hepatitis B vaccines can be administered during pregnancy, and individuals who have not previously been vaccinated should receive them **(AII).**

Data are limited regarding the role of medical or surgical interventions to reduce the risk of perinatal HCV transmission. Nearly all studies, including those in individuals with and without HIV, have found that elective cesarean delivery does not reduce the risk of perinatal HCV transmission.[116-119]

Moreover, there is an increased risk of maternal morbidity associated with cesarean compared with vaginal delivery, particularly in the setting of maternal HIV infection.[120-123] Thus, while elective cesarean delivery in individuals with HIV/HCV coinfection can be considered based on HIV-related indications, data do not support its routine use for the prevention of HCV transmission.

The current standard of care for treatment of HCV infection, regardless of duration, is DAA combination therapy. In real-world studies, SVR rates are similar to those from registration trials,[124,125] and are consistently >90%. DAAs have not been sufficiently studied in pregnant women with HCV infection. In a pilot study of ledipasvir/sofosbuvir in pregnant women (without HIV infection), treatment was started in the end of the second/beginning of the third trimester and found to be safe and resulted in cure in nine women.[126] Pharmacokinetic measurements did not identify clinically significant changes.

Historically, while not studied in this population, DAA drugs have not demonstrated significant fetal toxicity concerns in animal studies, in contrast to when interferon and ribavirin were the standard of care. Interferon is no longer used for the treatment of HCV infection and ribavirin is used infrequently and usually in complex treatment or retreatment scenarios. Ribavirin is an FDA category X drug because of its teratogenicity at low doses in multiple animal species. Defects noted in animals include limb abnormalities, craniofacial defects, exencephaly, and anophthalmia.

Ribavirin **should not be used** during pregnancy **(AII).** Women of childbearing potential and men receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy **(AIII).** Inadvertent pregnancy during paternal exposure was not associated with adverse events in two newborns.[127] For now, treatment with DAA during pregnancy **is not recommended (CIII);** more safety data are needed.

Recommendations for Treatment of Hepatitis C Virus Infections

For Treatment-Naive Patients Without Cirrhosis (Any Genotype or No Pre-Treatment Genotype)

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AI) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks (AI)

Note: Characteristics that exclude people with HIV from receiving simplified therapy are outlined in Box 1.

For Treatment-Naive Patients with Compensated Cirrhosis (Recommendations Based on Genotypes)

Genotypes 1, 2, 4–6

Preferred Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AIII) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks (AI)

Alternative Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 12 weeks (CI)

Genotype 3

Preferred Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AIII)

Alternative Therapy

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 12 weeks (CI) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily, with or without ribavirin for 12 weeks pending results of NS5A RAS testing (CI)

For Treatment of Acute HCV Infection

- Three (glecaprevir 100 mg/pibrentasvir 40 mg per tablet) tablets daily for 8 weeks (AII) *or*
- One (sofosbuvir 400 mg/velpatasvir 100 mg per tablet) tablet daily for 12 weeks (AII)

Recommendations for treatment after DAA failure are not provided; see the corresponding section in the AASLD/IDSA HCV treatment guidance.

Key: AASLD = American Association for the Study of Liver Diseases; DAA = direct-acting antivirals; FDC = fixed-dose combination; HCV = hepatitis C virus; IDSA = Infectious Diseases Society of America; RAS = resistance-associated substitutions

References

1. Davis C, Mgomella GS, da Silva Filipe A, et al. Highly diverse hepatitis C strains detected in Sub-Saharan Africa have unknown susceptibility to direct-acting antiviral treatments. *Hepatology*. 2019;69(4):1426-1441. Available at: https://pubmed.ncbi.nlm.nih.gov/30387174.

2. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. *Hepatology*. 2014;59(1):318-327. Available at: https://pubmed.ncbi.nlm.nih.gov/24115039.

3. Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology*. 2015;61(1):77-87. Available at: https://pubmed.ncbi.nlm.nih.gov/25069599.

4. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. Towards ending viral hepatitis. World Health Organization. 2016. Available at: https://apps.who.int/iris/handle/10665/246177.

5. Hofmeister MG, Rosenthal EM, Barker LK, et al. Estimating prevalence of hepatitis C virus infection in the United States, 2013–2016. *Hepatology*. 2019;69(3):1020-1031. Available at: https://pubmed.ncbi.nlm.nih.gov/30398671.

6. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med*. 2014;160(5):293-300. Available at: https://pubmed.ncbi.nlm.nih.gov/24737271.

7. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *MMWR Morb Mortal Wkly Rep*. 2015;64(17):453-458. Available at: https://pubmed.ncbi.nlm.nih.gov/25950251.

8. Van Handel MM, Rose CE, Hallisey EJ, et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. *J Acquir Immune Defic Syndr*. 2016;73(3):323-331. Available at: https://pubmed.ncbi.nlm.nih.gov/27763996.

9. Rosenberg ES, Rosenthal EM, Hall EW, et al. Prevalence of hepatitis C virus infection in U.S. states and the District of Columbia, 2013 to 2016. *JAMA Netw Open*. 2018;1(8):e186371. Available at: https://pubmed.ncbi.nlm.nih.gov/30646319.

10. Centers for Disease Control and Prevention. 2019 viral hepatitis surveillance report. 2019. Available at: https://www.cdc.gov/hepatitis/statistics/2019surveillance/index.htm.

11. Hall EW, Schillie S, Vaughan AS, et al. County-level variation in hepatitis C virus mortality and trends in the United States, 2005–2017. *Hepatology*. 2021;74(2):582-590. Available at: https://pubmed.ncbi.nlm.nih.gov/33609308.

12. Platt L, Easterbrook P, Gower E, et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. *Lancet Infect Dis*. 2016;16(7):797-808. Available at: https://pubmed.ncbi.nlm.nih.gov/26922272.

13. Bosh KA, Coyle JR, Hansen V, et al. HIV and viral hepatitis coinfection analysis using surveillance data from 15 U.S. states and two cities. *Epidemiol Infect*. 2018;146(7):920-930. Available at: https://pubmed.ncbi.nlm.nih.gov/29636119.

14. Prussing C, Chan C, Pinchoff J, et al. HIV and viral hepatitis co-infection in New York City, 2000–2010: prevalence and case characteristics. *Epidemiol Infect*. 2015;143(7):1408-1416. Available at: https://pubmed.ncbi.nlm.nih.gov/25170631.

15. Centers for Disease Control and Prevention. About the Division of Viral Hepatitis. 2021. Available at: https://www.cdc.gov/hepatitis/aboutus.htm.

16. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V, 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One*. 2014;9(7):e101554. Available at: https://pubmed.ncbi.nlm.nih.gov/24988388.

17. Zuckerman A, Douglas A, Nwosu S, Choi L, Chastain C. Increasing success and evolving barriers in the hepatitis C cascade of care during the direct acting antiviral era. *PLoS One*. 2018;13(6):e0199174. Available at: https://pubmed.ncbi.nlm.nih.gov/29912944.

18. World Health Organization. Hepatitis C. 2021. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c.

19. Berenguer J, Rodríguez-Castellano E, Carrero A, et al. Eradication of hepatitis C virus and non-liver-related non-acquired immune deficiency syndrome-related events in human immunodeficiency virus/hepatitis C virus coinfection. *Hepatology*. 2017;66(2):344-356. Available at: https://pubmed.ncbi.nlm.nih.gov/28109003.

20. Boerekamps A, Newsum AM, Smit C, et al. High treatment uptake in human immunodeficiency virus/hepatitis C virus-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. *Clin Infect Dis*. 2018;66(9):1352-1359. Available at: https://pubmed.ncbi.nlm.nih.gov/29186365.

21. Boerekamps A, van den Berk GE, Lauw FN, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. *Clin Infect Dis*. 2018;66(9):1360-1365. Available at: https://pubmed.ncbi.nlm.nih.gov/29186320.

22. Doyle JS, van Santen DK, Iser D, et al. Microelimination of hepatitis C among people with human immunodeficiency virus coinfection: declining incidence and prevalence accompanying a multicenter treatment scale-up trial. *Clin Infect Dis*. 2021;73(7):e2164-e2172. Available at: https://pubmed.ncbi.nlm.nih.gov/33010149.

23. Liu CH, Kao JH. Last mile to microelimination of hepatitis C virus infection among people living with human immunodeficiency virus. *Clin Infect Dis*. 2021;73(7):e2172-e2174. Available at: https://pubmed.ncbi.nlm.nih.gov/33005954.

24. Smit C, Boyd A, Rijnders BJA, et al. HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study. *Lancet HIV*. 2021;8(2):e96-e105. Available at: https://pubmed.ncbi.nlm.nih.gov/33357835.

25. Alter MJ. Epidemiology of hepatitis C virus infection. *World J Gastroenterol*. 2007;13(17):2436-2441. Available at: https://pubmed.ncbi.nlm.nih.gov/17552026.

26. Paintsil E, He H, Peters C, Lindenbach BD, Heimer R. Survival of hepatitis C virus in syringes: implication for transmission among injection drug users. *J Infect Dis*. 2010;202(7):984-990. Available at: https://pubmed.ncbi.nlm.nih.gov/20726768.

27. Sulkowski MS, Moore RD, Mehta SH, Chaisson RE, Thomas DL. Hepatitis C and progression of HIV disease. *JAMA*. 2002;288(2):199-206. Available at: https://pubmed.ncbi.nlm.nih.gov/12095384.

28. Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. *J Hepatol*. 2006;45(4):607-616. Available at: https://pubmed.ncbi.nlm.nih.gov/16901579.

29. Cotte L, Hocqueloux L, Lefebvre M, et al. Microelimination or not? The changing epidemiology of human immunodeficiency virus-hepatitis C virus coinfection in France 2012–2018. *Clin Infect Dis*. 2021;73(9):e3266-e3274. Available at: https://pubmed.ncbi.nlm.nih.gov/33400777.

30. Crespo J, Cuadrado A, Perelló C, et al. Epidemiology of hepatitis C virus infection in a country with universal access to direct-acting antiviral agents: data for designing a cost-effective elimination policy in Spain. *J Viral Hepat*. 2020;27(4):360-370. Available at: https://pubmed.ncbi.nlm.nih.gov/31755634.

31. Liu L, Wang L, Zhang H, et al. Changing epidemiology of hepatitis B virus and hepatitis C virus coinfection in a human immunodeficiency virus-positive population in China: results from the Third and Fourth Nationwide Molecular Epidemiologic Surveys. *Clin Infect Dis*. 2021;73(4):642-649. Available at: https://pubmed.ncbi.nlm.nih.gov/34398954.

32. van de Laar TJ, Matthews GV, Prins M, Danta M. Acute hepatitis C in HIV-infected men who have sex with men: an emerging sexually transmitted infection. *AIDS*. 2010;24(12):1799-1812. Available at: https://pubmed.ncbi.nlm.nih.gov/20601854.

33. Hoornenborg E, Achterbergh RCA, Schim van der Loeff MF, et al. MSM starting preexposure prophylaxis are at risk of hepatitis C virus infection. *AIDS*. 2017;31(11):1603-1610. Available at: https://pubmed.ncbi.nlm.nih.gov/28657964.

34. Krakower DS, Mayer KH. Routine screening for hepatitis C in MSM on HIV PrEP. *Nat Rev Urol*. 2019;16(5):272-274. Available at: https://pubmed.ncbi.nlm.nih.gov/30783262.

35. Ades AE, Gordon F, Scott K, et al. Overall vertical transmission of HCV, transmission net of clearance, and timing of transmission. *Clin Infect Dis*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35403676.

36. Eyster ME, Alter HJ, Aledort LM, Quan S, Hatzakis A, Goedert JJ. Heterosexual co-transmission of hepatitis C virus (HCV) and human immunodeficiency virus (HIV). *Ann Intern Med*. 1991;115(10):764-768. Available at: https://pubmed.ncbi.nlm.nih.gov/1656825.

37. Lissen E, Alter HJ, Abad MA, et al. Hepatitis C virus infection among sexually promiscuous groups and the heterosexual partners of hepatitis C virus infected index cases. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):827-831. Available at: https://pubmed.ncbi.nlm.nih.gov/7509282.

38. Terrault NA, Dodge JL, Murphy EL, et al. Sexual transmission of hepatitis C virus among monogamous heterosexual couples: the HCV partners study. *Hepatology*. 2013;57(3):881-889. Available at: https://pubmed.ncbi.nlm.nih.gov/23175457.

39. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. *Clin Infect Dis*. 2014;59(6):765-773. Available at: https://pubmed.ncbi.nlm.nih.gov/24928290.

40. Terrault NA, Levy MT, Cheung KW, Jourdain G. Viral hepatitis and pregnancy. *Nat Rev Gastroenterol Hepatol*. 2021;18(2):117-130. Available at: https://pubmed.ncbi.nlm.nih.gov/33046891.

41. Conte D, Fraquelli M, Prati D, Colucci A, Minola E. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology*. 2000;31(3):751-755. Available at: https://pubmed.ncbi.nlm.nih.gov/10706568.

42. Domínguez-Rodríguez S, Prieto L, Fernández McPhee C, et al. Perinatal HCV transmission rate in HIV/HCV coinfected women with access to ART in Madrid, Spain. *PLoS One*. 2020;15(4):e0230109. Available at: https://pubmed.ncbi.nlm.nih.gov/32271775.

43. Zelenev A, Li J, Mazhnaya A, Basu S, Altice FL. Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study. *Lancet Infect Dis*. 2018;18(2):215-224. Available at: https://pubmed.ncbi.nlm.nih.gov/29153265.

44. Bethea ED, Chen Q, Hur C, Chung RT, Chhatwal J. Should we treat acute hepatitis C? A decision and cost-effectiveness analysis. *Hepatology*. 2018;67(3):837-846. Available at: https://pubmed.ncbi.nlm.nih.gov/29059461.

45. Rockstroh JK, Boesecke C. Hepatitis C virus treatment as prevention: challenges and opportunities in men who have sex with men. *J Infect Dis*. 2020;222(Suppl 9):S782-s788. Available at: https://pubmed.ncbi.nlm.nih.gov/33245348.

46. Tong MJ, el-Farra NS, Reikes AR, Co RL. Clinical outcomes after transfusion-associated hepatitis C. *N Engl J Med*. 1995;332(22):1463-1466. Available at: https://pubmed.ncbi.nlm.nih.gov/7739682.

47. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet*. 1997;349(9055):825-832. Available at: https://pubmed.ncbi.nlm.nih.gov/9121257.

48. Koretz RL, Abbey H, Coleman E, Gitnick G. Non-A, non-B post-transfusion hepatitis. Looking back in the second decade. *Ann Intern Med*. 1993;119(2):110-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8512159.

49. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Elevated liver enzymes following initiation of antiretroviral therapy. *JAMA*. 2000;283(19):2526-2527. Available at: https://pubmed.ncbi.nlm.nih.gov/10815113.

50. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. *Hepatology*. 1999;30(4):1054-1058. Available at: https://pubmed.ncbi.nlm.nih.gov/10498659.

51. Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. *Hepatology*. 2001;34(6):1193-1199. Available at: https://pubmed.ncbi.nlm.nih.gov/11732009.

52. Pineda JA, Romero-Gómez M, Díaz-García F, et al. HIV coinfection shortens the survival of patients with hepatitis C virus-related decompensated cirrhosis. *Hepatology*. 2005;41(4):779-789. Available at: https://pubmed.ncbi.nlm.nih.gov/15800956.

53. Ragni MV, Eghtesad B, Schlesinger KW, Dvorchik I, Fung JJ. Pretransplant survival is shorter in HIV-positive than HIV-negative subjects with end-stage liver disease. *Liver Transpl*. 2005;11(11):1425-1430. Available at: https://pubmed.ncbi.nlm.nih.gov/16237709.

54. Lo Re V, 3rd, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. *Ann Intern Med*. 2014;160(6):369-379. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24723077.

55. Salmon-Ceron D, Lewden C, Morlat P, et al. Liver disease as a major cause of death among HIV infected patients: role of hepatitis C and B viruses and alcohol. *J Hepatol*. 2005;42(6):799-805. Available at: https://pubmed.ncbi.nlm.nih.gov/15973779.

56. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641. Available at: https://pubmed.ncbi.nlm.nih.gov/16908797.

57. Smith JA, Aberle JH, Fleming VM, et al. Dynamic coinfection with multiple viral subtypes in acute hepatitis C. *J Infect Dis*. 2010;202(12):1770-1779. Available at: https://pubmed.ncbi.nlm.nih.gov/21067369.

58. Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. *MMWR Morb Mortal Wkly Rep*. 2013;62(18):362-365. Available at: https://pubmed.ncbi.nlm.nih.gov/23657112.

59. American Association for the Study of Liver Diseases IDSoA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. 2021. Available at: https://www.hcvguidelines.org.

60. Centers for Disease Control and Prevention. HIV guidelines: preventing new HIV infections. Available at: https://www.cdc.gov/hiv/guidelines/preventing.html.

61. Chamie G, Bonacini M, Bangsberg DR, et al. Factors associated with seronegative chronic hepatitis C virus infection in HIV infection. *Clin Infect Dis*. 2007;44(4):577-583. Available at: https://pubmed.ncbi.nlm.nih.gov/17243063.

62. Mattsson L, Grillner L, von Sydow M, Bergdahl S, Weiland O. Seroconversion to hepatitis C virus antibodies in patients with acute posttransfusion non-A, non-B hepatitis in Sweden. *Infection*. 1991;19(5):309-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1666063.

63. Thomson EC, Nastouli E, Main J, et al. Delayed anti-HCV antibody response in HIV-positive men acutely infected with HCV. *AIDS*. 2009;23(1):89-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19050390.

64. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med*. 2003;138(3):197-207. Available at: https://pubmed.ncbi.nlm.nih.gov/12558359.

65. Feld JJ. Hepatitis C virus diagnostics: the road to simplification. *Clin Liver Dis (Hoboken)*. 2018;12(5):125-129. Available at: https://pubmed.ncbi.nlm.nih.gov/30988927.

66. Taylor JL, Johnson S, Cruz R, Gray JR, Schiff D, Bagley SM. Integrating harm reduction into outpatient opioid use disorder treatment settings: harm reduction in outpatient addiction treatment. *J Gen Intern Med*. 2021;36(12):3810-3819. Available at: https://pubmed.ncbi.nlm.nih.gov/34159545.

67. Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. *Cochrane Database Syst Rev*. 2017;9(9):Cd012021. Available at: https://pubmed.ncbi.nlm.nih.gov/28922449.

68. Schulte B, Schmidt CS, Strada L, et al. Hepatitis C virus prevalence and incidence in a large nationwide sample of patients in opioid substitution treatment in Germany: a prospective cohort study. *Clin Infect Dis*. 2020;70(10):2199-2205. Available at: https://pubmed.ncbi.nlm.nih.gov/31631215.

69. Jin F, Dore GJ, Matthews G, et al. Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2021;6(1):39-56. Available at: https://pubmed.ncbi.nlm.nih.gov/33217341.

70. Vanhommerig JW, Lambers FA, Schinkel J, et al. Risk factors for sexual transmission of hepatitis C virus among human immunodeficiency virus-infected men who have sex with men: a case-control study. *Open Forum Infect Dis*. 2015;2(3):ofv115. Available at: https://pubmed.ncbi.nlm.nih.gov/26634219.

71. Hampel B, Kusejko K, Kouyos RD, et al. Chemsex drugs on the rise: a longitudinal analysis of the Swiss HIV Cohort Study from 2007 to 2017. *HIV Med*. 2020;21(4):228-239. Available at: https://pubmed.ncbi.nlm.nih.gov/31849182.

72. Naggie S, Holland DP, Sulkowski MS, Thomas DL. Hepatitis C virus postexposure prophylaxis in the healthcare worker: why direct-acting antivirals don't change a thing. *Clin Infect Dis*. 2017;64(1):92-99. Available at: https://pubmed.ncbi.nlm.nih.gov/27682067.

73. Page K, Melia MT, Veenhuis RT, et al. Randomized trial of a vaccine regimen to prevent chronic HCV infection. *N Engl J Med*. 2021;384(6):541-549. Available at: https://pubmed.ncbi.nlm.nih.gov/33567193.

74. Lambers FA, Brinkman K, Schinkel J, et al. Treatment of acute hepatitis C virus infection in HIV-infected MSM: the effect of treatment duration. *AIDS*. 2011;25(10):1333-1336. Available at: https://pubmed.ncbi.nlm.nih.gov/21516025.

75. Piroth L, Larsen C, Binquet C, et al. Treatment of acute hepatitis C in human immunodeficiency virus-infected patients: the HEPAIG study. *Hepatology*. 2010;52(6):1915-1921. Available at: https://pubmed.ncbi.nlm.nih.gov/21064156.

76. Martin NK, Thornton A, Hickman M, et al. Can hepatitis C virus (HCV) direct-acting antiviral treatment as prevention reverse the HCV epidemic among men who have sex with men in the United Kingdom? Epidemiological and modeling insights. *Clin Infect Dis*. 2016;62(9):1072-1080. Available at: https://pubmed.ncbi.nlm.nih.gov/26908813.

77. Vento S. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *J Viral Hepat*. 2000;7 Suppl 1:7-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10866837.

78. Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28(3):805-809. Available at: https://pubmed.ncbi.nlm.nih.gov/9731576.

79. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2018;68(2):723-750. Available at: https://pubmed.ncbi.nlm.nih.gov/29624699.

80. Merchante N, Giron-Gonzalez JA, Gonzalez-Serrano M, et al. Survival and prognostic factors of HIV-infected patients with HCV-related end-stage liver disease. *AIDS*. 2006;20(1):49-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16327319.

81. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004;351(5):438-450. Available at: https://pubmed.ncbi.nlm.nih.gov/15282351.

82. Chung RT, Andersen J, Volberding P, et al. Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med*. 2004;351(5):451-459. Available at: https://pubmed.ncbi.nlm.nih.gov/15282352.

83. Solomon SS, Wagner-Cardoso S, Smeaton L, et al. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. *Lancet Gastroenterol Hepatol*. 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/35026142.

84. Dore GJ, Feld JJ, Thompson A, et al. Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir, a randomised non-inferiority trial. *J Hepatol*. 2020;72(3):431-440. Available at: https://pubmed.ncbi.nlm.nih.gov/31655134.

85. Butt AA, Yan P, Shaikh OS, Chung RT, Sherman KE. Treatment adherence and virological response rates in hepatitis C virus infected persons treated with sofosbuvir-based regimens: results from ERCHIVES. *Liver Int*. 2016;36(9):1275-1283. Available at: https://pubmed.ncbi.nlm.nih.gov/26928927.

86. Ward KM, Falade-Nwulia O, Moon J, et al. Non-adherence to LDV/SOF did not predict SVR in a randomized controlled trial of HIV/HCV coinfected persons who use drugs. *J Infect Dis*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/34543417.

87. Cunningham EB, Hajarizadeh B, Amin J, et al. Adherence to once-daily and twice-daily direct-acting antiviral therapy for hepatitis C infection among people with recent injection drug use or current opioid agonist therapy. *Clin Infect Dis*. 2020;71(7):e115-e124. Available at: https://pubmed.ncbi.nlm.nih.gov/31677262.

88. Schmid P, Bregenzer A, Huber M, et al. Progression of liver fibrosis in HIV/HCV co-infection: a comparison between non-invasive assessment methods and liver biopsy. *PLoS One*. 2015;10(9):e0138838. Available at: https://pubmed.ncbi.nlm.nih.gov/26418061.

89. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Ann Intern Med*. 2013;159(5):372. Available at: https://pubmed.ncbi.nlm.nih.gov/24026329.

90. Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients treated in routine practice. *Clin Infect Dis*. 2017;64(12):1711-1720. Available at: https://pubmed.ncbi.nlm.nih.gov/28199525.

91. Kim HN, Nance RM, Williams-Nguyen JS, et al. Effectiveness of direct-acting antiviral therapy in patients with human immunodeficiency virus-hepatitis C virus coinfection in routine clinical care: a multicenter study. *Open Forum Infect Dis*. 2019;6(4):ofz100. Available at: https://pubmed.ncbi.nlm.nih.gov/30949539.

92. Amele S, Peters L, Rodger A, et al. Effectiveness and safety of interferon-free direct-acting antiviral hepatitis C virus therapy in HIV/hepatitis C virus coinfected individuals: results from a pan-European study. *J Acquir Immune Defic Syndr*. 2021;86(2):248-257. Available at: https://pubmed.ncbi.nlm.nih.gov/33079903.

93. Panel on Antiretroviral Guidelines for Adults and Adolescents. Hepatitis C virus/HIV coinfection. 2022. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/hepatitis-c-virus-hiv-coinfection?view=full.

94. Kosloski MP, Oberoi R, Wang S, et al. Drug-drug interactions of glecaprevir and pibrentasvir coadministered with human immunodeficiency virus antiretrovirals. *J Infect Dis*. 2020;221(2):223-231. Available at: https://pubmed.ncbi.nlm.nih.gov/31504702.

95. Mogalian E, Stamm LM, Osinusi A, et al. Drug-drug interaction studies between hepatitis C virus antivirals sofosbuvir/velpatasvir and boosted and unboosted human immunodeficiency virus antiretroviral regimens in healthy volunteers. *Clin Infect Dis*. 2018;67(6):934-940. Available at: https://pubmed.ncbi.nlm.nih.gov/29522076.

96. Rockstroh JK, Lacombe K, Viani RM, et al. Efficacy and safety of glecaprevir/pibrentasvir in patients coinfected with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study. *Clin Infect Dis*. 2018;67(7):1010-1017. Available at: https://pubmed.ncbi.nlm.nih.gov/29566246.

97. Wyles D, Bräu N, Kottilil S, et al. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfected with human immunodeficiency virus type 1: an open-label, Phase 3 study. *Clin Infect Dis*. 2017;65(1):6-12. Available at: https://pubmed.ncbi.nlm.nih.gov/28369210.

98. Brown RS, Jr., Buti M, Rodrigues L, et al. Glecaprevir/pibrentasvir for 8 weeks in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: the EXPEDITION-8 trial. *J Hepatol*. 2020;72(3):441-449. Available at: https://pubmed.ncbi.nlm.nih.gov/31682879.

99. Cornberg M, Jimenez AMA, Aghemo A, et al. Safety and effectiveness using 8 weeks of glecaprevir/pibrentasvir in HCV-infected treatment-naive patients with compensated cirrhosis: the CREST study. *Hepatology*. 2021;74:575A-576A. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9239949.

100. Popping S, Hullegie SJ, Boerekamps A, et al. Early treatment of acute hepatitis C infection is cost-effective in HIV-infected men-who-have-sex-with-men. *PLoS One*. 2019;14(1):e0210179. Available at: https://pubmed.ncbi.nlm.nih.gov/30629662.

101. Bourlière M, Gordon SC, Flamm SL, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376(22):2134-2146. Available at: https://pubmed.ncbi.nlm.nih.gov/28564569.

102. Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. *Hepatology*. 2017;66(2):389-397. Available at: https://pubmed.ncbi.nlm.nih.gov/28128852.

103. Wyles D, Weiland O, Yao B, et al. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. *J Hepatol*. 2019;70(5):1019-1023. Available at: https://pubmed.ncbi.nlm.nih.gov/30857780.

104. Lok AS, Sulkowski MS, Kort JJ, et al. Efficacy of glecaprevir and pibrentasvir in patients with genotype 1 hepatitis C virus infection with treatment failure after NS5A inhibitor plus sofosbuvir therapy. *Gastroenterology*. 2019;157(6):1506-1517.e1501. Available at: https://pubmed.ncbi.nlm.nih.gov/31401140.

105. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. *J Viral Hepat*. 2019;26(8):980-990. Available at: https://pubmed.ncbi.nlm.nih.gov/31012179.

106. Llaneras J, Riveiro-Barciela M, Lens S, et al. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. *J Hepatol*. 2019;71(4):666-672. Available at: https://pubmed.ncbi.nlm.nih.gov/31203153.

107. Degasperi E, Spinetti A, Lombardi A, et al. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. *J Hepatol*. 2019;71(6):1106-1115. Available at: https://pubmed.ncbi.nlm.nih.gov/31433303.

108. Papaluca T, Roberts SK, Strasser SI, et al. Efficacy and safety of sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus (HCV) NS5A-inhibitor experienced patients with difficult to cure characteristics. *Clin Infect Dis*. 2021;73(9):e3288-e3295. Available at: https://pubmed.ncbi.nlm.nih.gov/32887983.

109. The American College of Obstetricians and Gynecologists. Viral hepatitis in pregnancy. 2022. Available at: https://www.acog.org/en/clinical/clinical-guidance/practice-bulletin/articles/2007/10/viral-hepatitis-in-pregnancy.

110. Prasad M. Risk factors for mother to child transmission of hepatitis C (HCV): a prospective observational study. *American Journal of Obstetrics & Gynecology*. 2022;226(S5). Available at: https://www.ajog.org/article/S0002-9378(21)01238-2/fulltext.

111. Rossi RM, Wolfe C, Brokamp R, et al. Reported prevalence of maternal hepatitis C virus infection in the United States. *Obstet Gynecol*. 2020;135(2):387-395. Available at: https://pubmed.ncbi.nlm.nih.gov/31923064.

112. Patrick SW, Bauer AM, Warren MD, Jones TF, Wester C. Hepatitis C virus infection among women giving birth - Tennessee and United States, 2009–2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(18):470-473. Available at: https://pubmed.ncbi.nlm.nih.gov/28493860.

113. The American College of Obstetricians and Gynecologists. Routine hepatitis C virus screening in pregnant individuals. 2021. Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2021/05/routine-hepatitis-c-virus-screening-in-pregnant-individuals.

114. Jhaveri R, Broder T, Bhattacharya D, Peters MG, Kim AY, Jonas MM. Universal screening of pregnant women for hepatitis C: the time is now. *Clin Infect Dis*. 2018;67(10):1493-1497. Available at: https://pubmed.ncbi.nlm.nih.gov/30215670.

115. Chaillon A, Rand EB, Reau N, Martin NK. Cost-effectiveness of universal hepatitis C virus screening of pregnant women in the United States. *Clin Infect Dis*. 2019;69(11):1888-1895. Available at: https://pubmed.ncbi.nlm.nih.gov/30689769.

116. McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol*. 2008;199(3):315.e311-315. Available at: https://pubmed.ncbi.nlm.nih.gov/18771997.

117. Ghamar Chehreh ME, Tabatabaei SV, Khazanehdari S, Alavian SM. Effect of cesarean section on the risk of perinatal transmission of hepatitis C virus from HCV-RNA+/HIV-

mothers: a meta-analysis. *Arch Gynecol Obstet*. 2011;283(2):255-260. Available at: https://pubmed.ncbi.nlm.nih.gov/20652289.

118. Mariné-Barjoan E, Berrébi A, Giordanengo V, et al. HCV/HIV co-infection, HCV viral load and mode of delivery: risk factors for mother-to-child transmission of hepatitis C virus? *AIDS*. 2007;21(13):1811-1815. Available at: https://pubmed.ncbi.nlm.nih.gov/17690581.

119. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005;192(11):1872-1879. Available at: https://pubmed.ncbi.nlm.nih.gov/16267757.

120. Read JS, Tuomala R, Kpamegan E, et al. Mode of delivery and postpartum morbidity among HIV-infected women: the women and infants transmission study. *J Acquir Immune Defic Syndr*. 2001;26(3):236-245. Available at: https://pubmed.ncbi.nlm.nih.gov/11242196.

121. Grubert TA, Reindell D, Kästner R, et al. Rates of postoperative complications among human immunodeficiency virus-infected women who have undergone obstetric and gynecologic surgical procedures. *Clin Infect Dis*. 2002;34(6):822-830. Available at: https://pubmed.ncbi.nlm.nih.gov/11850864.

122. Grubert TA, Reindell D, Kästner R, Lutz-Friedrich R, Belohradsky BH, Dathe O. Complications after caesarean section in HIV-1-infected women not taking antiretroviral treatment. *Lancet*. 1999;354(9190):1612-1613. Available at: https://pubmed.ncbi.nlm.nih.gov/10560681.

123. Fiore S, Newell ML, Thorne C. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. *AIDS*. 2004;18(6):933-938. Available at: https://pubmed.ncbi.nlm.nih.gov/15060441.

124. D'Ambrosio R, Pasulo L, Puoti M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. *J Hepatol*. 2019;70(3):379-387. Available at: https://pubmed.ncbi.nlm.nih.gov/30472321.

125. Mangia A, Milligan S, Khalili M, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: Analysis of 5,552 patients from 12 cohorts. *Liver Int*. 2020;40(8):1841-1852. Available at: https://pubmed.ncbi.nlm.nih.gov/32449966.

126. Chappell CA, Scarsi KK, Kirby BJ, et al. Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. *Lancet Microbe*. 2020;1(5):e200-e208. Available at: https://pubmed.ncbi.nlm.nih.gov/32939459.

127. Hegenbarth K, Maurer U, Kroisel PM, Fickert P, Trauner M, Stauber RE. No evidence for mutagenic effects of ribavirin: report of two normal pregnancies. *Am J Gastroenterol*. 2001;96(7):2286-2287. Available at: https://pubmed.ncbi.nlm.nih.gov/11467687.

Herpes Simplex Virus

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Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Among people aged 14 to 49 years in the United States as of 2016, the HSV-1 seroprevalence is 47.8%, and the HSV-2 seroprevalence is 11.9%.[1] Although most cases of recurrent genital herpes are due to HSV-2, HSV-1 has become an increasing cause of first-episode genital herpes, causing up to 42% of infections in young adult heterosexual women and 76% of infections in young adult men who have sex with men in Sydney, Australia between 1992 to 2006.[2] In one study earlier in the HIV epidemic, approximately 60% of people with HIV were HSV-2 seropositive, and 96% were seropositive for either HSV-1 or HSV-2.[3,4] HSV-2 infection increases the risk of HIV acquisition two- to threefold.[5,6] In HIV-1/HSV-2 coinfected people not taking effective antiretroviral therapy (ART), the rate of HSV-2 reactivation and shedding is increased,[7] and HSV-2 reactivation is associated with increased HIV RNA levels in plasma and genital secretions.[8]

Clinical Manifestations

The majority of clinically evident infections with herpes simplex virus (HSV) manifest as mucocutaneous lesions, occurring in either perioral or genital distributions.

Orolabial herpes (commonly known as cold sores or fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations of oral HSV-1 include a sensory prodrome in the affected area, rapidly followed by lesions on lips and oral mucosa that evolve in stages from papule to vesicle, ulcer, and crust. The course of illness in untreated persons is 5 to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight and physiologic stress.[9]

The majority of individuals with HSV-2 seropositivity have clinically silent infection.[10] Genital herpes is typically caused by HSV-2 and is the most common manifestation of symptomatic HSV-2 infection, though HSV-2 can also cause orolabial herpes. Genital herpes caused by HSV-1 is clinically indistinguishable from HSV-2 infection, although recurrences and viral shedding occur less often with genital HSV-1 infection.[11] Typical genital mucosal or skin lesions evolve through stages of papule to vesicle, ulcer, and crust. Ulcerative lesions are usually the only stage observed on mucosal surfaces, but vesicles are commonly seen on skin on or around the genitals (e.g., the penile shaft, mons pubis, thighs). Local symptoms might include a sensory prodrome consisting of pain and pruritus. Mucosal genital disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.[12] Fever can also occur in primary infection. These classic manifestations occur in some people, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized. Regardless of the clinical severity of infection, viral shedding on mucosal surfaces occurs frequently and can result in transmission. HSV shedding occurs more frequently in people with HIV with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3 than in those without HIV or with higher CD4 counts.[13,14]

HSV-1 and HSV-2 are significant causes of proctitis in men with HIV who have sex with men and may occur in the absence of external anal ulcers.[15] In profoundly immunocompromised people (CD4 counts <100 cells/mm^3), extensive, deep, nonhealing ulcerations can occur. Perirectal HSV lesions are more likely to be resistant to acyclovir compared to lesions at other locations.[16] In addition, atypical presentations, such as hypertrophic genital HSV,[17,18] which mimics neoplasia and requires biopsy for diagnosis, may be seen in people with HIV.

HSV esophagitis presents similarly in people with and without HIV, aside from extended symptom duration.[19] The manifestations of other non-mucocutaneous or disseminated HSV infections (e.g., acute retinal necrosis, keratitis, meningitis, encephalitis, Bell's palsy, hepatitis, herpetic whitlow) are similar to those observed in people without HIV. Disseminated HSV infection is rare, even in profoundly immunosuppressed people, such as recipients of hematopoietic stem cell transplant[20] and solid organ transplant.[21]

Diagnosis

Because mucocutaneous HSV infections cannot be diagnosed accurately by clinical examination alone, a laboratory diagnosis of all suspected HSV mucocutaneous infections should be pursued.[22] HSV DNA polymerase chain reaction (PCR) is the preferred method for mucocutaneous lesions potentially caused by HSV. PCR is the most sensitive method of diagnosis; viral culture sensitivity decreases as lesions heal.[23] Testing for other sexually transmitted infections and infectious causes of ulcerative disease—including varicella zoster virus, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, and mpox—is also advised based on local endemicity and patient risk factors.

For suspected central nervous system (CNS) infection, PCR can be run directly on cerebral spinal fluid specimens. Differentiation between CNS infection with HSV-1 and HSV-2 should be pursued to guide conversations about risk of recurrence. HSV PCR of the blood should not be used to diagnose mucosal HSV unless there is concern for disseminated disease. HSV detected in genital and oral lesions should be tested for both HSV-1 and HSV-2 for purposes of counseling on recurrence and transmission. Testing for other manifestations of HSV (e.g., esophagitis, meningitis, encephalitis, hepatitis, keratitis, etc.) is the same in people with and without HIV.

Type-specific serum and point-of-care immunoglobulin G serologic assays are commercially available and can be used for the diagnosis of HSV-2 infection in asymptomatic individuals or those with atypical lesions. Type-specific serologic screening for HSV-2 can be considered for people with HIV, particularly for those with history of genital ulcer disease, atypical genital lesions that were not confirmed as HSV by PCR or culture, and for those whose sexual partners have HSV-2 infection.[22] However, providers should be aware that there are some important limitations of currently available serologic tests. False negative serologies can occur in early infection; repeat testing 12 weeks following suspected exposure is warranted. False positive HSV-2 serologic test results occur with the enzyme immunoassay antibody tests, particularly at low index values (1.1–3.0).[24-26] In such situations, confirmatory testing with a second serologic test using a different antigen is recommended.[27] Serologic screening for HSV-1 infection is not useful due to high prevalence, and HSV-1 or HSV-2 immunoglobulin M (IgM) is not useful because IgM testing is not type-specific.[22]

A diagnosis of genital herpes should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2021 CDC Sexually Transmitted Infections Treatment Guidelines.

Preventing Exposure

Although earlier in the HIV epidemic most people with HIV were found to also have HSV-1 and HSV-2 infections,[4] more recent prevalence is not known, and preventing HSV-2 acquisition in those who do not already have HSV-2 is important. In heterosexual HIV-negative but HSV-2-serodifferent couples, disclosure of HSV-2 status is associated with reduced risk of HSV-2 transmission.[28] Consistent use of condoms reduces HSV-2 acquisition in heterosexual couples and should be encouraged to prevent transmission of HSV-2 and other sexually transmitted pathogens **(AII).**[29] The association between consistent condom use and the reduction of HSV-2 acquisition in men who have sex with men has not been studied, but consistent condom use should be encouraged **(AIII).**

Sexual transmission of HSV most often occurs during episodes of asymptomatic viral shedding. People with HIV should avoid sexual contact with partners who have overt genital or orolabial herpetic lesions **(AII).**

The value of using suppressive antiviral therapy to prevent transmission of HSV-2 might vary according to HIV status. In people with symptomatic HSV-2 without HIV, suppressive antiviral therapy with valacyclovir 500 mg once daily reduced HSV-2 transmission to susceptible heterosexual partners by 48%.[30] However, in people seropositive for HSV-2 and HIV-1 but not taking ART, suppressive acyclovir at 400 mg twice daily did not prevent HSV-2 transmission to HSV-2–seronegative partners.[31] It is unknown if the lack of efficacy in the latter study was related to HIV-1 infection, uncontrolled HIV-1 viremia, the suppressive regimen, or because HSV-2 seropositive patients did not need to have a history of genital ulcer disease to participate. Extrapolating from the HSV-2 transmission trial among people without HIV, use of suppressive anti-HSV therapy used only for the purpose of preventing HSV-2 transmission to seronegative partners can be considered as part of a shared-decision-making conversation with applicable patients and partners particularly if there is a history of genital ulcer disease **(BIII).** Patients should be made aware that this strategy may be of modest benefit in preventing transmission, and other methods of risk reduction should also be considered to maximize protection **(BIII).** There are no data available regarding the use of suppressive therapy to prevent genital HSV-1 transmission.

Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection **is not recommended (AIII).** In clinical trials, pre-exposure prophylaxis with vaginal tenofovir gel and oral tenofovir disoproxil fumarate (TDF) or with TDF/emtricitabine has been associated with reduced risk of HSV-2 acquisition in people without HIV.[32-34] However, HSV-2 seronegative people with HIV on TDF-containing ART regimens are at similar risk of acquiring HSV-2 as those on non-TDF-containing ART regimens,[35] suggesting that TDF is not effective in preventing HSV-2 acquisition in people with HIV. The dose, duration, timing, and efficacy of anti-HSV prophylaxis after known or suspected exposure to HSV have not been evaluated. No vaccine for prevention of HSV infection is available. Some studies have shown that medical male circumcision decreased the risk of HSV-2 acquisition in African men without HIV,[36,37] and may be associated with decreased risk of HSV-2 transmission to female partners.[38] However, medical male circumcision to decrease risk of HSV-2 acquisition and transmission has not been studied among men with HIV and therefore **is not recommended** for the sole purpose of preventing HSV acquisition **(AIII).**

Treating Disease

Recommendations for Treating Herpes Simplex Virus Infections

Note: Compared to acyclovir, valacyclovir has improved bioavailability and requires less frequent dosing.

Orolabial Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day (AIII), *or*
- Famciclovir 500 mg PO twice a day (AIII), *or*
- Acyclovir 400 mg PO three times a day (AIII)

Initial Genital Lesions (Duration: 7–10 Days) or Recurrent Genital Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO twice a day (AI), *or*
- Famciclovir 500 mg PO twice a day (AI), *or*
- Acyclovir 400 mg PO three times a day (AI)

Severe Mucocutaneous and Visceral or Disseminated HSV Infections

- For initial therapy, acyclovir 10 mg/kg IV every 8 hours for 10–14 days (AIII)
- For mucocutaneous lesions, change to oral therapy (dose as above) once lesions begin to regress (AIII); continue oral treatment until lesions have completely healed (AIII)
- Some clinicians will elect to extend the course of treatment for visceral or disseminated disease based on clinical response and degree of immunosuppression.

Ophthalmic HSV Disease

- Consultation with an ophthalmologist experienced in the management of patients with HSV ocular disease is strongly recommended (AIII).

Epithelial Keratitis

- Valacyclovir 1 g PO twice a day for 5–10 days (BIII), *or*
- Acyclovir 400 mg PO 5 times a day for 5–10 days (BIII), *or*
- Trifluridine eye drops: 1 drop in affected eye every 2 hours while awake (maximum nine times per day) until complete re-epithelialization, then 1 drop every 4 hours while awake (minimum five times per day) for an additional 7 days (BIII), *or*
- Ganciclovir 0.15% gel: 1 drop to affected eye five times a day (every 3 hours while awake) until re-epithelialization has occurred; then 1 drop 3 times a day for an additional 7 days (BIII)

Note: Topical steroids are not recommended in the management of active epithelial keratitis (AIII).

Stromal Keratitis (Duration of Antivirals: ≥1 Year)

- Acyclovir 400 mg PO twice a day (AII) *or* valacyclovir 500 mg PO once daily (AIII), *plus*
- Prednisolone 1% 1 drop to affected eye 6–8 times per day for at least 10 weeks followed by taper; exact course should be managed by ophthalmologist based on individual patient course (AIII)

HSV of the Central Nervous System

HSV Meningitis (Duration: 10–14 Days) (AIII)

- For initial therapy, acyclovir 10 mg/kg IV every 8 hours
- After clinical improvement, change to valacyclovir 1 g PO three times a day

HSV Encephalitis (Duration: 14–21 Days) (CIII)

- Acyclovir 10 mg/kg IV every 8 hours
- Some clinicians will elect to extend the course based on clinical response and degree of immunosuppression.

Treatment of Acyclovir-Resistant Mucocutaneous HSV Infections

Treatment failure due to acyclovir resistance should be suspected if lesions do not begin to resolve within 7–10 days after initiation of anti-HSV therapy. All acyclovir-resistant strains are also resistant to valacyclovir, and most are resistant to famciclovir.

Treatment of acyclovir-resistant HSV should be given in consultation with an infectious disease expert (AIII).

Preferred Therapy

- IV foscarnet 40 mg/kg every 8–12 hours until clinical response (AI)

Alternative Therapy

- Topical imiquimod 5% cream three times a week (BIII), *or*
- Topical cidofovir 1% gel once daily (BIII), *or*
- Topical trifluridine 1% three times a day (BIII), *or*
- Topical foscarnet 1% five times a day (BIII), *or*
- IV cidofovir 5 mg/kg once weekly for 2 weeks, then every other week (CIII)
  - Administer probenecid 2 g PO 3 hours before each cidofovir dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g). Administer 1 L of normal saline before and, if additional fluid load can be tolerated, administer another 1 L of normal saline after each cidofovir infusion.
  - Note: Cidofovir should be avoided in patients with sulfonamide allergy because of cross-hypersensitivity with probenecid.

Duration

- Based on clinical response; typically 21–28 days or longer

Notes

- An expanded access program of oral pritelivir is available for immunocompromised people with acyclovir-resistant HSV infection; see the Managing Treatment Failure in Mucocutaneous Disease section for more information.
- Topical formulations of trifluridine, cidofovir, and foscarnet are not commercially available. Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet.
- Recurrences following episodes of acyclovir-resistant HSV can be caused by either acyclovir-resistant or acyclovir-sensitive strains; after resolution of the acyclovir-resistant episode, suppressive therapy with acyclovir can be considered to prevent additional recurrences (CIII).

Pregnancy Considerations

- Acyclovir is an option for treatment during pregnancy, including during the first trimester (AII).
- Given its simplified dosing schedule, valacyclovir is also an option for treatment during pregnancy (BII).

Key: HSV = herpes simplex virus; IV = intravenous; PO = oral

People with HSV infections can be treated with episodic antiviral therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. Acyclovir, valacyclovir, and famciclovir are all effective for suppressive and episodic therapy. Valacyclovir is a prodrug of acyclovir, and famciclovir is a prodrug of penciclovir (only available topically); both have improved oral bioavailability and allow for decreased dosing frequency compared to acyclovir, making them preferred oral regimens for patient dosing convenience and adherence, if available. Episodic treatment for individual recurrences of genital ulcer disease does not influence the natural history of genital HSV-2 infection.

People with orolabial HSV lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for 5 to 10 days **(AIII).** First episodes of genital HSV lesions should be treated with oral valacyclovir, famciclovir, or acyclovir for 7 to 10 days; recurrences can be treated for 5 to 10 days **(AI).**

Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir for 10 to 14 days **(AIII).**[16,39] Once the lesions begin to regress, those being treated can be switched to oral antiviral therapy **(AIII).** Therapy should be continued until the lesions have completely healed **(AIII).**

HSV infections of the corneal epithelium (epithelial keratitis) are due to active viral infection and should be treated with oral valacyclovir 1,000 mg twice daily or acyclovir 400 mg five times daily for 5 to 10 days, or with a topical antiviral agent until resolution of dendritic lesions and re-epithelialization **(BIII).** Treatment by either route is effective; use of both oral and topical agents in combination is not necessary.[40] For topical treatment, ophthalmic trifluridine drops **(BIII)** or ganciclovir gel **(BIII)** can be used, though there are limitations to each. While it is not expected that treatment would be required beyond 2 weeks, using trifluridine beyond this time frame may result in toxicity to the corneal epithelium; ganciclovir can be cost prohibitive. Acyclovir ophthalmic ointment is also an appropriate option but is not currently available in the United States. Topical steroids are not recommended in the management of active epithelial keratitis **(AIII).**

For patients who also have stromal keratitis, largely due to inflammation rather than replicating virus, topical steroids are the mainstay of treatment. Prednisolone 1% eye drops (1 drop to affected eye 6–8 times a day) is given for at least 10 weeks, followed by a slow taper. Steroids should be given in conjunction with acyclovir 400 mg twice daily **(AII)**[41] or valacyclovir 500 mg daily **(AIII)** for at least one year to decrease the risk of recurrent stromal inflammation. Topical antivirals should not be used for extended durations to prevent recurrence, as this can cause toxicity to the eye that can be confused with persistent infection. As HSV keratitis exists along a continuum between epithelial viral replication and stromal inflammation, all cases should be managed by an ophthalmologist **(AIII).** Management is focused on striking a balance between viral clearance, control of inflammation, and prevention of reactivation.

For HSV meningitis, initial treatment with acyclovir IV 10 mg/kg every 8 hours is recommended, with step-down to high-dose oral valacyclovir 1 g three times daily following clinical improvement, for a total duration of 10 to 14 days **(AIII).**

People with visceral or disseminated HSV disease should be treated with acyclovir 10 mg/kg IV every 8 hours for at least 10 to 14 days **(AIII);** those with HSV encephalitis should be treated with acyclovir 10 mg/kg IV every 8 hours for at least 14 to 21 days **(CIII).** Some clinicians will elect to extend the course based on clinical response and degree of immunosuppression.

Special Considerations Regarding Antiretroviral Therapy Initiation

Orolabial and genital HSV should not influence the decision to start ART in people with HIV. Transient increases in HSV-2–associated genital ulcers have been observed during the first 6 months after initiation of ART in HIV/HSV-2 coinfected people, particularly in those with low CD4 counts.[42,43] In such cases, suppressive anti-HSV therapy can be considered. The frequency and severity of clinical episodes of genital herpes are often reduced in individuals after immune reconstitution on ART. However, immune reconstitution does not reduce the frequency of genital HSV shedding.[44]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed for people receiving episodic or suppressive HSV therapy unless they have advanced renal impairment. However, for people receiving IV acyclovir, cidofovir, or foscarnet, monitoring of renal function and dose adjustment as necessary is recommended at initiation of treatment and at least once or twice weekly for the duration of treatment, if stable (see Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections that Require Dosage Adjustment in Adults With Renal Insufficiency for renal dosing information and the Cytomegalovirus Disease chapter for additional foscarnet and cidofovir monitoring recommendations).

See Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections for additional information on adverse drug reactions.

Mucocutaneous lesions that are atypical and occasionally recalcitrant to therapy have been reported in individuals initiating ART and have been attributed to immune reconstitution inflammatory syndrome (IRIS).[45]

Managing Treatment Failure in Mucocutaneous Disease

Treatment failure due to acyclovir resistance should be suspected if herpes-related lesions do not begin to resolve within 7 to 10 days after initiation of anti-HSV therapy. Risk factors for acyclovir-resistant HSV include prolonged use of acyclovir, suboptimal acyclovir dosing, immunosuppression, and ongoing HSV replication.[46]

In people with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing should then be conducted to confirm drug resistance **(AII).**[47] Phenotypic testing of viral isolates has been the gold-standard method for assessing HSV resistance; genotypic testing is not widely available but may available at the University of Washington Department of Laboratory Medicine and Pathology.

All acyclovir-resistant strains are also resistant to valacyclovir, and the majority are resistant to famciclovir. Therefore, the treatment of choice for acyclovir-resistant HSV is IV foscarnet **(AI).**[48,49] IV cidofovir is a potential alternative **(CIII).** Systemic foscarnet and cidofovir are nephrotoxic medications; treatment should be given in consultation with an infectious diseases specialist **(AIII)** and with frequent laboratory monitoring (see Table 5).[50] Topical imiquimod, cidofovir, trifluridine, and foscarnet also have been used successfully to treat external lesions **(BIII),** although prolonged application for 21 to 28 days or longer may be required. Topical cidofovir, foscarnet, and trifluridine must be compounded in a pharmacy.[51,52]

A novel oral agent, the helicase-primase inhibitor pritelivir, is currently being tested in clinical trials for treatment of acyclovir-resistant HSV in immunocompromised people (*ClinicalTrials.gov* Identifier: NCT03073967). There is an Expanded Access Program available for oral pritelivir in these populations (also see *ClinicalTrials.gov* Identifier: NCT05844436 for more information).

Preventing Recurrence of Mucocutaneous Disease

Recommendations for Preventing Recurrence of Mucocutaneous Disease
Chronic Suppressive Therapy
Indications • For people with severe or frequent recurrences (AI), *or* • For people who want to minimize the frequency of recurrences (AI), *or* • To reduce the risk of genital ulcer disease in people with CD4 counts <250 cells/mm^3 who are starting ART (BI) Preferred Therapy • Valacyclovir 500 mg PO twice a day (AI) Alternative Therapy • Acyclovir 400 mg PO twice a day (AI), *or* • Famciclovir 500 mg PO twice a day (AI), *or* • Valacyclovir 500 mg or 1,000 mg PO once a day (CIII) o Valacyclovir 500 mg daily is less likely to be effective in people with ≥10 recurrences per year. o Valacyclovir 1,000 mg daily can be considered in people with HIV with more preserved immunologic functioning if they are unable to adhere to twice-daily dosing. Note: In people with prior acyclovir resistance, suppressive acyclovir therapy should be offered after resolution of the episode (CIII). See text below for more information. Duration • May be continued indefinitely, without regard to improved CD4 count; however, the need for continued therapy should be re-evaluated at least annually, particularly if immune reconstitution has occurred (BIII).
Pregnancy Considerations
• Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks gestation for pregnant women with past genital herpes (AI). • Suppressive therapy for pregnant women who are seropositive for HSV-2 but without history of genital lesions is not recommended (BIII).

- Due to increased renal clearance, the recommended dose of acyclovir used for suppressive therapy for HSV infection in pregnancy is 400 mg three times a day (AII).
- Given its simplified dosing schedule, valacyclovir 500 mg twice a day is an option for suppressive therapy during pregnancy (BII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; HSV = herpes simplex virus; IV = intravenous; PO = oral

Suppressive therapy reduces the frequency of recurrences of HSV lesions by nearly 80% and improves quality of life.[53] When deciding on suppressive therapy for genital HSV-2 infection in persons with HIV and HSV-2 coinfection, factors to consider include the frequency and severity of HSV recurrences and risk for genital ulcer disease when initiating ART.[44] Suppressive therapy should be offered to people who have severe or frequent HSV recurrences **(AI)** or who want to minimize the frequency of recurrences **(AI).**[22,54] Suppressive therapy may also be offered to those with CD4 counts <250 cells/mm^3 who are initiating ART due to the increased risk of herpes outbreaks after ART initiation **(BI).**

Oral acyclovir, valacyclovir, and famciclovir are all effective; selection of a suppressive antiviral is often based largely on convenience of dosing, making valacyclovir a preferred option by patients.[50] Valacyclovir can be given at 500 mg twice daily **(AI),** 500 mg once daily **(CIII)**, or 1,000 mg once daily **(CIII)** for suppression. The 500-mg daily dose is less likely to be effective in people with 10 or more recurrences per year.[55] Valacyclovir 500 mg twice daily is the only dose specifically studied in people with HIV.[54] Valacyclovir 1,000 mg daily can be considered in people with HIV with more preserved immune function if they are unable to adhere to twice-daily dosing. Oral acyclovir 400 mg twice a day and oral famciclovir 250 mg twice a day are also acceptable options for suppressive therapy **(AI).** Suppressive therapy for HSV may be continued indefinitely, without regard to improved CD4 count, although the need for continued therapy should be addressed at least annually, particularly if immune reconstitution has occurred **(BIII).**

People with HIV are less likely to experience acyclovir-resistant HSV than hematopoietic stem cell recipients.[46,48] With the latter population, the risk of developing acyclovir-resistant HSV was lower with daily suppressive acyclovir therapy than with episodic therapy.[56] Recurrences following episodes of acyclovir-resistant herpes can be caused by either acyclovir-resistant or acyclovir-sensitive strains.[48] Therefore, even in people with prior acyclovir resistance, suppressive acyclovir therapy should be offered after resolution of the episode **(CIII).** It is not expected, however, that acyclovir resistance will wane during a clinical episode, and thus acyclovir should not be used as until resolution of the episode in this setting. If a person with prior acyclovir resistance develops a recurrence while taking acyclovir suppressive therapy, susceptibility testing should be done.

In people with HIV who are not taking effective ART, suppressive anti-HSV therapy decreases HIV RNA levels in plasma, anal, and genital secretions, as well as lowers risk of HIV progression;[57] however, suppressive anti-HSV medications should not be used in place of ART to delay or reduce the risk of HIV progression **(AIII).** In people who are taking ART, suppressive HSV antivirals do not delay HIV progression, improve CD4 recovery, or decrease markers of systemic inflammation[58,59] and are not useful for these outcomes.

Special Considerations During Pregnancy

Laboratory testing to diagnose mucocutaneous HSV infections is the same during pregnancy as for other people with HIV. During pregnancy with primary HSV disease, antiviral therapy should be administered orally for 7 to 10 days (or longer, if lesions are incompletely healed) to reduce the

duration and severity of the symptoms and to reduce the duration of viral shedding. For treatment of severe genital HSV infections or disseminated infections, IV acyclovir may be administered during pregnancy. Pregnant women with recurrent outbreaks should also be given antiviral treatment to reduce symptoms and viral shedding.[22]

Disseminated disease, such as HSV hepatitis, is rare but may be more likely to occur in pregnancy and can be fatal;[60,61] providers should consider disseminated HSV in the differential diagnosis of patients with appropriate clinical and laboratory presentations. Acyclovir is the antiviral drug with the most reported experience in pregnancy, and both animal and human data suggest it is safe in pregnancy, including in the first trimester **(AII).**[62] Due to increased renal clearance in pregnancy, the recommended dose of acyclovir used for suppressive therapy is 400 mg three times daily, higher than the corresponding dose in nonpregnant people.[63] Valacyclovir is rapidly converted to acyclovir after hepatic metabolism and has a safety profile similar to acyclovir;[63] given its simplified dosing schedule, valacyclovir is an option for treatment and suppressive therapy during pregnancy **(BII).** There are limited data on the use of famciclovir during pregnancy.

A case–control study suggested a higher risk of gastroschisis associated with both genital herpes and acyclovir use during the first trimester of pregnancy.[64] The use of valacyclovir and famciclovir during pregnancy has been described, and these antiviral drugs also appear to be safe and well tolerated during the first trimester.[63] Cidofovir is teratogenic and should not be used during pregnancy **(AIII).**

An important concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate, which can result in serious adverse events, including death or long-term neurologic sequelae. Transplacental transmission may occur in very rare cases, resulting in congenital infection, including microcephaly, hepatosplenomegaly, intrauterine growth restriction, and stillbirth; however, most neonatal herpes is acquired during the intrapartum period through exposure to the virus in the maternal genital tract, especially in the presence of active lesions. Approximately one-third to one-half of cases of neonatal herpes are caused by HSV-1.[65,66]

The rate of neonatal HSV transmission is highest with primary HSV-1 or HSV-2 genital infection during late pregnancy.[67] Cesarean delivery is recommended for pregnant women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor **(AII).**[22] Risk of neonatal transmission is reduced in previously HSV-2–seropositive pregnant women or those with prior genital episodes. Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks gestation for pregnant women with past genital herpes **(AI).** Although neonatal HSV disease has been reported in infants born to women treated with antenatal suppressive antiviral therapy,[68] it has been shown to reduce the risk of both asymptomatic shedding as well as clinical recurrence of HSV at the time of delivery and need for cesarean birth.[66,69] For primary outbreaks that occur in the third trimester, continuing antiviral therapy until delivery may be considered. All of these interventions are likely to be similarly effective in people with HIV as in those without. Suppressive therapy for pregnant women who are seropositive for HSV-2 but without history of genital lesions **is not recommended (BIII).** Postnatal transmission can occur rarely. To prevent postnatal transmission, pregnant women with herpetic lesions on any part of the body should take special precautions with handwashing prior to handling the neonate. Maternal genital herpes was a risk factor for perinatal HIV transmission in the pre-ART era.[70] Whether HSV facilitates HIV transmission in pregnant women taking effective ART is unknown.

References

1. McQuillan G, Kruszon-Moran D, Flagg EW, Paulose-Ram R. Prevalence of Herpes Simplex Virus Type 1 and Type 2 in Persons Aged 14-49: United States, 2015-2016. *NCHS Data Brief*. 2018(304):1-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29442994.

2. Ryder N, Jin F, McNulty AM, Grulich AE, Donovan B. Increasing role of herpes simplex virus type 1 in first-episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992-2006. *Sex Transm Infect*. 2009;85(6):416-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19273479.

3. Stamm WE, Handsfield HH, Rompalo AM, Ashley RL, Roberts PL, Corey L. The association between genital ulcer disease and acquisition of HIV infection in homosexual men. *Jama*. 1988;260(10):1429-1433. Available at: https://pubmed.ncbi.nlm.nih.gov/3404600/.

4. Patel P, Bush T, Mayer KH, et al. Prevalence and risk factors associated with herpes simplex virus-2 infection in a contemporary cohort of HIV-infected persons in the United States. *Sex Transm Dis*. 2012;39(2):154-160. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22249305.

5. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis*. 2002;185(1):45-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11756980.

6. Looker KJ, Elmes JAR, Gottlieb SL, et al. Effect of HSV-2 infection on subsequent HIV acquisition: an updated systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17(12):1303-1316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28843576.

7. Mbopi-Keou FX, Gresenguet G, Mayaud P, et al. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis*. 2000;182(4):1090-1096. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10979904.

8. Nagot N, Ouedraogo A, Konate I, et al. Roles of clinical and subclinical reactivated herpes simplex virus type 2 infection and human immunodeficiency virus type 1 (HIV-1)-induced immunosuppression on genital and plasma HIV-1 levels. *J Infect Dis*. 2008;198(2):241-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18593294.

9. Arduino PG, Porter SR. Herpes Simplex Virus Type 1 infection: overview on relevant clinico-pathological features. *J Oral Pathol Med*. 2008;37(2):107-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18197856.

10. Tronstein E, Johnston C, Huang ML, et al. Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection. *JAMA*. 2011;305(14):1441-1449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21486977.

11. Johnston C, Magaret A, Son H, et al. Viral shedding 1 year following first-episode genital HSV-1 infection. *JAMA*. 2022;328(17):1730-1739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36272098.

12. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med*. 1983;98(6):958-972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6344712.

13. Schiffer JT, Swan DA, Magaret A, Schacker TW, Wald A, Corey L. Mathematical modeling predicts that increased HSV-2 shedding in HIV-1 infected persons is due to poor immunologic control in ganglia and genital mucosa. *PLoS One*. 2016;11(6):e0155124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27285483.

14. Mostad SB, Kreiss JK, Ryncarz A, et al. Cervical shedding of herpes simplex virus and cytomegalovirus throughout the menstrual cycle in women infected with human immunodeficiency virus type 1. *Am J Obstet Gynecol*. 2000;183(4):948-955. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11035345.

15. Bissessor M, Fairley CK, Read T, Denham I, Bradshaw C, Chen M. The etiology of infectious proctitis in men who have sex with men differs according to HIV status. *Sex Transm Dis*. 2013;40(10):768-770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24275725.

16. Safrin S, Elbeik T, Phan L, et al. Correlation between response to acyclovir and foscarnet therapy and in vitro susceptibility result for isolates of herpes simplex virus from human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 1994;38(6):1246-1250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8092821.

17. Yudin MH, Kaul R. Progressive hypertrophic genital herpes in an HIV-infected woman despite immune recovery on antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2008;2008:592532. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18784844.

18. Sbidian E, Battistella M, Legoff J, et al. Recalcitrant pseudotumoral anogenital herpes simplex virus type 2 in HIV-infected patients: evidence for predominant B-lymphoplasmocytic infiltration and immunomodulators as effective therapeutic strategy. *Clin Infect Dis*. 2013;57(11):1648-1655. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24065320.

19. Hoversten P, Kamboj AK, Wu TT, Katzka DA. Variations in the clinical course of patients with herpes simplex virus esophagitis based on immunocompetence and presence of underlying esophageal disease. *Dig Dis Sci*. 2019;64(7):1893-1900. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30725296.

20. Johnson JR, Egaas S, Gleaves CA, Hackman R, Bowden RA. Hepatitis due to herpes simplex virus in marrow-transplant recipients. *Clin Infect Dis*. 1992;14(1):38-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1571460.

21. Basse G, Mengelle C, Kamar N, et al. Disseminated herpes simplex type-2 (HSV-2) infection after solid-organ transplantation. *Infection*. 2008;36(1):62-64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18165863.

22. Workowski KA, Bachmann LH, Chan PA, et al. Sexually Transmitted Infections Treatment Guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34292926.

23. Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. *J Infect Dis*. 2003;188(9):1345-1351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14593592.

24. Agyemang E, Le QA, Warren T, et al. Performance of Commercial Enzyme-Linked Immunoassays for Diagnosis of Herpes Simplex Virus-1 and Herpes Simplex Virus-2 Infection in a Clinical Setting. *Sex Transm Dis*. 2017;44(12):763-767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28876290.

25. Golden MR, Ashley-Morrow R, Swenson P, Hogrefe WR, Handsfield HH, Wald A. Herpes simplex virus type 2 (HSV-2) Western blot confirmatory testing among men testing positive for HSV-2 using the focus enzyme-linked immunosorbent assay in a sexually transmitted disease clinic. *Sex Transm Dis*. 2005;32(12):771-777. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16314775.

26. Morrow RA, Friedrich D, Meier A, Corey L. Use of "biokit HSV-2 Rapid Assay" to improve the positive predictive value of Focus HerpeSelect HSV-2 ELISA. *BMC Infect Dis*. 2005;5:84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16225691.

27. Centers for Disease Control and Prevention. Genital herpes. 2022. Available at: https://www.cdc.gov/std/treatment-guidelines/herpes.htm

28. Wald A, Krantz E, Selke S, Lairson E, Morrow RA, Zeh J. Knowledge of partners' genital herpes protects against herpes simplex virus type 2 acquisition. *J Infect Dis*. 2006;194(1):42-52. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16741881.

29. Martin ET, Krantz E, Gottlieb SL, et al. A pooled analysis of the effect of condoms in preventing HSV-2 acquisition. *Arch Intern Med*. 2009;169(13):1233-1240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19597073.

30. Corey L, Wald A, Patel R, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med*. 2004;350(1):11-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14702423.

31. Mujugira A, Magaret AS, Celum C, et al. Daily acyclovir to decrease herpes simplex virus type 2 (HSV-2) transmission from HSV-2/HIV-1 coinfected persons: a randomized controlled trial. *J Infect Dis*. 2013;208(9):1366-1374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23901094.

32. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329(5996):1168-1174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20643915.

33. Celum C, Morrow RA, Donnell D, et al. Daily oral tenofovir and emtricitabine-tenofovir preexposure prophylaxis reduces herpes simplex virus type 2 acquisition among heterosexual HIV-1-uninfected men and women: a subgroup analysis of a randomized trial. *Ann Intern Med*. 2014;161(1):11-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24979446.

34. Marrazzo JM, Rabe L, Kelly C, et al. Tenofovir gel for prevention of herpes simplex virus type 2 acquisition: findings from the VOICE trial. *J Infect Dis*. 2019;219(12):1940-1947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30753642.

35. Celum C, Hong T, Cent A, et al. Herpes simplex virus type 2 acquisition among HIV-1-infected adults treated with tenofovir disoproxyl fumarate as part of combination antiretroviral therapy: results from the ACTG A5175 PEARLS study. *J Infect Dis*. 2017;215(6):907-910. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28453835.

36. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med*. 2009;360(13):1298-1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19321868.

37. Sobngwi-Tambekou J, Taljaard D, Lissouba P, et al. Effect of HSV-2 serostatus on acquisition of HIV by young men: results of a longitudinal study in Orange Farm, South Africa. *J Infect Dis*. 2009;199(7):958-964. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19220143.

38. Grund JM, Bryant TS, Jackson I, et al. Association between male circumcision and women's biomedical health outcomes: a systematic review. *Lancet Glob Health*. 2017;5(11):e1113-e1122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29025633.

39. Meyers JD, Wade JC, Mitchell CD, et al. Multicenter collaborative trial of intravenous acyclovir for treatment of mucocutaneous herpes simplex virus infection in the immunocompromised host. *Am J Med*. 1982;73(1A):229-235. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7048914.

40. Collum LM, McGettrick P, Akhtar J, Lavin J, Rees PJ. Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration. *Br J Ophthalmol*. 1986;70(6):435-438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3521717.

41. Acyclovir for the prevention of recurrent herpes simplex virus eye disease. Herpetic Eye Disease Study Group. *N Engl J Med*. 1998;339(5):300-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9696640.

42. Graham SM, Masese L, Gitau R, et al. Increased risk of genital ulcer disease in women during the first month after initiating antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2009;52(5):600-603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19648822.

43. Tobian AA, Grabowski MK, Serwadda D, et al. Reactivation of herpes simplex virus type 2 after initiation of antiretroviral therapy. *J Infect Dis*. 2013;208(5):839-846. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23812240.

44. Posavad CM, Wald A, Kuntz S, et al. Frequent reactivation of herpes simplex virus among HIV-1-infected patients treated with highly active antiretroviral therapy. *J Infect Dis*. 2004;190(4):693-696. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15272395.

45. Couppie P, Sarazin F, Clyti E, et al. Increased incidence of genital herpes after HAART initiation: a frequent presentation of immune reconstitution inflammatory syndrome (IRIS) in HIV-infected patients. *AIDS Patient Care STDS*. 2006;20(3):143-145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16548710.

46. Schalkwijk HH, Snoeck R, Andrei G. Acyclovir resistance in herpes simplex viruses: Prevalence and therapeutic alternatives. *Biochemical Pharmacology*. 2022;206. Available at: https://pubmed.ncbi.nlm.nih.gov/36309081/.

47. Balfour HH, Jr. Antiviral drugs. *N Engl J Med*. 1999;340(16):1255-1268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10210711.

48. Safrin S, Crumpacker C, Chatis P, et al. A controlled trial comparing foscarnet with vidarabine for acyclovir-resistant mucocutaneous herpes simplex in the acquired immunodeficiency syndrome. The AIDS Clinical Trials Group. *N Engl J Med*. 1991;325(8):551-555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1649971.

49. Levin MJ, Bacon TH, Leary JJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. *Clin Infect Dis*. 2004;39 Suppl 5:S248-257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15494896.

50. Hammond SP, Rangaraju M, Sumner M, Timmler B, Chandrasekar P, Avery RK. A Multicenter Assessment of the Outcomes and Toxicities of Foscarnet for Treatment of Acyclovir-Resistant Mucocutaneous Herpes Simplex in Immunocompromised Patients. *Open Forum Infect Dis*. 2024;11(3):ofae046. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38444818.

51. Javaly K, Wohlfeiler M, Kalayjian R, et al. Treatment of mucocutaneous herpes simplex virus infections unresponsive to acyclovir with topical foscarnet cream in AIDS patients: a phase I/II study. *J Acquir Immune Defic Syndr*. 1999;21(4):301-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10428108.

52. Lascaux AS, Caumes E, Deback C, et al. Successful treatment of aciclovir and foscarnet resistant Herpes simplex virus lesions with topical imiquimod in patients infected with human immunodeficiency virus type 1. *J Med Virol*. 2012;84(2):194-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22170537.

53. Romanowski B, Marina RB, Roberts JN, Valtrex HSSG. Patients' preference of valacyclovir once-daily suppressive therapy versus twice-daily episodic therapy for recurrent genital herpes: a randomized study. *Sex Transm Dis*. 2003;30(3):226-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12616141.

54. DeJesus E, Wald A, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in human immunodeficiency virus-infected subjects. *J Infect Dis*. 2003;188(7):1009-1016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14513421.

55. Reitano M, Tyring S, Lang W, et al. Valaciclovir for the suppression of recurrent genital herpes simplex virus infection: a large-scale dose range-finding study. International Valaciclovir HSV Study Group. *J Infect Dis*. 1998;178(3):603-610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9728526.

56. Erard V, Wald A, Corey L, Leisenring WM, Boeckh M. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. *J Infect Dis*. 2007;196(2):266-270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17570114.

57. Lingappa JR, Baeten JM, Wald A, et al. Daily acyclovir for HIV-1 disease progression in people dually infected with HIV-1 and herpes simplex virus type 2: a randomised placebo-controlled trial. *Lancet*. 2010;375(9717):824-833. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20153888.

58. Yi TJ, Walmsley S, Szadkowski L, et al. A randomized controlled pilot trial of valacyclovir for attenuating inflammation and immune activation in HIV/herpes simplex virus 2-coinfected adults on suppressive antiretroviral therapy. *Clin Infect Dis*. 2013;57(9):1331-1338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23946220.

59. Van Wagoner N, Geisler WM, Bachmann LH, Hook EW. The effect of valacyclovir on HIV and HSV-2 in HIV-infected persons on antiretroviral therapy with previously unrecognised HSV-2. *Int J STD AIDS*. 2015;26(8):574-581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25147236.

60. Kang AH, Graves CR. Herpes simplex hepatitis in pregnancy: a case report and review of the literature. *Obstet Gynecol Surv*. 1999;54(7):463-468. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10394584.

61. Allen RH, Tuomala RE. Herpes simplex virus hepatitis causing acute liver dysfunction and thrombocytopenia in pregnancy. *Obstet Gynecol*. 2005;106(5 Pt 2):1187-1189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16260566.

62. Stone KM, Reiff-Eldridge R, White AD, et al. Pregnancy outcomes following systemic prenatal acyclovir exposure: Conclusions from the international acyclovir pregnancy registry, 1984-1999. *Birth Defects Res A Clin Mol Teratol*. 2004;70(4):201-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15108247.

63. Pasternak B, Hviid A. Use of acyclovir, valacyclovir, and famciclovir in the first trimester of pregnancy and the risk of birth defects. *JAMA*. 2010;304(8):859-866. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20736469.

64. Ahrens KA, Anderka MT, Feldkamp ML, et al. Antiherpetic medication use and the risk of gastroschisis: findings from the National Birth Defects Prevention Study, 1997-2007. *Paediatr Perinat Epidemiol*. 2013;27(4):340-345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23772935.

65. Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA*. 2003;289(2):203-209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12517231.

66. Management of Genital Herpes in Pregnancy: ACOG Practice Bulletinacog Practice Bulletin, Number 220. *Obstet Gynecol*. 2020;135(5):e193-e202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32332414.

67. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med*. 2009;361(14):1376-1385. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19797284.

68. Pinninti SG, Angara R, Feja KN, et al. Neonatal herpes disease following maternal antenatal antiviral suppressive therapy: a multicenter case series. *J Pediatr*. 2012;161(1):134-138 e131-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22336576.

69. Hollier LM, Wendel GD. Third trimester antiviral prophylaxis for preventing maternal genital herpes simplex virus (HSV) recurrences and neonatal infection. *Cochrane Database Syst Rev*. 2008(1):CD004946. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18254066.

70. Chen KT, Segu M, Lumey LH, et al. Genital herpes simplex virus infection and perinatal transmission of human immunodeficiency virus. *Obstet Gynecol*. 2005;106(6):1341-1348. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16319261.

Histoplasmosis

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Epidemiology

Histoplasmosis is a fungal infection caused by the dimorphic fungus *Histoplasma capsulatum (H. capsulatum)*. The fungal infection is endemic to the central and south-central United States, where it is especially common in the Ohio and Mississippi River valleys. Microfoci of infection exist elsewhere in the eastern United States. Histoplasmosis is also found in Latin America and the Caribbean, Asia, and Africa. In some Latin American countries, histoplasmosis is one of the most common opportunistic infections in people with HIV, even during the era of highly active antiretroviral therapy (ART).[1-3] A CD4 T lymphocyte (CD4) cell count <150 cells/mm^3 is associated with an increased risk of symptomatic illness in people with HIV.[4,5] The risk for and incidence of symptomatic disease is generally higher at lower CD4 counts in people with HIV, but disease can present with counts as high as 350 cells/mm^3.

Histoplasmosis is acquired by the inhalation of microconidia that form in the mycelial phase of the fungus in the environment. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. Diminished cellular immunity can lead to a reactivation of a quiescent focal infection acquired years earlier; this is the presumed mechanism for disease occurrence in nonendemic areas.

Clinical Manifestations

There is a spectrum of disease from asymptomatic and self-limited pulmonary disease to disseminated disease in those with low CD4 counts (≤200 cells/mm^3). In people with advanced HIV, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough and dyspnea occur in approximately 50% of patients.[4,6] Gastrointestinal (GI) disease usually manifests as fever, nausea and vomiting, diarrhea, abdominal pain, and weight loss.[7] In a case series of people with HIV in Panama, diarrhea with or without fever was seen in 50% of the patients with histoplasmosis,[8] and in another series from French Guiana, GI symptoms occurred in 70% of patients with histoplasmosis.[3] Central nervous system (CNS) and cutaneous manifestations occur in no more than 20% of patients. People with CNS histoplasmosis typically experience fever and headache; if brain involvement is present, they may also experience seizures, focal neurological deficits, septic meningitis, or changes in mental status.[4] Approximately 10% of patients with low CD4 counts experience septic shock, multiorgan failure, and/or pericardial effusion and pericarditis requiring rapid therapy.[4] In such cases, blood cultures and *Histoplasma* antigen tests of serum and urine are helpful diagnostically.[4,9] In patients with CD4 counts >200 cells/mm^3, histoplasmosis is often limited to the respiratory tract, and they may present with cough, pleuritic chest pain, and/or fever.[9]

Diagnosis

The detection of *Histoplasma* antigen in blood or urine (the detection method preferred by the World Health Organization) is a sensitive method for the rapid diagnosis of disseminated histoplasmosis in people with HIV.[10] This test should be obtained for any person with HIV and low CD4 counts who

has the above-mentioned symptoms and who lives, or has previously lived, in an area in which *H. capsulatum* is commonly found.

In a study using a certain quantitative enzyme immunoassay (EIA), *Histoplasma* antigen was detected in 100% of urine samples and 92% of serum samples from people with AIDS and disseminated histoplasmosis.[11] Another EIA employs a monoclonal antibody to detect *Histoplasma* galactomannan and has been reported to have a sensitivity of 91% and a specificity of 91%.[12] A lateral flow assay for the detection of *Histoplasma* antigen in urine was reported to have a sensitivity of 96% and specificity of 96%.[13] Antigen detection in bronchoalveolar lavage fluid may also be a useful method for the diagnosis of pulmonary histoplasmosis.[14]

In people with severe disseminated histoplasmosis, peripheral blood smears might occasionally show the organisms engulfed by white blood cells if observed with careful attention. Histopathological examination of biopsy material from involved tissues often demonstrates small yeast cells 2 to 4 μm in diameter, which are characteristic of histoplasmosis.

In >85% of people with HIV and disseminated histoplasmosis, *H. capsulatum* can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions, or samples from other involved sites; however, the organism requires several weeks to grow before final results can be interpreted.[15] Serologic tests for antibodies are less useful than antigen assays for people with HIV and disseminated histoplasmosis but may be helpful for those with pulmonary disease and reasonably intact immune responses.[15,16]

The diagnosis of *Histoplasma* meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[17] In a review of CNS histoplasmosis that included people with HIV, cultures were positive in 38% of study participants.[18] *Histoplasma* antigen can be detected in CSF in a far greater number of cases, and antibodies against *H. capsulatum* are seen in at least one-half of cases.[18] A positive antigen or antibody test result from CSF is diagnostic for histoplasmosis. In cases in which none of these specific tests are positive, a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not attributable to another cause.

Preventing Exposure

People with HIV who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to *H. capsulatum*, but those with CD4 counts <200 cells/mm^3 should be counseled to minimize exposure to activities associated with an increased risk for histoplasmosis **(BIII).** These activities include creating dust when working with surface soil; cleaning chicken coops; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing buildings; and exploring caves.[19]

Preventing Disease

Preventing the First Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)
Indications for Initiating Primary Prophylaxis (BI)
• People with CD4 count <150 cells/mm^3 and who are at high risk because of occupational histoplasmosis exposure *or* who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 person-years)
Preferred Therapy
• Itraconazole 200 mg PO once daily (BI)
Criteria for Discontinuing Primary Prophylaxis (BIII)
• Stable ART, *and*
• CD4 count ≥150 cells/mm^3 for 6 months, *and*
• Undetectable HIV-1 viral load
Indication for Restarting Primary Prophylaxis
• CD4 count <150 cells/mm^3 (BIII)

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the incidence of histoplasmosis, although not mortality, in people who have advanced HIV (CD4 counts <150 cells/mm^3) and live in areas where histoplasmosis is highly endemic.[20] Based on these data, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) continues to recommend itraconazole at a dose of 200 mg daily as primary prophylaxis **(BI)** to people with CD4 counts <150 cells/mm^3 who are at high risk because of occupational histoplasmosis exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 person-years) **(BI).** However, as with other opportunistic infections in the current era of more effective ART, it may be reasonable to consider withholding primary prophylaxis if ART can be immediately initiated and there is an accompanying rise in CD4 cell count above the threshold of risk **(CIII).** Fluconazole has yet to show activity in a prophylaxis setting for histoplasmosis. The role of screening for *Histoplasma* antigen to define people at risk for developing infection has not been studied.

If used, primary prophylaxis should be discontinued in people on ART once CD4 counts are ≥150 cells/mm^3 for 6 months and HIV-1 viral loads are undetectable **(BIII).** Prophylaxis should be restarted if the CD4 count falls to <150 cells/mm^3 **(BIII).**

Treating Disease

Treating *Histoplasma capsulatum* Infections
Treating Severe Disseminated Disease
Induction Therapy (≥2 Weeks or Until Clinically Improved)
Preferred Therapy
• Liposomal amphotericin B 3 mg/kg IV daily (AI)

Alternative Therapy

- Amphotericin B lipid complex 5 mg/kg IV daily (AIII)

Maintenance Therapy (**≥12** Months)

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day (AII)

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole and only moderately ill.

- Posaconazole 300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily (BIII), *or*
- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII), *or*
- Fluconazole 800 mg PO once daily (CII)

Treating Mild-to-Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in People With CD4 <300 cells/mm^3

Induction and Maintenance Therapy (≥12 Months)

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day (AII)

Alternative Therapy

- Posaconazole 300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily (BIII), *or*
- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII), *or*
- Fluconazole 800 mg PO once daily (CII)

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks Depending on Symptom Resolution and Improvement of CSF Findings)

Preferred Therapy

- Liposomal amphotericin B 5 mg/kg IV daily (AIII)

Alternative Therapy

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (BIII)

Maintenance Therapy **(≥12** Months and Until Resolution of Abnormal CSF Findings)

Preferred Therapy

- Itraconazole 200 mg PO two or three times a day (AIII)

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole and only moderately ill.

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII), *or*
- Fluconazole 800 mg PO once daily (CII)—for people who cannot tolerate both itraconazole and voriconazole

Long-Term Suppressive Therapy

Indications

- Severe disseminated or CNS infection after completing maintenance therapy for ≥12 months of treatment (AIII), *or*
- Relapse despite appropriate initial therapy (after reinduction therapy) (BIII)

Preferred Therapy

- Itraconazole 200 mg PO once daily (AIII)

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole.

- Fluconazole 400 mg PO once daily (CII), *or*
- Voriconazole 200 mg PO twice daily (BIII), *or*
- Posaconazole 300 mg PO daily (BIII)

Criteria for Discontinuing Long-Term Suppressive Therapy (AII)

- Receipt of azole treatment for >1 year, *and*
- Negative fungal blood cultures, *and*
- Serum or urine *Histoplasma* antigen below the level of quantification, *and*
- Undetectable HIV viral load on stable ART, *and*
- CD4 count ≥150 cells/mm^3 and on ART for ≥6 months

Indication for Restarting Long-Term Suppressive Therapy

- CD4 count <150 cells/mm^3 (BIII)

Other Considerations

- Random itraconazole serum concentrations should be measured in all patients after 2 weeks of therapy (the time it usually takes to reach a steady state) to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions (AIII).
- Random serum concentrations (itraconazole plus hydroxyitraconazole) should be between 1 and 2 μg/mL. Concentrations ≥5 μg/mL are associated with an increased frequency and severity of adverse effects.
- Oral itraconazole liquid solution is preferred over the capsule formulation because of improved absorption but is less well tolerated. However, it is not necessary to use the liquid solution if random serum itraconazole concentration is ≥1.0 μg/mL with the capsule formulation (AIII).
- Trough voriconazole serum concentrations should be measured after 5 days of therapy (the time it usually takes to reach a steady state) with the goal of achieving a concentration of 1 to 5 μg/mL. Concentrations are highly variable among patients, and for individual patients, concentrations can vary because of drug–drug interactions. Neurotoxicity and hepatotoxicity are associated with serum concentrations >5 μg/mL, but some patients can experience adverse effects with lower serum concentrations (AIII).
- Trough posaconazole serum concentrations should be measured after 5 days of therapy (the time it usually takes to reach a steady state) to ensure adequate absorption, with a goal of achieving a concentration >1 μg/mL (AIII).
- Acute pulmonary histoplasmosis in patients with HIV and CD4 count ≥300 cells/mm^3 should be managed the same as in immunocompetent patients (AIII).

• All triazole antifungals have the potential to interact with certain ART agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Drug–Drug Interactions section in the Adult and Adolescent Antiretroviral Guidelines lists these interactions and recommends dose adjustments where feasible. The University of Liverpool HIV Drug Interactions Database provides more detailed information on interactions.
Pregnancy Considerations
• Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis during pregnancy, especially during the first trimester (AIII). • In the second and third trimester of pregnancy, itraconazole can be considered if the benefit outweighs the potential risk (CIII). • Azole antifungals **should be avoided** during the first trimester of pregnancy (BIII). • Use of fluconazole, voriconazole, and posaconazole **should be avoided** in pregnancy, especially in the first trimester (AIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system, CSF = cerebrospinal fluid; IV = intravenous; PO = orally

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) induced a more rapid and complete response, lowered mortality rates, and reduced toxicity more efficaciously than standard IV amphotericin B deoxycholate (0.7 mg/kg daily) for the treatment of histoplasmosis associated with AIDS.[21] Based on these findings, patients with symptomatic severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for ≥2 weeks or until they clinically improve **(AI).** IV amphotericin B lipid complex (5 mg/kg daily) can be used if cost is a concern, or if the patient cannot tolerate liposomal amphotericin B **(AIII).**

Step-down therapy to oral itraconazole, 200 mg three times a day for 3 days followed by 200 mg two times a day, should be given for ≥12 months **(AII).**[22] Because absorption of itraconazole can be erratic and because of potential drug interactions between itraconazole and protease inhibitors, efavirenz, rilpivirine, etravirine, and many other drugs that are cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, random serum concentration of itraconazole should be measured 2 weeks after the start of therapy (see The University of Liverpool HIV Drug Interactions Database) **(AIII).** Combined serum itraconazole and hydroxyitraconazole concentrations should be 1 to 2 μg/mL. Adverse events become more frequent and severe as concentrations increase, with a 26% increase observed when concentrations exceed 5 μg/mL.[23] Itraconazole is a moderately strong CPY3A4 inhibitor, so ART effectiveness also must be considered.

In patients with mild-to-moderate disseminated histoplasmosis, oral itraconazole, 200 mg three times daily for 3 days followed by 200 mg twice daily for ≥12 months, is an appropriate initial therapy **(AII).**[22,24] The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption **(AIII).** However, the capsule formulation of itraconazole is better tolerated than the liquid formulation. If a serum random itraconazole concentration of 1.0 to 2.0 μg/mL has been achieved with the capsule formulation, it is not necessary to use the liquid solution. The capsule formulation should be given with food and cannot be used when the patient requires gastric acid–inhibiting drugs. A formulation of itraconazole, SUBA-itraconazole, has improved absorption and is most likely of all formulations to achieve random itraconazole level (≥1.0 μg/mL).[25] Although this agent likely will prove useful in treating histoplasmosis, SUBA-itraconazole cannot be routinely recommended due to cost and the need for further clinical data on its use for this purpose .

Acute pulmonary histoplasmosis in a person with HIV who has a CD4 count ≥300 cells/mm^3 should be managed the same way as acute pulmonary histoplasmosis in an immunocompetent person **(AIII).**[22] For acute pulmonary histoplasmosis in a person with HIV who has a CD4 count <300 cells/mm^3, the patient should receive therapy similar to that of mild-to-moderate disseminated disease **(AIII).**

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dose of 5 mg/kg IV daily for 4 to 6 weeks depending on the resolution of symptoms and improvement of abnormal CSF findings **(AIII).** Amphotericin B deoxycholate 0.7 to 1.0 mg/kg IV daily can be used as an alternative if liposomal amphotericin B is not available **(BIII).** A reduction in *Histoplasma* antigen is encouraging. This initial IV therapy with amphotericin B should be followed by maintenance therapy with oral itraconazole at a dose of 200 mg two or three times daily for ≥12 months with dose adjustment based on interactions with ART and itraconazole serum concentration until abnormal CSF findings are resolved **(AIII).**[22] Voriconazole is an alternative to itraconazole for *Histoplasma* meningitis **(BIII).** The Panel recommends fluconazole 800 mg daily as an alternative maintenance therapy for those who are intolerant of itraconazole and voriconazole **(CII).**[26]

Oral posaconazole and voriconazole have been reported to be effective in treating histoplasmosis in a small number of people with HIV or other immunosuppressive conditions[27-30] and are therefore recommended as alternatives for those who are only moderately ill and intolerant of itraconazole **(BIII).** Oral voriconazole should be administered at a dose of 400 mg two times a day for 1 day, then 200 mg two times a day **(BIII).** If voriconazole is used, trough serum concentrations should be measured after 5 days of therapy, with a goal of achieving a serum concentration of l to 5 μg/mL **(AIII).** Concentrations are highly variable among different people and over time within a given person and may vary because of absorption issues and drug–drug interactions (see The University of Liverpool HIV Drug Interactions Database). Neurotoxicity and hepatotoxicity are associated with serum concentrations >5 μg/mL, but individual patients can experience adverse effects, such as hepatitis and neurotoxicity, even with lower serum concentrations. Oral posaconazole should be administered at a dose of 300 mg of extended-release tablets twice daily for 1 day, then 300 mg once daily **(BIII).** Posaconazole serum concentrations should be measured after 5 days of therapy to ensure adequate absorption, with a goal of achieving a concentration of >1 μg/mL **(AIII).**

Fluconazole is less effective than itraconazole for the treatment of histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily **(CII).**[26] Isavuconazole has been used in too few patients with histoplasmosis to be routinely recommended at this time but might be considered when other triazoles such as itraconazole, voriconazole, and posaconazole cannot be used. The echinocandins do not have activity against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis **(AIII).**

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining a response to therapy. Antigen titers should be checked monthly for the first 3 months and then every 3–4 months, until negative. Blood titers will drop faster than urine titers, and titers will drop faster with polyene treatment compared to azole treatment.[31] A significant rise in antigen level suggests relapse and consideration for treatment changes.

People with HIV diagnosed with histoplasmosis should start ART as soon as possible after initiating antifungal therapy **(AIII).** Life-threatening immune reconstitution inflammatory syndrome (IRIS) has been uncommonly reported in people with HIV who have histoplasmosis.[32,33] Therefore, ART should not be withheld because of concern for the possible development of IRIS **(AIII).**[34]

All triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. Refer to Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for a list of interactions and recommendations for dose adjustments, where feasible. Itraconazole has caused worsening heart failure, adrenal insufficiency, and transaminitis. Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections provides a list of antifungal adverse reactions.

Managing Treatment Failure

Liposomal amphotericin B should be used in patients who are severely ill or who have failed to respond to initial azole antifungal therapy **(AIII).** Oral posaconazole and oral voriconazole are recommended as reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII);**[27-30] fluconazole at a dose of 800 mg daily also can be used **(CII).**[26] Drug interactions may limit the use of voriconazole in patients who are taking certain non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, etravirine) or protease inhibitors. Posaconazole has fewer known drug interactions with ART medications than voriconazole.

Prevention of Relapse

Long-term suppressive therapy with oral itraconazole (200 mg daily) should be administered to people with severe disseminated infection or CNS infection for ≥12 months after completing induction therapy **(AIII)** or after reinduction therapy to those whose disease relapsed despite initial receipt of an appropriate therapy **(BIII).**[35,36] Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily **(CII).**[26,37] Although the role of voriconazole or posaconazole has not been evaluated in sufficiently powered studies, they may be reasonable options for patients who received these drugs as maintenance therapy **(BIII).** Long-term therapy is started after symptoms have abated and antigen titer is decreasing.

A study sponsored by the AIDS Clinical Trials Group (ACTG) reported that it was safe to discontinue itraconazole treatment for histoplasmosis in people who had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum or urine antigen <4.1 units, and a CD4 count >150 cells/mm^3; and had been on ART for 6 months.[35] No relapses were evident among 32 study participants who were followed for a median of 24 months. Thus, it appears safe to discontinue suppressive azole antifungal therapy in patients who have a serum or urine antigen below the limit of quantification in ng/mL, with CD4 count ≥150 cells/mm^3, on ART for 6 months, and who have an undetectable HIV viral load **(AII).** Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^3 **(BIII).**[35]

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis during pregnancy, especially during the first trimester **(AIII).** Extensive clinical

experience with amphotericin B has not documented teratogenicity. Because amphotericin B crosses the placenta, infants born to those treated with amphotericin B should be evaluated for adverse effects, including renal dysfunction and hypokalemia.[38]

Although the safety of amphotericin B in pregnancy is well established, less is known about itraconazole. The drug is known to be embryotoxic and teratogenic in rodents. Teratogenic effects included major skeletal defects, encephaloceles, and macroglossia. Because of this, the manufacturer recommends that people of childbearing potential use contraceptives during and for 2 months after treatment.[39] Interestingly, prospective cohort studies of more than 200 women with first trimester itraconazole exposure did not show an increased risk of congenital malformation, but these studies reported uncontrolled doses and durations and have low power to detect differences.[40,41] In the second and third trimester of pregnancy, itraconazole can be considered if the benefit outweighs the potential risk **(CIII).**[40,41] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII).**[42] Although several cohort studies and a systematic review have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short-term exposure to fluconazole.[43-45] Reports of increased birth defects associated with fluconazole use include data from the Quebec Pregnancy Cohort, a population-based cohort with a prospective data collection on all pregnancies covered by Quebec Prescription Drug Insurance from 1998 to 2015, which demonstrated an association between higher fluconazole exposures (>150 mg dosing) during the first trimester and cardiac septal closure defects.[46] In addition, five cases of fluconazole embryopathy—a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures—have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[47-50] Additionally, fluconazole use in the first trimester has been associated with an increased risk of spontaneous abortion and stillbirth.[51] Data derived from the Quebec Pregnancy Cohort supported an increased risk of spontaneous loss with fluconazole use at low doses but found no association with risk of stillbirth.[46] A recent analysis of registry data from Sweden and Norway did not find an increase in stillbirth or neonatal death associated with exposure to fluconazole at any dose during pregnancy.[52]

In animals, voriconazole (at doses lower than recommended human doses) and posaconazole are teratogenic and embryotoxic. No adequately controlled studies have been conducted of these drugs in humans. Use of fluconazole, voriconazole, and posaconazole **should be avoided** in pregnancy, especially in the first trimester **(AIII).**

References

1. Cano-Torres JO, Olmedo-Reneaum A, Esquivel-Sanchez JM, et al. Progressive disseminated histoplasmosis in Latin America and the Caribbean in people receiving highly active antiretroviral therapy for HIV infection: a systematic review. *Med Mycol*. 2019;57(7):791-799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30668766.

2. Nacher M, Drak Alsibai K, Valdes A, et al. Risk factors for mortality among HIV-infected patients with disseminated histoplasmosis. *J Fungi (Basel)*. 2020;6(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33266199.

3. Nacher M, Valdes A, Adenis A, et al. Disseminated histoplasmosis in HIV-infected patients: a description of 34 years of clinical and therapeutic practice. *J Fungi (Basel)*. 2020;6(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32906589.

4. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine (Baltimore)*. 1990;69(6):361-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2233233.

5. McKinsey DS, Spiegel RA, Hutwagner L, et al. Prospective study of histoplasmosis in patients infected with human immunodeficiency virus: incidence, risk factors, and pathophysiology. *Clin Infect Dis*. 1997;24(6):1195-1203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9195082.

6. Baddley JW, Sankara IR, Rodriquez JM, Pappas PG, Many WJ, Jr. Histoplasmosis in HIV-infected patients in a southern regional medical center: poor prognosis in the era of highly active antiretroviral therapy. *Diagn Microbiol Infect Dis*. 2008;62(2):151-156. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18597967.

7. Assi M, McKinsey DS, Driks MR, et al. Gastrointestinal histoplasmosis in the acquired immunodeficiency syndrome: report of 18 cases and literature review. *Diagn Microbiol Infect Dis*. 2006;55(3):195-201. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16545932.

8. Gutierrez ME, Canton A, Sosa N, Puga E, Talavera L. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. *Clin Infect Dis*. 2005;40(8):1199-1202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15791523.

9. Wheat LJ, Chetchotisakd P, Williams B, Connolly P, Shutt K, Hajjeh R. Factors associated with severe manifestations of histoplasmosis in AIDS. *Clin Infect Dis*. 2000;30(6):877-881. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10854363.

10. World Health Organization. Guidelines for diagnosing and managing disseminated histoplasmosis among people living with HIV. World Health Organization. April 2020. Available at: https://www.who.int/publications/i/item/9789240006430.

11. Connolly PA, Durkin MM, Lemonte AM, Hackett EJ, Wheat LJ. Detection of histoplasma antigen by a quantitative enzyme immunoassay. *Clin Vaccine Immunol*. 2007;14(12):1587-1591. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17913863.

12. Martinez-Gamboa A, Niembro-Ortega MD, Torres-Gonzalez P, et al. Diagnostic accuracy of antigen detection in urine and molecular assays testing in different clinical samples for the diagnosis of progressive disseminated histoplasmosis in patients living with HIV/AIDS: a prospective multicenter study in Mexico. *PLoS Negl Trop Dis*. 2021;15(3):e0009215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33684128.

13. Caceres DH, Gomez BL, Tobon AM, et al. Validation and concordance analysis of a new lateral flow assay for detection of histoplasma antigen in urine. *J Fungi (Basel)*. 2021;7(10). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34682221.

14. Hage CA, Davis TE, Fuller D, et al. Diagnosis of histoplasmosis by antigen detection in BAL fluid. *Chest*. 2010;137(3):623-628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19837826.

15. Wheat LJ. Approach to the diagnosis of the endemic mycoses. *Clin Chest Med*. 2009;30(2):379-389, viii. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19375642.

16. Tobon AM, Agudelo CA, Rosero DS, et al. Disseminated histoplasmosis: a comparative study between patients with acquired immunodeficiency syndrome and non-human immunodeficiency virus-infected individuals. *Am J Trop Med Hyg*. 2005;73(3):576-582. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16172484.

17. Wheat LJ, Musial CE, Jenny-Avital E. Diagnosis and management of central nervous system histoplasmosis. *Clin Infect Dis*. 2005;40(6):844-852. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15736018.

18. Wheat J, Myint T, Guo Y, et al. Central nervous system histoplasmosis: multicenter retrospective study on clinical features, diagnostic approach and outcome of treatment. *Medicine (Baltimore)*. 2018;97(13):e0245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29595679.

19. Su CP, de Perio MA, Cummings KJ, McCague AB, Luckhaupt SE, Sweeney MH. Case investigations of infectious diseases occurring in workplaces, United States, 2006–2015. *Emerg Infect Dis*. 2019;25(3):397-405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30789129.

20. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. National Institute of Allergy and Infectious Diseases Mycoses Study Group. *Clin Infect Dis*. 1999;28(5):1049-1056. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10452633.

21. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med*. 2002;137(2):105-109. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12118965.

22. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America.

Clin Infect Dis. 2007;45(7):807-825. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17806045.

23. Lestner JM, Roberts SA, Moore CB, Howard SJ, Denning DW, Hope WW. Toxicodynamics of itraconazole: implications for therapeutic drug monitoring. *Clin Infect Dis*. 2009;49(6):928-930. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19681707.

24. Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. *Am J Med*. 1995;98(4):336-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7709945.

25. Thompson GR, 3rd, Lewis P, Mudge S, Patterson TF, Burnett BP. Open-label crossover oral bioequivalence pharmacokinetics comparison for a 3-day loading dose regimen and 15-day steady-state administration of SUBA-itraconazole and conventional itraconazole capsules in healthy adults. *Antimicrob Agents Chemother*. 2020;64(8). Available at: https://www.ncbi.nlm.nih.gov/pubmed/32457106.

26. Wheat J, MaWhinney S, Hafner R, et al. Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. *Am J Med*. 1997;103(3):223-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9316555.

27. Freifeld A, Proia L, Andes D, et al. Voriconazole use for endemic fungal infections. *Antimicrob Agents Chemother*. 2009;53(4):1648-1651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19139290.

28. Restrepo A, Tobon A, Clark B, et al. Salvage treatment of histoplasmosis with posaconazole. *J Infect*. 2007;54(4):319-327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16824608.

29. Freifeld AG, Iwen PC, Lesiak BL, Gilroy RK, Stevens RB, Kalil AC. Histoplasmosis in solid organ transplant recipients at a large Midwestern university transplant center. *Transpl Infect Dis*. 2005;7(3-4):109-115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16390398.

30. Al-Agha OM, Mooty M, Salarieh A. A 43-year-old woman with acquired immunodeficiency syndrome and fever of undetermined origin. Disseminated histoplasmosis. *Arch Pathol Lab Med*. 2006;130(1):120-123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16390228.

31. Hage CA, Kirsch EJ, Stump TE, et al. Histoplasma antigen clearance during treatment of histoplasmosis in patients with AIDS determined by a quantitative antigen enzyme immunoassay. *Clin Vaccine Immunol*. 2011;18(4):661-666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21307278.

32. Passos L, Talhari C, Santos M, Ribeiro-Rodrigues R, Ferreira LC, Talhari S. Histoplasmosis-associated immune reconstitution inflammatory syndrome. *An Bras Dermatol*. 2011;86(4 Suppl 1):S168-172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22068802.

33. Breton G, Adle-Biassette H, Therby A, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients with disseminated histoplasmosis. *AIDS*. 2006;20(1):119-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16327328.

34. Melzani A, de Reynal de Saint Michel R, Ntab B, et al. Incidence and trends in immune reconstitution inflammatory syndrome associated with histoplasma capsulatum among people living with human immunodeficiency virus: a 20-year case series and literature review. *Clin Infect Dis*. 2020;70(4):643-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30921453.

35. Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clin Infect Dis*. 2004;38(10):1485-1489. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15156489.

36. Hecht FM, Wheat J, Korzun AH, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. *J Acquir Immune Defic Syndr Human Retrovirol*. 1997;16(2):100-107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9358104.

37. Norris S, Wheat J, McKinsey D, et al. Prevention of relapse of histoplasmosis with fluconazole in patients with the acquired immunodeficiency syndrome. *Am J Med*. 1994;96(6):504-508. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8017447.

38. Dean JL, Wolf JE, Ranzini AC, Laughlin MA. Use of amphotericin B during pregnancy: case report and review. *Clin Infect Dis*. 1994;18(3):364-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8011817.

39. Janssen Pharmaceutical Companies. SPORANOX®(itraconazole) Capsules. 2023. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPORANOX-Capsules-pi.pdf.

40. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19338381.

41. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. 2000;183(3):617-620. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10992182.

42. Pilmis B, Jullien V, Sobel J, Lecuit M, Lortholary O, Charlier C. Antifungal drugs during pregnancy: an updated review. *J Antimicrob Chemother*. 2015;70(1):14-22. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25204341.

43. Nørgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother*. 2008;62(1):172-176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18400803.

44. Mastroiacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol*. 1996;175(6):1645-1650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8987954.

45. Alsaad AM, Kaplan YC, Koren G. Exposure to fluconazole and risk of congenital malformations in the offspring: a systematic review and meta-analysis. *Reprod Toxicol*. 2015;52:78-82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25724389.

46. Bérard A, Sheehy O, Zhao JP, et al. Associations between low- and high-dose oral fluconazole and pregnancy outcomes: 3 nested case-control studies. *CMAJ*. 2019;191(7):E179-E187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30782643.

47. Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet*. 1997;72(3):253-256. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9332650.

48. Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22(2):336-340. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8838193.

49. Lee BE, Feinberg M, Abraham JJ, Murthy AR. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J*. 1992;11(12):1062-1064. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1461702.

50. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol*. 2005;73(11):919-923. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16265639.

51. Mølgaard-Nielsen D, Svanstrom H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26746458.

52. Pasternak B, Wintzell V, Furu K, Engeland A, Neovius M, Stephansson O. Oral fluconazole in pregnancy and risk of stillbirth and neonatal death. *JAMA*. 2018;319(22):2333-2335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29896619.

Human Herpesvirus-8 Disease

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Epidemiology

The seroprevalence of human herpesvirus-8 (HHV-8)—also known as Kaposi sarcoma–associated herpesvirus (KSHV)—varies worldwide and is estimated to be 3% to 7% in the general U.S. population[1-4] compared with 16% in China,[5] 10% to 20% in several Mediterranean countries, and 30% to more than 90% in parts of sub-Saharan Africa.[6-10] In the United States, men who have sex with men (MSM) and people with HIV are at increased risk for HHV-8 infection.[11,12] Among MSM without HIV, the HHV-8 seroprevalence ranges from 13% to 20%, and it increases to 30% to 68% among MSM with HIV, with particularly high rates among MSM in the southern United States.[13,14] Injection drug and methamphetamine use may also be a risk factor for HHV-8 seropositivity,[15] although this association has not been observed consistently.[11-13,16]

HHV-8 is etiologically associated with all forms of Kaposi sarcoma (KS), including classic, endemic, transplant-associated, and HIV-associated (also known as "epidemic" KS). HHV-8 causes a plasmablastic form of multicentric Castleman's disease (MCD), which is a lymphoproliferative disorder. HHV-8 is also associated with primary effusion lymphoma (PEL), both its effusion-based and extra cavitary forms. Approximately 80% of PEL cases are also coinfected with Epstein-Barr virus.[17] Another type of HHV-8-associated lymphoma is known as HHV-8 positive diffuse large B-cell lymphoma (HHV-8 DLBCL), not otherwise specified.[18] Although the precise pathogenesis for these tumors remains unclear, infection with HHV-8 precedes their development.[19] HHV-8 is also related to an inflammatory syndrome known as KSHV-associated inflammatory cytokine syndrome (KICS), which is a diagnosis of exclusion.[20]

The overall prevalence of KS in the United States was as high as 30% among patients with AIDS prior to the advent of effective antiretroviral therapy (ART).[21] The incidence of KS rose steeply in the United States between 1981 and 1987 and then gradually declined, even prior to the widespread availability of highly effective combination ART.[22] Considerable geographic disparity of KS exists within the United States and worldwide. Higher rates of KS occur in the southern United States,[23] where higher mortality has been reported among Black men than in other populations.[14,24] KS is a common cancer in sub-Saharan Africa,[25] where it presents as epidemic and endemic KS. Importantly, KS incidence has declined only modestly in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.[26-28] PEL and MCD remain rare relative to KS[29,30]; however, the rarity of these conditions may be related to underdiagnosis.

Clinical Manifestations

Most individuals latently infected with HHV-8 are asymptomatic.[31] Immunocompetent children and organ transplant recipients newly infected with HHV-8 may develop a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.[32,33]

KS: KS manifestations vary widely, but most patients have nontender, hyperpigmented, macular or nodular skin lesions. Oral lesions occur at initial presentation in approximately one-quarter of

people[34,35] and are predictors of pulmonary involvement and less favorable treatment outcomes.[36-39] Lymphatic involvement is also common and may lead to debilitating lower extremity edema, even after successful treatment with chemotherapy. Persistent lymphedema, particularly of the legs, may be complicated by reduced mobility, contractures, diffuse serous drainage, skin ulceration, and recurrent cellulitis.[40,41] Involvement of internal viscera occurs in up to 50% of cases and may be difficult to diagnose. Patients with visceral involvement may either be asymptomatic or manifest with shortness of breath, painless rectal bleeding or melena, or other nonspecific pulmonary and gastrointestinal symptoms.[42-47] Involvement of organs, including the brain and heart, and extensive lytic bone lesions can also occur.[48,49] Of note, KS lesions can occur on the eyelid skin or conjunctiva. In one study conducted prior to the introduction of potent ART, 20 of 100 individuals with AIDS and KS had ophthalmic lesions.[50] In some individuals, eyelid or conjunctival lesions will be the first and initially the only clinically apparent site of KS.

MCD: MCD routinely manifests with systemic symptoms, including fever and night sweats, and findings upon examination, including generalized adenopathy, fever, and hepatosplenomegaly.[29,51] MCD may mimic nonspecific inflammatory conditions, including sepsis with hypotension and laboratory abnormalities associated with a systemic inflammatory response such as cytopenia (thrombocytopenia, anemia) and low albumin, and progress to multi-organ failure if untreated.[29,52,53] The clinical manifestations of MCD can be relapsing and remitting in nature. HHV8-associated MCD occurs in people with HIV with concurrent KS (cutaneous and/or visceral) in up to 50% of cases and can occur at high CD4 T lymphocyte (CD4) cell counts.[54]

PEL: PEL characteristically presents with effusions isolated within the pleural, pericardial, or abdominal cavities,[55] but mass lesions and "extra cavitary" disease within skin, hematopoietic organs, and the gastrointestinal tract have been described.[56-58] Patients with PEL may also present with concurrent KS (either cutaneous and/or visceral KS) and/or MCD, which may complicate diagnosis and treatment.

HHV-8 DLBCL: This type of lymphoma typically involves lymph nodes but can disseminate to extranodal sites.[59-61] Patients present with fevers and night sweats, with evidence of systemic inflammation. Patients may have massive splenomegaly as HHV-8 DLBCL may arise concurrently with MCD.[62]

KICS: KICS has been described primarily in patients with concurrent KS.[20,63,64] In the initial report of this syndrome, patients had specific signs and symptoms associated with inflammation and displayed MCD-like inflammatory symptoms but did not have pathological findings of MCD. Patients with KICS frequently are critically ill and demonstrate marked elevations in interleukin-6 (IL-6) and interleukin-10, as well as high plasma HHV-8 viral loads. It is important to note that patients with PEL meet criteria for KICS, but as a distinct pathologic process with unique oncologic management, it is essential to appropriately work up and exclude PEL among individuals who meet KICS criteria.[65] Therefore, KICS is a diagnosis of exclusion, and it is essential to rule out other HHV-8 conditions, including both MCD and PEL, which have different treatment paradigms.[66]

Overlapping HHV-8 Disorders: KS can present concurrently with MCD, PEL, or KICS. Individuals with MCD may have a concurrent lymphoma or KS at presentation or experience the emergence of KS following MCD treatment.[67] Consequently, a thorough diagnostic workup (including imaging and histologic evaluation) must be undertaken to appropriately diagnose any other concurrent HHV8-associated disorders, as treatment may vary depending on the diagnosis.

Diagnosis

Kaposi Sarcoma

Clinical diagnosis alone generally is not sufficient for KS, and tissue examination is needed to confirm diagnosis.[68,69] Diagnosis of KS requires histologic confirmation of suspected KS lesions. KS diagnosis is confirmed by immunohistochemical (IHC) staining of tumors with antibodies recognizing the HHV-8-encoded latency-associated nuclear antigen (LANA). Polymerase chain reaction (PCR) to identify HHV-8 DNA within tumor tissue may augment IHC, but the role of PCR in KS diagnosis remains under evaluation.[70,71] In settings where biopsy is not available, referral to a center where a biopsy can be safely obtained is important.

Bronchoscopy for visualization of endobronchial KS lesions and CT of the chest should be performed if there is concern for pulmonary KS (respiratory symptoms or abnormal chest X-ray); however, transbronchial biopsies or biopsies of endobronchial lesions are not recommended because of the vascular nature of these tumors and risk of bleeding. CT abdomen and upper endoscopy and colonoscopy should be performed if there is suspicion for gastrointestinal (GI) KS (GI symptoms, iron deficiency anemia, or positive fecal occult blood). GI biopsy of KS lesions is feasible and important for establishing the diagnosis of KS or other opportunistic infections, such as cytomegalovirus, which may impact management. Conjunctival KS remains a clinical diagnosis due to potential complications of obtaining conjunctival biopsies.

Kaposi Sarcoma Staging

The AIDS Clinical Trials Group (ACTG) criteria is the most widely used KS staging system and is based on tumor extent (T), immunologic status as measured by CD4 count (I), and the presence of systemic illness (S). “Good risk” tumor stage (T0) is defined as KS confined to the skin and/or lymph nodes and/or minimal oral disease. “Poor risk” tumor stage (T1) is defined as KS with tumor-associated edema and/or ulceration, extensive oral disease, or visceral KS.[72,73]

Multicentric Castleman’s Disease

The diagnosis of MCD requires a lymph node biopsy. Histology demonstrates monotypic, lambda restricted plasmablasts that are HHV-8-infected (LANA positive) and are primarily located in the mantle cell zones and/or abutting the germinal centers.[59] Lymph node biopsies may also demonstrate concurrent KS. Research studies examining flow cytometry studies of peripheral blood and effusions from patients with MCD during episodes of flare have shown HHV-8 positive lambda restricted plasmablasts or viroblasts that may be indicative of this diagnosis.[74,75] Histologic biopsy of lymph nodes remains the standard for MCD diagnosis.

Primary Effusion Lymphoma

PEL diagnosis requires measurement of cytologic and immunologic cell markers by flow cytometry analyses, as well as histology confirmation for cases of suspected extracavitary PEL.

HHV-8 Diffuse Large B-Cell Lymphoma

HHV-8 DLCBL requires pathologic confirmation of involved nodal or extranodal sites.

KSHV-Associated Inflammatory Cytokine Syndrome

KICS may occur concurrently in patients with KS. Criteria for KICS include:

1. Clinical manifestations
    a. Symptoms (e.g., fever, fatigue, respiratory and/or gastrointestinal symptoms)
    b. Laboratory abnormalities (e.g., pancytopenia, low albumin)
    c. Radiographic abnormalities (e.g., organomegaly, body cavity effusions, lymphadenopathy)
2. Evidence of systemic inflammation (elevated C-reactive protein)
3. Elevated HHV-8 DNA levels in the plasma or peripheral blood mononuclear cells (PBMCs)
4. Absence of a pathologic diagnosis of MCD or PEL, which would require lymph node assessment or sampling of body cavity effusions

The working KICS criteria requires the presence of at least two clinical manifestations drawn from at least two different categories (1a, b, and c) and meeting criteria 2 through 4.[20,76]

Other Diagnostic Considerations for HHV-8-Related Disease

Serologic testing for HHV-8 antibodies is not used for either diagnostic testing or routine screening for HHV-8-related illnesses. The lack of a standardized role for HHV-8 serology is in part due to the poor sensitivity and specificity of the current assays.[77]

Measurement of plasma HHV-8 is useful for diagnosis and monitoring of some HHV-8-related diseases. In one study from South Africa, patients with KS with elevated HHV-8 viral levels in the blood were often associated with S1 stage, or the presence of systemic illness, and indicative of a concurrent HHV-8 inflammatory syndrome.[78] A prospective study in Uganda also found that a higher HHV-8 copy number in plasma at KS diagnosis was associated with worse survival outcomes in epidemic and endemic KS.[79] For patients with KICS, detection of HHV-8 in blood is part of the diagnostic criteria.[80] HHV-8 DNA levels in the PBMCs are elevated in patients with active MCD and PEL,[17,80,81] and an undetectable plasma HHV-8 DNA may exclude a diagnosis of MCD.[80] Among patients with MCD, PBMC HHV-8 DNA levels decrease following a flare.[67] A retrospective study demonstrated that whole blood HHV-8 DNA levels appeared to be higher in patients with MCD than in patients with KS.[82]

Preventing Exposure

The mode(s) of transmission of HHV-8 remains unclear, but epidemiologic and virologic data suggest that saliva is a source of infectious virus and may be an important route of transmission. Asymptomatic HHV-8 infection is often associated with HHV-8 shedding in the saliva and occasional shedding in genital secretions.[31,83,84] In a study of 50 MSM with HHV-8 infection in the United States, HHV-8 was detected by PCR in the saliva of 39% of participants on more than 35% of days on which samples were obtained.[83] HHV-8 shedding is also common among persons in sub-Saharan Africa. Among adults with HHV-8 without KS in Uganda, 22% had HHV-8 DNA detected in saliva and 3% in genital secretions; HHV-8 also was detected in saliva of 68% of commercial sex

workers in Kenya.[85,86] Based on these observations, viral shedding may result in HHV-8 transmission to uninfected partners through behaviors associated with exposure to saliva or genital secretions.[13] HHV-8 transmission through blood transfusion has been reported in Uganda, where HHV-8 is endemic[87]; however, studies from the United States and Western Europe have not found evidence to support HHV-8 transmission through blood transfusion.[88,89] Perinatal transmission from the placenta or during delivery or peripartum also occurs.

Recommendations to prevent exposure to HHV-8 do not yet exist; screening patients for HHV-8 serostatus or behavioral modifications to limit potential exposures have not been validated and are not currently recommended.

Preventing Disease

Recommendation for Preventing Development of Kaposi Sarcoma
• Administer ART to all people with HIV to reduce the likelihood that KS will develop (AI).

Key: ART = antiretroviral therapy; KS = Kaposi sarcoma

Because strong risk factors for the development of KS in people with HIV include both low CD4 count[90] and uncontrolled viremia,[91] the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) recommends early initiation of ART to reduce the risk of KS **(AI).**[92,93] Although epidemiologic data are somewhat conflicting, no antiretroviral agents have proven clearly superior to others for the prevention of KS.[88-91,94,95]

Although ganciclovir inhibits HHV-8 replication, insufficient evidence exists to support the use of ganciclovir for prophylaxis of HHV-8 disease.[96] Therefore, the Panel recommends against the use of ganciclovir or valganciclovir in preventing HHV-8 disease **(AIII).**

Treating Disease

Recommendations for Treating HHV-8-Associated Diseases—Kaposi Sarcoma, Primary Effusion Lymphoma, Multicentric Castleman's Disease
General Treatment Considerations
• Treatment for HHV-8-associated diseases should be undertaken in consultation with guidance from both oncology and infectious disease specialists, with additional input from centers specifically caring for people with HIV and cancer (AIII).
• Among people with HIV, all HHV-8-specific treatments should be given with ART, which is an essential component of managing these diseases (AI).
• ART given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug–drug interactions and additive toxicities (AIII).
Kaposi Sarcoma
ACTG StageT0 (localized involvement of skin and/or lymph nodes and/or minimal oral disease only):
• ART (AII) alone, *or*
• ART plus liposomal doxorubicin (AIII), if disease does not respond to ART alone; *or*

ACTG stage T1 [extensive and/or symptomatic KS skin lesions, extensive oral disease, tumor-associated edema, and/or ulceration or any visceral involvement]:

- Preferred Therapy
  - ART plus liposomal doxorubicin (AI)
- Alternative Therapy
  - ART plus paclitaxel, if liposomal doxorubicin is not available (AI), or to treat recurrence after treatment with liposomal doxorubicin (AII), *or*
  - ART with oral pomalidomide plus thromboprophylaxis (e.g., low-dose aspirin 81 mg daily) (BII)

Note: Concurrent use of systemic corticosteroids or other immunosuppressants in patients with KS should either be avoided or used under close observation, given the potential for exacerbation of KS (AIII).

Multicentric Castleman's Disease

Preferred Therapy

- MCD without KS: ART plus rituximab (BII)
- MCD with KS: ART plus rituximab with liposomal doxorubicin (AII)

Alternative Therapy

- ART plus IV ganciclovir (or oral valganciclovir) with or without high-dose zidovudine—not for use in cases of multi-organ failure, such as renal and/or hepatic failure (CII)

Primary Effusion Lymphoma or HHV-8 Diffuse Large B-Cell Lymphoma (with or without KS)

Preferred Therapy

- PEL or HHV-8-associated DLBCL: ART plus combination chemotherapy, such as EPOCH (AIII)
- PEL or HHV-8-associated DLBCL with MCD: ART plus dose-adjusted EPOCH and rituximab (CII)

KSHV-Associated Inflammatory Cytokine Syndrome

- After excluding MCD and PEL, ART plus rituximab with combination chemotherapy for concurrent KS (CII)

Key: ACTG = AIDS Clinical Trials Group; ART = antiretroviral therapy; DLBCL = diffuse large B-cell lymphoma; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin combination therapy; HHV-8 = human herpesvirus 8; IV = intravenous; KS = Kaposi sarcoma; KSHV = Kaposi sarcoma–associated herpesvirus; MCD = multicentric Castleman's disease; PEL = primary effusion lymphoma; T1 = "Poor risk" tumor stage

General Treatment Considerations for All Patients With HHV-8-Associated Disorders

Treatment for HHV-8-associated diseases should be undertaken in consultation with an experienced specialist with appropriate guidance from both oncology and infectious disease specialists with additional input from centers specifically caring for people with HIV and cancer **(AIII).** Among people with HIV, all HHV-8-specific treatments should be given with ART, which is an essential component of managing these disorders **(AI).** ART given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug–drug interactions and additive toxicities **(AIII).** Consider referral for clinical trials for all HHV-8-associated disorders, including patients with persistent or recurrent KS.

Kaposi Sarcoma

Initiating ART alone, without chemotherapy, can effectively treat KS in people with HIV with ACTG T0 tumor stage (limited cutaneous KS and no visceral disease) and is therefore recommended as initial therapy **(AII).**[97] Of note, a multicenter trial in sub-Saharan Africa and South America found that initiating ART in combination with chemotherapy (oral etoposide) reduced the risk of suspected KS-immune reconstitution inflammatory syndrome (IRIS) and/or early KS progression compared with ART alone, but it did not provide durable clinical benefit as measured by death, KS progression, or initiation of chemotherapy, other than etoposide.[98,99] Liposomal doxorubicin, along with ART, can be administered in consultation with a specialist in cases where T0 tumor stage disease does not resolve with ART alone **(AIII).**

Chemotherapy, in combination with ART in people with HIV, should be administered in patients with ACTG T1 tumor stage, defined as extensive and/or symptomatic KS skin lesions, extensive oral disease, tumor-associated edema and/or ulceration, or any visceral involvement of KS **(AI).**[79,94,95,98,100,101]

Although liposomal doxorubicin and paclitaxel exhibit comparable response rates and progression-free survival, liposomal doxorubicin exhibits less high-grade toxicity relative to paclitaxel.[94] In limited resource settings, where liposomal doxorubicin is not available, data have demonstrated benefits in using paclitaxel over other available regimens, such as bleomycin and vincristine or etoposide.[102] Therefore, liposomal doxorubicin is recommended as first-line therapy **(AI);** when liposomal doxorubicin is unavailable, paclitaxel is a recommended alternative **(AI).** Paclitaxel is also recommended to treat recurrent KS following treatment with liposomal doxorubicin **(AII).**[100]

Pomalidomide, an oral immunomodulatory drug, has been investigated in patients with KS with and without HIV. Among people with HIV, pomalidomide was approved for use by the U.S. Food and Drug Administration if KS is not responsive to ART alone **(BII).** Pomalidomide was administered with ART and aspirin 81 mg (for thromboprophylaxis) with response rates of 67% among people with HIV in a Phase 1/2 study.[103] In this study, 83% of participants had received prior chemotherapy at baseline. Adherence to oral therapy and thromboprophylaxis is important while using pomalidomide.

KS may be recurrent despite ART adherence and re-treatment with the same systemic KS treatment options may be feasible. However, for patients with persistent or worsening KS despite chemotherapy, other concurrent HHV-8 diseases, specifically PEL or MCD, should be considered **(BIII).**

Local Therapy

For individuals with large, bulky eyelid or conjunctival lesions, local treatment may be necessary to improve eyelid function, relieve associated pain, and prevent complications from ocular surface exposure. In cases of stage T0 disease, local treatments of eyelid or conjunctival lesions reported to be effective include surgical excision, cryotherapy alone, low-dose radiation, and topical or intralesional injections of interferon-alfa-2a or -2b **(CIII).**[50,104-106] Each approach has been reported to cause complete lesion regression, with minimal side effects, but no comparative studies have been reported that identify the most effective local treatment. Similarly, for stage T0 skin disease, local therapies have been used.[107,108] However, these studies were done prior to the introduction use of

effective ART. Overall, as KS may recur despite local therapies, options for systemic therapy should be sought, especially in cases with T1 disease **(AI).**

Other Agents

Concurrent use of systemic corticosteroids or other immunosuppressants in patients with KS should either be avoided or used under close observation, given the potential for exacerbation of KS **(AIII).**[109-111]

The antiviral agents ganciclovir, foscarnet, and cidofovir exhibit *in vitro* activity against HHV-8.[112,113] Available data indicate that these antiviral drugs have limited efficacy for the treatment of KS[114,115] and HHV-8-associated hemophagocytosis.[116,117] Therefore, antiviral agents with activity against HHV-8 are not recommended for KS treatment **(AII).**

Multicentric Castleman's Disease

Rituximab is recommended as first-line treatment for MCD **(BII),**[118,119] although up to one-third of patients receiving rituximab may have subsequent exacerbations or emergence of KS.[120,121]

For patients with concurrent diagnoses of KS and MCD, use of both rituximab and liposomal doxorubicin is recommended **(AII).**[51,67]

Other Agents

Monoclonal antibodies targeting either IL-6 or the IL-6 receptor are approved for patients with idiopathic MCD, but this is not applicable in patients with HHV8-associated MCD.[122-124] Use of tocilizumab in HHV-8-associated MCD resulted in five of eight participants having a response in MCD; however, duration of the response was only 3.2 months, and seven of the study participants received rituximab for subsequent MCD flares.[125] Currently, insufficient evidence exists to recommend monitoring IL-6 levels for diagnostic or prognostic purposes.

A 3-week course of twice-daily intravenous (IV) ganciclovir or oral valganciclovir was associated with remissions in MCD in one report,[126] and a combination of valganciclovir and high-dose zidovudine (ZDV) has led to durable clinical remissions[127]; therefore, IV ganciclovir or oral valganciclovir may be considered when treating MCD without multi-organ dysfunction, either with or without high-dose ZDV **(CII).** Additionally, studies have explored the role of maintenance oral valganciclovir with tocilizumab or ZDV with valganciclovir and rituximab-based therapies. Among those treated with rituximab with liposomal doxorubicin and maintenance ZDV/valganciclovir, the 5-year progression-free survival was 89%.[67] The role of maintenance therapies in MCD is unclear given the relapsing and remitting nature of this disease, and they are therefore not recommended.

Although corticosteroids appear to be effective as an adjunctive therapy for MCD, they should be used with caution or avoided, especially in patients with concurrent KS, given potential for exacerbation of life-threatening KS **(AIII).**[109-111] In patients with MCD who have emergence of KS or worsening KS, KS-directed therapy should be continued beyond MCD management **(BII).**[128]

Primary Effusion Cell Lymphoma and HHV-8 Diffuse Large B-cell Lymphoma

Combination chemotherapy regimens used for other B-cell lymphomas, in combination with ART, should be administered to patients with PEL with curative intent **(AIII).** Due to the rarity of this

disease, limited data are available from prospective randomized clinical trials. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in combination with ART has demonstrated some benefit, albeit still limited, for PEL. The combination of etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) demonstrated superior survival relative to CHOP in one pooled analysis [129,130] Therefore, ART with EPOCH should be given as first-line treatment for PEL or HHV-8 DLBCL with or without concurrent KS **(AIII).**

Rituximab and dose-adjusted EPOCH **(CII)** should be considered in patients with PEL or HHV8-DLBCL and concurrent diagnosis of MCD with or without concurrent KS [131,132] One retrospective observational study of 20 patients (19 treated with EPOCH regimen with or without rituximab, bevacizumab, and/or high-dose methotrexate as combinations) has shown a 3-year cancer-specific survival of 47%.[17]

KSHV-Associated Inflammatory Cytokine Syndrome

Because of the overlapping clinical and laboratory features between KICS and MCD, rituximab in combination with chemotherapy has been evaluated as a therapeutic option for KICS, which is commonly observed with concurrent KS. This has led to improvement in clinical symptoms in case reports and case series.[76,133] In a larger prospective evaluation of patients with KICS, in 18 patients administered rituximab in combination with chemotherapy for concurrent KS, 55% of patients had a response per the clinical benefit response criteria, which includes laboratory findings and symptoms associated with KICS.[66] Therefore, rituximab with combination chemotherapy to treat KS is recommended for patients with KICS **(CII).** As rituximab is associated with the onset or deterioration of KS, careful management of concurrent KS is imperative.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

When initiating ART, IRIS may occur among patients with HHV-8-related KS, PEL, or MCD.

KS: KS-IRIS is characterized by either first presentation of KS ("unmasking") or paradoxical worsening of pre-existing KS and can be associated with significant morbidity and mortality.[134] Studies in the United States and Europe reveal that KS is the most commonly reported form of IRIS, occurring in 6% to 29% of patients with KS and HIV who are initiating ART.[135,136] In sub-Saharan Africa, exacerbations of KS compatible with KS-IRIS have been reported in 18% to 31% of adults initiating ART.[137-139]

Risk factors for developing KS-IRIS include advanced KS tumor stage (T1), pre-treatment HIV viral load >5 $\log_{10}$ copies/mL, detectable pre-treatment plasma HHV-8, and initiation of ART alone without concurrent chemotherapy.[134,135] Therefore, an accurate staging of KS prior to starting ART without chemotherapy is necessary.

Treatment of KS-IRIS includes systemic chemotherapy and supportive measures. Steroids are strongly discouraged for managing KS-IRIS because corticosteroid therapy has been associated with exacerbation of pre-existing KS in people with HIV **(AIII).**[111,140]

KS may present concurrently with other HHV-8 diseases, such as PEL, MCD, or KICS, which may mimic features of KS-IRIS.

MCD and PEL: Little information exists about the frequency of IRIS in terms of unmasking or paradoxical worsening of MCD or PEL.[136,141]

Preventing Recurrence

ART should be continued lifelong as with all people with HIV. Suppression of HIV replication may prevent recurrence and is recommended for patients with KS and MCD **(AIII),** as well as those with HHV-8-associated malignant lymphoproliferative disorders **(AIII).**

Special Considerations During Pregnancy

The seroprevalence of HHV-8 infection among pregnant women with HIV varies by geographic area, ranging from 1.7% among U.S.-born and 3.6% among Haitian-born women in New York City to 2.4% to 6.0% among pregnant women from four other U.S. cities.[142,143] One study from Brazil of 131 pregnant women with HIV found HHV-8 antibodies in 0.8% and no HHV-8 DNA was detected.[144] However, given the much higher HHV-8 prevalence and occurrence of KS among African populations[3], including among pregnant women,[145] clinicians should have a lower threshold for consideration of HHV-8-related diagnoses with consistent clinical presentations among pregnant African immigrants with HIV. Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,[146] although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.[147] HHV-8 seropositivity does not appear to influence pregnancy outcome.

Routine screening for HHV-8 by PCR or serology is not recommended during pregnancy **(AIII).**

Antiviral therapy with cidofovir, ganciclovir, or foscarnet or other antivirals targeting HHV-8 infection in pregnancy is not recommended **(AIII).**

Given the rarity of KS, PEL, and MCD in pregnancy and the potential toxicity of the drugs used for treatment, when these conditions occur in pregnancy, they should be managed with consultations among the obstetrician, infectious disease specialist, and oncologist. With limited disease, treatment may be deferred until after delivery.[148]

In vitro models suggest that beta-human chorionic gonadotropin induces regression of KS tumors, but clinical reports on the incidence and natural history of KS in pregnancy are conflicting.[149-152] Perinatal transmission of HHV-8 occurs infrequently. Evidence supporting perinatal transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth,[153,154] higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),[155] and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.[156] Maternal HIV infection was associated with decreased transplacental transfer of antibodies to HHV-8 and lower cord blood levels of HHV-8 antigens, as compared to mothers without HIV; however, there was no effect on age of infection in the child.[157] Data indicate increased mortality through age 24 months among infants with HIV born to HHV-8-seropositive mothers compared with HHV-8-seronegative mothers,[153-155,158-163] but these studies could not completely account for other confounding factors affecting infants with HIV. The majority of studies document a substantially higher rate of HHV-8 seropositivity among children born to HHV-8 antibody-positive women compared with HHV-8 antibody-negative women.[158-163]

References

1. Pellett PE, Wright DJ, Engels EA, et al. Multicenter comparison of serologic assays and estimation of human herpesvirus 8 seroprevalence among US blood donors. *Transfusion*. 2003;43(9):1260-1268. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12919429.

2. Hudnall SD, Chen T, Rady P, Tyring S, Allison P. Human herpesvirus 8 seroprevalence and viral load in healthy adult blood donors. *Transfusion*. 2003;43(1):85-90. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12519435.

3. Engels EA, Atkinson JO, Graubard BI, et al. Risk factors for human herpesvirus 8 infection among adults in the United States and evidence for sexual transmission. *The Journal of Infectious Disease*. 2007;196(2):199–207. Available at: https://academic.oup.com/jid/article/196/2/199/871873.

4. Qu L, Jenkins F, Triulzi DJ. Human herpesvirus 8 genomes and seroprevalence in United States blood donors. *Transfusion*. 2010;50(5):1050-1056. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1537-2995.2009.02559.x.

5. Fang Y, Li W, Zhang Y, et al. Seroprevalence of Kaposi's sarcoma-associated herpesvirus and risk factors in Jiuquan area, China. *J Med Virol*. 2022;94(12):6016-6022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35922376.

6. Dollard SC, Butler LM, Jones AM, et al. Substantial regional differences in human herpesvirus 8 seroprevalence in sub-Saharan Africa: insights on the origin of the "Kaposi's sarcoma belt". *Int J Cancer*. 2010;127(10):2395-2401. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20143397.

7. Malonga GA, Dienta S, Traore FT, et al. Human herpesvirus 8 seroprevalence among blood donors in Mali. *J Med Virol*. 2022;94(9):4554-4558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35546445.

8. Cesarman E, Damania B, Krown SE, Martin J, Bower M, Whitby D. Kaposi sarcoma. *Nat Rev Dis Primers*. 2019;5(1):9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30705286.

9. Newton R, Labo N, Wakeham K, et al. Kaposi sarcoma–associated herpesvirus in a rural Ugandan cohort, 1992–2008. *The Journal of Infectious Disease*. 2018;217(2):263–269. Available at: https://academic.oup.com/jid/article/217/2/263/4584515.

10. Nalwoga A, Webb EL, Muserere C, et al. Variation in KSHV prevalence between geographically proximate locations in Uganda. *Infect Agent Cancer*. 2020;15:49. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32714434.

11. Liu Z, Fang Q, Zuo J, et al. Global epidemiology of human herpesvirus 8 in men who have sex with men: a systematic review and meta-analysis. *J Med Virol*. 2018;90(3):582-591. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28975631.

12. Labo N, Miley W, Benson CA, Campbell TB, Whitby D. Epidemiology of Kaposi's sarcoma-associated herpesvirus in HIV-1-infected US persons in the era of combination antiretroviral therapy. *AIDS*. 2015;29(10):1217-1225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26035321.

13. Knights SM, Salyards M, Kendall N, et al. High seroprevalence of Kaposi sarcoma-associated herpesvirus in men who have sex with men with HIV in the southern United States. *Open Forum Infect Dis*. 2023;10(4):ofad160. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37096147.

14. Knights SM, Lazarte SM, Kainthla R, Chiao EY, Nijhawan AE. Mortality disparities among patients with HIV-associated Kaposi's sarcoma in the southern United States. *AIDS*. 2022;36(5):721-728. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34930860.

15. Cannon MJ, Dollard SC, Smith DK, et al. Blood-borne and sexual transmission of human herpesvirus 8 in women with or at risk for human immunodeficiency virus infection. *N Engl J Med*. 2001;344(9):637-643. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11228278.

16. Renwick N, Dukers NH, Weverling GJ, et al. Risk factors for human herpesvirus 8 infection in a cohort of drug users in the Netherlands, 1985-1996. *J Infect Dis*. 2002;185(12):1808-1812. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12085330.

17. Lurain K, Polizzotto MN, Aleman K, et al. Viral, immunologic, and clinical features of primary effusion lymphoma. *Blood*. 2019;133(16):1753-1761. Available at: https://www.pubmed.ncbi.nlm.nih.gov/30782610.

18. International Agency for Research on Cancer. WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: 2017.Available at: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017.

19. Gao SJ, Kingsley L, Hoover DR, et al. Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. *N Engl J Med*. 1996;335(4):233-241. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8657239.

20. Polizzotto MN, Uldrick TS, Wyvill KM, et al. Clinical features and outcomes of patients with symptomatic Kaposi sarcoma herpesvirus (KSHV)-associated inflammation: prospective characterization of KSHV inflammatory cytokine syndrome (KICS). *Clin Infect Dis*. 2016;62(6):730-738. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26658701.

21. Beral V. The epidemiology of cancer in AIDS patients. *AIDS*. 1991;5 Suppl 2:S99-103. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1845066.

22. Eltom MA, Jemal A, Mbulaiteye SM, Devesa SS, Biggar RJ. Trends in Kaposi's sarcoma and non-Hodgkin's lymphoma incidence in the United States from 1973 through 1998. *J Natl Cancer Inst*. 2002;94(16):1204-1210. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12189223.

23. Royse KE, El Chaer F, Amirian ES, et al. Disparities in Kaposi sarcoma incidence and survival in the United States: 2000–2013. *PLoS One*. 2017;12(8):e0182750. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28829790.

24. White DL, Oluyomi A, Royse K, et al. Incidence of AIDS-related Kaposi sarcoma in all 50 United States from 2000 to 2014. *J Acquir Immune Defic Syndr*. 2019;81(4):387-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31242141.

25. Forman D, Bray F, Brewster DH, et al., ed^eds. Cancer incidence in five continents. ed. Lyon: International Agency for Research on Cancer; 2014. ed^eds.; No. X.

26. Casper C. The increasing burden of HIV-associated malignancies in resource-limited regions. *Annu Rev Med*. 2011;62:157-170. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20868276.

27. Mutyaba I, Phipps W, Krantz EM, et al. A population-level evaluation of the effect of antiretroviral therapy on cancer incidence in Kyadondo County, Uganda, 1999–2008. *J Acquir Immune Defic Syndr*. 2015;69(4):481-486. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25844696.

28. Semeere AS, Busakhala N, Martin JN. Impact of antiretroviral therapy on the incidence of Kaposi's sarcoma in resource-rich and resource-limited settings. *Curr Opin Oncol*. 2012;24(5):522-530. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22729153.

29. Casper C. The aetiology and management of Castleman disease at 50 years: translating pathophysiology to patient care. *Br J Haematol*. 2005;129(1):3-17. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15801951.

30. Bhutani M, Polizzotto MN, Uldrick TS, Yarchoan R. Kaposi sarcoma-associated herpesvirus-associated malignancies: epidemiology, pathogenesis, and advances in treatment. *Semin Oncol*. 2015;42(2):223-246. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25843728.

31. Casper C, Krantz E, Selke S, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. *J Infect Dis*. 2007;195(1):30-36. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17152006.

32. Andreoni M, Sarmati L, Nicastri E, et al. Primary human herpesvirus 8 infection in immunocompetent children. *JAMA*. 2002;287(10):1295-1300. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11886321.

33. Luppi M, Barozzi P, Schulz TF, et al. Bone marrow failure associated with human herpesvirus 8 infection after transplantation. *N Engl J Med*. 2000;343(19):1378-1385. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11070102.

34. Fatahzadeh M, Schwartz RA. Oral Kaposi's sarcoma: a review and update. *Int J Dermatol*. 2013;52(6):666-672. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23679875.

35. Lager I, Altini M, Coleman H, Ali H. Oral Kaposi's sarcoma: a clinicopathologic study from South Africa. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2003;96(6):701-710. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14676761.

36. Reichart PA. Oral manifestations in HIV infection: fungal and bacterial infections, Kaposi's sarcoma. *Med Microbiol Immunol*. 2003;192(3):165-169. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12684760.

37. Rohrmus B, Thoma-Greber EM, Bogner JR, Rocken M. Outlook in oral and cutaneous Kaposi's sarcoma. *Lancet*. 2000;356(9248):2160. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11191549.

38. Gorsky M, Epstein JB. A case series of acquired immunodeficiency syndrome patients with initial neoplastic diagnoses of intraoral Kaposi's sarcoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2000;90(5):612-617. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11077385.

39. Yoo DJ, Lee KH, Munderi P, Shin KC, Lee JK. Clinical and bronchoscopic findings in Ugandans with pulmonary Kaposi's sarcoma. *Korean J Intern Med*. 2005;20(4):290-294. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16491826.

40. Ramaswami R, Lurain K, Yarchoan R. Oncologic treatment of HIV-associated Kaposi sarcoma 40 years on. *J Clin Oncol*. 2022;40(3):294-306. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34890242.

41. Volkow-Fernandez P, Islas-Munoz B, Alatorre-Fernandez P, Cornejo-Juarez P. Cellulitis in patients with chronic lower-limb lymphedema due to HIV-related Kaposi sarcoma. *Int J STD AIDS*. 2022;33(3):296-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34965797.

42. Phipps W, Ssewankambo F, Nguyen H, et al. Gender differences in clinical presentation and outcomes of epidemic Kaposi sarcoma in Uganda. *PLoS One*. 2010;5(11):e13936. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21103057.

43. Imran TF, Al-Khateeb Z, Jung J, Peters S, Dever LL. Pulmonary Kaposi's sarcoma as the initial presentation of human immunodeficiency virus infection. *IDCases*. 2014;1(4):78-81. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26839780.

44. Lee AJ, Brenner L, Mourad B, Monteiro C, Vega KJ, Munoz JC. Gastrointestinal Kaposi's sarcoma: case report and review of the literature. *World J Gastrointest Pharmacol Ther*. 2015;6(3):89-95. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26261737.

45. Buchbinder A, Friedman-Kien AE. Clinical aspects of epidemic Kaposi's sarcoma. *Cancer Surv*. 1991;10:39-52. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1821322.

46. Hengge UR, Ruzicka T, Tyring SK, et al. Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 1: epidemiology, environmental predispositions, clinical manifestations, and therapy. *Lancet Infect Dis*. 2002;2(5):281-292. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12062994.

47. Sissolak G, Mayaud P. AIDS-related Kaposi's sarcoma: epidemiological, diagnostic, treatment and control aspects in sub-Saharan Africa. *Trop Med Int Health*. 2005;10(10):981-992. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16185232.

48. Isenbarger DW, Aronson NE. Lytic vertebral lesions: an unusual manifestation of AIDS-associated Kaposi's sarcoma. *Clin Infect Dis*. 1994;19(4):751-755. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7803643.

49. Andrews JR, Cho-Park YA, Ferry J, Abramson JS, Robbins GK. Kaposi's sarcoma-associated herpesvirus-related solid lymphoma involving the heart and brain. *AIDS Res Treat*. 2011;2011:729854. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21541215.

50. Shuler JD, Holland GN, Miles SA, Miller BJ, Grossman I. Kaposi sarcoma of the conjunctiva and eyelids associated with the acquired immunodeficiency syndrome. *Arch Ophthalmol*. 1989;107(6):858-862. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2471496.

51. Uldrick TS, Polizzotto MN, Aleman K, et al. Rituximab plus liposomal doxorubicin in HIV-infected patients with KSHV-associated multicentric Castleman disease. *Blood*. 2014;124(24):3544-3552. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25331113.

52. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and management of Castleman disease. *Cancer Control*. 2014;21(4):266-278. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25310208.

53. Anderson S, Sasson SC, Lee FJ, Cooper W, Larsen S, Garsia R. Episodic fevers and vasodilatory shock mimicking urosepsis in a patient with HIV-associated multicentric Castleman's Disease: a case report. *BMC Infect Dis*. 2016;16:53. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26831502.

54. Bower M. How I treat HIV-associated multicentric Castleman disease. *Blood*. 2010;116(22):4415-4421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20688959.

55. Patel S, Xiao P. Primary effusion lymphoma. *Arch Pathol Lab Med*. 2013;137(8):1152-1154. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23899073.

56. Pielasinski U, Santonja C, Rodriguez-Pinilla SM, Requena L. Extracavitary primary effusion lymphoma presenting as a cutaneous tumor: a case report and literature review. *J Cutan Pathol*. 2014;41(9):745-753. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24917369.

57. Courville EL, Sohani AR, Hasserjian RP, Zukerberg LR, Harris NL, Ferry JA. Diverse clinicopathologic features in human herpesvirus 8-associated lymphomas lead to diagnostic problems. *Am J Clin Pathol*. 2014;142(6):816-829. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25389336.

58. Liao G, Cai J, Yue C, Qing X. Extracavitary/solid variant of primary effusion lymphoma presenting as a gastric mass. *Exp Mol Pathol*. 2015;99(3):445-448. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26407759.

59. Chadburn A, Said J, Gratzinger D, et al. HHV8/KSHV-positive lymphoproliferative disorders and the spectrum of plasmablastic and plasma cell neoplasms: 2015 SH/EAHP Workshop report-part 3. *Am J Clin Pathol*. 2017;147(2):171-187. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28395104.

60. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma. *Blood*. 2000;95(4):1406-1412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10666218.

61. Vega F, Miranda RN, Medeiros LJ. KSHV/HHV8-positive large B-cell lymphomas and associated diseases: a heterogeneous group of lymphoproliferative processes with significant clinicopathological overlap. *Mod Pathol*. 2020;33(1):18-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31527708.

62. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood*. 2002;99(7):2331-2336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11895764.

63. Uldrick TS, Wang V, O'Mahony D, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without multicentric Castleman disease. *Clin Infect Dis*. 2010;51(3):350-358. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20583924.

64. Polizzotto MN, Uldrick TS, Hu D, Yarchoan R. Clinical manifestations of Kaposi sarcoma herpesvirus lytic activation: multicentric Castleman disease (KSHV-MCD) and the KSHV inflammatory cytokine syndrome. *Front Microbiol*. 2012;3:73. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22403576.

65. Patel R, Lurain K, Yarchoan R, Ramaswami R. Clinical management of Kaposi sarcoma herpesvirus-associated diseases: an update on disease manifestations and treatment strategies. *Expert Rev Anti Infect Ther*. 2023;21(9):929-941. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37578202.

66. Ramaswami R, Lurain K, Polizzotto M, et al. Study of characteristics and outcomes of KSHV inflammatory cytokine syndrome (KICS). Presented at: Conference on Retroviruses and Opportunistic Infections (CROI). 2023. Seattle, WA. Available at: https://www.croiconference.org/croi-2023-resources/#program-guide.

67. Ramaswami R, Lurain K, Polizzotto MN, et al. Characteristics and outcomes of KSHV-associated multicentric Castleman disease with or without other KSHV diseases. *Blood Advances*. 2021;5(6):1660-1670. Available at: https://pubmed.ncbi.nlm.nih.gov/33720337.

68. Patel RM, Goldblum JR, Hsi ED. Immunohistochemical detection of human herpes virus-8 latent nuclear antigen-1 is useful in the diagnosis of Kaposi sarcoma. *Mod Pathol*. 2004;17(4):456-460. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14990970.

69. Amerson E, Woodruff CM, Forrestel A, et al. Accuracy of clinical suspicion and pathologic diagnosis of Kaposi sarcoma in East Africa. *J Acquir Immune Defic Syndr*. 2016;71(3):295-301. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26452066.

70. Pak F, Mwakigonja AR, Kokhaei P, et al. Kaposi's sarcoma herpesvirus load in biopsies of cutaneous and oral Kaposi's sarcoma lesions. *Eur J Cancer*. 2007;43(12):1877-1882. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17627810.

71. Pak F, Pyakural P, Kokhaei P, et al. HHV-8/KSHV during the development of Kaposi's sarcoma: evaluation by polymerase chain reaction and immunohistochemistry. *J Cutan Pathol*. 2005;32(1):21-27. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15660651.

72. Okuku F, Krantz EM, Kafeero J, et al. Evaluation of a predictive staging model for HIV-associated Kaposi sarcoma in Uganda. *J Acquir Immune Defic Syndr*. 2017;74(5):548-554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28107226.

73. Krown SE, Testa MA, Huang J. AIDS-related Kaposi's sarcoma: prospective validation of the AIDS Clinical Trials Group staging classification. AIDS Clinical Trials Group Oncology Committee. *J Clin Oncol*. 1997;15(9):3085-3092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9294471.

74. Martin de Fremont G, Vanjak A, Sbihi Z, et al. Characteristics of circulating KSHV-infected viroblasts during active KSHV+ multicentric Castleman disease. *Blood Adv*. 2023;7(9):1682-1691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36508281.

75. Zhou T, Yuan CM, Lurain K, et al. A novel approach for characterization of KSHV-associated multicentric Castleman disease from effusions. *Br J Haematol*. 2023;200(4):462-475. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36264007.

76. Cantos VD, Kalapila AG, Ly Nguyen M, Adamski M, Gunthel CJ. Experience with Kaposi sarcoma herpesvirus inflammatory cytokine syndrome in a large urban HIV clinic in the United States: case series and literature review. *Open Forum Infect Dis*. 2017;4(4):ofx196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29766014.

77. Morrison BJ, Labo N, Miley WJ, Whitby D. Serodiagnosis for tumor viruses. *Semin Oncol*. 2015;42(2):191-206. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25843726.

78. Tibenderana RM, Blumenthal MJ, Bukajumbe E, Schafer G, Mohamed Z. Clinical significance of elevated KSHV viral load in HIV-related Kaposi's sarcoma patients in South Africa. *Viruses*. 2024;16(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/38399965.

79. Phipps W, Adams SV, Mooka P, et al. A prospective study of clinical outcomes of HIV-associated and HIV-negative Kaposi sarcoma in Uganda. *AIDS*. 2023;37(1):51-59. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36083142.

80. Haq IU, Pria AD, Papanastasopoulos P, et al. The clinical application of plasma Kaposi sarcoma herpesvirus viral load as a tumour biomarker: results from 704 patients. *HIV Med*. 2016;17(1):56-61. Available at: https://onlinelibrary.wiley.com/doi/10.1111/hiv.12273.

81. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. *Blood*. 2000;96(6):2069-2073. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10979949.

82. Jary A, Leducq V, Palich R, et al. Usefulness of Kaposi's sarcoma-associated herpesvirus (KSHV) DNA viral load in whole blood for diagnosis and monitoring of KSHV-associated diseases. *J Clin Microbiol*. 2018;56(6). Available at: https://www.pubmed.ncbi.nlm.nih.gov/29643199.

83. Pauk J, Huang ML, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. *N Engl J Med*. 2000;343(19):1369-1377. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11070101.

84. Casper C, Redman M, Huang ML, et al. HIV infection and human herpesvirus-8 oral shedding among men who have sex with men. *J Acquir Immune Defic Syndr*. 2004;35(3):233-238. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15076237.

85. Johnston C, Orem J, Okuku F, et al. Impact of HIV infection and Kaposi sarcoma on human herpesvirus-8 mucosal replication and dissemination in Uganda. *PLoS One*. 2009;4(1):e4222. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19156206.

86. Phipps W, Saracino M, Selke S, et al. Oral HHV-8 replication among women in Mombasa, Kenya. *J Med Virol*. 2014;86(10):1759-1765. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24692069.

87. Hladik W, Dollard SC, Mermin J, et al. Transmission of human herpesvirus 8 by blood transfusion. *N Engl J Med*. 2006;355(13):1331-1338. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17005950.

88. Cannon MJ, Operskalski EA, Mosley JW, Radford K, Dollard SC. Lack of evidence for human herpesvirus-8 transmission via blood transfusion in a historical US cohort. *J Infect Dis*. 2009;199(11):1592-1598. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19385734.

89. Schennach H, Schonitzer D, Wachter H, Fuchs D. Blood donations and viruses. *Lancet*. 1997;349(9061):1327-1328. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9142092.

90. Lodi S, Guiguet M, Costagliola D, et al. Kaposi sarcoma incidence and survival among HIV-infected homosexual men after HIV seroconversion. *J Natl Cancer Inst*. 2010;102(11):784-792. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20442214.

91. Dubrow R, Qin L, Lin H, et al. Association of CD4+ T-cell count, HIV-1 RNA viral load, and antiretroviral therapy with Kaposi sarcoma risk among HIV-infected persons in the United States and Canada. *J Acquir Immune Defic Syndr*. 2017;75(4):382-390. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28394855.

92. Borges AH, Neuhaus J, Babiker AG, et al. Immediate antiretroviral therapy reduces risk of infection-related cancer during early HIV infection. *Clin Infect Dis*. 2016;63(12):1668-1676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27609756.

93. Silverberg MJ, Neuhaus J, Bower M, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS*. 2007;21(14):1957-1963. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17721103.

94. Cianfrocca M, Lee S, Von Roenn J, et al. Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. *Cancer*. 2010;116(16):3969-3977. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20564162.

95. Cooley T, Henry D, Tonda M, Sun S, O'Connell M, Rackoff W. A randomized, double-blind study of pegylated liposomal doxorubicin for the treatment of AIDS-related Kaposi's sarcoma. *Oncologist*. 2007;12(1):114-123. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17227906.

96. Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis.* 2008;198(1):23-30. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18491970.

97. Bower M, Dalla Pria A, Coyle C, et al. Prospective stage-stratified approach to AIDS-related Kaposi's sarcoma. *J Clin Oncol*. 2014;32(5):409-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24378415.

98. Hosseinipour MC, Kang M, Krown SE, et al. As-needed vs. immediate etoposide chemotherapy in combination with antiretroviral therapy for mild-to-moderate AIDS-associated Kaposi sarcoma in resource-limited settings: A5264/AMC-067 randomized clinical trial. *Clin Infect Dis.* 2018;67(2):251-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29365083.

99. Nyirenda M, Ngongondo M, Kang M, et al. Early progression and immune reconstitution inflammatory syndrome during treatment of mild-to-moderate Kaposi sarcoma in sub-Saharan Africa and South America: incidence, long-term Ootcomes, and effects of early chemotherapy. *J Acquir Immune Defic Syndr*. 2020;84(4):422-429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32265361.

100. Tulpule A, Groopman J, Saville MW, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. *Cancer*. 2002;95(1):147-154. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12115328.

101. Cheung TW, Remick SC, Azarnia N, Proper JA, Barrueco JR, Dezube BJ. AIDS-related Kaposi's sarcoma: a phase II study of liposomal doxorubicin. The TLC D-99 Study Group. *Clin Cancer Res.* 1999;5(11):3432-3437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10589755.

102. Krown SE, Moser CB, MacPhail P, et al. Treatment of advanced AIDS-associated Kaposi sarcoma in resource-limited settings: a three-arm, open-label, randomised, non-inferiority trial. *Lancet*. 2020;395(10231):1195-1207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32145827.

103. Ramaswami R, Polizzotto MN, Lurain K, et al. Safety, activity, and long-term outcomes of pomalidomide in the treatment of Kaposi sarcoma among individuals with or without HIV infection. *Clin Cancer Res.* 2022;28(5):840-850. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34862247.

104. Jeng BH, Holland GN, Lowder CY, Deegan WF, 3rd, Raizman MB, Meisler DM. Anterior segment and external ocular disorders associated with human immunodeficiency virus disease. *Surv Ophthalmol*. 2007;52(4):329-368. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17574062.

105. Kohanim S, Daniels AB, Huynh N, Chodosh J. Local treatment of Kaposi sarcoma of the conjunctiva. *Int Ophthalmol Clin*. 2011;51(4):183-192. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21897150.

106. Ghabrial R, Quivey JM, Dunn JP, Jr., Char DH. Radiation therapy of acquired immunodeficiency syndrome-related Kaposi's sarcoma of the eyelids and conjunctiva. *Arch Ophthalmol*. 1992;110(10):1423-1426. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1417543.

107. Walmsley S, Northfelt DW, Melosky B, Conant M, Friedman-Kien AE, Wagner B. Treatment of AIDS-related cutaneous Kaposi's sarcoma with topical alitretinoin (9-cis-retinoic acid) gel. Panretin Gel North American Study Group. *J Acquir Immune Defic Syndr*. 1999;22(3):235-246. Available at: https://pubmed.ncbi.nlm.nih.gov/10770343.

108. Klein E, Schwartz RA, Laor Y, Milgrom H, Burgess GH, Holtermann OA. Treatment of kaposi's sarcoma with vinblastine. *Cancer*. 1980;45(3):427-431. Available at: https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/1097-0142%2819800201%2945%3A3%3C427%3A%3AAID-CNCR2820450304%3E3.0.CO%3B2-1.

109. Volkow PF, Cornejo P, Zinser JW, Ormsby CE, Reyes-Teran G. Life-threatening exacerbation of Kaposi's sarcoma after prednisone treatment for immune reconstitution inflammatory syndrome. *AIDS*. 2008;22(5):663-665. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18317012.

110. Jinno S, Goshima C. Progression of Kaposi sarcoma associated with iatrogenic Cushing syndrome in a person with HIV/AIDS. *AIDS Read*. 2008;18(2):100-104. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18333287.

111. Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during corticosteroid therapy. *Cancer*. 1993;72(5):1779-1783. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8348508.

112. Kedes DH, Ganem D. Sensitivity of Kaposi's sarcoma-associated herpesvirus replication to antiviral drugs. Implications for potential therapy. *J Clin Invest*. 1997;99(9):2082-2086. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9151779.

113. Medveczky MM, Horvath E, Lund T, Medveczky PG. In vitro antiviral drug sensitivity of the Kaposi's sarcoma-associated herpesvirus. *AIDS*. 1997;11(11):1327-1332. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9302441.

114. Little RF, Merced-Galindez F, Staskus K, et al. A pilot study of cidofovir in patients with kaposi sarcoma. *J Infect Dis*. 2003;187(1):149-153. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12508160.

115. Krown SE, Dittmer DP, Cesarman E. Pilot study of oral valganciclovir therapy in patients with classic Kaposi sarcoma. *J Infect Dis*. 2011;203(8):1082-1086. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21450998.

116. Luppi M, Barozzi P, Rasini V, et al. Severe pancytopenia and hemophagocytosis after HHV-8 primary infection in a renal transplant patient successfully treated with foscarnet. *Transplantation*. 2002;74(1):131-132. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12134112.

117. Low P, Neipel F, Rascu A, et al. Suppression of HHV-8 viremia by foscarnet in an HIV-infected patient with Kaposi's sarcoma and HHV-8 associated hemophagocytic syndrome. *Eur J Med Res.* 1998;3(10):461-464. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9753702.

118. Bower M, Newsom-Davis T, Naresh K, et al. Clinical features and outcome in HIV-associated multicentric Castleman's disease. *J Clin Oncol*. 2011;29(18):2481-2486. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21555697.

119. Marcelin AG, Aaron L, Mateus C, et al. Rituximab therapy for HIV-associated Castleman disease. *Blood*. 2003;102(8):2786-2788. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12842986.

120. Gerard L, Berezne A, Galicier L, et al. Prospective study of rituximab in chemotherapy-dependent human immunodeficiency virus associated multicentric Castleman's disease: ANRS 117 CastlemaB Trial. *J Clin Oncol*. 2007;25(22):3350-3356. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17664482.

121. Bower M, Powles T, Williams S, et al. Brief communication: rituximab in HIV-associated multicentric Castleman disease. *Ann Intern Med*. 2007;147(12):836-839. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18087054.

122. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood*. 2005;106(8):2627-2632. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15998837.

123. Nagao A, Nakazawa S, Hanabusa H. Short-term efficacy of the IL6 receptor antibody tocilizumab in patients with HIV-associated multicentric Castleman disease: report of two cases. *J Hematol Oncol*. 2014;7:10. Available at: https://www.pubmed.ncbi.nlm.nih.gov/24438824.

124. van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. *J Clin Oncol*. 2010;28(23):3701-3708. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20625121.

125. Ramaswami R, Lurain K, Peer CJ, et al. Tocilizumab in patients with symptomatic Kaposi sarcoma herpesvirus-associated multicentric Castleman disease. *Blood*. 2020;135(25):2316-2319. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32276276.

126. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood*. 2004;103(5):1632-1634. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14615380.

127. Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. *Blood*. 2011;117(26):6977-6986. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21487108.

128. Ramaswami R, Lurain K, Polizzotto MN, et al. Characteristics and outcomes of KSHV-associated multicentric Castleman disease with or without other KSHV diseases. *Blood Adv*. 2021;5(6):1660-1670. Available at: https://pubmed.ncbi.nlm.nih.gov/33720337.

129. Boulanger E, Gerard L, Gabarre J, et al. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. *J Clin Oncol*. 2005;23(19):4372-4380. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15994147.

130. Barta SK, Lee JY, Kaplan LD, Noy A, Sparano JA. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. *Cancer*. 2012;118(16):3977-3983. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22180164.

131. Lim ST, Rubin N, Said J, Levine AM. Primary effusion lymphoma: successful treatment with highly active antiretroviral therapy and rituximab. *Ann Hematol*. 2005;84(8):551-552. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15800785.

132. Jessamy K, Ojevwe FO, Doobay R, Naous R, Yu J, Lemke SM. Primary effusion lymphoma: is dose-adjusted-EPOCH worthwhile therapy? *Case Rep Oncol*. 2016;9(1):273-279. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27462227.

133. Spezia-Lindner NJ, Kondapi D, DiNardo AR, Ramaswami R, Chiao E, Clark EH. The importance of early recognition of KSHV-mediated syndromes: a case report. *Am J Med*. 2021;134(10):e503-e506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33989604.

134. Letang E, Lewis JJ, Bower M, et al. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK. *AIDS*. 2013;27(10):1603-1613. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23462220.

135. Bower M, Nelson M, Young AM, et al. Immune reconstitution inflammatory syndrome associated with Kaposi's sarcoma. *J Clin Oncol*. 2005;23(22):5224-5228. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16051964.

136. Achenbach CJ, Harrington RD, Dhanireddy S, Crane HM, Casper C, Kitahata MM. Paradoxical immune reconstitution inflammatory syndrome in HIV-infected patients treated with combination antiretroviral therapy after AIDS-defining opportunistic infection. *Clin Infect Dis*. 2012;54(3):424-433. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22095568.

137. Mosam A, Shaik F, Uldrick TS, et al. A randomized controlled trial of highly active antiretroviral therapy versus highly active antiretroviral therapy and chemotherapy in therapy-naive patients with HIV-associated Kaposi sarcoma in South Africa. *J Acquir Immune Defic Syndr*. 2012;60(2):150-157. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22395672.

138. Borok M, Fiorillo S, Gudza I, et al. Evaluation of plasma human herpesvirus 8 DNA as a marker of clinical outcomes during antiretroviral therapy for AIDS-related Kaposi sarcoma in Zimbabwe. *Clin Infect Dis.* 2010;51(3):342-349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20572760.

139. Letang E, Almeida JM, Miro JM, et al. Predictors of immune reconstitution inflammatory syndrome-associated with kaposi sarcoma in mozambique: a prospective study. *J Acquir Immune Defic Syndr.* 2010;53(5):589-597. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19801945.

140. Chabria S, Barakat L, Ogbuagu O. Steroid-exacerbated HIV-associated cutaneous Kaposi's sarcoma immune reconstitution inflammatory syndrome: 'where a good intention turns bad'. *Int J STD AIDS.* 2016;27(11):1026-1029. Available at: https://www.pubmed.ncbi.nlm.nih.gov/26769754.

141. Aaron L, Lidove O, Yousry C, Roudiere L, Dupont B, Viard JP. Human herpesvirus 8-positive Castleman disease in human immunodeficiency virus-infected patients: the impact of highly active antiretroviral therapy. *Clin Infect Dis.* 2002;35(7):880-882. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12228826.

142. Goedert JJ, Charurat M, Blattner WA, et al. Risk factors for Kaposi's sarcoma-associated herpesvirus infection among HIV-1-infected pregnant women in the USA. *AIDS.* 2003;17(3):425-433. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12556697.

143. Goedert JJ, Kedes DH, Ganem D. Antibodies to human herpesvirus 8 in women and infants born in Haiti and the USA. *Lancet.* 1997;349(9062):1368. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9149705.

144. Lopes AO, Lima LRP, Tozetto-Mendoza TR, et al. Low prevalence of human gammaherpesvirus 8 (HHV-8) infection among HIV-infected pregnant women in Rio De Janeiro, Brazil. *J Matern Fetal Neonatal Med.* 2021;34(20):3458-3461. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31747817.

145. Bacha JM, El-Mallawany NK, Slone JS, Wilkinson JP, Mehta PS, Campbell LR. Recommendations for treating life-threatening Kaposi sarcoma during pregnancy in HIV-positive women in low income countries. *Int J STD AIDS.* 2020;31(8):724-734. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32493141.

146. Huang LM, Huang SY, Chen MY, et al. Geographical differences in human herpesvirus 8 seroepidemiology: a survey of 1,201 individuals in Asia. *J Med Virol.* 2000;60(3):290-293. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10630961.

147. Lisco A, Barbierato M, Fiore JR, et al. Pregnancy and human herpesvirus 8 reactivation in human immunodeficiency virus type 1-infected women. *J Clin Microbiol.* 2006;44(11):3863-3871. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16943357.

148. Adeyemo A, Wood C, Govind A. Kaposi's sarcoma in pregnancy after initiation of highly active antiretroviral therapy: a manifestation of immune reconstitution syndrome. *Int J STD AIDS.* 2012;23(12):905-906. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23258835.

149. Berger P, Dirnhofer S. Kaposi's sarcoma in pregnant women. *Nature*. 1995;377(6544):21-22. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7659155.

150. Lunardi-Iskandar Y, Bryant JL, Zeman RA, et al. Tumorigenesis and metastasis of neoplastic Kaposi's sarcoma cell line in immunodeficient mice blocked by a human pregnancy hormone. *Nature*. 1995;375(6526):64-68. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7723844.

151. Rabkin CS, Chibwe G, Muyunda K, Musaba E. Kaposi's sarcoma in pregnant women. *Nature*. 1995;377(6544):21; author reply 22. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7659154.

152. Schulz TF, Weiss RA. Kaposi's sarcoma. A finger on the culprit. *Nature*. 1995;373(6509):17-18. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7800029.

153. Gutierrez-Ortega P, Hierro-Orozco S, Sanchez-Cisneros R, Montano LF. Kaposi's sarcoma in a 6-day-old infant with human immunodeficiency virus. *Arch Dermatol*. 1989;125(3):432-433. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2923454.

154. McCarthy GA, Kampmann B, Novelli V, Miller RF, Mercey DE, Gibb D. Vertical transmission of Kaposi's sarcoma. *Arch Dis Child*. 1996;74(5):455-457. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8669966.

155. Sitas F, Newton R, Boshoff C. Increasing probability of mother-to-child transmission of HHV-8 with increasing maternal antibody titer for HHV-8. *N Engl J Med*. 1999;340(24):1923. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10375309.

156. Mbulaiteye S, Marshall V, Bagni RK, et al. Molecular evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus in Uganda and K1 gene evolution within the host. *J Infect Dis*. 2006;193(9):1250-1257. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16586362.

157. Sabourin KR, Ogolla S, Reyes GS, et al. Effects of maternal HIV infection on early Kaposi sarcoma-associated herpesvirus seroconversion in a Kenyan mother-infant cohort. *J Infect Dis*. 2023;228(10):1357-1366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37536370.

158. Mantina H, Kankasa C, Klaskala W, et al. Vertical transmission of Kaposi's sarcoma-associated herpesvirus. *Int J Cancer*. 2001;94(5):749-752. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11745472.

159. Serraino D, Locatelli M, Songini M, et al. Human herpes virus-8 infection among pregnant women and their children: results from the Sardinia-IDDM Study 2. *Int J Cancer*. 2001;91(5):740-741. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11267990.

160. Gessain A, Mauclere P, van Beveren M, et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. *Int J Cancer*. 1999;81(2):189-192. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10188717.

161. Bourboulia D, Whitby D, Boshoff C, et al. Serologic evidence for mother-to-child transmission of Kaposi sarcoma-associated herpesvirus infection. *JAMA*. 1998;280(1):31-32. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9660357.

162. Whitby D, Smith NA, Matthews S, et al. Human herpesvirus 8: seroepidemiology among women and detection in the genital tract of seropositive women. *J Infect Dis.* 1999;179(1):234-236. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9841845.

163. Plancoulaine S, Abel L, van Beveren M, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. *Lancet*. 2000;356(9235):1062-1065. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11009141.

Human Papillomavirus Disease

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Recommendations for Cervical Cancer Screening for People With HIV

Figure 1. Screening Algorithm for Cervical Cancer in People With HIV Aged 21 to 29 Years

Figure 2. Screening Algorithm for Cervical Cancer in People With HIV Aged 30 Years and Older

Recommendations for Anal Cancer Screening for People With HIV

Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV

Figure 4. Assessment of Anal Cytology and HPV Results in People With HIV

Epidemiology

At least 12 human papillomavirus (HPV) types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.[1-3] HPV68 is considered "probably oncogenic," and several other HPV types are considered "possibly oncogenic." HPV16 alone accounts for approximately 53% to 73% of cervical cancers in the general population and HPV18 for another 12% to 21%.[4] The other oncogenic HPV types each account for under 5% of cervical cancers.[4] Anal cancer and a subset of tumors of the vulva, vagina, penis, and oropharyngeal carcinoma (OPC) are also associated with HPV, and HPV16 and 18 are the most commonly detected in noncervical HPV-positive tumors.[2,5-14]

While anal cancer and OPC occur in both women and men with HIV, these two tumors disproportionally affect males with HIV, as well as African Americans.[15-18] Data also suggest that the distribution of oncogenic HPV types detected in cervical and anal cancers among people with HIV may differ from those in the general population.[19,20]

HPV infection is the major risk factor for development of cervical cancer,[5,21] the fourth most common cancer in women worldwide.[22] Nearly all cervical cancers contain oncogenic HPV DNA sequences.[23-25] While HPV is a common sexually transmitted cervical infection, most of these infections resolve spontaneously.[26-30] Cervical tumorigenesis occurs mostly, if not exclusively, in the presence of persistent oncogenic HPV infection.[1,5,31] Women with HIV have high incidence and persistence of HPV relative to women without HIV, as well as high rates of cervical intraepithelial neoplasia (CIN), cervical precancer (CIN 3), and invasive cancer.[32-40] Rates of cervical cancer in women with HIV were elevated significantly compared with the general population—3 to 4 times overall (95% confidence interval [CI], 3.13–3.70).[41] Most of these relative risks increase with decreasing CD4 T lymphocyte (CD4) cell counts, and cervical cancer is itself associated with advanced HIV.[42-54] The percentage with adenocarcinoma histology compared with squamous cell carcinoma is lower in women with HIV than in the general population. Several studies found decreased incident detection, persistence, and progression of HPV and CIN with effective

antiretroviral therapy (ART) use,[55,56] including one study that distinguished between adherent versus nonadherent or effective versus ineffective ART use (based on HIV RNA level).

In a report from the HIV/AIDS Cancer Match Study (2002–2016)—which included a population of 164,084 women with HIV—552 cases of invasive cervical cancer (ICC) occurred in 1.16 million person-years of follow-up (rate = 47.7 per 100,000). By age group, the highest incidence rates occurred in the 40- to 44- and 35- to 39-year-old age groups (rate = 66.1 and 64.5 per 100,000, respectively). No cases of ICC were identified in the under 25-year-old age group during 69,900 person-years of follow-up (standardized incidence ratio [SIR] = 0; 95% CI, 0,7.1).[41]

People with HIV have an increased incidence of anogenital tumors (vulva, vagina, penis) and OPC relative to the general population.[23,57-60] Low CD4 counts in people with HIV have been associated with increased risk of anal cancer,[61-63] as well as high-grade anal intraepithelial neoplasia (AIN; the likely anal cancer precursor lesion),[64-66] anal and genital warts, and vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).[67-69] Registry-based data indicate a downward trend in anal cancer incidence relative to the general population (i.e., a reduction in SIR from approximately SIR ~40 in 1996 to SIR ~20 in 2012; $P = 0.0001$),[59] as well as a possible ($P = 0.09$) decrease in cervical cancer from SIR ~5 in 1996 to SIR ~3 in 2012, and a nonsignificant decrease in OPC.[70,71] Other HPV-related tumors are less common, and less is known about trends in their incidence.

The elevated risk of HPV-associated cancers in people with HIV continues into older age (>50 years of age).[39] Registry-based data show that the 5-year risk (cumulative incidence) of anal cancer was 0.65% and 0.33% in men aged 45 to 59 years with HIV who have sex with men with and without AIDS, respectively, whereas the results were 0.10% and 0.04% for men with HIV who do not have sex with men, and 0.20% and 0.08% for women with HIV.[70] Similar results were obtained in a recent meta-analysis of available studies.[72] The ANCHOR study estimated the cumulative 4-year progression from high-grade squamous intraepithelial lesion (HSIL) to anal cancer was 1.8%.[73]

Anogenital warts have very low carcinogenic potential but are an important HPV-associated disease in people with HIV. These lesions are common, and more likely to be persistent in people with HIV than in the general population. Approximately 80% to 90% of anogenital warts are caused by non-oncogenic HPV types 6 or 11.[74] HPV types 6 and 11 also have been associated with conjunctival, nasal, oral, and laryngeal warts. In the United States, prior to the introduction of HPV vaccination, the incidence of anogenital warts was 60.2 per 10,000 women (aged 20–24 years) and 53.8 per 10,000 men (aged 20–24 years),[75-77] but with several-fold greater rates in people with HIV.[67] Low-grade vulvar lesions and genital warts were both found to decrease with ART.[67]

Clinical Manifestations

The principal clinical manifestations of mucosal HPV infection are genital, anal, and oral warts; CIN; VIN; VAIN; AIN; anogenital squamous cell cancers; and cervical adenocarcinomas. A subset of oropharyngeal cancers is also caused by HPV.[78]

Oral, genital (condyloma acuminata), and anal warts are usually flat, papular, or pedunculated growths on the mucosa or epithelium. The lesions may measure a few millimeters to 1 to 2 centimeters in diameter. Most warts are asymptomatic, but warts can be associated with itching or discomfort. In cases associated with more severe immunosuppression, marked enlargement may cause dyspareunia or dyschezia. Lesions of any size may cause cosmetic concerns.

Low-grade squamous intraepithelial lesions (LSIL) and HSIL in the cervix, vagina, vulva, and anal canal are often asymptomatic but may manifest with bleeding or itching. Related cancers also may be asymptomatic or may manifest with bleeding, pain, odor, or a visible/palpable mass. External lesions may be visible or palpable. Similarly, squamous cell cancers at these sites also can be asymptomatic or may manifest with bleeding, pain, or a visible/palpable mass.[79]

Preventing HPV Infection

Recommendations for Preventing HPV Infection
• HPV vaccine is recommended for routine vaccination at age 11 or 12 years. o Administer three doses of 9-valent HPV vaccine (Gardasil 9) at 0, 1 to 2, and 6 months (AIII). Ideally, the series should have been initiated at age 11 or 12 years but may be started as early as age 9 years. The two-dose series is not recommended in people with HIV. • For all people with HIV aged 13 to 26 years who were not vaccinated previously: o Administer three doses of 9-valent HPV vaccine (Gardasil 9) at 0, 1 to 2, and 6 months (AIII). The two-dose series is not recommended in people with HIV. • For people with HIV aged 27 to 45 years who were not adequately vaccinated previously: o HPV vaccine is not routinely recommended; instead, shared clinical decision-making regarding HPV vaccination is recommended for people who may be at risk for a new HPV infection (AIII). • For people who were adequately vaccinated with bivalent or quadrivalent HPV vaccine: o Some experts would consider additional vaccination with 9-valent HPV vaccine, but data are lacking to define the efficacy and cost-effectiveness of this approach (CIII). • HPV vaccination is not recommended during pregnancy (CIII).

HPV Vaccine

HPV vaccination prevents HPV infection and is ideally administered before sexual exposure to HPV. Although HPV vaccine is most effective in people with few or no sex partners prior to vaccination, HPV vaccination in people with multiple lifetime sex partners can still prevent HPV infection from subtypes they have not been exposed to yet. Three U.S. Food and Drug Administration (FDA)–approved HPV vaccines are licensed: bivalent, quadrivalent, and 9-valent. Currently, only the 9-valent vaccine (9vHPV, protective against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58) is available in the United States.[14,80] This vaccine has an FDA indication for prevention of cervical, vaginal, vulvar, and anal cancer; genital warts, and oropharyngeal and other head and neck cancers[81] based on randomized clinical trial (RCT) data; however, these studies were not conducted in people with HIV.[82-88] These RCTs evaluated several endpoints accepted by FDA and established the safety of the vaccine in children as young as 9 years of age and young people aged 16 to 26, as well as older women (aged 27–45 years).[89,90] Although no clinical trials have been conducted to demonstrate HPV vaccine efficacy in prevention of oropharyngeal cancers, some evidence exists that the prevalence of oral HPV infections from types contained in the vaccines are reduced with vaccination.[91,92] Protection against more subtypes might be more useful in people with HIV because there is more diversity of oncogenic subtypes of HPV.[14,80]

Routine HPV vaccination with the 9-valent vaccine should be initiated at age 11 or 12 years but may be started as early as age 9 years.[93,94] Although the Centers for Disease Control and

Prevention (CDC) Advisory Committee on Immunization Practices recommends a two-dose series,[95] the Panel recommends that people with HIV receive a three-dose series (0, 1–2, and 6 months) because their immune response to vaccination might be attenuated **(AIII).** Because HPV vaccination is safe and immunogenic and has the potential benefit of preventing HPV-associated disease and cancer, catch-up HPV vaccination is recommended for people with HIV aged 13 to 26 years **(AIII).** Although routine vaccination beyond age 26 is not recommended, shared clinical decision-making regarding HPV vaccination is recommended for adults aged 27 to 45 years who are not adequately vaccinated and are at risk for a new HPV infection **(AIII).**[94] Considerations to help guide shared clinical decision-making are available on the CDC website.

For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, some experts would give an additional full series (three doses) of vaccination with the 9-valent vaccine **(CIII),** however no data exist to define who might benefit or how cost-effective this approach might be.

Several studies have established the safety and immunogenicity of HPV vaccines in a broad range of people with HIV.[95-97] Some studies have demonstrated lower antibody levels in people with HIV than in those who do not have HIV; however, the clinical significance of this observation is unknown.[98-100] Studies have shown that HPV vaccination induces an anamnestic response in children and adults with HIV.[83,96,101] Immune responses appear stronger among those with higher CD4 counts and suppressed HIV viral loads.[97,102]

Although HPV vaccine clinical trials in people with HIV reported appropriate immunogenicity and safety,[95-104] few, if any, RCTs have utilized clinical endpoints, such as CIN 3 or incident persistent infection with vaccine HPV types. There is also a paucity of prospective epidemiologic studies using these endpoints.[105] One randomized, double-blind clinical trial evaluated the efficacy of the quadrivalent HPV vaccine (4vHPV) in a population of people with HIV who were older than 27 years with high rates of prior and current HPV infection. The trial did not show efficacy for prevention of new anal HPV infections or improvement in anal HSIL outcomes.[106] Anal cancer endpoints, including anal HSIL and anogenital wart incidence, were studied in another RCT of 4vHPV that involved 129 men who have sex with men (MSM) and who were on ART with a mean age of 38.8 years and who had history of AIDS.[107] Although the vaccine and placebo arms did not differ by HSIL or genital wart incidence, vaccine HPV types were less common in the vaccine arm, and in secondary analyses the investigators found that those with the longest time since immunization had significantly reduced risk of HSIL. A one-arm study of 260 MSM with HIV, aged 18 to 26 years, who received 4vHPV and were followed with high-resolution anoscopy at 7, 12, and 24 months found that no participants who were naive at baseline for one or more 4vHPV types developed LSIL or HSIL related to those HPV.[108] Conversely, a Phase 3 4vHPV RCT involving older males and females with HIV (aged ≥27 years) ended early due to an insufficient vaccine effect to meet stopping rules.[106] This trial did, however, suggest efficacy for short-term prevention of oral HPV infection, which decreased significantly from 88% to 32% after 6 months. A prospective observational cohort study of female youth who received 4vHPV showed unexpectedly high rates of abnormal cervical cytology, occurring in 33 of 56 youth who acquired HIV perinatally and only 1 of 7 of youth who were exposed but uninfected and yielding incidence rates of 100 person-years of 15 (10.9–29.6) and 2.9 (0.4–22.3), respectively. The majority of the diagnoses were LSIL or less, and the genotypes associated with these abnormal cytology results were unknown.[103]

People with HIV who have been vaccinated should continue routine cervical cancer screening because the vaccine does not prevent all HPV types that may be precursors to cervical cancer, and

because the vaccine may be less effective in people with HIV (especially those with low CD4 counts) than in people without HIV.

Condom Use

The use of male latex condoms is strongly recommended for preventing transmission or acquisition of HPV infection, as well as for preventing HIV and other sexually transmitted infections (STIs) **(AII).**[109-111] Latex condoms provide a sufficient barrier to prevent passage of particles the size of HPV. Consistent and proper use of latex male condoms has been associated with 70% lower incidence of oncogenic HPV infection among women.[111] Similarly, cross-sectional data suggested that among heterosexual men with no steady sex partner, consistent condom use was associated with 50% lower odds of HPV infection of the penis.[112] A meta-analysis found that condom use was associated with reduced risk of genital warts and, in women, with lower rates of CIN.[109] An RCT of condom use in heterosexual couples found significantly more frequent clearance of CIN and HPV among women randomized to condom use and of penile lesions among their male partners.[113,114] Male condoms have benefits in reducing risk of transmission of nearly all STIs (including HIV infection) during heterosexual intercourse and same-sex intercourse between men. In circumstances when a male condom cannot be used properly, a female condom (e.g., an FC1 or FC2 Female Condom) should be considered for heterosexual vaginal intercourse **(AII)** and for heterosexual or male same-sex anal intercourse **(BIII).** Data on FC1 and FC2 Female Condoms suggest that the devices are protective against STIs.[110]

Male Circumcision

There is evidence that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from RCTs and observational studies.[115-118] Observational studies in the general population also suggest that circumcision is associated with lower risk of penile cancer and of cervical cancer in sexual partners. Relevant data in men with HIV, however, are limited; findings to date suggest that the effects of circumcision against HPV infection (while protective) may be less in people with HIV than in those without. Furthermore, no clinical trials have assessed whether circumcision of men who have HIV reduces the risk of genital or anal HPV-related cancer or precancer (such as AIN) or oncogenic HPV infection of the anal or oral mucosa for them or their sexual partners. Evidence is insufficient to recommend adult male circumcision solely to reduce the risk of oncogenic HPV infection in men with HIV or their sex partners.

Preventing Disease

Cervical Cancer Screening Recommendations

Figure 1. Screening Algorithm for Cervical Cancer in People With HIV Aged 21 to 29 Years

Figure 2. Screening Algorithm for Cervical Cancer in People With HIV Aged 30 Years and Older

The same cytology and colposcopic techniques with biopsy are used to detect CIN among people with and without HIV (see section on Preventing Disease). At the time of cytology screening, the genitalia and anal canal should be inspected carefully for visual signs of warts or invasive cancer.

Available HPV tests can detect up to 14 oncogenic HPV types in clinical specimens and are sensitive for the detection of cervical cancer precursors. Some commercially available HPV tests will specify whether the oncogenic HPV includes genotypes HPV16 or HPV16/18. The available tests for oncogenic HPV have been incorporated into the screening algorithms. HPV testing is always for oncogenic HPV types only; there is no role for non-oncogenic HPV testing.

Observational epidemiologic studies in people with HIV have been instrumental in the decisions to adopt several cervical cancer screening guidelines that had been validated in large clinical trials in the general population. This included studies that supported the incorporation of cervical HPV testing for determining referral to colposcopy versus retesting in 1 year or during routine follow-up. For example, despite the very high prevalence of HPV in women with HIV, normal cytology with negative HPV co-testing had a strong negative predictive value, with low 3- to 5-year incidence of cervical intraepithelial neoplasia grade 2 (CIN 2+) regardless of CD4 count.[119,120] Conversely, the risk of precancer was high in women with HIV who tested positive for oncogenic HPV despite normal cervical cytology results and several-fold greater still if HPV16 was specifically detected.[121] Additional studies showed that oncogenic HPV testing had high sensitivity and negative predictive value in the triage of borderline cervical cytology results (i.e., atypical squamous cells of uncertain significance [ASC-US]).[122,123]

Possible cervical cytology results include the following:

- Normal (negative for intraepithelial lesion or malignancy)
- LSIL or CIN 1 (cervical intraepithelial neoplasia grade 1)
- HSIL or CIN 2, 3
- ASC-US
- ASC-H (atypical squamous cells, cannot rule out a high-grade lesion)
- AGC (atypical glandular cells)

For people with HIV, cervical cancer screening and treatment of precancer are, in and of themselves, a major burden. Positive HPV screening tests are several-fold more common in women with HIV than in the general population, and as many as 16% of women with HIV have abnormal cervical cytology with ASC-US or worse at each clinical visit.[124] This often leads to repeated colposcopy and biopsy, although most of these colposcopies and biopsies in people with HIV find LSIL rather than clinically relevant disease (e.g., HSIL, cancer). A study of "primary oncogenic HPV screening"—which uses HPV testing as the initial screening method and, if positive, often reflex-triage (e.g., HPV16/18-genotyping, cervical cytology)—found that this approach reduced unnecessary colposcopies by almost half relative to currently recommended HPV/cervical cytology co-testing for women with HIV.[125] However, these findings require confirmation. There is also a significant need for technical advancement to improve the positive predictive value of the screening tests—especially as many women with HIV exceed the age for routinely recommended HPV vaccination.[125]

People With HIV Aged 21 to 29 Years

Cervical cytology is the primary mode for cervical cancer screening for women with HIV under 30 years of age. People aged 21 to 29 years with HIV should have cervical cytology at the time of initial diagnosis with HIV **(AII).** See Figure 1. Screening Algorithm for Cervical Cancer in People With HIV Aged 21 to 29 Years for detailed recommendations. The absolute incidence of ICC is

exceedingly low among women with HIV under 25 years; therefore, cervical cancer screening is recommended to start at age 21. The rationale for beginning screening at age 21 is to provide a 3- to 5-year window prior to age 25, when the risk of ICC in women with HIV exceeds that of the general population.[41] Co-testing (cervical cytology and HPV test) and reflex high-risk HPV (hr-HPV) testing (HPV testing in the presence of abnormal cytology results) is routinely recommended for people without HIV and might be considered for people aged 25 to 29 years with HIV; however, there is a relatively high prevalence of transient HPV before age 30 years, which may lead to unnecessary colposcopy.[126] If cytology reveals ASC-US and reflex hr-HPV testing is performed, repeat cytology should be evaluated in 6 to 12 months **(AII).** If repeat cytology shows ASC-US and reflex hr-HPV is positive, individuals should be referred for colposcopy **(CIII).**

The American Society for Colposcopy and Cervical Pathology (ASCCP) and the American College of Obstetrics and Gynecology (ACOG) recommend screening for cervical cancer using cytology alone for women aged 21 to 29 years. The American Cancer Society (ACS) now recommends initiating cervical cancer screening at age 25 with primary HPV screening (hr-HPV testing alone) every 5 years in the general population. The FDA recently approved self-testing for HPV screening in clinical settings.[127] There are ongoing studies to evaluate the use self-testing for HPV screening in people with HIV. The U.S. Preventive Services Task Force (USPSTF) is reviewing its current recommendations and will issue an update soon regarding the use of primary HPV screening for cervical cancer.

People With HIV Aged 30 Years and Older

Cervical cancer screening in people with HIV should continue throughout their lifetime (and not, as in the general population, end at 65 years of age) **(BIII).** Either cytology only or cytology and HPV co-testing is acceptable for screening **(BIII).** See Figure 2. Screening Algorithm for Cervical Cancer in People With HIV Aged 30 Years and Older for detailed recommendations. Current guidelines from both the ACS and the USPSTF allow use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow a prolonged cervical cancer screening interval in women with HIV who are older than 29 years and have normal cervical cytology with concurrent negative HPV testing.

For people aged more than 65 years, it is recommended to continue cervical cancer screening because people with HIV are at higher risk for cervical cancer **(BIII).** However, clinicians should consider other factors, such as the life expectancy of the patient and the risk for developing cervical cancer at this age.[128]

Overview of Cervical Cancer Screening Guidelines					
	<21 Years	21–24 Years	25–29 Years	≥30 Years	Comments
NIH OAR Adult and Adolescent OI Guidelines (specific to people with HIV)	No screening recommended	Cytology Only • Cytology yearly o If normal cytology on 3 consecutive annual tests, adjust to every 3 years	Cytology Only • Cytology yearly o If normal cytology on 3 consecutive annual tests, adjust to every 3 years	Co-testing[a] • Co-testing yearly o If normal cytology and hr-HPV negative on 3 consecutive years, adjust to every 3 years. Cytology Only • Cytology yearly • If normal cytology on 3 consecutive years, adjust to every 3 years	
USPSTF (no HIV-specific guidance)	No screening recommended	• Cytology every 3 years	• Cytology every 3 years	Cytology Only • Every 3 years hr-HPV Testing Only • Every 5 years Co-testing[a] • Every 5 years	Not specific to people with HIV
ASCCP					Same as USPSTF
ACOG					Same as USPSTF
ACS (no HIV-specific guidance)	No screening recommended	No screening recommended	Preferred • Primary HPV test[b] every 5 years Acceptable • Co-testing every 5 years • Cytology alone every 3 years	Preferred • Primary HPV test[b] every 5 years Acceptable • Co-testing every 5 years • Cytology alone every 3 years	Updated July 2020 Not specific to people with HIV

Overview of Cervical Cancer Screening Guidelines					
WHO (HIV-specific guidance)	No screening recommended	No screening recommended	Preferred • Primary HPV test[b] (provider-obtained or self-collection) every 3–5 years	Preferred • Primary HPV test[b] (provider-obtained or self-collection every 3–5 years)	Updated July 2021

[a] Co-testing refers to combined cytology and high-risk HPV (hr-HPV) testing.

[b] Primary HPV testing is hr-HPV testing alone.

Key: ACOG = American College of Obstetricians and Gynecologists; ACS = American Cancer Society; ASCCP = American Society for Colposcopy and Cervical Pathology; HPV = human papillomavirus; hr-HPV = high-risk HPV; NIH OAR = National Institutes of Health Office of AIDS Research; OI = opportunistic infection; USPSTF = United States Preventive Services Task Force; WHO = World Health Organization

Preventing Vaginal and Vulvar Cancer

VAIN and VIN are recognized through visual inspection, including colposcopy and biopsy as needed. Most patients are asymptomatic, however. Abnormalities are usually detected after colposcopic examination and biopsy in response to abnormal cervical cytology. Following hysterectomy for benign disease, routine screening for vaginal cancer is not recommended for people with HIV **(AIII).** However, people with a history of high-grade CIN, adenocarcinoma *in situ*, or ICC are at increased risk and should be followed with annual vaginal cuff cervical cytology **(BIII).** For patients not known to have had a hysterectomy for a benign indication, continued screening is recommended since studies have shown that CIN is the most common indication for hysterectomy for people with HIV **(CIII).** Although vaginal cervical cytology results are often abnormal in women with HIV and more common than in women without HIV, VAIN 2+ and vaginal cancers are infrequent.[129] Another study in women with HIV with previous hysterectomy and no previous abnormal cervical cytology results, showed that among those with vaginal biopsies, 29% had VAIN 2 or VAIN 3.[130] However, this retrospective study was limited due to sample size. For patients with abnormal vaginal cuff cervical cytology results with no visible vaginal colposcopic abnormalities, the use of Lugol's iodine to stain the vagina is recommended **(AIII).** Vaginal colposcopy also is indicated in the presence of concomitant cervical and vulvar lesions. Classification of VAIN (i.e., VAIN 1, VAIN 2, and VAIN 3) parallels that of the cervix.

No screening procedure is available for vulvar cancer. However, biopsy or referral is indicated when inspection/palpation identifies lesions suspicious for VIN or cancer.

Screening for Anal Cancer

Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV

Figure 4. Assessment of Anal Cytology and HPV Results in People With HIV

Based on the high incidence of anal cancer in people with HIV, the high prevalence of anal HSIL in people with HIV, the high progression rate of anal HSIL to anal cancer in the absence of treatment, and efficacy in treating anal HSIL to reduce progression to anal cancer, screening for anal HSIL **(AII)**[73,131] and treatment of anal HSIL **(AI)** are recommended for people with HIV based on age.[73] See Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV and Figure 4. Assessment of Anal Cytology and HPV Results in People With HIV for detailed recommendations.

People with HIV, regardless of history of anal intercourse, should undergo annual assessment of anal symptoms (e.g., unexplained itching, anal bleeding, or pain; presence of perianal lesions). MSM and transgender women below the age of 35 and others below the age of 45 with anal symptoms should undergo digital anorectal examination (DARE) and standard anoscopy **(AIII).** See International Anal Neoplasia Society Guidelines for the Practice of Digital Anal Rectal Examination and Performing a Digital Anal Rectal Examination on how to perform a proper DARE.

MSM and transgender women aged 35 and above and all others with HIV aged 45 and above with symptoms or abnormal examinations should be referred to high-resolution anoscopy (HRA) if available **(BIII).** HRA identifies anal HSIL and (following biopsy for histopathologic confirmation) enables treatment of anal HSIL to prevent progression to anal cancer. If HRA is not available, patients should undergo standard anoscopy **(BIII)** and be referred for biopsy of identified lesions to determine level of histologic changes and to rule out invasive cancer**.** Standard anoscopy involves

visualization of the anal canal and perianal region through an anoscope without application of 5% acetic acid or Lugol's iodine to identify lesions. HRA requires specialized training and is performed with 5% acetic acid and Lugol's iodine to identify lesions under magnification typically provided by a colposcope. HRA allows flat lesions typical of HSIL or cancer to be identified with greater precision than standard anoscopy.

When to start screening for anal HSIL in asymptomatic individuals specifically should be based on the overall risk for anal cancer. The risk for anal cancer in people with HIV appears to differ based on age, sex at birth, and HIV exposure group, as evidenced by national estimates from the AIDS/Cancer Match Study, which links HIV/AIDS registries with data from the National Cancer Institute's Surveillance Epidemiology End Results (SEER), and by findings from a comprehensive meta-analysis of anal cancer screening and treatment studies (see figure on anal cancer incidence from this meta-analysis).[70,72]

Based on their incidence of anal cancer, and until definitive screening guidelines are available, experts in the field recommend that screening in asymptomatic people with HIV begin at different ages depending on sex and HIV risk group. Initiating screening for anal precancer and cancer is recommended at age 35 for MSM and transgender women who have HIV **(AII).** Screening for anal cancer should be initiated in all other persons with HIV at age 45 years **(AII).** MSM and transgender women aged 35 years and older, and other people with HIV aged 45 years and older, should continue to be assessed annually for anal symptoms and undergo DARE regardless of symptoms **(BIII).**

Older age, longer known duration of immune suppression and HIV infection, history of AIDS, smoking, positive HPV16 or 18 status, and higher grade of cytologic abnormality are associated with increased risk of anal cancer.[72,132-135] People with HIV who meet any of these criteria should be screened and referred for HRA as soon as feasible **(BIII).**

Screening can be performed using anal cytology alone or with hr-HPV co-testing. Screening individuals with anal cytology to identify those who need HRA with the goal of diagnosing and treating anal HSIL should be performed only when HRA and HRA-based treatment are available. There currently are no FDA-cleared anal HPV tests, but testing is available in many clinical laboratories. It is strongly recommended to use only clinical laboratories that have undergone CLIA certification to conduct anal HPV tests. If cytology will be obtained for screening, defer DARE until after swabbing anal canal to decrease potential for lubricant interfering with cytology results. Until further data on screening algorithms are available, the recommended screening approaches shown in Figure 3. Screening Algorithm for Anal Cancer in Asymptomatic People With HIV can be considered based on testing availability.

The International Anal Neoplasia Society (IANS) recently published recommendations for anal cancer screening including but not specific for people with HIV. We concur with the recommendation to screen for anal cancer for MSM and transgender women aged more than 35 years with HIV and all other people aged 45 years or above with HIV. We agree with the use of anal cytology or anal cytology with hr-HPV co-testing as screening modalities. In contrast to the IANS guidelines, we do not recommend HPV screening without cytology at this time due to insufficient supporting evidence in people with HIV **(BIII).** The prevalence of anal hr-HPV infection is very high among persons with HIV, and the specificity and positive predictive value for anal HSIL are expected to be low. Although screening for HPV16 or 18 specifically may improve the specificity and positive predictive value, anal cancer is associated with a broader spectrum of hr-HPV types in

people with HIV than in people without HIV; therefore, there may still be insufficient sensitivity for anal HSIL in people with HIV.[19]

Overview of Anal Cancer Screening Guidelines in People With HIV		
	NIH OAR Adult and Adolescent OI Guidelines	IANS Guidelines
Primary anal HPV testing alone without cytology as screening option	No	Yes
High-priority patients if HRA availability limited (no priority order specified in either guideline)	• Higher grade of cytologic abnormality • HPV16 on HPV testing • Smokers • >60 years of age • Longer known duration of HIV • History of AIDS	• Higher grade of cytologic abnormality • HPV16 on HPV testing

Key: HPV = human papillomavirus; HRA = high-resolution anoscopy; IANS = International Anal Neoplasia Society; NIH OAR = National Institutes of Health Office of AIDS Research; OI = opportunistic infection

If HSIL is identified on biopsy, treatment of the lesion should be performed to reduce the incidence of anal cancer among people with HIV **(AI).** Further details are presented in the section "Treating AIN and Anal Cancer."

Preventing Oropharyngeal Cancer

Although HPV DNA detection might be useful in identifying individuals at high risk of oropharyngeal cancer, no adequate methods currently exist to determine the site of HPV-associated oropharyngeal precancer or cancer to target biopsy or treatment, despite ongoing efforts. It also should be noted that rates of non-HPV-associated oral cancer also are increased in people with HIV,[15] and potentially malignant oral disorders can be diagnosed and followed by biopsy in some cases; the effectiveness of this approach has not been tested in RCTs.[136]

Diagnosis

Warts/Condyloma

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy. However, biopsy is needed only if the diagnosis is uncertain, the lesions do not respond to standard therapy, or the warts are pigmented, indurated, fixed, bleeding, or ulcerated. No data support the use of HPV testing for screening, diagnosis, or management of visible genital/oral warts or oral HPV disease in people with HIV.[137]

Cervical Neoplasia

The same cytology and colposcopic techniques with biopsy are used to detect CIN among patients without HIV and people with HIV (see section on Preventing Disease). At the time of cytology

screening, the genitalia and anal canal should be inspected carefully for visual signs of warts, mucosal abnormalities that may indicate intraepithelial neoplasia, or invasive cancer.

Anal and Vulvar/Vaginal Neoplasia

AIN, VAIN, and VIN are recognized through visual inspection, including high-resolution anoscopy, colposcopy, and biopsy as needed. A digital examination of the anal canal to feel for masses should be performed as part of routine evaluation.[138]

Treating Disease

Cancer-specific survival following treatment of anal cancer and OPC was reported to be similar in people with HIV and the general population, whereas cervical cancer survival following treatment was reported to be lower in women with HIV.[139,140] Another study found that although response to initial therapy for ICC (e.g., radiation treatment) was similar in women with HIV compared with others, HIV was associated with higher risk of relapse (hazard ratio [HR] 3.6; 1.86–6.98) and higher cervical cancer mortality.[141] Data from the AIDS Malignancy Consortium showed that women with HIV on ART with locally advanced cervical cancer in sub-Saharan Africa can complete routine cisplatin and radiation therapy. Furthermore, 1-year progression-free overall survival rates observed among women with high-risk advanced tumors were similar to reported studies of women without HIV with generally smaller tumors.[142]

Treating Genital and Oral Warts
Patient-Applied Treatments Options *For Uncomplicated External Warts That Can Be Easily Identified by Patients* • Topical imiquimod (5% cream) at bedtime 3 nonconsecutive nights a week, for up to 16 weeks (BII). Each treatment should be washed with soap and water 6 to 10 hours after application. • Topical podofilox (0.5% solution or gel) twice a day for 3 days, followed by 4 days of no therapy. Can be repeated, as necessary, up to four times (BIII). • Topical sinecatechins (15% ointment) three times a day for up to 16 weeks until warts are cleared completely and not visible (BIII) • Topical cidofovir 1% daily for 5 days per week for 8 weeks (CIII). Not commercially available but may be compounded in pharmacies with required equipment. Provider-Applied Treatment Options *For Complex or Multicentric Lesions, or Lesions Inaccessible to Patient, or Due to Patient or Provider Preference* • Cryotherapy (liquid nitrogen or cryoprobe) applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks until lesions are no longer visible (BIII). Some specialists recommend allowing the lesion to thaw and freezing a second time in each session (BIII). • TCA and BCA (80% to 90%) applied to warts only and allowed to dry until a white frosting develops. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible (BIII). • Intralesional cidofovir (15 mg/mL solution) injected directly into the wart (maximum 1 mL per session). May be repeated every 4 weeks for total of three to four treatments (CIII). • Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts (BIII). Laser surgery is an option but is usually more expensive (CIII). Note: Many treatments for anogenital warts cannot be used in the oral mucosa. Surgery is the most common treatment for oral warts that interfere with function or for aesthetic reasons.
Considerations in Pregnancy
• Topical treatments such as BCA and TCA, as well as ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy (AIII). • Obstetrical management should not change for people with genital warts unless extensive condylomata might impede vaginal delivery or cause extensive bleeding (AIII). • Cervical and anal cancer screening is recommended during pregnancy. • Endocervical curettage is contraindicated during pregnancy (AIII).

Key: BCA = bichloroacetic acid, TCA = trichloroacetic acid

Treating Genital and Oral Warts

People with HIV may have larger or more numerous warts, may not respond as well to therapy for genital warts as individuals who are immunocompetent, and may have more frequent recurrences after treatment. Genital warts are not life-threatening and may regress without therapy, even in people with HIV and especially in those whose immunity is relatively preserved. Treatments are available for genital warts, but none are effective or preferred uniformly. Lacking RCTs specific to people with HIV, guidelines for the treatment of STIs in people without HIV should be followed. More than one treatment option may be required for refractory or recurrent lesions in people with HIV. Histologic diagnosis should be obtained for refractory lesions to confirm the absence of high-

grade disease. Intra-anal, vaginal, urethral, or cervical warts should be treated and managed by a specialist.

Patient-applied treatments are recommended generally for uncomplicated external warts that can be identified easily and treated by the patient. Imiquimod (5% cream) is a topical cytokine inducer that should be applied at bedtime on 3 nonconsecutive nights per week, for up to 16 weeks, until lesions are no longer visible. The treatment area should be washed with soap and water 6 to 10 hours after the application **(BII).** Podofilox 0.5% solution or gel should be applied to visible anogenital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle can be repeated, as necessary, up to four times **(BIII).** Another option is sinecatechins (15% ointment), a topical botanical product that contains active catechins from green tea and should be applied three times daily for up to 16 weeks, until warts are cleared completely and not visible **(BIII).**[143] No clinical trials of this latter treatment option have been conducted in people with HIV. Topical application of cidofovir or intralesional cidofovir has reported activity against genital warts **(CIII).** Topical formulation is not commercially available but may be compounded in pharmacies with required equipment.[144-146]

Provider-applied treatments—such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery—typically are recommended for complex or multicentric lesions, lesions inaccessible to patient-applied therapy, or because of patient or provider preference.

Cryotherapy (liquid nitrogen or cryoprobe) destroys lesions by thermal-induced cytolysis and should be applied until each lesion is thoroughly frozen, with treatment repeated every 1 to 2 weeks for up to 4 weeks, until lesions are no longer visible **(BIII).** Some specialists recommend allowing the lesion to thaw and freezing a second time in each session **(BIII).**

TCA and BCA (80% to 90%) both act as caustic agents to destroy wart tissue and should be applied to warts only and allowed to dry until a white frosting develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap to remove unreacted acid. The treatment can be repeated weekly for up to 6 weeks, until lesions are no longer visible **(BIII).**

Surgical treatments (e.g., tangential scissor excision, tangential shave excision, curettage, electrosurgery, electrocautery, infrared coagulation) can be used for external genital and anal warts **(BIII).** Laser surgery is an option but is usually more expensive **(CIII).**

Intralesional interferon has been used for the treatment of genital warts, but because of cost, difficulty of administration, and potential for systemic adverse effects—such as fever, fatigue, myalgias, and leukopenia—it is not recommended for first-line treatment **(CIII).**

Podophyllin resin may be an alternative provider-applied treatment, with strict adherence to recommendations on application. It has inconsistent potency in topical preparations and can have toxicity that may limit routine use in clinical practice.

No consensus on optimal treatments of oral warts exists. Treatments for anogenital warts cannot be used in the oral mucosa. Given the lack of RCTs, surgical removal is the most common treatment for oral warts that interfere with function or need to be removed for aesthetic reasons.

These recommendations align with the CDC STI Treatment Guidelines.

Treating CIN and Cervical Cancer

People with HIV with CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in people with HIV should be managed according to ASCCP guidelines.

People with satisfactory colposcopy (transformation is fully visualized) and biopsy-confirmed high-grade CIN (CIN 2/3) can be treated with either ablation (e.g., cryotherapy, laser vaporization, electrocautery, diathermy, cold coagulation) or excisional methods (e.g., loop electrosurgical excision procedure, laser conization, cold knife conization), whereas people with unsatisfactory colposcopy should be treated only with excisional methods **(AII).** In patients with recurrent high-grade CIN, diagnostic excisional methods are recommended **(AII).** Hysterectomy is acceptable for treatment of recurrent or persistent biopsy-confirmed high-grade CIN **(BII);** if invasive disease is suspected, the patient should be managed in consultation with a gynecologic oncologist. The ASCCP guidelines for adolescents and young women aged 21 to 24 years should continue to be followed. In these patients, progression of lesions is more common, and so is recurrence. Therefore, close observation, as outlined in the guidelines, should be considered for management of CIN 1; CIN 2; CIN 2,3 not otherwise specified (when pathology is HSIL but does not specify if CIN 2 or 3); and histologic HSIL in adolescents and adults with HIV who are younger than 25 years **(BIII).** If concern for loss to follow-up, excisional methods of treatment for CIN 2; CIN 2,3; and HSIL may be preferred **(BIII).**

Management of ICC may follow National Comprehensive Cancer Network (NCCN) guidelines. Although complication and failure rates may be higher in people with HIV, standard treatment appears safe and efficacious.[142]

Treating VIN, Vulvar Cancer, VAIN, and Vaginal Cancer

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed the same as vulvovaginal warts. Treatment of high-grade VIN/VAIN should be individualized in consultation with a specialist and is dependent upon the patient's medical condition and the location and extent of the disease. Various treatment modalities are available for VIN, including local excision, laser vaporization, ablation, and topical therapies (e.g., imiquimod or cidofovir135 therapy). Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO_2 laser, and excisional procedures.[147-149]

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following NCCN guidelines.

Treating AIN and Anal Cancer

The ANCHOR study was not designed to compare different treatment modalities for efficacy. However, almost all participants were treated with office-based ablation of HSIL, most often hyfrecation. The rate of treatment-associated serious adverse events was very low. Office-based hyfrecation is therefore a reasonable first-line approach to treatment of anal HSIL **(AI).**[73] Those with anal cancer should be referred to Oncology for appropriate treatment.

Treating HPV-Associated Disease at Other Sites, Including the Penis and the Oropharynx

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ for men and women with and without HIV. Data suggest a more favorable prognosis for HPV-associated oropharyngeal cancers than for non-HPV-associated oropharyngeal cancers.[150-152] Surgery, chemotherapy, and radiation are treatment modalities used for oropharyngeal cancers.

Special Considerations Regarding Antiretroviral Therapy Initiation

Given the strong evidence that early ART initiation is clinically beneficial in reducing risk of AIDS and opportunistic infections (OIs), there is no reason to consider HPV-related oral, anal, or genital disease when deciding whether or when to initiate ART.

Monitoring Response to Therapy and Adverse Events (Including IRIS)

Monitoring by physical examination is required during and after treatment of genital warts to detect toxicity, persistence, or recurrence, all of which are common with each of the treatments. Because recurrences of CIN and cervical cancer after conventional therapy are more common with HIV, these individuals should be followed after treatment with frequent cytologic screening and colposcopic examination (see Preventing Disease and Treating Disease sections). Treatment of CIN with ablative and excisional modalities can be associated with several adverse events, such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis. Individualized treatment of adverse events is required.

Each of the treatment modalities for AIN described above is associated with adverse events, primarily pain, bleeding, ulceration, and, in rare cases, development of abscesses, fissures, or fistulas. Patients can be monitored for adverse events using the methods previously described.

Treatment for anal cancer with combination radiation and chemotherapy is associated with a high rate of morbidity, even when the treatment is successful. The most important complication is radiation-associated proctitis.

During IRIS, HPV may manifest as a paradoxical increase in warts after introduction of ART or by inflammation of existing warts.[153,154] A few studies also have shown the development of oral warts while starting ART.[155-158]

Managing Treatment Failure

For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered **(AIII).** Biopsy should be considered to exclude VIN. Genital warts often require more than one course of treatment.

Recurrent cytologic and histologic abnormalities after therapy for CIN should be managed according to ASCCP guidelines.

No consensus on the treatment of biopsy-proven recurrent VIN exists, and surgical excision can be considered.

Preventing Recurrence

Monitoring after therapy for cervical disease should follow ASCCP guidelines. In one study of women with HIV treated for high-grade CIN, low-dose intravaginal 5-FU (2 g twice weekly for 6 months) reduced the short-term risk of recurrence. Clinical experience with this therapy, however, is too limited to provide a recommendation for its use, and no follow-up study to confirm these observations has been reported. No guidelines exist regarding frequency of monitoring after therapy for VIN, but twice-yearly vulvar inspection appears reasonable for people who have been treated for VIN. People who have been treated for high-grade VAIN should be managed like those with CIN 2, that is, with cytology at 6 and 12 months after therapy, and annually thereafter.

No indication exists for secondary prophylaxis (chronic maintenance therapy) with any of the conventional modalities to prevent recurrence of genital warts, CIN, or AIN.

Special Considerations During Pregnancy

Pregnant women with HIV who have genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists, such as an obstetrician or gynecologist and an infectious disease provider. Pregnancy may be associated with an increased frequency and rate of growth of genital warts. Podofilox should not be used during pregnancy **(BIII).** At present, the evidence is insufficient to recommend imiquimod use during pregnancy. No anomalies have been observed with the use of imiquimod in animals during pregnancy. Several case series describe the use of imiquimod during pregnancy, also without any significant adverse effects.[159,160]

Other topical treatments—such as BCA and TCA—and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy **(AIII).**

Transmission of genital HPV6 and 11 from vaginal secretions at delivery is the presumed mechanism of juvenile-onset recurrent respiratory papillomatosis in children. This condition is rare but is seen more frequently among children born to women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children.[161] No change in obstetrical management is indicated for people with genital warts unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding **(AIII).**

Cervical and anal cancer screening is recommended during pregnancy. Cytobrush sampling can be done during pregnancy. Pregnant women with abnormal cervical cytology results should undergo colposcopy and cervical biopsy of lesions suspicious for high-grade disease or cancer **(BIII).** Increased bleeding may occur with cervical biopsy during pregnancy. Endocervical curettage is contraindicated during pregnancy **(AIII).**

During pregnancy, ASC-US or LSIL can be managed the same as for all people with HIV, although deferral of colposcopy until at least 6 weeks postpartum is acceptable **(CIII).** Treatment of CIN is not recommended during pregnancy unless invasive disease is suspected **(AIII).** Patients with suspected cervical cancer should be referred to a gynecologic oncologist for definitive diagnosis, treatment, and development of a delivery plan. Vaginal delivery is not recommended for people with ICC **(AIII).** For people with CIN and without suspicion of invasive disease, re-evaluation with co-testing and colposcopy is recommended after 6 weeks postpartum **(AIII).** People with CIN can deliver vaginally.

Pregnancy testing is not needed before vaccination. HPV vaccination is not recommended during pregnancy **(CIII),** as there are limited data for its use in pregnancy; however, no intervention is needed if inadvertently given.[162] In a combined analysis of five RCTs of the HPV6/11/16/18 vaccine, administration of the vaccine to women who became pregnant during the course of the trial did not appear to negatively affect pregnancy outcomes.[163] Additionally, in a population-based study in Denmark, no increased risk of spontaneous abortion, stillbirth, or infant mortality was observed in more than 5,200 pregnancies exposed to at least one dose of the quadrivalent HPV vaccine. Also in Denmark, an analysis of the Medical Birth Register and National Patient Register found that among 1,665 exposed pregnancies, quadrivalent HPV vaccination was not associated with a significantly increased risk of adverse pregnancy outcomes, including major birth defect, preterm birth, or low birth weight.[164] Data on the use of the 9-valent vaccine during pregnancy are more limited, but to date are also reassuring.[165-169]

The effects of treatment of AIN on pregnancy are unknown. Most experts recommend deferral of diagnosis and treatment of AIN until after delivery unless a strong clinical suspicion of anal cancer exists.

References

1. Schiffman M, Clifford G, Buonaguro FM. Classification of weakly carcinogenic human papillomavirus types: addressing the limits of epidemiology at the borderline. *Infect Agent Cancer*. 2009;4:8. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19486508.

2. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009;10(4):321-322. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19350698.

3. Castle PE. The evolving definition of carcinogenic human papillomavirus. *Infect Agent Cancer*. 2009;4:7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19432962.

4. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. *Lancet*. 2013;382(9895):889-899. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23618600.

5. World Health Organization International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: World Health Organization; 2007. Available at: https://monographs.iarc.who.int.

6. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine*. 2006;24 Suppl 3:S3/11-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16949997.

7. Chaturvedi AK. Beyond cervical cancer: burden of other HPV-related cancers among men and women. *J Adolesc Health*. 2010;46(4 Suppl):S20-26. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20307840.

8. Grulich AE, Jin F, Conway EL, Stein AN, Hocking J. Cancers attributable to human papillomavirus infection. *Sex Health*. 2010;7(3):244-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20719211.

9. Ye Y, Burkholder GA, Wiener HW, et al. Comorbidities associated with HPV infection among people living with HIV-1 in the southeastern US: a retrospective clinical cohort study. *BMC Infect Dis*. 2020;20(1):144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32059635.

10. Smith JS, Backes DM, Hoots BE, Kurman RJ, Pimenta JM. Human papillomavirus type-distribution in vulvar and vaginal cancers and their associated precursors. *Obstet Gynecol*. 2009;113(4):917-924. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19305339.

11. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. *Int J Cancer*. 2009;124(7):1626-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19115209.

12. Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol*. 2011;29(32):4294-4301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21969503.

13. Forman D, de Martel C, Lacey CJ, et al. Global burden of human papillomavirus and related diseases. *Vaccine*. 2012;30 Suppl 5:F12-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23199955.

14. Saraiya M, Unger ER, Thompson TD, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst*. 2015;107(6):djv086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25925419.

15. Beachler DC, Abraham AG, Silverberg MJ, et al. Incidence and risk factors of HPV-related and HPV-unrelated head and neck squamous cell carcinoma in HIV-infected individuals. *Oral Oncol*. 2014;50(12):1169-1176. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25301563.

16. Kahn JA, Belzer M, Chi X, et al. Pre-vaccination prevalence of anogenital and oral human papillomavirus in young HIV-infected men who have sex with men. *Papillomavirus Res*. 2019;7:52-61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30658128.

17. Castillejos-Garcia I, Ramirez-Amador VA, Carrillo-Garcia A, Garcia-Carranca A, Lizano M, Anaya-Saavedra G. Type-specific persistence and clearance rates of HPV genotypes in the oral and oropharyngeal mucosa in an HIV/AIDS cohort. *J Oral Pathol Med*. 2018;47(4):396-402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29380908.

18. Mendez-Martinez R, Maldonado-Frias S, Vazquez-Vega S, et al. High prevalent human papillomavirus infections of the oral cavity of asymptomatic HIV-positive men. *BMC Infect Dis*. 2020;20(1):27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31924186.

19. Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018;18(2):198-206. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5805865.

20. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Health*. 2020;8(2):e191-e203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31812369.

21. Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet*. 2007;370(9590):890-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17826171.

22. American Cancer Society. Global cancer facts & figures 3rd edition. Atlanta: American Cancer Society; 2015. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/global-cancer-facts-and-figures/global-cancer-facts-and-figures-3rd-edition.pdf.

23. Bosch FX, Manos MM, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. International biological study on cervical cancer (IBSCC) Study Group. *J Natl Cancer Inst*. 1995;87(11):796-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7791229.

24. Wheeler CM, Hunt WC, Joste NE, Key CR, Quint WG, Castle PE. Human papillomavirus genotype distributions: implications for vaccination and cancer screening in the United States. *J Natl Cancer Inst*. 2009;101(7):475-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19318628.

25. Munoz N, Bosch FX, de Sanjose S, et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med*. 2003;348(6):518-527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12571259.

26. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med*. 1998;338(7):423-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9459645.

27. Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA. Risk of female human papillomavirus acquisition associated with first male sex partner. *J Infect Dis*. 2008;197(2):279-282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18179386.

28. Bauer HM, Hildesheim A, Schiffman MH, et al. Determinants of genital human papillomavirus infection in low-risk women in Portland, Oregon. *Sex Transm Dis*. 1993;20(5):274-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8235925.

29. Wheeler CM, Parmenter CA, Hunt WC, et al. Determinants of genital human papillomavirus infection among cytologically normal women attending the University of New Mexico student health center. *Sex Transm Dis*. 1993;20(5):286-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8235927.

30. Burk RD, Ho GY, Beardsley L, Lempa M, Peters M, Bierman R. Sexual behavior and partner characteristics are the predominant risk factors for genital human papillomavirus infection in young women. *J Infect Dis*. 1996;174(4):679-689. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8843203.

31. Rodriguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. 2010;102(5):315-324. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20157096.

32. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst*. 2000;92(18):1500-1510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10995805.

33. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. *J Natl Cancer Inst*. 2009;101(16):1120-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19648510.

34. Simard EP, Engels EA. Cancer as a cause of death among people with AIDS in the United States. *Clin Infect Dis*. 2010;51(8):957-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20825305.

35. Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst*. 2005;97(6):425-432. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15770006.

36. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet*. 2007;370(9581):59-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17617273.

37. Dal Maso L, Polesel J, Serraino D, et al. Pattern of cancer risk in persons with AIDS in Italy in the HAART era. *Br J Cancer*. 2009;100(5):840-847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19223894.

38. Polesel J, Franceschi S, Suligoi B, et al. Cancer incidence in people with AIDS in Italy. *Int J Cancer*. 2010;127(6):1437-1445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20049835.

39. Abraham AG, D'Souza G, Jing Y, et al. Invasive cervical cancer risk among HIV-infected women: a North American multicohort collaboration prospective study. *J Acquir Immune Defic Syndr*. 2013;62(4):405-413. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23254153.

40. Stelzle D, Tanaka LF, Lee KK, et al. Estimates of the global burden of cervical cancer associated with HIV. *Lancet Glob Health*. 2021;9(2):e161-e169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33212031.

41. Stier EA, Engels E, Horner MJ, et al. Cervical cancer incidence stratified by age in women with HIV compared with the general population in the United States, 2002-2016. *AIDS*. 2021;35(11):1851-1856. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34049357.

42. Strickler HD, Burk RD, Fazzari M, et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2005;97(8):577-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15840880.

43. Moscicki AB, Ellenberg JH, Crowley-Nowick P, Darragh TM, Xu J, Fahrat S. Risk of high-grade squamous intraepithelial lesion in HIV-infected adolescents. *J Infect Dis*. 2004;190(8):1413-1421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15378433.

44. Schrager LK, Friedland GH, Maude D, et al. Cervical and vaginal squamous cell abnormalities in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1989;2(6):570-575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2555473.

45. Maiman M, Fruchter RG, Serur E, Remy JC, Feuer G, Boyce J. Human immunodeficiency virus infection and cervical neoplasia. *Gynecol Oncol*. 1990;38(3):377-382. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2227552.

46. Ahdieh L, Klein RS, Burk R, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. *J Infect Dis*. 2001;184(6):682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11517428.

47. Schuman P, Ohmit SE, Klein RS, et al. Longitudinal study of cervical squamous intraepithelial lesions in human immunodeficiency virus (HIV)-seropositive and at-risk HIV-seronegative women. *J Infect Dis*. 2003;188(1):128-136. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12825181.

48. Massad LS, Riester KA, Anastos KM, et al. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with HIV-1. Women's Interagency HIV Study Group. *J Acquir Immune Defic Syndr*. 1999;21(1):33-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10235512.

49. Feingold AR, Vermund SH, Burk RD, et al. Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. *J Acquir Immune Defic Syndr*. 1990;3(9):896-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2166784.

50. Wright TC, Jr., Ellerbrock TV, Chiasson MA, Van Devanter N, Sun XW. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors, and validity of Papanicolaou smears. New York Cervical Disease Study. *Obstet Gynecol*. 1994;84(4):591-597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8090399.

51. Sun XW, Ellerbrock TV, Lungu O, Chiasson MA, Bush TJ, Wright TC, Jr. Human papillomavirus infection in human immunodeficiency virus-seropositive women. *Obstet Gynecol*. 1995;85(5 Pt 1):680-686. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7724095.

52. Heard I, Jeannel D, Bergeron C, Saada M, Henrion R, Kazatchkine MD. Lack of behavioural risk factors for squamous intraepithelial lesions (SIL) in HIV-infected women. *Int J STD AIDS*. 1997;8(6):388-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9179650.

53. Delmas MC, Larsen C, van Benthem B, et al. Cervical squamous intraepithelial lesions in HIV-infected women: prevalence, incidence and regression. European Study Group on Natural History of HIV Infection in Women. *AIDS*. 2000;14(12):1775-1784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10985315.

54. Six C, Heard I, Bergeron C, et al. Comparative prevalence, incidence and short-term prognosis of cervical squamous intraepithelial lesions amongst HIV-positive and HIV-negative women. *AIDS*. 1998;12(9):1047-1056. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9662202.

55. Ahdieh-Grant L, Li R, Levine AM, et al. Highly active antiretroviral therapy and cervical squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Natl Cancer Inst*. 2004;96(14):1070-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15265968.

56. Minkoff H, Zhong Y, Burk RD, et al. Influence of adherent and effective antiretroviral therapy use on human papillomavirus infection and squamous intraepithelial lesions in human immunodeficiency virus-positive women. *J Infect Dis*. 2010;201(5):681-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20105077.

57. Simard EP, Pfeiffer RM, Engels EA. Spectrum of cancer risk late after AIDS onset in the United States. *Arch Intern Med*. 2010;170(15):1337-1345. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20696958.

58. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer*. 2008;123(1):187-194. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18435450.

59. Hernandez-Ramirez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. *Lancet HIV*. 2017;4(11):e495-e504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28803888.

60. Riddell Jt, Brouwer AF, Walline HM, et al. Oral human papillomavirus prevalence, persistence, and risk-factors in HIV-positive and HIV-negative adults. *Tumour Virus Res*. 2022;13:200237. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35460939.

61. Guiguet M, Boue F, Cadranel J, et al. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. *Lancet Oncol*. 2009;10(12):1152-1159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19818686.

62. Hernandez-Ramirez RU, Qin L, Lin H, et al. Association of immunosuppression and human immunodeficiency virus (HIV) viremia with anal cancer risk in persons living with HIV in the United States and Canada. *Clin Infect Dis*. 2020;70(6):1176-1185. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31044245.

63. Faber MT, Frederiksen K, Palefsky JM, Kjaer SK. A nationwide longitudinal study on risk factors for progression of anal intraepithelial neoplasia grade 3 to anal cancer. *Int J Cancer*. 2022;151(8):1240-1247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35657350.

64. Wilkin TJ, Palmer S, Brudney KF, Chiasson MA, Wright TC. Anal intraepithelial neoplasia in heterosexual and homosexual HIV-positive men with access to antiretroviral therapy. *J Infect Dis*. 2004;190(9):1685-1691. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15478076.

65. Kreuter A, Brockmeyer NH, Hochdorfer B, et al. Clinical spectrum and virologic characteristics of anal intraepithelial neoplasia in HIV infection. *J Am Acad Dermatol*. 2005;52(4):603-608. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15793509.

66. Palefsky JM, Holly EA, Efirdc JT, et al. Anal intraepithelial neoplasia in the highly active antiretroviral therapy era among HIV-positive men who have sex with men. *AIDS*. 2005;19(13):1407-1414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16103772.

67. Massad LS, Silverberg MJ, Springer G, et al. Effect of antiretroviral therapy on the incidence of genital warts and vulvar neoplasia among women with the human immunodeficiency virus. *Am J Obstet Gynecol*. 2004;190(5):1241-1248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15167825.

68. Conley LJ, Ellerbrock TV, Bush TJ, Chiasson MA, Sawo D, Wright TC. HIV-1 infection and risk of vulvovaginal and perianal condylomata acuminata and intraepithelial neoplasia: a prospective cohort study. *Lancet*. 2002;359(9301):108-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11809252.

69. Jamieson DJ, Paramsothy P, Cu-Uvin S, Duerr A, Group HIVERS. Vulvar, vaginal, and perianal intraepithelial neoplasia in women with or at risk for human immunodeficiency virus. *Obstet Gynecol*. 2006;107(5):1023-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648406.

70. Colon-Lopez V, Shiels MS, Machin M, et al. Anal cancer risk among people with HIV infection in the United States. *J Clin Oncol*. 2018;36(1):68-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29140774.

71. Shiels MS, Islam JY, Rosenberg PS, Hall HI, Jacobson E, Engels EA. Projected cancer incidence rates and burden of incident cancer cases in HIV-infected adults in the United States through 2030. *Ann Intern Med*. 2018;168(12):866-873. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29801099.

72. Clifford GM, Georges D, Shiels MS, et al. A meta-analysis of anal cancer incidence by risk group: Toward a unified anal cancer risk scale. *Int J Cancer*. 2021;148(1):38-47. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32621759.

73. Palefsky JM, Lee JY, Jay N, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. *N Engl J Med*. 2022;386(24):2273-2282. Available at: https://pubmed.ncbi.nlm.nih.gov/35704479/.

74. Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis*. 2005;191(5):731-738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15688287.

75. Flagg EW, Schwartz R, Weinstock H. Prevalence of anogenital warts among participants in private health plans in the United States, 2003-2010: potential impact of human papillomavirus vaccination. *Am J Public Health*. 2013;103(8):1428-1435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23763409.

76. Lewis RM, Laprise JF, Gargano JW, et al. Estimated prevalence and incidence of disease-associated human papillomavirus types among 15- to 59-Year-olds in the United States. *Sex Transm Dis*. 2021;48(4):273-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33492097.

77. Daugherty M, Byler T. Genital wart and human papillomavirus prevalence in men in the United States from penile swabs: results from national health and nutrition examination surveys. *Sex Transm Dis*. 2018;45(6):412-416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29750774.

78. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med*. 2007;356(19):1944-1956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494927.

79. Leslie SW, Sajjad H, Kumar S. Genital warts. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/pubmed/28722914.

80. Yusupov A, Popovsky D, Mahmood L, Kim AS, Akman AE, Yuan H. The nonavalent vaccine: a review of high-risk HPVs and a plea to the CDC. *Am J Stem Cells*. 2019;8(3):52-64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31976155.

81. Gardasil 9 [package insert]. Merck Sharp & Dohme Corp. 2020. Available at: https://www.fda.gov/media/90064/download.

82. Paavonen J, Naud P, Salmeron J, et al. Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women. *Lancet*. 2009;374(9686):301-314. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19586656.

83. Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007;356(19):1915-1927. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494925.

84. Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med*. 2015;372(8):711-723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25693011.

85. Palefsky JM, Giuliano AR, Goldstone S, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. *N Engl J Med*. 2011;365(17):1576-1585. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22029979.

86. Giuliano AR, Palefsky JM, Goldstone S, et al. Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. *N Engl J Med*. 2011;364(5):401-411. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21288094.

87. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet*. 2007;369(9574):1693-1702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17512854.

88. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356(19):1928-1943. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17494926.

89. Castellsague X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*. 2015;33(48):6892-6901. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26144901.

90. Kuehn B. Studies support HPV safety. *JAMA*. 2020;323(4):302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31990322.

91. Herrero R, Quint W, Hildesheim A, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. *PLoS One*. 2013;8(7):e68329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23873171.

92. Sonawane K, Suk R, Chiao EY, et al. Oral human papillomavirus infection: differences in prevalence between sexes and concordance with genital human papillomavirus infection, NHANES 2011 to 2014. *Ann Intern Med*. 2017;167(10):714-724. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29049523.

93. Petrosky E, Bocchini JA, Jr., Hariri S, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2015;64(11):300-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25811679.

94. Meites E, Szilagyi PG, Chesson HW, Unger ER, Romero JR, Markowitz LE. Human papillomavirus vaccination for adults: updated recommendations of the advisory committee on immunization practices. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):698-702. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31415491.

95. Levin MJ, Moscicki AB, Song LY, et al. Safety and immunogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine in HIV-infected children 7 to 12 years old. *J Acquir Immune Defic Syndr*. 2010;55(2):197-204. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20574412.

96. Wilkin T, Lee JY, Lensing SY, et al. Safety and immunogenicity of the quadrivalent human papillomavirus vaccine in HIV-1-infected men. *J Infect Dis*. 2010;202(8):1246-1253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20812850.

97. Kojic EM, Kang M, Cespedes MS, et al. Immunogenicity and safety of the quadrivalent human papillomavirus vaccine in HIV-1-infected women. *Clin Infect Dis*. 2014;59(1):127-135. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24723284.

98. Rainone V, Giacomet V, Penagini F, et al. Human papilloma virus vaccination induces strong human papilloma virus specific cell-mediated immune responses in HIV-infected adolescents and young adults. *AIDS*. 2015;29(6):739-743. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25849837.

99. Faust H, Toft L, Sehr P, et al. Human papillomavirus neutralizing and cross-reactive antibodies induced in HIV-positive subjects after vaccination with quadrivalent and bivalent HPV vaccines. *Vaccine*. 2016;34(13):1559-1565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26896686.

100. Money DM, Moses E, Blitz S, et al. HIV viral suppression results in higher antibody responses in HIV-positive women vaccinated with the quadrivalent human papillomavirus vaccine. *Vaccine*. 2016;34(40):4799-4806. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27544584.

101. Ellsworth GB, Lensing SY, Ogilvie CB, et al. A delayed dose of quadrivalent human papillomavirus vaccine demonstrates immune memory in HIV-1-infected men. *Papillomavirus Res*. 2018;6:11-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29807211.

102. Kahn JA, Xu J, Kapogiannis BG, et al. Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women. *Clin Infect Dis*. 2013;57(5):735-744. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23667266.

103. Moscicki AB, Karalius B, Tassiopoulos K, et al. Human papillomavirus antibody levels and quadrivalent vaccine clinical effectiveness in perinatally human immunodeficiency virus-infected and exposed, uninfected youth. *Clin Infect Dis.* 2019;69(7):1183-1191. Available at: https://pubmed.ncbi.nlm.nih.gov/30927547.

104. McClymont E, Lee M, Raboud J, et al. The efficacy of the quadrivalent human papillomavirus vaccine in girls and women living with human immunodeficiency virus. *Clin Infect Dis*. 2019;68(5):788-794. Available at: https://pubmed.ncbi.nlm.nih.gov/29985988.

105. Staadegaard L, Ronn MM, Soni N, et al. Immunogenicity, safety, and efficacy of the HPV vaccines among people living with HIV: A systematic review and meta-analysis. *EClinicalMedicine*. 2022;52:101585. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35936024.

106. Wilkin TJ, Chen H, Cespedes MS, et al. A randomized, placebo-controlled trial of the quadrivalent HPV vaccine in HIV-infected adults age 27 years or older: AIDS Clinical Trials Group protocol A5298. *Clin Infect Dis*. 2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29659751.

107. Hidalgo-Tenorio C, Pasquau J, Omar-Mohamed M, et al. Effectiveness of the quadrivalent HPV vaccine in preventing anal ≥ HSILs in a Spanish population of HIV+ MSM aged > 26 years. *Viruses*. 2021;13(2). Available at: https://pubmed.ncbi.nlm.nih.gov/33498165.

108. Palefsky JM, Lensing SY, Belzer M, et al. High prevalence of anal high-grade squamous intraepithelial lesions, and prevention through human papillomavirus vaccination, in young men

who have sex with men living with human immunodeficiency virus. *Clin Infect Dis*. 2021;73(8):1388-1396. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33991185.

109. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sex Transm Dis*. 2002;29(11):725-735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12438912.

110. Wiyeh AB, Mome RKB, Mahasha PW, Kongnyuy EJ, Wiysonge CS. Effectiveness of the female condom in preventing HIV and sexually transmitted infections: a systematic review and meta-analysis. *BMC Public Health*. 2020;20(1):319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32164652.

111. Winer RL, Hughes JP, Feng Q, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med*. 2006;354(25):2645-2654. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16790697.

112. Pierce Campbell CM, Lin HY, Fulp W, et al. Consistent condom use reduces the genital human papillomavirus burden among high-risk men: the HPV infection in men study. *J Infect Dis*. 2013;208(3):373-384. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23644283.

113. Bleeker MC, Hogewoning CJ, Voorhorst FJ, et al. Condom use promotes regression of human papillomavirus-associated penile lesions in male sexual partners of women with cervical intraepithelial neoplasia. *Int J Cancer*. 2003;107(5):804-810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14566831.

114. Hogewoning CJ, Bleeker MC, van den Brule AJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *Int J Cancer*. 2003;107(5):811-816. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14566832.

115. Auvert B, Sobngwi-Tambekou J, Cutler E, et al. Effect of male circumcision on the prevalence of high-risk human papillomavirus in young men: results of a randomized controlled trial conducted in Orange Farm, South Africa. *J Infect Dis*. 2009;199(1):14-19. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19086814.

116. Tobian AA, Serwadda D, Quinn TC, et al. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med*. 2009;360(13):1298-1309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19321868.

117. Serwadda D, Wawer MJ, Makumbi F, et al. Circumcision of HIV-infected men: effects on high-risk human papillomavirus infections in a randomized trial in Rakai, Uganda. *J Infect Dis*. 2010;201(10):1463-1469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20370481.

118. Gray RH, Serwadda D, Kong X, et al. Male circumcision decreases acquisition and increases clearance of high-risk human papillomavirus in HIV-negative men: a randomized trial in Rakai, Uganda. *J Infect Dis*. 2010;201(10):1455-1462. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20370483.

119. Keller MJ, Burk RD, Xie X, et al. Risk of cervical precancer and cancer among HIV-infected women with normal cervical cytology and no evidence of oncogenic HPV infection. *JAMA*. 2012;308(4):362-369. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22820789.

120. Robbins HA, Strickler HD, Massad LS, et al. Cervical cancer screening intervals and management for women living with HIV: a risk benchmarking approach. *AIDS*. 2017;31(7):1035-1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28323758.

121. Keller MJ, Burk RD, Massad LS, et al. Cervical precancer risk in HIV-infected women who test positive for oncogenic human papillomavirus despite a normal pap test. *Clin Infect Dis*. 2015;61(10):1573-1581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26187020.

122. D'Souza G, Burk RD, Palefsky JM, Massad LS, Strickler HD, Group WHW. Cervical human papillomavirus testing to triage borderline abnormal pap tests in HIV-coinfected women. *AIDS*. 2014;28(11):1696-1698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25232904.

123. Gilles C, Konopnicki D, Rozenberg S. The recent natural history of human papillomavirus cervical infection in women living with HIV: A scoping review of meta-analyses and systematic reviews and the construction of a hypothetical model. *HIV Med*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37062862.

124. Massad LS, Xie X, Minkoff H, et al. Longitudinal assessment of abnormal Papanicolaou test rates among women with HIV. *AIDS*. 2020;34(1):73-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31789890.

125. Strickler HD, Keller MJ, Hessol NA, et al. Primary HPV and molecular cervical cancer screening in U.S. women living with human immunodeficiency virus. *Clin Infect Dis*. 2021;72(9):1529-1537. Available at: https://pubmed.ncbi.nlm.nih.gov/32881999.

126. McHaro R, Lennemann T, France J, et al. HPV type distribution in HIV positive and negative women with or without cervical dysplasia or cancer in East Africa. *Front Oncol*. 2021;11:763717. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34917506.

127. FDA roundup: May 17, 2024 [press release]. U.S. Food & Drug Administration, May 17 2024. Available at: https://www.fda.gov/news-events/press-announcements/fda-roundup-may-17-2024.

128. Massad LS, Xie X, Minkoff HL, et al. Frequency of high-grade squamous cervical lesions among women over age 65 years living with HIV. *Am J Obstet Gynecol*. 2021;225(4):411.e411-411.e417. Available at: https://pubmed.ncbi.nlm.nih.gov/33957115/.

129. Massad LS, Xie X, Greenblatt RM, et al. Effect of human immunodeficiency virus infection on the prevalence and incidence of vaginal intraepithelial neoplasia. *Obstet Gynecol*. 2012;119(3):582-589. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22353957.

130. Smeltzer S, Yu X, Schmeler KM, Peters Y, Levison J. Abnormal vaginal pap test after hysterectomy in human immunodeficiency virus-infected women. *Obstet Gynecol*. 2016;127(Suppl 1):4S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28469285.

131. Clarke MA, Wentzensen N. Strategies for screening and early detection of anal cancers: A narrative and systematic review and meta-analysis of cytology, HPV testing, and other biomarkers. *Cancer Cytopathol*. 2018;126(7):447-460. Available at: https://pubmed.ncbi.nlm.nih.gov/29797691/.

132. Hoots BE, Palefsky JM, Pimenta JM, Smith JS. Human papillomavirus type distribution in anal cancer and anal intraepithelial lesions. *Int J Cancer*. 2009;124(10):2375-2383. Available at: https://pubmed.ncbi.nlm.nih.gov/19189402/.

133. Chowdhury S, Darragh TM, Berry-Lawhorn JM, et al. HPV type distribution in benign, high-grade squamous intraepithelial lesions and squamous cell cancers of the anus by HIV status. *Cancers (Basel)*. 2023;15(3). Available at: https://pubmed.ncbi.nlm.nih.gov/36765617/.

134. Daling JR, Madeleine MM, Johnson LG, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. *Cancer*. 2004;101(2):270-280. Available at: https://pubmed.ncbi.nlm.nih.gov/15241823/.

135. Keller K, Ramos-Cartagena JM, Guiot HM, et al. Association of smoking with anal high-risk HPV infection and histologically confirmed anal high-grade squamous intraepithelial lesions among a clinic-based population in Puerto Rico. *Cancer Treat Res Commun*. 2022;30:100503. Available at: https://pubmed.ncbi.nlm.nih.gov/34999478/.

136. Balasundaram I, Payne KF, Al-Hadad I, Alibhai M, Thomas S, Bhandari R. Is there any benefit in surgery for potentially malignant disorders of the oral cavity? *J Oral Pathol Med*. 2014;43(4):239-244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23750566.

137. Centers for Disease Control and Prevention. Sexually transmitted infections treatment guidelines, 2021: human papillomavirus (HPV) infection. 2021. Available at: https://www.cdc.gov/std/treatment-guidelines/hpv.htm.

138. Hillman RJ, Berry-Lawhorn JM, Ong JJ, et al. International anal neoplasia society guidelines for the practice of digital anal rectal examination. *J Low Genit Tract Dis.* 2019;23(2):138-146. Available at: https://pubmed.ncbi.nlm.nih.gov/30907777/.

139. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol*. 2015;33(21):2376-2383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26077242.

140. Ortiz AP, Engels EA, Nogueras-Gonzalez GM, et al. Disparities in human papillomavirus-related cancer incidence and survival among human immunodeficiency virus-infected Hispanics living in the United States. *Cancer*. 2018;124(23):4520-4528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30345506.

141. Ferreira MP, Coghill AE, Chaves CB, et al. Outcomes of cervical cancer among HIV-infected and HIV-uninfected women treated at the Brazilian National Institute of Cancer. *AIDS*. 2017;31(4):523-531. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28060014.

142. Einstein MH, Ndlovu N, Lee J, et al. Cisplatin and radiation therapy in HIV-positive women with locally advanced cervical cancer in sub-Saharan Africa: A phase II study of the AIDS malignancy consortium *Gynecol Oncol*. 2019;153(1):20-25. Available at: https://pubmed.ncbi.nlm.nih.gov/30773222/.

143. Tatti S, Swinehart JM, Thielert C, Tawfik H, Mescheder A, Beutner KR. Sinecatechins, a defined green tea extract, in the treatment of external anogenital warts: a randomized controlled trial. *Obstet Gynecol*. 2008;111(6):1371-1379. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18515521.

144. Matteelli A, Beltrame A, Graifemberghi S, et al. Efficacy and tolerability of topical 1% cidofovir cream for the treatment of external anogenital warts in HIV-infected persons. *Sex Transm Dis*. 2001;28(6):343-346. Available at: https://pubmed.ncbi.nlm.nih.gov/11403192.

145. Orlando G, Fasolo MM, Beretta R, Merli S, Cargnel A. Combined surgery and cidofovir is an effective treatment for genital warts in HIV-infected patients. *AIDS*. 2002;16(3):447-450. Available at: https://pubmed.ncbi.nlm.nih.gov/11834957.

146. Burgos J, Campany D, Garcia J, Landolfi S, Falco V, Curran A. Effectiveness of topical cidofovir for treatment of refractory anal high-grade squamous intraepithelial lesion. *AIDS*. 2023;37(9):1425-1429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37195272.

147. Bradbury M, Cabrera S, García-Jiménez A, et al. Vulvar intraepithelial neoplasia: clinical presentation, management and outcomes in women infected with HIV. *AIDS*. 2016;30(6):859-868. Available at: https://pubmed.ncbi.nlm.nih.gov/26959352/.

148. Bradbury M, Xercavins N, Garcia-Jimenez A, et al. Vaginal intraepithelial neoplasia: clinical presentation, management, and outcomes in relation to HIV infection status. *J Low Genit Tract Dis*. 2019;23(1):7-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30161052.

149. Fiascone S, Vitonis AF, Feldman S. Topical 5-fluorouracil for women with high-grade vaginal intraepithelial neoplasia. *Obstet Gynecol*. 2017;130(6):1237-1243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29112645.

150. Craig SG, Anderson LA, Schache AG, et al. Recommendations for determining HPV status in patients with oropharyngeal cancers under TNM8 guidelines: a two-tier approach. *Br J Cancer*. 2019;120(8):827-833. Available at: https://pubmed.ncbi.nlm.nih.gov/30890775/.

151. Nauta IH, Rietbergen MM, van Bokhoven A, et al. Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. *Ann Oncol*. 2018;29(5):1273-1279. Available at: https://pubmed.ncbi.nlm.nih.gov/29438466/.

152. Lechner M, Liu J, Masterson L, Fenton TR. HPV-associated oropharyngeal cancer: epidemiology, molecular biology and clinical management. *Nat Rev Clin Oncol*. 2022;19(5):306-327. Available at: https://pubmed.ncbi.nlm.nih.gov/35105976/.

153. Meys R, Gotch FM, Bunker CB. Human papillomavirus in the era of highly active antiretroviral therapy for human immunodeficiency virus: an immune reconstitution-associated disease? *Br J Dermatol*. 2010;162(1):6-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19709102.

154. Moussa R, Stephenson I, Fisk P, Dhar J, Nicholson KG, Wiselka MJ. Buschke-Loewenstein lesion: another possible manifestation of immune restoration inflammatory syndrome? *AIDS*. 2004;18(8):1221-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15166544.

155. Greenspan D, Canchola AJ, MacPhail LA, Cheikh B, Greenspan JS. Effect of highly active antiretroviral therapy on frequency of oral warts. *Lancet*. 2001;357(9266):1411-1412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11356441.

156. King MD, Reznik DA, O'Daniels CM, Larsen NM, Osterholt D, Blumberg HM. Human papillomavirus-associated oral warts among human immunodeficiency virus-seropositive patients

in the era of highly active antiretroviral therapy: an emerging infection. *Clin Infect Dis*. 2002;34(5):641-648. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11803508.

157. Iarikov D, Duke W, Skiest D. Extensive development of flat warts as a cutaneous manifestation of immune reconstitution syndrome. *AIDS Read*. 2008;18(10):524-527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18975443.

158. Weiss DA, Yang G, Myers JB, Breyer BN. Condyloma overgrowth caused by immune reconstitution inflammatory syndrome. *Urology*. 2009;74(5):1013-1014. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19616289.

159. Patel VM, Schwartz RA, Lambert WC. Topical antiviral and antifungal medications in pregnancy: a review of safety profiles. *J Eur Acad Dermatol Venereol*. 2017;31(9):1440-1446. Available at: https://pubmed.ncbi.nlm.nih.gov/28449377.

160. Einarson A, Costei A, Kalra S, Rouleau M, Koren G. The use of topical 5% imiquimod during pregnancy: a case series. *Reprod Toxicol*. 2006;21(1):1-2. Available at: https://pubmed.ncbi.nlm.nih.gov/16039826.

161. Chatzistamatiou K, Sotiriadis A, Agorastos T. Effect of mode of delivery on vertical human papillomavirus transmission - A meta-analysis. *J Obstet Gynaecol*. 2016;36(1):10-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26367314.

162. Markowitz LE, Dunne EF, Saraiya M, et al. Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2014;63(RR-05):1-30. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25167164.

163. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol*. 2009;114(6):1179-1188. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19935017.

164. Scheller NM, Pasternak B, Molgaard-Nielsen D, Svanstrom H, Hviid A. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *N Engl J Med*. 2017;376(13):1223-1233. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28355499.

165. Kharbanda EO, Vazquez-Benitez G, DeSilva MB, et al. Association of inadvertent 9-valent human papillomavirus vaccine in pregnancy with spontaneous abortion and adverse birth outcomes. *JAMA Netw Open*. 2021;4(4):e214340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33818618.

166. Moreira ED, Block SL, Ferris D, et al. Safety profile of the 9-valent HPV vaccine: a combined analysis of 7 Phase III clinical trials. *Pediatrics*. 2016;138(2). Available at: https://pubmed.ncbi.nlm.nih.gov/27422279.

167. Murphy EC, Alimena S, Pelletier A, et al. Human papillomavirus inpatient postpartum vaccination clinical guideline implementation. *Obstetrics and Gynecology*. 2023;142(1):108-116. Available at: https://pubmed.ncbi.nlm.nih.gov/37348091.

168. Meng R, Ma R, Wang J, et al. Post-marketing surveillance for the safety of the 9-valent human papillomavirus vaccine: a retrospective real-world study in China. *Expert Rev Vaccines*. 2023;22(1):696-703. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37497832.

169. Berenson AB, Panicker G, Unger ER, Rupp RE, Kuo YF. Immunogenicity of 2 or 3 doses of 9vHPV vaccine in U.S. female individuals 15 to 26 years of age. *NEJM Evid*. 2024;3(2):EVIDoa2300194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38320488.

Immunizations for Preventable Diseases in Adults and Adolescents With HIV

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Overview

The Advisory Committee on Immunization Practices (ACIP) recommends immunizing people with HIV similarly to the general population, with a few key exceptions.

- The following live virus vaccines **are contraindicated** in people with HIV:
  - For CD4 T lymphocyte (CD4) cell count <200 cells/mm^3:
    - Measles
    - Mumps
    - Rubella
    - Varicella (VAR)
    - Live attenuated typhoid Ty21a
    - Yellow fever
  - For any CD4 counts:
    - Live attenuated influenza vaccine (LAIV)
    - Live attenuated smallpox vaccine (ACAM2000)
- The following vaccines have specific recommendations related to HIV status:
  - COVID-19
  - Hepatitis A (HAV)
  - Hepatitis B (HBV)
  - Meningococcus serogroup A, C, W, Y (MenACWY)
  - Pneumococcal vaccines
  - Human papillomavirus

The National Institutes of Health/Infectious Diseases Society of America/HIV Medicine Association recommendations described here may differ from ACIP recommendations when the committees interpret data differently or when one guideline has been updated more recently than the other. Please see the Recommended Adult Immunization Schedule by Medical Condition and Other Indications table and Recommended Immunization Schedule for Adults and Adolescents With HIV figure at the end of this chapter for a full overview of vaccines for adults with HIV, including standard vaccines recommended for all individuals.

Specific Immunizations

COVID-19 Vaccine

Available Vaccines

- mRNA vaccines (Spikevax, Moderna; Comirnaty, Pfizer-BioNTech)
- Adjuvanted protein subunit vaccine (Novavax)

Summary of Recommendations

- For adults and children >5 years of age with HIV, administer a dose of the updated COVID-19 vaccine (once available) regardless of their CD4 count or HIV viral load **(AII).**
- Individuals with advanced or untreated HIV are considered moderately or severely immunocompromised and may receive one additional dose at least 8 weeks after the last COVID-19 vaccine dose **(AIII).**
    - Note: Advanced HIV is defined as people with CD4 count <200 cells/mm^3, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV.
- For current COVID-19 vaccination recommendations, please visit the Centers for Disease Control and Prevention (CDC) website on the Use of COVID-19 Vaccines in the United States.

Evidence Summary

Worse outcomes for people with HIV and COVID-19, including high COVID-19 mortality rates, have been reported in cohort studies from the United States, the United Kingdom, and South Africa.[1-8] HIV was independently associated with an increased risk of severe and critical COVID-19 in a large trial from the World Health Organization's Global Clinical Platform, which included data from 38 countries.[9] In a multicenter cohort study of 286 people with HIV and COVID-19 in the United States, a lower CD4 count (i.e., <200 cells/mm^3) was associated with a higher risk for the composite endpoint of intensive care unit admission, invasive mechanical ventilation, or death. This increased risk was observed even in patients who had achieved virologic suppression of HIV.[6] Similarly, a multisite clinical cohort of people with HIV in clinical care in the United States showed an association between lower current (<350 cells/mm^3) and nadir (<200 cells/mm^3) CD4 counts and risk of hospitalization, intubation, or death, without an association between viral load suppression and COVID-19 disease severity.[10]

Most people with HIV develop antibody responses to vaccination comparable to those measured in people without HIV.[11-16] However, responses may be lower and antibody titers decline faster, particularly for individuals[13-15] with CD4 counts <200 cells/mm^3. Rates of breakthrough infections after vaccination are higher among individuals with HIV, with vaccine efficacy declining sooner than in HIV-negative matched cohorts.[17-19] Breakthrough infections showed no association with viral load suppression, though fewer breakthroughs[17] were seen in individuals with CD4 counts ≥500 cells/mm^3. Vaccine efficacy against more severe outcomes (e.g., hospitalization, intensive care unit admission, death) has been more robust than protection against infection or mild disease.[20]

For individuals with advanced or untreated HIV, the lower seroresponse rates and reduced vaccine effectiveness compared with individuals without immunocompromise support recommendations for additional booster doses.[21]

Three COVID-19 vaccines are available in the United States: two mRNA formulations (Moderna and Pfizer) and one adjuvanted recombinant protein (Novavax). Since 2023, the original vaccines are no longer authorized and have been replaced with updated versions that better match circulating variants. Primary and booster vaccines have been harmonized to a single strain, and annual assessments are anticipated to update vaccine composition and scheduling recommendations.[22]

All adults and adolescents, regardless of their CD4 count or HIV viral load, should receive a dose of the newest updated COVID-19 vaccine when available (at least 4–8 weeks after last dose).[21,23] Those with severe immunosuppression may have a diminished immune response to the vaccine and therefore may receive one additional dose at least 8 weeks after the last COVID-19 vaccine dose. For current COVID-19 vaccination recommendations, please visit the CDC website on the Use of COVID-19 Vaccines in the United States.

Hepatitis A Vaccine

See the "Hepatitis A Virus (HAV)" section in the table below for detailed guidance on immunization against HAV.

Available Vaccines

- Single-antigen inactivated hepatitis A vaccines
  - HepA (Havrix, GSK)
  - HepA (Vaqta, Merck)
- Combination inactivated hepatitis A vaccine and recombinant hepatitis B vaccine
  - HepA-HepB (Twinrix, GSK)

Summary of Recommendations

For Vaccination

- Administer a two-dose series (dosing interval depends on the vaccine used: at 0 and 6–12 months for Havrix **[AII]** or 0 and 6–18 months for Vaqta **[AIII]**) of single-antigen hepatitis A vaccine (HepA) or a three-dose series (0, 1, and 6 months) of the combined hepatitis A and hepatitis B vaccine (HepA-HepB, Twinrix) to any person without evidence of immunity to HAV (and for the combined vaccine, without evidence of immunity to HAV or HBV) **(AII).**
- For travelers, some clinicians recommend a four-dose accelerated regimen (0, 7, 21–30 days, and 12 months) of HepA-HepB **(BII).**
- For people with HIV and CD4 count ≥200 cells/mm^3, assess antibody response 1 to 2 months after completion of the series. If negative, a third dose may be administered **(BIII).**
- People with HIV with CD4 count <200 cells/mm^3 who have ongoing risk for HAV should be immunized at entry to care and assessed for antibody response 1 to 2 months after completion of the series. If negative, revaccinate when their CD4 count is >200 cells/mm^3 **(BIII).**

- For people with HIV with CD4 count <200 cells/mm^3 who do not have ongoing risk for HAV, waiting for a CD4 count >200 cells/mm^3 prior to immunization is an option **(BIII).**
- One study showed lower seroresponse to HAV when coadministered with pneumococcal conjugate vaccine. For patients who need both, clinicians may choose to separate by 1 month (**CIII).**[24]

For Pre-Exposure Prophylaxis (Travel)

- For people with HIV who are nonimmune and traveling within 2 weeks to countries with endemic HAV, consider administering immunoglobulin G (IgG) 0.1 mL/kg if duration of travel is <1 month. If duration of travel is 1 to 2 months, administer IgG 0.2 mL/kg. If duration of travel is ≥2 months, IgG 0.2 mL/kg should be repeated every 2 months.

For Post-Exposure Prophylaxis

- For people with HIV who are nonimmune, administer HAV vaccine and IgG 0.1 mL/kg simultaneously in different anatomical sites as soon as possible, ideally within 2 weeks of exposure. Complete the HAV vaccine series following the dosing intervals for the selected vaccine.

Hepatitis B Vaccine

See the "Preventing Disease" section in Hepatitis B Virus (HBV) Infection for detailed guidance on immunization against HBV, as well as the evidence summary.

Available Vaccines

- Recombinant hepatitis B vaccine, CpG-adjuvanted
  - HepBCpG (Heplisav-B, Dynavax)
- Recombinant hepatitis B vaccines (conventional monovalent)
  - HepB (Engerix-B, GSK)
  - HepB (Recombivax HB, Merck)
- Combination inactivated hepatitis A and recombinant hepatitis B recombinant vaccine
  - HepA-HepB (Twinrix, GSK)

Summary of Recommendations

For Vaccination

- Indications for Hepatitis B Vaccination
  - People without chronic HBV infection and without immunity to HBV infection (negative for hepatitis B surface antigen, hepatitis B core antibody [anti-HBc], and hepatitis B surface antibody [anti-HBs]) **(AII).**
  - Although vaccine response is better in people with CD4 count >350 cells/mm^3, vaccination should not be deferred in people with a lower CD4 count who are at increased risk of

acquiring HBV infection, because some people with CD4 <350 cells/mm^3 do respond to vaccination **(AII).**

- Preferred
  - Heplisav-B intramuscularly (IM) at 0 and 4 weeks **(AII)**
- Alternative (if HepBCpG [Heplisav-B] is unavailable)
  - Engerix-B 40 mcg (two simultaneous injections of 20 mcg each) at 0, 1, and 6 months (these doses are considered a "double-dose," three-dose series) **(AII);** *or*
  - Recombivax HB 20 mcg (two injections of 10 mcg each) at 0, 1, and 6 months (these doses are considered a "double-dose," three-dose series) **(AII);** *or*
  - Twinrix combined HepA and HepB vaccine (1 mL IM) as a three-dose series (at 0, 1, and 6 months) **(AII)**
- Vaccination Schedule for Prior Non-Responders (Anti-HBs <10 mIU/ml) 1 Month After Complete Vaccine Series
  - If prior Engerix-B or Recombivax HB vaccination failed, administer HepBCpG (Heplisav-B) IM at 0 and 4 weeks **(AI),** with consideration for a third dose of HepBCpG at 24 weeks **(BIII).**
  - If prior two-dose HepBCpG (Heplisav-B) vaccination failed, there are no data but clinicians can consider a third dose of HepBCpG (Heplisav-B) IM at 24 weeks after first dose **(BIII).**
- Assess for Vaccine Response
  - Anti-HBs should be obtained 4 weeks after completion of the vaccine series to document response to HepB vaccination, defined as anti-HBs ≥10 mIU/ml **(AII).**
- Vaccination Schedule for People With Isolated Anti-HBc
  - One standard dose of any Hepatitis B vaccine followed by testing for quantitative anti-HBs 1 to 2 months post-dose
    - If the titer is >100 mIU/mL, no further vaccination is needed.*
    - If the titer is ≤100 mIU/mL, a complete series of hepatitis B vaccine should be completed (see above for Vaccination Schedule), followed by repeat anti-HBs testing **(BII).**
    - If an anti-HBs quantitative titer is not available, then a complete hepatitis B vaccine series is recommended, followed by qualitative anti-HBs testing **(BII).**

    ***** See text in the Hepatitis B Virus (HBV) Infection regarding rationale for >100 mIU/mL.

For Post-Exposure Prophylaxis

- For people who have been exposed and were vaccinated previously with a complete HepB vaccine series and have documented antibody response, no additional vaccine is needed.
- For people who have been exposed and who received a complete HepB vaccine series without documentation of antibody response, administer a single dose of HepB vaccine.
- For people who have been exposed and have not received any HepB vaccine or have not received a complete HepB vaccine series, administer or complete an HepB vaccine series and administer one dose of hepatitis B immune globulin at a separate anatomical site as soon as possible after

exposure (ideally within 24 hours, but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure).

Human Papillomavirus Vaccine

See the "HPV Vaccine" section in Human Papillomavirus (HPV) Disease for detailed guidance on immunization against human papillomavirus (HPV), as well as the evidence summary.

Available Vaccine

- 9-valent inactivated recombinant vaccine (Gardasil 9, Merck)

Summary of Recommendations

- Routine HPV vaccination is recommended for people with HIV. Ideally, the series should be initiated at age 11 or 12 years but may be started as early as age 9 years. For all people with HIV who are aged 13 to 26 years and who were not vaccinated previously, regardless of sex, administer three doses of the recombinant HPV nonavalent vaccine (Gardasil 9) at 0, 1 to 2, and 6 months **(AIII).** The two-dose series **is not recommended** for people with HIV.
- Shared clinical decision-making regarding HPV vaccination is recommended for people with HIV who are aged 27 to 45 years and who were not adequately vaccinated previously **(AIII).**
- At present, vaccination with commercially available HPV vaccine **is not recommended** during pregnancy **(CIII).** However, in post-hoc analyses of clinical trials and population-based studies, HPV vaccines have not been linked to adverse pregnancy outcomes.[25-28]
- For people who have completed a vaccination series with the recombinant HPV bivalent or quadrivalent vaccine, some experts would consider additional vaccination with recombinant HPV nonavalent vaccine, but data are lacking for defining the efficacy and cost-effectiveness of this approach **(CIII).**

Influenza Vaccine

Available Vaccines*

- Inactivated Influenza vaccine (IIV3) (standard-dose, egg-based vaccine)
  - Afluria (Seqirus)
  - Fluarix (GSK)
  - FluLaval (GSK)
  - Fluzone (Sanofi Pasteur)
- ccIIV3 (standard-dose, cell culture–based vaccine)
  - Flucelvax (Seqirus)
- HD-IIV3 (high-dose, egg-based vaccine)
  - Fluzone High-Dose (Sanofi Pasteur)

- aIIV3 (standard-dose, egg-based vaccine with MF59 adjuvant)
  - Fluad (Seqirus)
- RIV3 (recombinant hemagglutinin [HA] vaccine)
  - Flublok (Sanofi Pasteur)
- LAIV3 (live attenuated, egg-based vaccine)
  - FluMist (AstraZeneca)

* Vaccine formulations are updated yearly to reflect circulating strains.

Summary of Recommendations

- For all adults and adolescents with HIV, administer age-appropriate inactivated influenza vaccine or recombinant influenza vaccine annually **(AI).**
- For pregnant women with HIV, administer inactivated influenza or recombinant vaccine at any time during pregnancy **(AI).**
- LAIV administered via nasal spray **is contraindicated** in people with HIV **(AIII).**
- High-dose, recombinant, and adjuvanted influenza vaccines are recommended for people with HIV aged 65 years or older over standard-dose unadjuvanted inactivated vaccines **(AII).**[29]

Evidence Summary

Influenza is a common respiratory disease in adults and adolescents. Annual epidemics of seasonal influenza typically occur in the United States between October and April. Influenza A and B are most frequently implicated in human epidemics. Influenza A viruses are categorized into subtypes based on characterization of two surface antigens: HA and neuraminidase (NA). Although vaccine-induced immunity to the surface antigens HA and NA reduces the likelihood of infection,[30,31] the frequent emergence of antigenic variants through antigenic drift[32] (i.e., point mutations and recombination events within a subtype) is the virologic basis for seasonal epidemics and necessitates revaccination each season.[33]

Some studies of influenza have noted higher hospitalization rates[34-37] and increased mortality[37,38] among people with HIV; however, these findings have not been observed in all settings.[39] Increased morbidity may be greatest for people with HIV not on antiretroviral (ARV) drugs or with advanced disease. People with HIV are at high risk of serious influenza-related complications. For more information, see the CDC's website on Flu and People Living With HIV.

In general, people with HIV with minimal AIDS-related symptoms and normal or near-normal CD4 counts who receive inactivated influenza vaccine (IIV) develop adequate antibody responses.[40-42] Among people with a low CD4 count or who have advanced HIV disease, IIV might not induce protective antibody titers.[42-44] In one study, markers of inflammation in older people (≥60 years) with HIV were associated with lower post-vaccination influenza antibody titers.[45] In people with HIV, a second dose of vaccine does not improve immune response,[43,46] and intradermal influenza vaccine dosing did not improve the immune response compared with intramuscular dosing.[47]

Influenza vaccines are trivalent (two A components and one B component) with formulations that change from season to season. Two clinical studies have evaluated influenza vaccine efficacy in people with HIV. In an investigation of an influenza A outbreak at a residential facility for people with HIV,[34] vaccination was most effective at preventing influenza-like illness among people with a CD4 count >100 cells/mm^3 and among those with HIV RNA <30,000 copies/mL. In a randomized placebo-controlled trial conducted in South Africa among 506 people with HIV, including 349 people on ARV treatment and 157 who were ARV treatment naive, efficacy of trivalent IIV for prevention of culture- or reverse transcription–polymerase chain reaction–confirmed influenza illness was 75% (95% confidence interval, 9% to 96%).[48]

Several clinical studies also have evaluated the immunogenicity of influenza vaccine in people with HIV. In a randomized study[49] comparing the immunogenicity of high-dose (60 mcg of antigen per strain) versus standard-dose (15 mcg of antigen per strain) trivalent IIV among 195 adults with HIV aged ≥18 years (10% of whom had a CD4 count <200 cells/mm^3), seroprotection rates were higher in the high-dose group for influenza A (96% vs. 87%; $P = 0.029$) and influenza B (91% vs. 80%; $P = 0.030$). However, in a comparative study of 41 children and young adults with HIV, high-dose trivalent IIV was no more immunogenic than the standard dose among the recipients with HIV.[50]

Although booster doses can make the influenza vaccine more effective, that benefit is limited to specific groups, such as solid-organ transplant recipients.[51] One study in people with HIV assessed the effectiveness of a two-dose regimen of IIV and found that the second dose of vaccine did not significantly increase the frequency or magnitude of antibody responses.[46] Based on this study, influenza booster immunizations **are not recommended** for people with HIV.

Optimally, influenza vaccination should occur before onset of influenza activity in the community because it takes about 2 weeks after vaccination for protective antibodies to develop.[29] Health care providers should offer vaccination by the end of October if possible, and vaccination should continue to be offered as long as influenza viruses are circulating. Information on currently available influenza vaccines is obtainable through the CDC's recommendations on the 2024–2025 influenza season. For adults aged ≥65 years, high-dose IIV,[52] adjuvanted IIV,[53] or recombinant influenza vaccine[54] are preferentially recommended over standard-dose unadjuvanted vaccines based on data suggesting higher efficacy in preventing invasive pneumococcal disease (IPD) in this age group.[55]

Although a LAIV is available, it **is contraindicated** for people with HIV because of the paucity of safety data and the availability of alternative vaccines.[56] Although unintentional administration of LAIV to adults with HIV has been well tolerated,[57] **it is not recommended** for people with HIV.

IIVs can be administered to people receiving influenza antiviral drugs for treatment or chemoprophylaxis. Concurrent administration of influenza vaccine does not interfere with the immune response to other inactivated vaccines or to live vaccines.

Measles, Mumps, and Rubella Vaccine

Available Vaccines

- Live attenuated measles, mumps, and rubella (MMR) combination vaccine
  - M-M-R II (Merck)
  - Priorix (GSK)

Summary of Recommendations

For Vaccination

- Administer two doses of MMR vaccine at least 1 month apart to people with a CD4 count ≥200 cells/mm^3 and who have no evidence of immunity to MMR (evidence of immunity is defined as: patient was born before 1957 and/or had documentation of receipt of MMR vaccine and/or has laboratory evidence of immunity or disease) **(AIII).**
- The MMR vaccine **is not recommended** during pregnancy.
- Women of childbearing potential who get the MMR vaccine should wait 4 weeks before getting pregnant.
- For pregnant women without immunity to rubella, **delay immunization until after pregnancy,** and then administer two doses of the MMR vaccine at least 1 month apart if the CD4 count is ≥200 cells/mm^3 and on combination antiretroviral therapy (ART) **(AIII).**
- If no serologic evidence of immunity exists after two doses of MMR vaccine, consider repeating the two-dose MMR vaccine series, especially if the person is vaccinated while not virologically suppressed **(CIII).**
- **Do not administer** MMR vaccine to people with HIV with CD4 count <200 cells/mm^3 or uncontrolled HIV (not on ART or virologic failure) **(AIII).**

For Post-Exposure Prophylaxis

- For measles exposure of nonimmune individuals with CD4 count ≥200 cells/mm^3, administer the MMR vaccine within 72 hours of exposure **or** immunoglobulin (IG) within 6 days of exposure. Do not administer the MMR vaccine and IG simultaneously.
- For measles exposure of nonimmune individuals with CD4 count <200 cells/mm^3 or who are pregnant, administer IG within 6 days of exposure.

Evidence Summary

Measles is a highly contagious and potentially life-threatening disease. Measles is particularly virulent in the immunocompromised host, with a reported mortality rate as high as 40% in people with advanced HIV.[58] Worldwide, the incidence of measles has continued to rise, with several ongoing outbreaks. The World Health Organization reported that its European region experienced greater than 30,000 cases in 2022, up from fewer than 1,000 in 2021, and 51 countries had large disruptive outbreaks in 2023. The increase in cases is largely attributable to decreased rates of vaccination. Current information regarding outbreaks can be found on the CDC website Measles Cases and Outbreaks.[59]

With a resurgence of measles both domestically[60] and globally,[61] people with HIV should be assessed for immunity or prior vaccination. Acceptable evidence of immunity includes being born before 1957, documented evidence of two doses of the MMR vaccine, or presence of positive antibody titers.

Several studies from the 1990s found that 90% to 95% of adults with HIV were immune to measles.[62-64] In these studies, serostatus did not vary by CD4 count, suggesting that people with HIV

retained protective immunity even in the context of advanced disease. However, in a more recent study, the measles seroprevalence rate was 70.3%. Similarly, people with HIV appear to retain immunity to mumps and rubella even after acquisition of HIV.[65]

Individuals who do not fulfill any criteria for immunity and have CD4 counts ≥200 cells/mm^3 should receive two doses of MMR vaccine separated by at least 28 days. The combination measles, mumps, rubella, and varicella (MMRV) vaccine has not been studied in immunocompromised hosts and should **not be administered** to people with HIV.

The MMR vaccine **is contraindicated** for people with HIV with CD4 counts <200 cells/mm^3 because the MMR vaccine is a live attenuated formulation that has been linked to fatal cases of measles-associated pneumonitis following administration to people with HIV with a low CD4 count.[66,67] For people with HIV with CD4 count ≥200 cells/mm^3, the vaccine has been shown to be safe, although antibody response may be lower than for patients without HIV.[65,68,69] The MMR vaccine is also contraindicated for people with other immunocompromised conditions.

For more detailed information regarding post-exposure prophylaxis, please see the CDC webpage Measles (Rubeola).

Meningococcal Vaccine

Available Vaccines

- Quadrivalent meningococcal conjugate vaccine (MenACWY)
  - Menveo (GSK)
  - MenQuadfi (Sanofi Pasteur)
- Recombinant meningococcal group B vaccine (MenB)
  - Bexsero (GSK)
  - Trumenba (Pfizer)
- Pentavalent meningococcal vaccine (MenABCWY; combines conjugated MenACWY with recombinant MenB)
  - Penbraya (Pfizer)
  - Penmenvy (GSK)

Summary of Recommendations

- Administer two doses of quadrivalent meningococcal conjugate vaccine (MenACWY) at least 8 weeks apart to adolescents and adults with HIV who have not been vaccinated previously **(AII).**
- For people with HIV who have been vaccinated previously, repeat vaccination every 5 years throughout life **(BIII).**

- Serogroup B meningococcal vaccination (MenB) is not routinely indicated for all people with HIV unless they have additional risks for meningococcal disease (e.g., complement component deficiency, asplenia, or receipt of a complement inhibitor) or are at risk during a serogroup B outbreak.
- Adolescents and young adults with HIV (aged 16–23 years) can be offered MenB vaccination with shared decision-making **(CIII).**[70]
- Adults may receive a single dose of pentavalent meningococcal conjugate vaccine (MenABCWY) as an alternative to separate administration of MenACWY and MenB when both vaccines would be given on the same clinic day **(BIII).**

Evidence Summary

Meningococcal meningitis, caused by *Neisseria meningitidis*, is the most common cause of bacterial meningitis among children and young adults in the United States. Surveillance data collected from 1998 to 2007 identified 2,262 cases of meningococcal disease from a sample of 13% of the U.S. population from several states. All available formulations of meningococcal vaccine are inactivated. Two quadrivalent MenACWY vaccines and two pentavalent MenABCWY meningococcal vaccines are currently licensed and available in the United States. The quadrivalent vaccines include (1) meningococcal groups A, C, W, and Y oligosaccharide diphtheria CRM197 conjugate vaccine (MenACWY-CRM, Menveo) and (2) meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT, MenQuadfi). The pentavalent vaccines include (1) a combination of MenACWY-TT plus meningococcal group B recombinant FHbp antigens (MenACWY-TT plus MenB-FHbp; Penbraya) and (2) MenACWY plus meningococcal group B four component recombinant protein vaccine (MenACWY plus MenB-4C; Penmenvy). Meningococcal groups ACWY polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D, Menactra) is no longer available. A two-dose series of quadrivalent meningococcal vaccination is recommended for all adolescents, with the first dose at age 11 or 12 years and a second dose at age 16 years. Adolescents and adults with HIV who have not had this primary meningococcal vaccination series should receive two doses of MenACWY vaccine at least 8 weeks apart **(AII).** Repeated MenACWY boosters are recommended every 5 years **(BIII).** MenACWY vaccines are licensed in the United States for one booster dose. Repeated boosters every 5 years is an off-label use but endorsed by ACIP.[71]

A growing body of evidence supports an increased risk of meningococcal disease in people with HIV. Studies have shown a fivefold to 24-fold increased risk of meningococcal disease in people with HIV compared with people without HIV[72-74]; low CD4 count and high HIV viral load are associated with increased risk.[75,76] From 2000 to 2011, the average annual incidence rate of invasive meningococcal disease was 0.39 cases per 100,000 people. People with HIV with a lower CD4 count are at higher risk of invasive disease.[75] Most meningococcal infections among people with HIV in the United States have been caused by serogroups C, W, or Y.[76] In addition, a cohort study found that uptake of the MenACWY vaccine among people with a new diagnosis of HIV infection was low, and time to receipt of first vaccination was long.[77]

The safety and immunogenicity of MenACWY-D vaccine have been evaluated only in people with HIV who are aged 11 to 24 years. Patients with CD4 percentage ≥15% received either one or two doses (at 0 and 24 weeks) of vaccine, and those with CD4 percentage <15% received two doses (at 0 and 24 weeks). Among people with HIV who received one dose of vaccine, 21% to 63% developed an antibody titer of ≥1:128 at 72 weeks after vaccination. Antibody responses at 72 weeks in

individuals with CD4 percentage <15% were less robust,[78] with only 6% to 28% achieving titers ≥1:128. Local site reactions—such as pain and tenderness at the injection site—were uncommon (3.1%), as were grade 3 or greater events (2.2%). No vaccine-related deaths or cases of meningitis were noted. No safety or immunogenicity studies are available for quadrivalent MenACWY-CRM vaccine or the pentavalent vaccine in people with HIV, and clinical outcome data for both vaccines in people with HIV are lacking, as well.

MenB is not routinely indicated for all people with HIV unless they have additional risks for meningococcal disease. Adolescents and young adults (aged 16–23 years) with HIV can be offered MenB vaccination with shared decision-making **(CIII).**[70] MenB vaccine provides short-term protection against most strains of serogroup B meningococcal disease and has been used for patients at increased risk (e.g., those living in dormitories or barracks) and during outbreaks. People with functional or anatomic asplenia (including sickle cell disease), with persistent complement component deficiency, or using a complement inhibitor (e.g., eculizumab, ravulizumab) should receive MenB vaccination.[71] Two MenB vaccines are available: MenB-4C (Bexsero) and MenB-FHbp (Trumenba). People with HIV should receive the three-dose series for MenB, given at 0, 1–2, and 6 months, rather than the two-dose option recommended for healthy adolescents and young adults. MenB-FHbp consists of two purified recombinant lipidated FHbp antigens. MenB-4C consists of three recombinant proteins in addition to outer membrane vesicles that contain outer membrane protein porin A. MenB vaccines are not interchangeable; the same product must be used for all doses in the series. A MenB vaccine booster may be indicated if a person previously vaccinated is identified as being at increased risk during a MenB outbreak. In this situation, a single dose of the same vaccine is recommended ≥1 year after the MenB primary series completion and every 2 to 3 years thereafter.

Urban outbreaks of meningococcal meningitis have been reported in the United States among men both with and without HIV who have sex with men. Several outbreaks were associated with clubs and bathhouses. Some public health jurisdictions now recommend meningococcal vaccine for all men who have sex with men, regardless of HIV status; however, ACIP has not adopted this recommendation for men without HIV who have sex with men.[79]

During pregnancy and when lactating, women with HIV should receive MenACWY vaccine if indicated **(AIII).** No safety signals related to maternal and neonatal adverse events (including spontaneous abortion and birth defects) with MenACWY vaccine are evident in clinical trials or post-licensure surveillance.[80-84] Because only limited data are available for MenB vaccination during pregnancy, vaccination with MenB should be deferred unless the pregnant woman is at increased risk and, after consultation with their health care provider, the benefits of vaccination are considered to outweigh the potential risks **(CIII).**[71]

Mpox Vaccine

Available Vaccines

- Live nonreplicating smallpox and mpox vaccine
  - JYNNEOS (Bavarian Nordic)

Summary of Recommendations

For Vaccination

- Indications
  - Regardless of CD4 count, all people with HIV and no prior mpox infection should be offered mpox vaccination if they have or anticipate potential exposure to mpox, per CDC clinical considerations **(BII).**[85]
  - JYNNEOS should be provided to any other people with HIV who request vaccination **(CII).**
  - People who have received smallpox vaccination should receive mpox vaccination **(CIII).**
- Vaccine
  - Modified vaccinia Ankara-Bavarian Nordic (MVA-BN) vaccine, sold in the United States as JYNNEOS, is the preferred vaccine before mpox exposure for people with HIV because it uses a live attenuated, non-replicating virus **(AII).**
  - Administer JYNNEOS in two doses 28 days apart either 0.5 mL subcutaneously (SQ) or 0.1 mL intradermally (ID). SQ administration is preferred for people with a history of keloids and recommended for people aged <18 years.
  - In situations where the second dose was not administered during the recommended interval, administer a second dose as soon as possible **(CIII).** Restarting or adding doses to the series when an extended interval between doses occurs is not necessary **(CIII).**
  - At this time, booster doses, including for people with prior mpox or who were vaccinated at CD4 counts <200 cells/mm^3, are **not recommended (CIII).**
  - Administration of the smallpox vaccine (ACAM2000, a live replicating vaccinia vaccine) to people with HIV **is contraindicated (AII).**
  - Available human data on JYNNEOS administered to pregnant women are limited, and the risks and benefits of JYNNEOS should be discussed with the patient using shared decision-making **(CIII).**
  - If mpox vaccination is sought during pregnancy or while breastfeeding, administer JYNNEOS because it contains nonreplicating virus **(AII).**

For Post-Exposure Prophylaxis

- Indications
  - Post-exposure vaccination is recommended for all unvaccinated people with HIV who experience a known or presumed exposure **(BII).**
  - Post-exposure vaccination is recommended as soon as possible, ideally within 4 days after exposure; however, administration 4 to 14 days after exposure may still provide some protection against mpox and should be offered **(BII).**
- Vaccine
  - JYNNEOS is the preferred vaccine before mpox exposure for people with HIV because it uses a live attenuated, nonreplicating virus **(AII).**

- Administer JYNNEOS in two doses 28 days apart either 0.5 mL SQ or 0.1 mL ID. SQ administration is preferred for people with a history of keloids and recommended for people aged <18 years.
- When there is adequate supply of JYNNEOS, clinicians may preferentially administer via SQ route. Local side effects may be less severe with SQ administration than with ID administration.
- People who have received smallpox vaccination should still receive mpox post-exposure vaccination **(CIII).**

Evidence Summary

Mpox (formerly monkeypox) is a zoonotic viral disease caused by monkeypox virus (MPXV) that belongs to the *Orthopoxvirus* genus of the Poxviridae family, which also includes the causative agent of smallpox. Two main clades of MPXV have been described in different geographic regions of Africa; clade I (previously called Congo Basin clade) was classically associated with more severe disease and more human-to-human transmission than clade II (previously called West African clade).[86-88]

Vaccination is the principal biomedical means of preventing mpox, regardless of clade. Vaccines active against clade II mpox are expected to be equally active against clade I. Indications for mpox vaccination are the same for people with and without HIV. Mpox vaccination should be offered to all people with HIV who have not had prior mpox and who have or anticipate potential exposure to mpox, regardless of CD4 count.[85]

People with HIV who are eligible for vaccination against mpox should receive MVA-BN vaccines **(AII).** These are live attenuated, nonreplicating viral vaccines sold as JYNNEOS in the United States and as IMVANEX or IMVAMUNE elsewhere. JYNNEOS consists of two doses given 4 weeks (28 days) apart. The CDC's interim clinical considerations for mpox vaccination recommend either SQ or ID vaccine administration; both routes of administration have been shown to be similarly effective.[89] SQ administration of JYNNEOS is preferred for people with a history of keloids and recommended for people aged <18 years.

JYNNEOS has been demonstrated to be both safe for people with HIV and equally immunogenic compared with people without HIV.[90-92] Several studies indicate that JYNNEOS is effective against mpox.[93-98] Matched case control study data indicate that vaccine effectiveness against symptomatic infection ranges from 36% to 75% after one dose to 66% to 89% after two doses.[94,97,98]

However, these studies were limited to virologically suppressed people with CD4 counts ≥100 cells/mm^3. Studies to date have had insufficient data to assess the effectiveness of JYNNEOS against mpox stratified by CD4 count, although one study reported high effectiveness regardless of CD4 count.[99] Immunogenicity among people with HIV who are not virologically suppressed or who have lower CD4 counts remains unknown.

The durability of immunity after mpox vaccination is unknown, including among people with HIV. Serological studies have shown declining antibody titers post-vaccination. However, the roles of innate and cell-mediated immunity remain unclear, and immunologic correlates of protection have not yet been established.[100] Breakthrough infections are rare but have been documented after vaccination.[101] A global case study from nine countries described 29 individuals who experienced

mpox infections following completion of two appropriately spaced doses of JYNNEOS vaccine; of these individuals, eight had HIV and were virologically suppressed[102] with a median CD4 count of 555 cells/mm^3. Data collected from May 2022 to May 2024 during the clade II outbreak in the United States observed 271 cases (<1% of people vaccinated) occurring at disparate time intervals after vaccination; this low proportion of post-vaccination infections suggests that immunity is not waning to date.[103] In both reports, vaccine-breakthrough cases experienced less severe illness with fewer lesions. Hence, at this time, booster doses are **not recommended,** including for people who were vaccinated at CD4 counts <200 cells/mm^3 **(CIII).**

People with a prior history of mpox infection, including people with HIV, are not recommended to be vaccinated because mpox infection confers immunity **(CIII).**[85] No clinical correlates of immunity have yet been established to guide when additional vaccination might be needed following prior mpox infection. Although the durability of immunity is unknown, reinfection with mpox remains very rare. Observational data indicate that people with acquired immunity after initial infection tend to have a self-limited illness with a lower burden of lesions that can be managed in outpatient settings.[101,102] At this time, people who had mpox with moderate-to-severe immune suppression (CD4 <200 cells/mm^3) are also **not recommended (CIII)** to receive additional vaccinations after they achieve immune reconstitution on HIV treatment.

Available human data on JYNNEOS administered during pregnancy are insufficient to determine vaccine-associated risks. Animal studies of JYNNEOS have shown no evidence of harm to the developing fetus.[104] The risks and benefits of JYNNEOS should be discussed with the patient using shared decision-making **(CIII).** If vaccination is sought during pregnancy or breastfeeding, JYNNEOS should be used because it contains nonreplicating virus **(AII).** Vaccination with ACAM2000, which contains a replication-competent virus, **is contraindicated** during pregnancy or while breastfeeding due to risk of pregnancy loss, congenital defects, and vaccinia virus infection in fetuses and newborns and the availability of an alternative nonreplicating viral vaccine **(AII).**[105]

Pneumococcal Vaccine

Available Vaccines

- Pneumococcal conjugate vaccines (PCVs)
  - PCV15 (Vaxneuvance, Merck)
  - PCV20 (Prevnar 20, Pfizer)
  - PCV21 (Capvaxive, Merck)
- Pneumococcal polysaccharide vaccine (PPSV)
  - PPSV23 (Pneumovax, Merck)

Summary of Recommendations

Our recommendations are generally consistent with ACIP.[106] All people with HIV without history of pneumococcal vaccination or with unknown vaccine history should be vaccinated as follows:

- Administer PCV21, PCV20, or PCV15 **(AII).** After PCV21 or PCV20, no additional pneumococcal vaccine is currently recommended.

- In the expert opinion of the CAP Section Group of the Adult and Adolescent Opportunistic Infection Guidelines Panel, PCV21 is not recommended for adults with HIV if the prevalence of serotype 4 is over 30% in the region.[107] As of September 2024 high levels of serotype 4 have been reported in Alaska, Colorado, the Navajo Nation, New Mexico, and Oregon. In these locations, people with HIV should receive PCV20 or, if PCV20 is not available, PCV15 **(AIII).** This guidance will be reviewed and updated as pneumococcal disease epidemiology evolves and data from other geographic areas becomes available.

- If PCV15 is used, administer a dose of PPSV23 at least 8 weeks later **(AII).** No additional pneumococcal vaccine doses are recommended.
- For people with HIV who previously started or completed a pneumococcal vaccination series, there is no need to restart the series. Specific cases are as follows:
- Adults who have received both PCV13 and PPSV23:
  - Adults who received PPSV23 before the age of 65 can be administered PCV21 or PCV20 at least 5 years after the last pneumococcal vaccine dose
  - Adults who received PPSV23 at age 65 or older do not require further doses of PPSV23. Their pneumococcal vaccination can be considered complete.
    - Shared clinical decision-making is recommended regarding administration of PCV21 or PCV20 for immunocompromised persons aged ≥65 years who completed their vaccine series with both PCV13 and PPSV23. If a decision to administer PCV21 or PCV20 is made, it should be given at least 5 years after the last pneumococcal vaccine dose **(CIII).**
- Adults who previously received only PCV13 may receive one dose of PCV21 or PCV20 at least 1 year later **(BIII)**
- Adults who have only received PPSV23 may receive PCV21 or PCV20 (or PCV15 if the former are not available) at least 1 year after their last PPSV23 dose to complete their pneumococcal vaccination series **(BIII).**

Evidence Summary

Some observational studies have reported benefits of PPSV against IPD[108,109] (e.g., bacteremia, meningitis) and all-cause pneumonia[110-112] in people with HIV; however, results have been variable.[108,113-115] One randomized placebo-controlled trial of PPSV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia, and there was no evidence of reduced risk of IPD among vaccinated participants.[116] Follow-up of this cohort confirmed the increase in pneumonia in vaccinated participants but also showed a decrease in all-cause mortality, although participants in this study were not treated with ART.[117] A study[118] evaluating the impact of PCV13 vaccination on the rates of IPD in adults with HIV between 2008 and 2018 found that IPD rates remained high despite reductions with the introduction of PCV13. However, use of higher-valent conjugate vaccines may reduce IPD: 11.2% of cases of IPD consisted of additional serotypes contained in PCV15 but not PCV13, and 16.5% of cases of IPD consisted of serotypes in PCV20 but not in PCV15.

In 2021, PCV15 and PCV20 were licensed by the U.S. Food and Drug Administration (FDA) for use in adults[119] based on safety and immunogenicity data compared with data on PCV13 or PPSV23. Effectiveness data of these vaccines against pneumococcal disease or their durability in providing

immunoprotection in adults with HIV currently are not available. One Phase 3 clinical trial of PCV15 followed by PPSV23 8 weeks later in people with HIV demonstrated safety and immunogenicity of this approach.[120] No clinical data exist for the use of PCV20 in people with HIV.

In 2024, PCV21, which was developed specifically for adults, was approved in the United States. It includes the serotypes that are currently responsible for most cases of IPD in adults.[121] Overall, 77% to 85% of IPD cases in adults are due to serotypes in PCV21, compared with 54% to 62% in PCV20 and 60% to 67% in PPSV23. However, PCV21 does not include some serotypes contained in previously approved vaccines. One example is serotype 4, which is included in all other PCV formulations and in PPSV23; serotype 4 has recently reemerged in certain geographic areas (Alaska, Colorado, the Navajo Nation, New Mexico, and Oregon), causing outbreaks of pneumococcal disease, especially among people with certain risk factors that often are more common in people with HIV (e.g., homelessness, alcoholism, cigarette smoking, injection drug use, chronic lung disease).

Immune responses to PCV21 were evaluated among adults aged ≥18 years with HIV in one study. When recipients of PCV15 followed by PPSV23 8 weeks later were compared with recipients of PCV21 followed by placebo 8 weeks later, immunogenicity for shared serotypes was comparable, and PCV21 was immunogenic for unique serotypes.[122] There are currently no data on clinical effectiveness of PCV21 in people with HIV.

Recommendations for PCV and PPSV23 in people with HIV depend on their age, receipt of prior doses of pneumococcal vaccine, number of prior doses, and specific vaccines received. In addition, the region's prevalence of IPD (>30% of IPD cases) caused by serotype 4, patients' risk factors, and local health department recommendations need to be considered when deciding between PCV21 or PCV20 for vaccine-naive individuals. For people with HIV and CD4 counts >200 cells/mm^3, pneumococcal vaccination should not be delayed while awaiting a response to ART. For people with HIV who have a CD4 count <200 cells/mm^3, immunogenicity may be improved if pneumococcal vaccination is administered when the CD4 count increases to 200 cells/mm^3 or higher on ART. However, data are inconsistent. In some studies, immune responses have been shown to be decreased in response to PCV or to PPSV23 among people with HIV and lower CD4 counts (e.g., <200 or <350 cells/mm^3);[123,124] other studies have demonstrated no difference according to CD4 count at the time of vaccination or with delaying vaccinations until after 6 months of ART.[125-127] Thus, delaying administration of pneumococcal vaccines to optimize immune response in those with CD4 counts <200 cells/mm^3 must be considered against an increased risk of pneumococcal disease and IPD in this group and any potential barriers to retention in care.

Respiratory Syncytial Virus Vaccine

Available Vaccines

- Adjuvanted protein subunit vaccine (Arexvy, GSK)
- Bivalent protein subunit vaccine (Abrysvo, Pfizer)
- mRNA vaccine (mRESVIA, Moderna)

Summary of Recommendations

- Administration of a single respiratory syncytial virus (RSV) vaccine (Abrysvo, Arexvy, or mRESVIA) to all people with HIV aged ≥75 years is recommended **(CIII).**

- Administration of a single RSV vaccine for people ages 60 to 74 with HIV and CD4 count <200 cells/mm^3 or with comorbid chronic conditions that increase risk for severe RSV disease is recommended.
- For pregnant women with HIV, administration of a single RSV vaccine (Abrysvo) between 32 and 36 weeks gestation with seasonal administration during September through January in most of the continental United States is recommended **(CIII).**
- No booster doses are currently recommended (**CIII).**

Evidence Summary

RSV is a significant cause of lower respiratory tract infection and bronchiolitis worldwide in children aged <5 years and adults aged ≥60 years. RSV vaccine development began in the 1960s; however, early formaldehyde-inactivated RSV vaccines induced a life-threatening inflammatory response during subsequent natural RSV infection in infants.[128] Following an improved understanding of the structure of RSV, modern vaccine research has developed a myriad of safer approaches, including live attenuated, chimeric, vector-based, subunit proteins, nanoparticle, and nucleic acid vaccines.[129] Currently, at least 19 RSV vaccines are in clinical trials evaluating efficacy in pediatric, maternal, and adult populations.[130]

In May 2023, the FDA approved the first two RSV vaccines for adults aged ≥60 years: RSVPreF3 (Arexvy) and RSVpreF (Abrysvo). Both vaccines target the prefusion F protein on the viral surface.[131]

RSVPreF3 (Arexvy) is an AS01$_E$-adjuvanted RSV prefusion F protein–based vaccine, approved based on results of a large clinical trial comparing the candidate vaccine to placebo over a median follow-up of 6.7 months.[132] The study included 17,922 participants. People with HIV were excluded from the study. Relative to placebo, RSVPreF3 was efficacious in reducing RSV-related lower respiratory tract disease, severe lower respiratory tract disease, and acute respiratory infection by 83%, 94%, and 72%, respectively. Further, this vaccine was generally safe, with most adverse events being transient, mild to moderate, and related to local pain and fatigue. Rare inflammatory neurologic events were reported in three trial participants within 42 days of receipt of the RSVPreF3; all events occurred in trials without a placebo arm. These included one case of Guillain-Barré syndrome (GBS) and two cases of acute disseminated encephalomyelitis (ADEM). Both ADEM cases were based on symptoms and clinical findings, and one case was fatal.

RSVpreF (Abrysvo) is a bivalent RSV prefusion F protein–based vaccine that demonstrated efficacy in a large, randomized clinical trial with a mean follow-up of 7 months.[133] Immunocompromised patients were excluded from this trial. People with well-controlled HIV (viral load <50 copies/mL and CD4 counts >200 cells/mm^3 on ART) were eligible, but the number of people with HIV in the trial is not reported. Compared to placebo, RSVpreF reduced RSV-related lower respiratory tract illness with at least two signs or symptoms and with at least three signs or symptoms, by 67% and 86%, respectively. RSVpreF reduced RSV-associated acute respiratory illness by 62%. RSVpreF was relatively safe, with higher rates of local reactions in the vaccine (12%) versus placebo (7%), but rates of systemic events were similar. Rare inflammatory neurologic events were reported in three of 34,284 participants, including one case of GBS, one case of Miller Fisher syndrome (GBS variant), and one case of undifferentiated motor-sensory axonal polyneuropathy. A separate clinical trial evaluated maternal RSVpreF versus placebo to determine efficacy in reducing RSV-related illness in newborns and infants.[134] In interim analysis, RSVpreF was effective in reducing medically attended

severe RSV-associated lower respiratory tract illness in infants within 90 days after birth, and no safety concerns were identified. Pregnant women with HIV were excluded from this trial.

mRNA-1345 (mRESVIA) is an mRNA-based RSV vaccine encoding the stabilized RSV prefusion F glycoprotein. In a trial of more than 35,000 participants aged ≥60 years, the vaccine demonstrated greater than 80% efficacy against RSV-related lower respiratory tract disease.[135] Participants with HIV and CD4 count ≥350 cells/mm^3 and an undetectable HIV viral load within the past year were permitted to enroll in the trial. The vaccine was generally well tolerated, and no cases of ADEM or GBS were observed.

In June 2024, ACIP recommended that adults aged ≥75 years and adults aged 60 to 74 years with comorbid conditions that increase risk for severe RSV disease receive a single dose of an approved RSV vaccine. A full list of qualifying conditions can be found on the CDC's Clinical Overview of RSV webpage.[136] In September 2023, ACIP and the American College of Gynecology both recommended seasonal administration of one dose of RSV vaccine for pregnant women during weeks 32 through 36 of pregnancy, ideally at least 14 days before delivery.

In the absence of additional data regarding immunologic response, clinical efficacy, and safety in patients with HIV, these recommendations are aligned with the ACIP guidance for the general population. For people with HIV, offer a single RSV vaccine (Abrysvo, Arexvy, or mRESVIA) to individuals aged ≥75 years and those aged 60 to 74 years with qualifying comorbid conditions **(CIII).** Individuals aged 60 to 74 years with HIV and CD4 <200 cells/mm^3 are eligible for RSV vaccination, although the vaccines have not been studied in this population, and many clinicians may choose to wait for immune reconstitution prior to administering the vaccine **(CIII).** Optimally, vaccination should occur before the onset of the fall and winter RSV season.

For pregnant women with HIV, administer a single RSV vaccine (Abrysvo) between 32 to 36 weeks gestation with seasonal administration during September through January in most of the continental United States **(CIII).** The adjuvanted vaccine, Arexvy, and the mRNA vaccine, mRESVIA, have not been studied in pregnancy and should not be used as an alternative. In locations where the seasonality of RSV differs from the continental United States (e.g., tropical climates, the Southern hemisphere), providers should follow local guidance on timing of administration. Data regarding immunologic response to the vaccine and clinical outcomes are notably lacking in people with HIV.

Tetanus, Diphtheria, and Pertussis Vaccine

Available Vaccines

- Tdap: Tetanus, diphtheria, and pertussis
  - Adacel (Sanofi Pasteur)
  - Boostrix (GSK)
- Td: Tetanus and diphtheria
  - TENIVAC (Sanofi Pasteur)

Note: DTaP vaccines (diphtheria, tetanus, and pertussis) are only for babies and young children and therefore are not covered in these guidelines.

Summary of Recommendations

- Administer the combination tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) once if the person with HIV has not been vaccinated at age 11 or older, and then tetanus and diphtheria toxoids vaccine (Td) or Tdap every 10 years thereafter **(AII).**
- For pregnant women with HIV, administer one dose of Tdap during each pregnancy, preferably between 27 weeks and 36 weeks gestation **(AIII).**
- For adolescents and adults with HIV who have not received the primary vaccination series for tetanus, diphtheria, or pertussis, administer one dose of Tdap followed by one dose of Td or Tdap at least 4 weeks after Tdap, and another dose of Td or Tdap 6 months to 12 months after the last Td or Tdap. Tdap can be substituted for any Td dose and is always preferred as the first dose **(AIII).**

Evidence Summary

Antibody response to tetanus and diphtheria vaccination varies by CD4 count. For individuals with advanced HIV and a low CD4 count, immunologic response is attenuated for both tetanus and diphtheria when compared to HIV-uninfected controls.[137,138] For people with CD4 count >300 cells/mm^3, antibody response to tetanus vaccination is similar to the general population, whereas response to diphtheria remains diminished.[137-139] Limited data exist on the efficacy of pertussis vaccination in this population.

Two Tdap vaccines for individuals aged ≥10 years are available in the United States (Adacel and Boostrix). Both vaccines are inactivated and considered safe to administer at any CD4 count. People with HIV should receive vaccination for tetanus, diphtheria, and pertussis on the same schedule as individuals without HIV. All adults not previously vaccinated should receive a single dose of Tdap, followed by a Td or Tdap booster every 10 years.

Varicella Vaccine

See "Vaccination to Prevent Primary Infection (Varicella)" in the Varicella-Zoster Virus Disease section for detailed guidance on immunization against varicella, as well as the evidence summary.

Available Vaccines

- Live attenuated varicella vaccine
  - Varivax (Merck)

Summary of Recommendations

- People with HIV with any of the following have presumed immunity to varicella: receipt of two doses of varicella vaccine (Varivax or MMRV), diagnosis of varicella or herpes zoster (shingles) by a health care provider, or laboratory evidence of immunity or disease.
- For people with HIV who are varicella nonimmune with CD4 count ≥200 cells/mm^3, administer two doses of varicella vaccine (VAR) 4 to 8 weeks apart **(BIII).**
- VAR **is contraindicated** for people with HIV with CD4 count <200 cells/mm^3 **(AIII).**

- VAR **is not recommended** during pregnancy **(AIII).**

Herpes Zoster Vaccine

See "Vaccination to Prevent Reactivation Disease (Herpes Zoster)" in the Varicella-Zoster Virus Disease section for detailed guidance on immunization against zoster, as well as the evidence summary. Herpes zoster vaccine has not been studied for prevention against primary varicella infection.

Available Vaccines

- Recombinant adjuvanted zoster vaccine (RZV)
  - Shingrix (GSK)

Summary of Recommendations

- For people with HIV aged ≥18 years, administer two doses of RZV at 0 and 2 to 6 months **(AIII).**
- Consider delaying vaccination until the patient is virologically suppressed on ART **(CIII)** or until the CD4 count is ≥200 cells/mm^3 to ensure a robust vaccine response **(CIII).**
- People with HIV aged ≥18 years should receive RZV regardless of previous history of herpes zoster or previous receipt of zoster vaccine live (no longer available).
- Do not give RZV (Shingrix) during an acute episode of herpes zoster **(AIII).**
- RZV **is not recommended** during pregnancy **(AIII).**

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
COVID-19	All people regardless of CD4 count or viral load (AII)	People with HIV should receive a complete COVID-19 vaccine series regardless of their CD4 count or HIV viral load or their pregnancy or breastfeeding status (AIII). Information on current COVID-19 vaccination recommendations are available on CDC's COVID-19 Vaccines webpage.	People with advanced or untreated HIV are considered moderately or severely immunocompromised and may get a second dose of the updated vaccine at least 8 weeks after the first (AIII).	No difference in recommendations
Hepatitis A Virus (HAV)	HAV nonimmune (AIII)	Two-dose series of either single-antigen vaccine: • Havrix: 1.0 mL IM (0, 6–12 months) (AII); *or* • Vaqta: 1.0 mL IM (0, 6–18 months) (AIII) Alternative for individuals susceptible to both HAV and HBV: • Twinrix: 1.0 mL IM in three-dose series (0, 1, 6 months) (AII)	Assess total antibody response (IgG and IgM) 4 weeks after completion of the series, and if negative, revaccinate, preferably after the CD4 count is ≥200 cells/mm^3 (BIII). For travelers, some clinicians recommend— • Twinrix: four-dose series (0, 7, 21–30 days, 12 months) (BII) One study showed lower seroresponse to Hep A vaccine when co-administered with pneumococcal conjugate vaccine. For patients who need both, clinicians may choose to separate by 1 month.	No difference in recommendations
	Post-exposure prophylaxis	Administer HAV vaccine and HepA IgG (0.1 mg/kg) simultaneously in different anatomical sites as soon as possible within 2 weeks of exposure to HAV to people who are nonimmune. Complete the HAV vaccine series following the dosing intervals for the selected vaccine.		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Hepatitis B Virus (HBV)	HBV nonimmune and no active HBV (i.e., negative for HBsAg, anti-HBc, and anti-HBs)	Preferred: • Heplisav-B IM at 0 and 4 weeks (AII) Alternative (if Heplisav-B is unavailable): • Engerix-B (40 mcg): three-dose series (0, 1, 6 months) (AII); *or* • Recombivax HB (20 mcg): three-dose series (0, 1, 6 months) (AII); *or* • Twinrix 1.0 mL IM: three-dose series (0, 1, 6 months) (AII)	Anti-HBs should be obtained 4 weeks after completion of the vaccine series to document response to HepB vaccination, defined as anti-HBs ≥10 mIU/mL (AII). Vaccinate individuals with isolated anti-HBc with one standard dose of HepB (BII) and check anti-HBs titers 1–2 months afterward. If anti-HBs ≥100 mIU/mL, no further vaccination is needed, but if the titer is <100 mIU/mL, then vaccinate with a complete series of HepB (double dose) followed by anti-HBs testing (BII). If titers are not available, then give a complete vaccine series followed by anti-HBs testing (BII). If a significant delay occurs between doses, there is no need to restart the series. For travelers, some clinicians recommend an accelerated schedule: • Twinrix: four-dose series (0, 7, 21–30 days, 12 months) (BII).	ACIP does not recommend the use of double-dose Engerix-B or Recombivax HB high-dose for people with HIV. ACIP includes a four-dose series of Engerix-B 40 mcg at 0, 1, 2, and 6 months. This approach has not been demonstrated to be superior to a double-dose, three-dose series, so it is not included as a regimen in our guidelines.
	Vaccine nonresponder (if anti-HBs <10 mIU/mL after complete series)	If failed prior Engerix-B or Recombivax HB: • Heplisav-B IM at 0 and 4 weeks (AI) with consideration for third dose of HepBCpG at 24 weeks (BIII) If failed two-dose Heplisav-B, there are no data but can consider: • Third dose of Heplisav-B IM at 24 weeks after first dose (BIII)		
	Post-exposure prophylaxis	For exposed people who have been previously vaccinated with a complete series and have documented antibody response, no additional vaccine is needed.		

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
		For exposed people who have received complete series without documentation of antibody response, administer a single dose of HepB vaccine. For exposed people who have not received a vaccine or have not received the complete series, administer or complete the HepB vaccine series and administer a dose of HBIG at a separate anatomical site as soon as possible after exposure (ideally within 24 hours but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure).		
Human Papillomavirus (HPV)	Adults and adolescents through age 26 years	Recombinant 9-valent human papillomavirus vaccine (Gardasil 9): • 0.5 mL IM three-dose series (0, 1–2, and 6 months) (AIII)	If a significant delay occurs between doses, there is no need to restart the series. Some people with HIV ages 27–45 years may benefit from vaccination, and shared clinical decision-making between the provider and patient is recommended in these situations. Vaccination is not recommended during pregnancy (CIII). Delay until after pregnancy.	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Adults and adolescents who previously received bivalent or quadrivalent vaccine	For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, no recommendations exist for additional vaccinations; some experts would give an additional full series of recombinant 9-valent vaccine, but no data currently define who might benefit or how cost effective this approach might be (CIII).		
Influenza	All	One dose of age-appropriate IIV or RIV annually (AI) LAIV is contraindicated (AIII).	Influenza vaccines are trivalent, with formulations that change from season to season. Information on currently available influenza vaccines is available through the CDC's recommendations on the 2024–2025 influenza season. Adults aged ≥65 years are recommended to receive high-dose IIV (Fluzone High-Dose), RIV (Flublok), or adjuvanted IIV (FLUAD) over standard-dose unadjuvanted vaccine (AII). People aged ≥18 years also may use RIV (Flublok). For people with egg allergy, use IIV or RIV appropriate for age (if the allergy is more severe than hives, give the vaccine in a medical setting appropriate to manage severe allergic reaction). For pregnant women with HIV, administer IIV or RIV at any time during pregnancy (AI).	No difference in recommendations

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Measles, Mumps, and Rubella (MMR)	CD4 count ≥200 cells/mm^3 and no evidence of immunity to MMR	Two-dose series (0.5 mL SQ) of MMR vaccine at least 1 month apart (AIII) MMR vaccine **is contraindicated** if CD4 count <200 cells/mm^3 (AIII). MMR vaccine **is not recommended** during pregnancy.	Evidence of immunity to MMR vaccine • Birth date before 1957, *or* • Documentation of receipt of MMR vaccine, *or* • Laboratory evidence of immunity or disease for each pathogen For pregnant women without immunity to rubella, after pregnancy, administer two doses of MMR vaccine at least 1 month apart if CD4 count ≥200 cells/mm^3 and on ART (AIII).	No difference in recommendations
	Post-exposure prophylaxis	For measles, nonimmune individuals with CD4 count ≥200 cells mm^3, administer MMR vaccine within 72 hours of exposure **or** IG within 6 days of exposure. Do not administer MMR vaccine and IG simultaneously. For measles, nonimmune individuals with CD4 count <200 cells mm^3 or who are pregnant, administer IG within 6 days of exposure.		
Meningococcus Serogroup A, C, W, Y (MenACWY)	No prior polyvalent meningococcal vaccine	MenACWY vaccine (Menveo or MenQuadfi): • Two-dose series (0.5 mL IM) given at least 8 weeks apart (AII)	MenACWY vaccine is routinely recommended. During pregnancy and when lactating, women with HIV should receive MenACWY vaccine if indicated (AIII).	No difference in recommendations

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Prior MenACWY vaccination	Administer a booster dose of MenACWY vaccine every 5 years (BIII). MenABCWY vaccine should be used if MenACWY and MenB vaccines are both indicated (BIII).	MenACWY vaccines are interchangeable; the same vaccine product is recommended, but not required, for all doses.	
Meningococcus Serogroup B (MenB)	No prior MenB vaccine and increased risk for serogroup B meningococcal disease from a medical condition (e.g., complement component deficiency, asplenia, receipt of a complement inhibitor) or an outbreak	Administer either MenB vaccine (Bexsero or Trumenba) as a three-dose series (0.5 mL IM) at 0, 1–2, and 6 months (AIII) • If the second dose was administered ≥6 months after the first dose, a third dose is not needed. • If the third dose is administered <4 months after the second dose, the dose should be repeated ≥4 months after the last dose.	Bexsero and Trumenba are not interchangeable. MenB vaccination during pregnancy should be deferred (CIII).	No difference in recommendations
	Prior MenB vaccination (≥1 year) and at increased risk during an outbreak	Administer booster dose of same MenB vaccine (CIII).	Licensed in the United States only for a primary series. Administration of booster doses is considered off-label.	
	Adolescents and young adults with HIV (aged 16–23 years) can be offered MenB vaccination with shared decision-making.	Administer either MenB vaccine as a three-dose series (0.5 mL IM) administered at 0, 1–2, and 6 months (CIII).		

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Mpox	All people with HIV, regardless of CD4 count, with no prior mpox infection but who have or anticipate exposure to mpox per CDC clinical considerations (BII), or those who request vaccination (CII)	Administer a two-dose series of JYNNEOS given 28 days apart (AII): • 0.5 mL SQ (preferred for people with a history of keloids or aged <18 years), *or* • 0.1 mL ID (alternative) In situations where the second dose was not administered during the recommended interval, administer a second dose as soon as possible (CIII). Administration of live replicating vaccinia vaccines (iACAM2000) is contraindicated in people with HIV (AII).	JYNNEOS can be coadministered with most other vaccines. Adolescent and young adult men might consider a 4-week interval between receiving JYNNEOS vaccine and a COVID-19 vaccine because of potential risk for myocarditis and pericarditis (CIII). People who have received smallpox vaccination should receive mpox vaccination (CIII). Booster doses, including for people with prior mpox or who were vaccinated at CD4 counts <200 cells/mm^3, are not recommended (CIII). Data on JYNNEOS administered to pregnant women are limited; if mpox vaccination is indicated, the risks and benefits of JYNNEOS should be discussed using shared decision-making (CIII).	No difference in recommendations
	Post-exposure prophylaxis	For unvaccinated people with HIV who experience a known or presumed exposure (BII), administer complete JYNNEOS series (see above), with the first dose given ideally as soon as possible or within 4 to 14 days after exposure (BII).		

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Pneumococcal	No prior pneumococcal vaccine or unknown vaccination history	Administer one of the following: • PCV21 (Capvaxive) 0.5 mL IM x 1 (AII); *or* • PCV20 (Prevnar20): 0.5 mL IM x 1 (AII); *or* • PCV15 (Vaxneuvance): 0.5 mL IM × 1 followed at least 8 weeks later by PPSV23 (Pneumovax) 0.5 mL IM × 1 (AII).	PCV21 is not recommended for adults with HIV if local prevalence of serotype 4 is more than 30% (as of September 2024, high rates of serotype 4 have been reported in Alaska, Colorado, the Navajo Nation, New Mexico, and Oregon).	
	Previously received PCV13 and PPSV23	If <65 years when received dose of PPSV23: • Administer PCV21 *or* PCV20 0.5 mL IM x 1 at least 5 years after the last pneumococcal vaccine (CIII).	PPSV23 is no longer recommended as preferred booster dose for patients who previously started the vaccine series.	
		If ≥65 years when received dose of PPSV23: • No further doses of PPSV23 are required. • Shared decision-making is recommended regarding administration of PCV21 or PCV20 for adults aged ≥65 years who have completed both PCV13 and PPSV23. If PCV21 or PCV20 given, administer at least 5 years after last pneumococcal vaccine dose (CIII).		

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Previously received only PCV13	Administer PCV21 *or* PCV20 0.5 mL IM x 1 at least 1 year after PCV13 (BIII).	PPSV23 is no longer recommended as preferred booster dose for patients who previously started the vaccine series.	
	Previously received only PPSV23	Administer either of the following at least 1 year after last PPSV23 dose: • PCV21: 0.5 mL IM x1 (BIII); *or* • PCV20: 0.5 mL IM x 1 (BIII); *or* • PCV15: 0.5 mL IM x 1 (BIII)	PPSV23 is no longer recommended as preferred booster dose for patients who previously started the vaccine series.	
Respiratory Syncytial Virus (RSV)	Age ≥75 years	One dose 0.5 mL IM of RSV vaccine (Arexvy, Abrysvo, or mRESVIA) (CIII)	Limited data on efficacy and safety for people with HIV.	No difference in recommendations
	Age 60–74 years with a comorbid condition increasing the risk for severe RSV disease	One dose 0.5 mL IM of RSV vaccine (Arexvy, Abrysvo, or mRESVIA) (CIII)	Individuals aged 60–74 years with CD4 count <200 cells/mm^3 are eligible, but limited data exist on immune response. Some clinicians may elect to wait for immune reconstitution prior to vaccination (CIII).	
	Pregnant women between 32 and 36 weeks' gestation	One dose 0.5 mL IM of RSV vaccine (Abrysvo) (CIII)	Limited data exist on efficacy and safety for people with HIV. Seasonal administration recommended. RSV season in the continental United States is typically September–January but differs by year and geography.	

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
			Ideally, dose should be given at least 14 days prior to delivery.	
Tetanus, Diphtheria, and Pertussis	Not previously vaccinated	One dose 0.5 mL IM Tdap (Adacel or Boostrix), followed by one dose of Td or Tdap at least 4 weeks after Tdap and another dose of Td or Tdap 6 months to 12 months later, then give Td or Tdap every 10 years (AII)	Tdap can be substituted for any Td dose and is always preferred as the first dose.	No difference in recommendations
	Did not receive Tdap at age 11 years or older	One dose 0.5 mL IM Tdap (Adacel or Boostrix), then Td or Tdap every 10 years (AII)	If indicated, give Tdap regardless of when the last dose of Td was given.	
	Pregnancy	Give Tdap preferably in early part of gestational weeks 27–36 (AIII). One dose of Tdap is indicated for each pregnancy.	Give Td or Tdap booster every 10 years after Tdap.	
Varicella (Chickenpox)	CD4 count ≥200 cells/mm^3 with no evidence of immunity to varicella	Two-dose (0.5 mL SQ) series of VAR 4–8 weeks apart (BIII) Varivax **is contraindicated** if CD4 count <200 cells/mm^3 (AIII). Varivax **is not recommended** in pregnancy (AIII).	Evidence of immunity to varicella: • Documented receipt of two doses of Varivax or MMRV; *or* • Diagnosis of varicella or zoster by a health care provider; *or* • Laboratory evidence of immunity or disease If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended (AIII).	No difference in recommendations

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Zoster	Age ≥18 years, regardless of a past episode of herpes zoster or receipt of attenuated ZVL (Zostavax)	Two-dose (0.5 mL IM) series of RZV (Shingrix) IM 2–6 months apart (AIII). RZV is not recommended in pregnancy (AIII).	To maximize immunologic response to the vaccine, consider delaying vaccination until patient is virologically suppressed on ART (CIII) or wait for immune reconstitution in those who had a CD4 count <200 cells/mm^3 (CIII). Do not give RZV (Shingrix) during an acute episode of herpes zoster (AIII).	ACIP recommends RZV for adults aged ≥19 years who are or will be at risk for herpes zoster. (This difference in age selected by ACIP was made to align with the age range in the adult immunization schedule.)

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine Preventable Infection	Indication	Recommendations	Additional Comments	ACIP Recommendations
Immunizations for Travel				
Cholera	Not routinely recommended for most travelers (CIII). Age 18–64 years with CD4 count >200 cells/mm^3 and traveling to an area where cholera has been epidemic or endemic within the past year	Lyophilized CVD 103-HgR (Vaxchora) single oral dose at least 10 days prior to potential exposure (CIII)	Safety and efficacy have not been established in people with HIV. No adverse effects reported with older formulation of vaccine in people with HIV without an AIDS diagnosis.	No current recommendations for people with HIV
Typhoid	At risk of *Salmonella* serotype Typhi infection (e.g., through travel, intimate exposure to a chronic carrier, occupational exposure) Revaccination only if continued or renewed exposure to *Salmonella* serotype Typhi is expected.	One dose 0.5 mL (25 mcg) IM Vi capsular polysaccharide vaccine (Typhim Vi) via IM injection at least 1 week before exposure (AIII) Revaccinate every 2 years if risk remains (BIII). The live attenuated oral typhoid vaccine (Vivotif) is contraindicated in people with HIV (AIII).	Provide education on other preventive measures against foodborne illness in addition to typhoid vaccination (AIII). Safety of typhoid vaccination in pregnancy is unknown. Consider avoiding during pregnancy or, if necessary, give Vi capsular polysaccharide vaccine (AIII).	ACIP has no position on the use of typhoid vaccine in people with HIV except not to give immunocompromised people the oral live attenuated typhoid vaccine.
Yellow Fever (YF)	Age ≤59 years and at risk for YF virus acquisition (e.g., by traveling to or living in areas at risk based on season, location, activities, and duration)	If indicated, provide vaccination at least 10 days prior to expected exposure. Age <59 years and asymptomatic with CD4 count >500 cells/mm^3: One dose of YF vaccine; revaccinate in >10 years if risk remains (BIII).	Provide vaccination as an adjunct to other protective measures against mosquito bites. Pregnancy and age ≥60 years may increase risk of complications from YF vaccine administration.	No difference in recommendations

		Any age and asymptomatic with CD4 count 200–499 cells/mm^3: YF vaccine may be considered depending on risk (BIII). YF vaccine is contraindicated for people with CD4 count <200 cells/mm^3. This recommendation is based on a theoretic increased risk for encephalitis in this population (AII).	If international travel requirements rather than an increased risk for acquiring YF infection are the only reason to vaccinate people with HIV, excuse the person from vaccination and issue a medical waiver to fulfill health regulations. Closely monitor people with HIV who have received YF vaccine for evidence of adverse events.	
Polio	Not routinely recommended (AIII)			No difference in recommendations
	Those at higher risk for exposure to poliovirus—such as those traveling to countries where polio is endemic—can be vaccinated with inactivated polio vaccine (IPV) (CIII).	Three doses IPV 0.5 ml IM at 0 and 1–2 months, with third dose given 6–12 months after second dose (CIII)		
	Previously vaccinated with one to two doses of vaccine	Give remaining doses of vaccine at recommended intervals (CIII).		

Key: ACIP = Advisory Committee on Immunization Practices; anti-HAV = hepatitis A virus antibody; anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; HAV = hepatitis A virus; HBIG = hepatitis B immune globulin; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; HPV = human papillomavirus; ID = intradermal; IG = immunoglobulin; IgG = immunoglobulin G; IgM = immunoglobulin M; IIV = inactivated influenza vaccine; IM = intramuscular; IPV = inactivated polio vaccine; LAIV = live attenuated influenza vaccine; MenACWY = meningococcus serogroup A, C, W, Y; MenB = serogroup B meningococcal vaccination; MMR = measles, mumps, and rubella; MMRV = measles, mumps, rubella, and varicella; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV15 = 15-valent pneumococcal conjugate vaccine; PCV20 = 20-valent pneumococcal conjugate vaccine; PCV21 = 21-valent pneumococcal conjugate vaccine; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; RIV = recombinant influenza vaccine; RSV = respiratory syncytial virus; RZV = recombinant zoster vaccine; SQ = subcutaneous; Td = tetanus and diphtheria toxoids vaccine; Tdap = combination tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; VAR = varicella vaccine; YF = yellow fever; ZVL = zoster vaccine live

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Recommended Immunization Schedule for Adults and Adolescents With HIV

Vaccine	All People With HIV	Where Varies by Age	Where Varies by Pregnancy Status	Where Varies by CD4 Cell Count (cells/mm3)	
				<200	≥200
COVID-19	For current COVID-19 vaccination recommendations, please visit the CDC's COVID-19 Vaccines website.			Recommendations differ with advanced or untreated HIV infection	
Hepatitis A (HepA, HepA-HepB)	Two to three doses (varies by formulation)				
Hepatitis B (HepBCpG, HepB, HepA-HepB)	Two to three doses (varies by formulation and indication)				
Human Papillomavirus (HPV)		Three doses for ages 18–26 years Consider for ages 27–45 years with shared decision-making	Not recommended during pregnancy		
Influenza (Multiple Vaccines)	One dose annually				
Measles, Mumps, Rubella (MMR)			Not recommended during pregnancy	Contraindicated	Two doses if born after 1956 and no history of vaccination or positive antibody titer
Meningococcal A, C, W, Y Conjugate (MenACWY)	Three doses				
Meningococcal B (MenB)	Three doses		Not recommended during pregnancy		
Mpox (MVA-BN, Attenuated)	Two doses	Subcutaneous route preferred for people aged <18 years	Shared decision-making		
Pneumococcal Conjugate (PCV15, PCV20, PCV21)	One dose				
Pneumococcal Polysaccharide (PPSV23)	One dose (if conjugate vaccine was PCV-15)				
Respiratory Syncytial Virus (RSV)		One dose for people aged ≥75 years or those aged 60–74 years with a comorbid condition that increases risk for severe RSV disease	One dose between 32 and 36 weeks gestation		
Tetanus, Diphtheria, Pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years		Recommend booster with each pregnancy		
Varicella (VAR)			Not recommended in pregnancy	Contraindicated	Two doses
Zoster Recombinant (RZV)		Two doses for people aged ≥18 years	Not recommended in pregnancy		

Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection.

Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances.

Contraindicated

Note: Recommendations may differ from the Advisory Committee on Immunization Practices.

References

1. Geretti AM, Stockdale AJ, Kelly SH, et al. Outcomes of coronavirus disease 2019 (COVID-19) related hospitalization among people with human immunodeficiency virus (HIV) in the ISARIC World Health Organization (WHO) Clinical Characterization Protocol (UK): a prospective observational study. *Clin Infect Dis*. 2021;73(7):e2095-e2106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33095853.

2. Bhaskaran K, Rentsch CT, MacKenna B, et al. HIV infection and COVID-19 death: a population-based cohort analysis of UK primary care data and linked national death registrations within the OpenSAFELY platform. *Lancet HIV*. 2021;8(1):e24-e32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33316211.

3. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases SA. Risk factors for coronavirus disease 2019 (COVID-19) death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis*. 2021;73(7):e2005-e2015. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32860699.

4. Tesoriero JM, Swain CE, Pierce JL, et al. COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York State. *JAMA Netw Open*. 2021;4(2):e2037069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33533933.

5. Hoffmann C, Casado JL, Harter G, et al. Immune deficiency is a risk factor for severe COVID-19 in people living with HIV. *HIV Med*. 2021;22(5):372-378. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33368966.

6. Dandachi D, Geiger G, Montgomery MW, et al. Characteristics, comorbidities, and outcomes in a multicenter registry of patients with human immunodeficiency virus and coronavirus disease 2019. *Clin Infect Dis*. 2021;73(7):e1964-e1972. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32905581.

7. Bertagnolio S TS, Silva R, et al. Clinical characteristics and prognostic factors in people living with HIV hospitalized with COVID-19: findings from the WHO Global Clinical Platform. Presented at: International AIDS Society.; 2021. Available at: https://theprogramme.ias2021.org/Abstract/Abstract/2498.

8. Sun J, Patel RC, Zheng Q, et al. COVID-19 disease severity among people with HIV infection or solid organ transplant in the United States: a nationally-representative, multicenter, observational cohort study. *medRxiv*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34341798.

9. Bertagnolio S, Thwin SS, Silva R, et al. Clinical features of, and risk factors for, severe or fatal COVID-19 among people living with HIV admitted to hospital: analysis of data from the WHO Global Clinical Platform of COVID-19. *Lancet HIV*. 2022;9(7):e486-e495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35561704.

10. Shapiro AE, Bender Ignacio RA, Whitney BM, et al. Factors associated with severity of COVID-19 disease in a multicenter cohort of people with HIV in the United States, March-December 2020. *J Acquir Immune Defic Syndr*. 2022;90(4):369-376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35364600.

11. Heftdal LD, Knudsen AD, Hamm SR, et al. Humoral response to two doses of BNT162b2 vaccination in people with HIV. *J Intern Med*. 2022;291(4):513-518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34841629.

12. Yin J, Chen Y, Li Y, Wang C, Zhang X. Immunogenicity and efficacy of COVID-19 vaccines in people living with HIV: a systematic review and meta-analysis. *Int J Infect Dis*. 2022;124:212-223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36241168.

13. Costiniuk CT, Singer J, Lee T, et al. COVID-19 vaccine immunogenicity in people with HIV. *AIDS*. 2023;37(1):F1-F10. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36476452.

14. Hensley KS, Jongkees MJ, Geers D, et al. Immunogenicity and reactogenicity of SARS-CoV-2 vaccines in people living with HIV in the Netherlands: a nationwide prospective cohort study. *PLoS Med*. 2022;19(10):e1003979. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36301821.

15. Antinori A, Cicalini S, Meschi S, et al. Humoral and cellular immune response elicited by mRNA vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in people living with human immunodeficiency virus receiving antiretroviral therapy based on current CD4 T-lymphocyte count. *Clin Infect Dis*. 2022;75(1):e552-e563. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35366316.

16. Lee A, Wong SY, Chai LYA, et al. Efficacy of covid-19 vaccines in immunocompromised patients: systematic review and meta-analysis. *BMJ*. 2022;376:e068632. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35236664.

17. Coburn SB, Humes E, Lang R, et al. Analysis of postvaccination breakthrough COVID-19 infections among adults with HIV in the United States. *JAMA Netw Open*. 2022;5(6):e2215934. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35671054.

18. Fowokan A, Samji H, Puyat JH, et al. Effectiveness of COVID-19 vaccines in people living with HIV in British Columbia and comparisons with a matched HIV-negative cohort: a test-negative design. *Int J Infect Dis*. 2023;127:162-170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36462571.

19. Puyat JH, Wilton J, Fowokan A, et al. COVID-19 vaccine effectiveness by HIV status and history of injection drug use: a test-negative analysis. *J Int AIDS Soc*. 2023;26(10):e26178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37885156.

20. Link-Gelles R, Weber ZA, Reese SE, et al. Estimates of bivalent mRNA vaccine durability in preventing COVID-19-associated hospitalization and critical illness among adults with and without immunocompromising conditions - VISION Network, September 2022–April 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(21):579-588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37227984.

21. Regan JJ, Moulia DL, Link-Gelles R, et al. Use of updated COVID-19 vaccines 2023–2024 formula for persons aged >/=6 months: recommendations of the Advisory Committee on Immunization Practices - United States, September 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(42):1140-1146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37856366.

22. Food and Drug Administration. Vaccines and related biological products advisory committee meeting: future vaccination regimens addressing COVID-19. 2023. Available at: https://www.fda.gov/media/164699/download

23. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States. 2023. Available at: https://www.cdc.gov/vaccines/covid-19/clinical-considerations/interim-considerations-us.html

24. Riekkinen M, Pakkanen SH, Hutse V, et al. Coadministered pneumococcal conjugate vaccine decreases immune response to hepatitis A vaccine: a randomized controlled trial. *Clin Microbiol Infect*. 2023;29(12):1553-1560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37572831.

25. Garland SM, Ault KA, Gall SA, et al. Pregnancy and infant outcomes in the clinical trials of a human papillomavirus type 6/11/16/18 vaccine: a combined analysis of five randomized controlled trials. *Obstet Gynecol*. 2009;114(6):1179-1188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19935017.

26. Scheller NM, Pasternak B, Molgaard-Nielsen D, Svanstrom H, Hviid A. Quadrivalent HPV vaccination and the risk of adverse pregnancy outcomes. *N Engl J Med*. 2017;376(13):1223-1233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28355499.

27. Kharbanda EO, Vazquez-Benitez G, DeSilva MB, et al. Association of inadvertent 9-valent human papillomavirus vaccine in pregnancy with spontaneous abortion and adverse birth outcomes. *JAMA Netw Open*. 2021;4(4):e214340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33818618.

28. Boudova S, Boelig RC. Safety of the 9-valent HPV vaccine in pregnancy base on adverse events reported in VAERS. *American Journal of Obstetrics and Gynecology*. 2023;228(1):S733-S733. Available at: https://www.sciencedirect.com/science/article/pii/S000293782202107X?via%3Dihub.

29. Grohskopf LA, Blanton LH, Ferdinands JM, Chung JR, Broder KR, Talbot HK. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices - United States, 2023–24 influenza season. *MMWR Recomm Rep*. 2023;72(2):1-25. Available at: https://www.cdc.gov/mmwr/volumes/72/rr/rr7202a1.htm?s_cid=rr7202a1_w.

30. Clements ML, Betts RF, Tierney EL, Murphy BR. Serum and nasal wash antibodies associated with resistance to experimental challenge with influenza A wild-type virus. *J Clin Microbiol*. 1986;24(1):157-160. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3722363.

31. Potter CW, Oxford JS. Determinants of immunity to influenza infection in man. *Br Med Bull*. 1979;35(1):69-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/367490.

32. Cox NJ, Subbarao K. Influenza. *Lancet*. 1999;354(9186):1277-1282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10520648.

33. Couch RB, Kasel JA. Immunity to influenza in man. *Annu Rev Microbiol*. 1983;37:529-549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6357060.

34. Fine AD, Bridges CB, De Guzman AM, et al. Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City. *Clin Infect Dis*. 2001;32(12):1784-1791. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11360221.

35. Neuzil KM, Reed GW, Mitchel EF, Jr., Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. *JAMA*. 1999;281(10):901-907. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10078486.

36. Neuzil KM, Coffey CS, Mitchel EF, Jr., Griffin MR. Cardiopulmonary hospitalizations during influenza season in adults and adolescents with advanced HIV infection. *J Acquir Immune Defic Syndr*. 2003;34(3):304-307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14600576.

37. Cohen C, Moyes J, Tempia S, et al. Severe influenza-associated respiratory infection in high HIV prevalence setting, South Africa, 2009–2011. *Emerg Infect Dis*. 2013;19(11):1766-1774. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24209781.

38. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. *Arch Intern Med*. 2001;161(3):441-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11176770.

39. Peters PJ, Skarbinski J, Louie JK, et al. HIV-infected hospitalized patients with 2009 pandemic influenza A (pH1N1)—United States, spring and summer 2009. *Clin Infect Dis*. 2011;52 Suppl 1:S183-188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21342893.

40. Chadwick EG, Chang G, Decker MD, Yogev R, Dimichele D, Edwards KM. Serologic response to standard inactivated influenza vaccine in human immunodeficiency virus-infected children. *Pediatr Infect Dis J*. 1994;13(3):206-211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8177629.

41. Huang KL, Ruben FL, Rinaldo CR, Jr., Kingsley L, Lyter DW, Ho M. Antibody responses after influenza and pneumococcal immunization in HIV-infected homosexual men. *JAMA*. 1987;257(15):2047-2050. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3560380.

42. Staprans SI, Hamilton BL, Follansbee SE, et al. Activation of virus replication after vaccination of HIV-1-infected individuals. *J Exp Med*. 1995;182(6):1727-1737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7500017.

43. Kroon FP, van Dissel JT, de Jong JC, Zwinderman K, van Furth R. Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3-year study. *Vaccine*. 2000;18(26):3040-3049. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10825608.

44. Amoah S, Mishina M, Praphasiri P, et al. Standard-dose intradermal influenza vaccine elicits cellular immune responses similar to those of intramuscular vaccine in men with and those without HIV infection. *J Infect Dis*. 2019;220(5):743-751. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31045222.

45. George VK, Pallikkuth S, Pahwa R, et al. Circulating inflammatory monocytes contribute to impaired influenza vaccine responses in HIV-infected participants. *AIDS*. 2018;32(10):1219-1228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29683844.

46. Miotti PG, Nelson KE, Dallabetta GA, Farzadegan H, Margolick J, Clements ML. The influence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine. *JAMA*. 1989;262(6):779-783. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2787416.

47. Garg S, Thongcharoen P, Praphasiri P, et al. Randomized controlled trial to compare immunogenicity of standard-dose intramuscular versus intradermal trivalent inactivated influenza vaccine in HIV-infected men who have sex with men in Bangkok, Thailand. *Clin Infect Dis*. 2016;62(3):383-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26486702.

48. Madhi SA, Maskew M, Koen A, et al. Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis*. 2011;52(1):128-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21148531.

49. McKittrick N, Frank I, Jacobson JM, et al. Improved immunogenicity with high-dose seasonal influenza vaccine in HIV-infected persons: a single-center, parallel, randomized trial. *Ann Intern Med*. 2013;158(1):19-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23277897.

50. Hakim H, Allison KJ, Van de Velde LA, et al. Immunogenicity and safety of high-dose trivalent inactivated influenza vaccine compared to standard-dose vaccine in children and young adults with cancer or HIV infection. *Vaccine*. 2016;34(27):3141-3148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27129426.

51. Cordero E, Roca-Oporto C, Bulnes-Ramos A, et al. Two doses of inactivated influenza vaccine improve immune response in solid organ transplant recipients: results of TRANSGRIPE 1-2, a randomized controlled clinical trial. *Clin Infect Dis*. 2017;64(7):829-838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28362949.

52. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med*. 2014;371(7):635-645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25119609.

53. Van Buynder PG, Konrad S, Van Buynder JL, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. *Vaccine*. 2013;31(51):6122-6128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23933368.

54. Dunkle LM, Izikson R, Patriarca P, et al. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. *N Engl J Med*. 2017;376(25):2427-2436. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28636855.

55. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of U.S. nursing home residents admitted to hospital: a cluster-randomised trial. *Lancet Respir Med*. 2017;5(9):738-746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28736045.

56. Grohskopf LA, Ferdinands JM, Blanton LH, Broder KR, Loehr J. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices - United States, 2024–25 Influenza season. *MMWR Recomm Rep*. 2024;73(5):1-25. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39197095.

57. Menegay JL, Xu X, Sunil TS, Okulicz JF. Live versus attenuated influenza vaccine uptake and post-vaccination influenza-like illness outcomes in HIV-infected U.S. Air Force members. *J Clin Virol*. 2017;95:72-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28889083.

58. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. *JAMA*. 1992;267(9):1237-1241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1538561.

59. Global measles threat continues to grow as another year passes with millions of children unvaccinated [press release]. World Health Organization., November 16, 2023.

60. Patel M, Lee AD, Redd SB, et al. Increase in measles cases—United States, January 1–April 26, 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(17):402-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31048672.

61. Mahase E. Measles cases rise 300% globally in first few months of 2019. *BMJ*. 2019;365:l1810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30992273.

62. Kemper CA, Gangar M, Arias G, Kane C, Deresinski SC. The prevalence of measles antibody in human immunodeficiency virus-infected patients in northern California. *J Infect Dis*. 1998;178(4):1177-1180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9806055.

63. Kemper CA, Zolopa AR, Hamilton JR, Fenstersheib M, Bhatia G, Deresinski SC. Prevalence of measles antibodies in adults with HIV infection: possible risk factors of measles seronegativity. *AIDS*. 1992;6(11):1321-1325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1472336.

64. Wallace MR, Hooper DG, Graves SJ, Malone JL. Measles seroprevalence and vaccine response in HIV-infected adults. *Vaccine*. 1994;12(13):1222-1224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7839728.

65. Stermole BM, Grandits GA, Roediger MP, et al. Long-term safety and serologic response to measles, mumps, and rubella vaccination in HIV-1 infected adults. *Vaccine*. 2011;29(16):2874-2880. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21352938.

66. Centers for Disease Control and Prevention. Measles pneumonitis following measles-mumps-rubella vaccination of a patient with HIV infection, 1993. *MMWR Morb Mortal Wkly Rep*. 1996;45(28):603-606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8676852.

67. Angel JB, Walpita P, Lerch RA, et al. Vaccine-associated measles pneumonitis in an adult with AIDS. *Ann Intern Med*. 1998;129(2):104-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9669968.

68. Scott P, Moss WJ, Gilani Z, Low N. Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. *J Infect Dis*. 2011;204 Suppl 1:S164-178. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21666158.

69. Sprauer MA, Markowitz LE, Nicholson JK, et al. Response of human immunodeficiency virus-infected adults to measles-rubella vaccination. *J Acquir Immune Defic Syndr (1988)*. 1993;6(9):1013-1016. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8340890.

70. Centers for Disease Control and Prevention. Shared clinical decision-making meningococcal B vaccination. 2022. Available at: https://www.cdc.gov/vaccines/vpd/mening/hcp/references-resources.html

71. Mbaeyi SA, Bozio CH, Duffy J, et al. Meningococcal vaccination: recommendations of the advisory committee on immunization practices, United States, 2020. *MMWR Recomm Rep*. 2020;69(9):1-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33417592.

72. Simmons RD, Kirwan P, Beebeejaun K, et al. Risk of invasive meningococcal disease in children and adults with HIV in England: a population-based cohort study. *BMC Med*. 2015;13:297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26654248.

73. Stephens DS, Hajjeh RA, Baughman WS, Harvey RC, Wenger JD, Farley MM. Sporadic meningococcal disease in adults: results of a 5-year population-based study. *Ann Intern Med*. 1995;123(12):937-940. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7486489.

74. Cohen C, Singh E, Wu HM, et al. Increased incidence of meningococcal disease in HIV-infected individuals associated with higher case-fatality ratios in South Africa. *AIDS*. 2010;24(9):1351-1360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20559040.

75. Miller L, Arakaki L, Ramautar A, et al. Elevated risk for invasive meningococcal disease among persons with HIV. *Ann Intern Med*. 2014;160(1):30-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24166695.

76. Harris CM, Wu HM, Li J, et al. Meningococcal disease in patients with human immunodeficiency virus infection: a review of cases reported through active surveillance in the United States, 2000–2008. *Open Forum Infect Dis*. 2016;3(4):ofw226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28018927.

77. Ghaswalla PK, Marshall GS, Bengtson LGS, et al. Meningococcal vaccination rates among people with a new diagnosis of HIV infection in the U.S. *JAMA Netw Open*. 2022;5(4):e228573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35486405.

78. Lujan-Zilbermann J, Warshaw MG, Williams PL, et al. Immunogenicity and safety of 1 vs 2 doses of quadrivalent meningococcal conjugate vaccine in youth infected with human immunodeficiency virus. *J Pediatr*. 2012;161(4):676-681.e672. Available at: https://pubmed.ncbi.nlm.nih.gov/22622049.

79. Bozio CH, Blain A, MacNeil J, et al. Meningococcal disease surveillance in men who have sex with men—United States, 2015–2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(38):1060-1063. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30260947.

80. Zheteyeva Y, Moro PL, Yue X, Broder K. Safety of meningococcal polysaccharide-protein conjugate vaccine in pregnancy: a review of the Vaccine Adverse Event Reporting System. *Am J Obstet Gynecol*. 2013;208(6):478 e471-476. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23453881.

81. Hansen J, Zhang L, Klein NP, et al. Post-licensure safety surveillance study of routine use of quadrivalent meningococcal diphtheria toxoid conjugate vaccine. *Vaccine*. 2017;35(49 Pt B):6879-6884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28941623.

82. Myers TR, McNeil MM, Ng CS, Li R, Lewis PW, Cano MV. Adverse events following quadrivalent meningococcal CRM-conjugate vaccine (Menveo®) reported to the Vaccine Adverse Event Reporting system (VAERS), 2010–2015. *Vaccine*. 2017;35(14):1758-1763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28262331.

83. Tapia MD, Sow SO, Tamboura B, et al. Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial. *Lancet Infect Dis*. 2016;16(9):1026-1035. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27261067.

84. MENVEO [Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine] solution for injection, for intramuscular use [Type]. Sovicille, Italy: GlaxoSmithKline; 2022.

85. Centers for Disease Control and Prevention. Vaccine for Mpox Prevention in the United States. 2024. Available at: https://www.cdc.gov/mpox/hcp/vaccine-considerations/index.html

86. Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology*. 2005;340(1):46-63. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16023693.

87. Likos AM, Sammons SA, Olson VA, et al. A tale of two clades: monkeypox viruses. *J Gen Virol*. 2005;86(Pt 10):2661-2672. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16186219.

88. McQuiston JH, Luce R, Kazadi DM, et al. U.S. Preparedness and response to increasing clade I mpox cases in the Democratic Republic of the Congo - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(19):435-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38753567.

89. Centers for Disease Control and Prevention. Interim clinical considerations for use of vaccine for mpox prevention in the United States. 2025. Available at: https://www.cdc.gov/mpox/hcp/vaccine-considerations/vaccination-overview.html

90. Overton ET, Lawrence SJ, Stapleton JT, et al. A randomized phase II trial to compare safety and immunogenicity of the MVA-BN smallpox vaccine at various doses in adults with a history of AIDS. *Vaccine*. 2020;38(11):2600-2607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32057574.

91. Overton ET, Stapleton J, Frank I, et al. Safety and immunogenicity of modified vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced human immunodeficiency virus-infected individuals: an open-label, controlled clinical Phase II trial. *Open Forum Infect Dis*. 2015;2(2):ofv040. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26380340.

92. Greenberg RN, Overton ET, Haas DW, et al. Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects. *J Infect Dis*. 2013;207(5):749-758. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23225902.

93. Wolff Sagy Y, Zucker R, Hammerman A, et al. Real-world effectiveness of a single dose of mpox vaccine in males. *Nat Med*. 2023;29(3):748-752. Available at: https://pubmed.ncbi.nlm.nih.gov/36720271/.

94. Dalton AF, Diallo AO, Chard AN, et al. Estimated effectiveness of JYNNEOS vaccine in preventing mpox: a multijurisdictional case-control study - United States, August 19, 2022–March 31, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):553-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37200229.

95. Payne AB, Ray LC, Cole MM, et al. Reduced risk for mpox after receipt of 1 or 2 doses of JYNNEOS vaccine compared with risk among unvaccinated persons - 43 U.S. jurisdictions, July 31-October 1, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(49):1560-1564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36480479.

96. Bertran M, Andrews N, Davison C, et al. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. *Lancet Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36924787.

97. Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. *N Engl J Med*. 2023;388(26):2434-2443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37199451.

98. Rosenberg ES, Dorabawila V, Hart-Malloy R, et al. Effectiveness of JYNNEOS vaccine against diagnosed mpox infection - New York, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):559-563. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37339074.

99. Montaño M, Shapiro AE, Whitney BM, et al. Mpox in People with uhman immunodeficiency virus: predictors of diagnosis, outcomes, and vaccine effectiveness in a multisite cohort. *Clinical Infectious Diseases*. 2024. Available at: https://doi.org/10.1093/cid/ciae464.

100. Priyamvada L, Carson WC, Ortega E, et al. Serological responses to the MVA-based JYNNEOS monkeypox vaccine in a cohort of participants from the Democratic Republic of Congo. *Vaccine*. 2022;40(50):7321-7327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36344361.

101. Faherty EAG, Holly T, Ogale YP, et al. Notes from the Field: emergence of an mpox cluster primarily affecting persons previously vaccinated against mpox - Chicago, Illinois, March 18–June 12, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(25):696-698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37347713.

102. Hazra A, Zucker J, Bell E, et al. Mpox in people with past infection or a complete vaccination course: a global case series. *Lancet Infect Dis*. 2024;24(1):57-64. Available at: https://pubmed.ncbi.nlm.nih.gov/37678309/.

103. Guagliardo SAJ, Kracalik I, Carter RJ, et al. Monkeypox Virus Infections After 2 Preexposure Doses of JYNNEOS Vaccine - United States, May 2022–May 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(20):460-466. Available at: https://pubmed.ncbi.nlm.nih.gov/38781111/.

104. ^JYNNEOS [package insert]. Food and Drug Administration. 2022. https://www.fda.gov/media/131078/download

105. ^ACAM2000 [package insert]. Food and Drug Administration. 2018. https://www.fda.gov/media/75792/download

106. Kobayashi M, Pilishvili T, Farrar JL, et al. Pneumococcal vaccine for adults aged >/=19 years: recommendations of the Advisory Committee on Immunization Practices, United States, 2023. *MMWR Recomm Rep*. 2023;72(3):1-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37669242.

107. Stoecker C. Economic assessment of PCV21 in U.S. adults. Presented at: Meeting of the Advisory Committee on Immunization Practices (ACIP); 2024. Available at: https://www.cdc.gov/acip/downloads/slides-2024-06-26-28/02-Pneumococcal-Stoecker-508.pdf.

108. Hung CC, Chen MY, Hsieh SM, Hsiao CF, Sheng WH, Chang SC. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1-infected patients receiving highly active antiretroviral therapy: a prospective observational study. *Vaccine*. 2004;22(15-16):2006-2012. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15121313.

109. Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med*. 2005;165(13):1533-1540. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16009870.

110. Teshale EH, Hanson D, Flannery B, et al. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998–2003. *Vaccine*. 2008;26(46):5830-5834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18786586.

111. Rodriguez-Barradas MC, Goulet J, Brown S, et al. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. *Clin Infect Dis*. 2008;46(7):1093-1100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18444830.

112. Guerrero M, Kruger S, Saitoh A, et al. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. *AIDS*. 1999;13(14):1971-1975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10513657.

113. Marcus JL, Baxter R, Leyden WA, et al. Invasive pneumococcal disease among HIV-infected and HIV-uninfected adults in a large integrated healthcare system. *AIDS Patient Care STDS*. 2016;30(10):463-470. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27749111.

114. Veras MA, Enanoria WT, Castilho EA, Reingold AL. Effectiveness of the polysaccharide pneumococcal vaccine among HIV-infected persons in Brazil: a case control study. *BMC Infect Dis*. 2007;7:119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17956620.

115. Barry PM, Zetola N, Keruly JC, Moore RD, Gebo KA, Lucas GM. Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990-2003. *AIDS*. 2006;20(3):437-444. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16439878.

116. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet*. 2000;355(9221):2106-2111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10902624.

117. Watera C, Nakiyingi J, Miiro G, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS*. 2004;18(8):1210-1213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15166540.

118. Kobayashi M, Matanock A, Xing W, et al. Impact of 13-valent pneumococcal conjugate vaccine on Invasive pneumococcal disease among adults with HIV-United States, 2008-2018. *J Acquir Immune Defic Syndr*. 2022;90(1):6-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35384920.

119. Kobayashi M, Farrar JL, Gierke R, et al. Use of 15-valent pneumococcal conjugate vaccine and 20-valent pneumococcal conjugate vaccine among U.S. adults: updated recommendations of the Advisory Committee on Immunization Practices - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(4):109-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35085226.

120. Mohapi L, Pinedo Y, Osiyemi O, et al. Safety and immunogenicity of V114, a 15-valent pneumococcal conjugate vaccine, in adults living with HIV. *AIDS*. 2022;36(3):373-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34750291.

121. Beer L, Tie Y, Crim SM, et al. Progress toward achieving national HIV/AIDS strategy goals for quality of life among persons aged >/=50 years with diagnosed HIV - Medical Monitoring Project, United States, 2017–2023. *MMWR Morb Mortal Wkly Rep*. 2024;73(36):781-787. Available at: https://www.ncbi.nlm.nih.gov/pubmed/39264841.

122. Kobayashi M, Leidner AJ, Gierke R, et al. Use of 21-valent pneumococcal conjugate vaccine among U.S. adults: recommendations of the Advisory Committee on Immunization Practices,United States. *MMWR Morb Mortal Wkly Rep*. 2024;73(36):793–798. Available at: https://www.cdc.gov/mmwr/volumes/73/wr/mm7336a3.htm#contribAff.

123. Slayter KL, Singer J, Lee TC, Kayhty H, Schlech WF. Immunization against pneumococcal disease in HIV-infected patients: conjugate versus polysaccharide vaccine before or after reconstitution of the immune system (CTN-147). *Int J STD AIDS*. 2013;24(3):227-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23535358.

124. Song JY, Cheong HJ, Noh JY, Choi MJ, Yoon JG, Kim WJ. Immunogenicity and safety of 13-valent pneumococcal conjugate vaccine in HIV-infected adults in the era of highly active antiretroviral therapy: analysis stratified by CD4 T-cell count. *Hum Vaccin Immunother*. 2020;16(1):169-175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31441710.

125. Garcia Garrido HM, Schnyder JL, Haydari B, et al. Immunogenicity of the 13-valent pneumococcal conjugate vaccine followed by the 23-valent pneumococcal polysaccharide vaccine in people living with HIV on combination antiretroviral therapy. *Int J Antimicrob Agents*. 2022;60(2):106629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35760223.

126. Kvale D, Aaberge IS, Froland SS. Predictive value of immunologic parameters and HIV RNA in relation to humoral pneumococcal polysaccharide vaccine responses in patients with HIV infection. *Eur J Clin Microbiol Infect Dis*. 2002;21(9):688-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12373505.

127. Leggat DJ, Iyer AS, Ohtola JA, et al. Response to pneumococcal polysaccharide vaccination in newly diagnosed HIV-positive individuals. *J AIDS Clin Res*. 2015;6(2). Available at: https://www.ncbi.nlm.nih.gov/pubmed/25908995.

128. Higgins D, Trujillo C, Keech C. Advances in RSV vaccine research and development - a global agenda. *Vaccine*. 2016;34(26):2870-2875. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27105562.

129. Graham BS. The journey to RSV vaccines - heralding an era of structure-based design. *N Engl J Med*. 2023;388(7):579-581. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36791157.

130. PATH. RSV vaccine and mAb snapshot. 2023. Available at: https://media.path.org/documents/RSV-snapshot_02JUN2023_clinical-stage_dBtD8W3.pdf

131. Venkatesan P. First RSV vaccine approvals. *Lancet*. 2023;4(8):E577. Available at: https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(23)00195-7/fulltext#%20.

132. Papi A, Ison MG, Langley JM, et al. Respiratory syncytial virus prefusion F protein vaccine in older adults. *N Engl J Med*. 2023;388(7):595-608. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36791160.

133. Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med*. 2023;388(16):1451-1464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37018474.

134. Walsh EE, Marc GP, Zareba AM, et al. Efficacy and safety of a bivalent RSV prefusion F vaccine in older adults. *N Engl J Med*. 2023;388:1465-1477. Available at: https://www.nejm.org/doi/full/10.1056/NEJMoa2213836.

135. Wilson E, Goswami J, Baqui AH, et al. Efficacy and safety of an mRNA-based RSV PreF vaccine in older adults. *N Engl J Med*. 2023;389(24):2233-2244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38091530.

136. Centers for Disease Control and Prevention. Healthcare providers: RSV vaccination for adults 60 years of age and over. 2024. Available at: https://www.cdc.gov/vaccines/vpd/rsv/hcp/older-adults.html#risk-factors

137. Kroon FP, van Dissel JT, de Jong JC, van Furth R. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD4+ lymphocytes. *AIDS*. 1994;8(4):469-476. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7912086.

138. Kroon FP, van Dissel JT, Labadie J, van Loon AM, van Furth R. Antibody response to diphtheria, tetanus, and poliomyelitis vaccines in relation to the number of CD4+ T lymphocytes in adults infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21(5):1197-1203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8589143.

139. Kerneis S, Launay O, Turbelin C, Batteux F, Hanslik T, Boelle PY. Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2014;58(8):1130-1139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24415637.

Leishmaniasis

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Epidemiology

Leishmaniasis is caused by protozoa that survive and replicate within macrophages and other mononuclear cells. There are over 20 species within the *Leishmania* (*L*.) genus that cause human disease, the main forms of which are visceral, cutaneous, and mucosal disease.[1] Leishmaniasis occurs in 99 countries or territories in the tropics and subtropics (including the southern United States, most of Central and South America, and southern Europe), with an estimated incidence of 1 million new cases annually. In 2022, 12,842 incident cases of visceral leishmaniasis and 205,986 new cases of cutaneous leishmaniasis were reported to the World Health Organization (WHO).[2]

Prevalence of the different *Leishmania* species varies geographically. The main *Leishmania* species that cause visceral leishmaniasis are *L. donovani, L. infantum* (syn. *L. chagasi*), and the more recently recognized *L. (Mundinia) martiniquensis*. The visceral leishmaniasis-causing species in the Americas are *L. infantum* and *L. martiniquensis*. Cutaneous leishmaniasis acquired outside the Americas is commonly caused by *L. tropica, L. major,* and *L. aethiopica*. In the Americas, the prevalent species that cause cutaneous leishmaniasis are of the *L.* (*Viannia)* subgenera (*braziliensis, guyanensis, panamensis, peruviana), L. mexicana* and *L. amazonensis*.[3] In the United States, there have been fewer than 100 recognized autochthonous cases in the past 100 years, mainly *L. mexicana* cutaneous leishmaniasis acquired in Texas.[3]

As of 2021, HIV-leishmaniasis coinfection has been reported in 45 countries,[4] predominantly as HIV-visceral leishmaniasis coinfection.[4,5] The first cases of HIV-leishmaniasis coinfection were described in Spain in the late 1980s.[6] After the introduction of combination antiretroviral therapy (ART), the incidence decreased substantially in developed countries,[7,8] but HIV-leishmaniasis coinfection poses a growing problem in parts of Asia, Africa, and Latin America.[9-12] New species *Leishmania (Mundinia) martiniquensis,* associated with visceral and disseminated cutaneous leishmaniasis, and *L. (Mundinia) orientalis*, which causes cutaneous leishmaniasis, have been reported from Thailand in people with HIV.[11-13]

In endemic areas, leishmaniasis is usually spread by infected sand flies of the genera *Phlebotomus* and *Lutzomyia*. However, in southern Europe, HIV and *L. infantum* visceral leishmaniasis coinfections have been reported in association with injection drug use, suggesting that *Leishmania* (which can infrequently be transmitted via blood[14,15]) also may be acquired by needle sharing; contaminated syringes have been shown to be an epidemiologically significant component of the transmission cycle of *Leishmania* amastigotes.[16,17]

Clinical Manifestations

The term leishmaniasis encompasses multiple syndromes—most notably, cutaneous leishmaniasis and visceral leishmaniasis, but also related syndromes such as mucosal (or mucocutaneous) leishmaniasis, disseminated cutaneous leishmaniasis, diffuse cutaneous leishmaniasis (an anergic form), and post-kala-azar dermal leishmaniasis.[18] The most reported clinical presentation of leishmaniasis in people with HIV is a systemic visceral disease syndrome. However, the predominant

parasite species varies geographically. In Europe, visceral disease has been reported in 95% of people with HIV-leishmaniasis coinfection (87% typical visceral, 8% atypical visceral).[6] In Brazil, mucosal, visceral, and cutaneous forms have accounted for 43%, 37%, and 20% of reported leishmaniasis cases in people with HIV, respectively.[19]

Most *Leishmania* infections in immunocompetent hosts are asymptomatic. In many disease-endemic areas, 30% or more of the population has evidence of latent infection, as demonstrated by a positive leishmanin skin test.[20-22] After primary infection, *Leishmania* remain viable in healthy individuals for long periods, creating a population at risk of reactivation if CD4 T lymphocyte (CD4) cell depletion occurs. In people with HIV without severe CD4 cell depletion, disease manifestations are similar to those in immunocompetent individuals. In those with advanced immunosuppression (i.e., CD4 count <200 cells/mm^3), manifestations of leishmaniasis can be both atypical and more severe. Dermotrophic species can disseminate both in skin and through the reticuloendothelial system to visceralize.[23,24] Relapse after treatment—especially of visceral leishmaniasis—is common.[25,26] Atypical disseminated leishmaniasis in people with HIV is considered a WHO clinical stage 4 HIV criterion.[27]

Visceral Leishmaniasis

In people with HIV and visceral disease, the most common clinical and laboratory findings are fever (65% to 100%), systemic malaise (70% to 90%), splenomegaly (usually moderate) (54% to 90%), hepatomegaly without splenomegaly (34% to 85%), hepatosplenomegaly (68% to 73%), lymphadenopathy (12% to 57%), and pancytopenia (50% to 80%).[6,26] Anemia is usually marked, with <10 g hemoglobin/dL (50% to 100%); leukopenia is moderate, with <2,400 leukocytes/μL (56% to 95%); and thrombocytopenia is usually present (52% to 93%). Splenomegaly is less pronounced in people with HIV than in immunocompetent patients with visceral leishmaniasis.[26] In people with HIV with more profound CD4 cell depletion, atypical manifestations have been described, including mucosal involvement, such as masses, ulcers, mucositis of the upper and lower gastrointestinal tract, serositis in pleural and peritoneal cavities, and lung and skin lesions.[6,7,26,28,29] Esophageal involvement can lead to dysphagia and odynophagia and must be distinguished from other causes of esophagitis in people with HIV, such as candidiasis.[6] Amastigote infiltration of the duodenum often presents as chronic diarrhea.[7] Nonulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described in people with HIV and visceral leishmaniasis.[30-32] However, the presence of *Leishmania* amastigotes in skin can occur in the absence of lesions or in combination with other pathology, such as KS, and does not prove that the parasite is the cause of the lesions.[33,34]

Cutaneous Leishmaniasis

Cutaneous leishmaniasis in people with HIV varies depending on immune function. In people with HIV with well-controlled HIV and high CD4 counts, the presentation is not different than those without HIV except that there may be a higher rate of relapse.[35,36] In those with lower CD4 counts (e.g., <200 cells/mm^3), dermal leishmaniasis may disseminate in the skin, mucosa, and viscera.[37] Most have multiple skin lesions, often atypical (unusual morphology) for localized cutaneous leishmaniasis, and genital involvement seems more frequent.[37-39] Among people with HIV in Brazil, 68% had concomitant mucosal leishmaniasis, a rate much higher than those without HIV.[18] Additionally, as mentioned above, people with HIV and visceral leishmaniasis may present with cutaneous lesions.[40,41]

Mucosal Leishmaniasis

Mucosal leishmaniasis among people with HIV is most commonly associated with infections acquired in the New World, especially *L. braziliensis* and other species in the *L. (Viannia)* subgenera including *L. guyanensis* and *L. panamensis*.[19] Additionally, mucosal disease also has been reported with species that have geographic distribution beyond the Americas, including *L. infantum*, *L. aethiopica*, and *L. tropica*.[42] Presentation in people with HIV is similar to those without HIV and includes nasal septum destruction, obstructive masses in the nose, uvula erosion, ulcerated infiltrative lesions of the palate, and laryngeal involvement.[19,43-49] Mucosal leishmaniasis may occur concomitantly with cutaneous leishmaniasis or years after resolution of localized cutaneous leishmaniasis.[50]

Diagnosis

Demonstration of *Leishmania* parasites by histopathology, cultures, smears, and molecular methods in tissue specimens (such as scrapings, aspirates, and biopsies) is the standard for diagnosing cutaneous leishmaniasis in people with HIV. Coinfection of HIV and visceral leishmaniasis also can be diagnosed by demonstration of leishmanial parasites in the following: blood smears (approximately 50% sensitivity in expert hands); buffy-coat smear preparations; cultures from the peripheral blood; and smears, histopathology, and cultures from bone marrow (preferred) or splenic aspirates (significant procedural risk). Polymerase chain reaction (PCR) amplification can also be useful for detecting *Leishmania* nucleic acid in the blood or tissue of patients with HIV-leishmaniasis coinfection (>95% sensitivity).[51] Generally, PCR and *Leishmania* culture require specialty reference laboratory support. Assistance for conducting diagnostic tests for *Leishmania* is available by contacting the Centers for Disease Control and Prevention (CDC) at parasiteslab@cdc.gov.

Serologic tests that detect *Leishmania* antibodies have high sensitivity and can be used to support diagnosis of visceral leishmaniasis in immunocompetent patients.[51] They should be used only in those with a compatible clinical picture and an exposure history suggestive of visceral leishmaniasis. Serology has a lower sensitivity in people with HIV such that parasitological diagnosis should be sought when clinical suspicion has been raised.[6,52] The use of recombinant antigen in enzyme-linked immunosorbent assays (or ELISAs) may increase sensitivity for detection of *Leishmania* antibodies, but a proportion of people with HIV-leishmaniasis coinfection remain seronegative.[53] Immunoblotting with *L. infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of patients.[52]

Preventing Exposure

Prevention of exposure to leishmanial infection relies on reservoir host control in urban and periurban areas with zoonotic transmission (such as controlling visceral leishmaniasis in dogs) and vector control activities (such as indoor residual spraying, using insecticide-treated bed nets, and intervening in sand fly breeding sites).[54,55] Optimal control measures rely on local transmission characteristics, which vary by vector. For travelers to leishmaniasis-endemic areas, the best way to prevent infection is to protect themselves from sand fly bites. Personal protective measures include minimizing nocturnal outdoor activities, wearing protective clothing, and applying insect repellent to exposed skin.

People who inject drugs should undertake measures (such as the use of clean needles and injection equipment from syringe service programs) to decrease the risk of transmission of *Leishmania* parasites and other infectious agents.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended. No screening or preemptive therapy is appropriate for people with HIV who may have been exposed to leishmanial infection. No vaccine against leishmaniasis is available.

Treating Disease

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

- ART should be initiated as soon as possible (AIII). Initiation or optimization of ART may prevent reactivation of visceral leishmaniasis.

Leishmania infantum/chagasi

Preferred Therapy

- Liposomal amphotericin B*, achieving a total dose of 20–60 mg/kg (AII) via either
  - 3–5 mg/kg IV daily (AII), *or*
  - Interrupted schedule, such as 4 mg/kg IV on Days 1–5, 10, 17, 24, 31, and 38 (AII)

Alternative Therapy

- Amphotericin B deoxycholate* 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams (BII), *or*
- Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BII), currently available in the United States only by investigator-initiated investigational new drug application

Leishmania donovani

Preferred Therapy (Combination)

- Liposomal amphotericin B* 30 mg/kg IV total dose (5 mg/kg on Days 1, 3, 5, 7, 9, and 11), plus miltefosine 50 mg PO twice daily for 28 days (East Africa) or for 14 days (Southeast Asia) (BI)

Alternative Therapy

- Liposomal amphotericin B*, achieving a total dose of 20–60 mg/kg (AII) via either
  - 3–5 mg/kg IV daily (AII), *or*
  - Interrupted schedule, such as 4 mg/kg IV on Days 1–5, 10, 17, 24, 31, and 38 (AII)
- See Alternative Therapy for *L. infantum*, *or*
- For Indian *L. donovani*
  - Miltefosine (BII) (available in the United States via www.profounda.com), aiming for 2.5–3 mg/kg daily (maximum of 150 mg daily)
    - For patients who weigh 30–44 kg: 50 mg PO two times daily for 28 days
    - For patients who weigh ≥45 kg: 50 mg PO three times daily for 28 days

Chronic Maintenance Therapy for Visceral Leishmaniasis

Indication

- For patients with visceral leishmaniasis and CD4 count <200 cells/mm^3 (AII)

Preferred Therapy

- Liposomal amphotericin B* 4 mg/kg IV every 2–4 weeks (AII)

Alternative Therapy

- Amphotericin B lipid complex* 3 mg/kg every 21 days (BII), *or*
- Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM every 4 weeks (BII), *or*
- Pentamidine isethionate 4 mg/kg (maximum of 300 mg) IV every 2–4 weeks (BII)

Discontinuation of Chronic Maintenance Therapy

- Consider stopping secondary prophylaxis when the CD4 count is >350 cells/mm^3, HIV viral load has been undetectable for 6 months, and there are no symptoms of visceral leishmaniasis relapse (CIII).

Treating Cutaneous Leishmaniasis
• ART should be initiated as soon as possible (AIII). Initiation or optimization of ART may prevent reactivation of cutaneous leishmaniasis. *Preferred Therapy* • Liposomal amphotericin B* 4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) until a total dose of 20–60 mg/kg is achieved (BIII), *or* • Miltefosine 2.5 mg/kg/day PO in 2 or 3 divided doses for 28 days (*Viannia* subgenus); not well tolerated if more than 150 mg daily (BIII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BIII) *Alternative Therapy* • Other options for individual cases may include cryotherapy, topical paromomycin, intralesional pentavalent antimony (meglumine antimoniate) or pentamidine, fluconazole for *L. major* and *L. mexicana*, intravenous pentamidine or local heat therapy. Chronic Maintenance Therapy for Cutaneous Leishmaniasis • Indicated for immunocompromised patients with multiple relapses (CIII) • See drugs and doses for *Chronic Maintenance Therapy for Visceral Leishmaniasis*.
Pregnancy Considerations
• Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy (AIII). Amphotericin B deoxycholate can be given as alternative therapy (AIII). • In many uncomplicated cutaneous leishmaniasis cases, treatment can be delayed until postpartum (CIII). • In cases of severe cutaneous leishmaniasis with multiple and/or very large lesions, shared decision making with the patient is recommended to discuss the potential risks and benefits of deferring treatment until after pregnancy, treating with systemic therapy, or using local therapy as a temporizing approach (followed by systemic therapy to be given after pregnancy if the lesions do not resolve) (CIII). • Liposomal amphotericin B IV is the first choice for therapy of mucosal or severe cutaneous leishmaniasis in pregnancy (CIII).

* Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions (AII). Infusion-related adverse events may be ameliorated by pre-treatment with acetaminophen or diphenhydramine (CIII). An infusion of 1 L of saline 1 hour prior to drug infusion is recommended to help reduce the risk of renal dysfunction during treatment (BIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; IM = intramuscular; IV = intravenous; PO = orally

Visceral Leishmaniasis

The following medications have been used to treat visceral leishmaniasis: amphotericin B deoxycholate, liposomal amphotericin B, pentavalent antimonial drugs (e.g., meglumine antimoniate), and miltefosine (for *L. donovani*). Lower cure rates, higher drug toxicity, more relapses, and higher mortality summarize the treatment outcomes for people with HIV with visceral leishmaniasis. Amphotericin deoxycholate and lipid formulations of amphotericin B appear to be at least as effective as pentavalent antimonials.[56-58] Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than amphotericin B deoxycholate or pentavalent antimony (meglumine antimoniate).[59-61] The equivalent efficacy and better toxicity profile have led the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and

Adolescents With HIV (the Panel) to recommend liposomal amphotericin B as the preferred amphotericin formulation for treatment of visceral leishmaniasis in people with HIV **(AII).**[62] The optimal amphotericin B dosage has not been determined.[62,63]

Recommended regimens include liposomal preparations of 3 to 5 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight **(AII).** An alternative regimen of amphotericin B deoxycholate, 0.5 to 1.0 mg/kg body weight/day intravenously (IV), to achieve a total dose of 1.5 to 2.0 g, can be administered **(BII).**[56,57,64-67] Pentavalent antimony (meglumine antimoniate) 20 mg/kg/day IV or intramuscular (IM) for 28 consecutive days, is an alternative **(BII).** Pentavalent antimonial drugs require an investigator-initiated investigational new drug application in the United States (see Instructions for Acquiring Glucantime [Meglumine antimoniate] for Treatment of Leishmaniasis). Due to toxicity concerns with pentavalent antimonial drugs, a pregnancy test (beta-human chorionic gonadotropin [β-hCG]) should be obtained by individuals of childbearing potential prior to start of therapy, and effective contraception during treatment is advised.

Oral miltefosine monotherapy (available in the United States via www.profounda.com) is recommended as an alternative treatment option for Indian *L. donovani* visceral leishmaniasis in people with HIV[63,68] at a dose of approximately 2.5 to 3 mg/kg daily (maximum of 150 mg daily) for 28 days **(BII).**[69-72] Combination therapy using miltefosine and liposomal amphotericin in the treatment of HIV-*L. donovani* visceral leishmaniasis has also shown promise. A randomized clinical trial of liposomal amphotericin 30 mg/kg total dose and miltefosine 100 mg/day for 28 days was compared to liposomal amphotericin 40 mg/kg total dose monotherapy among patients with *L. donovani* visceral leishmaniasis and HIV coinfection in Ethiopia. Parasite clearance persisting to 58 days was found in 88% of the combination treatment group versus 55% in the monotherapy group.[73] In India, 150 people with HIV with *L. donovani* visceral leishmaniasis received total doses of liposomal amphotericin 40 mg/kg IV versus liposomal amphotericin 30 mg/kg IV with oral miltefosine 50 mg twice daily for 14 days. At Day 210 follow-up, 7% of patients in the monotherapy arm died versus 1.3% in the combination arm.[74] These data have led the WHO to update their 2022 HIV and visceral leishmaniasis coinfection treatment guidelines to conditionally recommend combination liposomal amphotericin and miltefosine treatment; those with HIV-visceral leishmaniasis coinfection in Eastern Africa (*L. donovani*) should be administered miltefosine for 28 days, and those with HIV-visceral leishmaniasis coinfection (*L. donovani*) in South East Asia should be administered miltefosine for 14 days.[75] Since miltefosine is teratogenic and is contraindicated in pregnancy, β-hCG should be checked prior to initiation and effective contraception should be continued for 5 months.[63]

Data supporting the use of miltefosine monotherapy in people with HIV are relatively limited and restricted to Indian *L. donovani*. For visceral leishmaniasis caused by *L. infantum* (e.g., in the Americas, Europe), Pan American Health Organization guidelines recommend against miltefosine monotherapy due to lower efficacy and limited evidence.[76] Further research is also needed to confirm the efficacy of drug combinations in people with HIV to treat other *Leishmania* species and severe or refractory cases of visceral leishmaniasis in other geographic regions. Currently, there is no recommendation for combination therapy in visceral leishmaniasis due to *L. infantum*.

Cutaneous Leishmaniasis

Few systematic data are available on the efficacy of treatment for cutaneous leishmaniasis, mucosal leishmaniasis, or diffuse cutaneous leishmaniasis in people with HIV. Based on data from individuals

without HIV with cutaneous leishmaniasis and case reports in people with HIV-cutaneous leishmaniasis, patients with HIV-cutaneous leishmaniasis should be treated with some form of systemic therapy, depending on the type of cutaneous leishmaniasis and the clinical response. Liposomal amphotericin B **(BIII),**[67] miltefosine (*Viannia* subgenus infections) **(BIII),** or pentavalent antimony (meglumine antimoniate) **(BIII)** are options for treatment.[77,78] Pentavalent antimonial drugs require an investigator-initiated investigational new drug application in the United States (see Instructions for Acquiring Glucantime [Meglumine antimoniate] for Treatment of Leishmaniasis).

Potential alternatives for cutaneous leishmaniasis include cryotherapy, topical paromomycin, intralesional pentavalent antimony or pentamidine isoethionate, intravenous pentamidine isethionate,[79,80] fluconazole for *L. major* and *L. mexicana*, or local heat therapy. The effectiveness of these modalities is known to be dependent upon the infecting species of *Leishmania*.[66,81-83] However, these alternatives are based on data from people without HIV, not those with HIV-cutaneous leishmaniasis coinfection. For example, although the Pan American Health Organization 2022 guidelines recommend intralesional pentavalent antimonial treatment as first-line use in immunocompetent patients, this treatment has not been tested in people with HIV and New World cutaneous leishmaniasis; because of this, there are concerns about how effectively it will prevent dissemination like mucosal leishmaniasis in people with HIV, who may be at increased risk.[76,84] Therefore, these alternatives could be considered in individualized circumstances in patients with high CD4 counts and controlled viral load.

Special Considerations Regarding ART Initiation

Appropriate use of ART has substantially improved the survival of patients with coinfection and decreased the likelihood of relapse after antileishmanial therapy.[8,26,85] Therefore, ART should be started as soon as patients are able to tolerate it **(AIII).**

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Patients treated with liposomal amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions **(AII).** Infusion-related adverse events may be ameliorated by pre-treatment with acetaminophen or diphenhydramine **(CIII).** An infusion of 1 L of saline 1 hour prior to drug infusion is recommended to help reduce the risk of glomerular function decline during treatment **(BIII).** The frequency of nephrotoxicity is lower for liposomal or lipid-associated preparations than for amphotericin B deoxycholate.[60]

Adverse events associated with miltefosine use include gastrointestinal symptoms (more commonly nausea or vomiting than diarrhea) that can result in prerenal azotemia, motion sickness-like symptoms, scrotal pain, thrombocytopenia, and hepatotoxicity. To decrease gastrointestinal symptoms, which are usually worse at the beginning of therapy, miltefosine should be administered in divided 50 mg doses during the day and taken with food containing some fat. Weekly assessment of renal and hepatic function and platelet counts is recommended.[67]

Patients receiving parenteral pentavalent antimony (meglumine antimoniate) should be monitored closely for adverse reactions.[77] Overall, at a dose of 20 mg/kg of body weight per day, more than 60% of patients have one or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase, or lipase, and clinical pancreatitis, in some patients. Weekly electrocardiograms are recommended during treatment, with careful monitoring for changes that may indicate early cardiotoxicity, such as prolonged QT intervals and T-wave inversion **(CIII).** Rarely, arrhythmias and sudden death have occurred.[58,66] Severe

adverse reactions to pentavalent antimony, including acute pancreatitis and leukopenia, appear to be more common in patients with coinfection than in those who do not have HIV.[86]

Cases of newly symptomatic visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis have been reported in association with immune reconstitution inflammatory syndrome (IRIS) following initiation of ART.[87-90] Several of these cases have resembled post-kala-azar dermal leishmaniasis or disseminated cutaneous leishmaniasis.[91-95] Existing experience with IRIS-associated leishmaniasis, however, is insufficient to provide data for specific management guidelines.

People with HIV who respond to initial treatment should be clinically monitored for relapse (any recurrence or new consistent skin lesions) for at least 6 months to 1 year after treatment for cutaneous leishmaniasis; those with infection with *L. (Viannia)* subspecies also should be followed for 2 to 5 years for any signs or symptoms of inflammation of the nasal mucosa. People with HIV successfully treated for visceral leishmaniasis should be clinically monitored for symptoms or signs of recurrence such as fever, constitutional symptoms, hepatomegaly, splenomegaly, or cytopenia. Routine follow-up via parasitological testing with repeat biopsies or longitudinally tracking antibody levels is generally not recommended for people with HIV with treated leishmaniasis who do not demonstrate clinical signs or symptoms of recurrence. A positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse in people with HIV-visceral leishmaniasis coinfection.[96]

Managing Treatment Failure

For patients who fail to respond to initial therapy or who experience a relapse after initial treatment, a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy, should be used as previously outlined **(AIII).** The response rate for retreatment appears to be similar to that for initial therapy, although some patients evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies.[97]

In a pharmacokinetic substudy of antileishmanial drugs for treatment of visceral leishmaniasis in people with HIV, blood concentrations of amphotericin were found to be twofold-lower than those measured in studies among those with visceral leishmaniasis without HIV. Additionally, lower observed miltefosine concentrations were likely due in part to lower weight-based dosing when compared to other studies, emphasizing the need to use a weight-based dosage approximating 2.5 mg/kg/day in adults. However, no relationship between amphotericin and miltefosine concentrations and treatment outcome was observed.[98]

Expert assistance to health care providers for clinical care for leishmaniasis is available at the CDC's Parasitic Diseases Hotline at (404) 718-4745 or parasites@cdc.gov.

Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of antileishmanial therapy in people with HIV, and relapse is more frequent in those with lower CD4 count.[99] Reported associations with relapse are prior episode of visceral leishmaniasis, CD4 count <100 cells/mm^3 at time of primary visceral leishmaniasis, and no increase in CD4 count at follow-up.[99] In people with HIV-visceral leishmaniasis coinfection who were not receiving or responding to ART, the risk of relapse at 6 and 12 months was 60% and 90%, respectively, in the absence of secondary prophylaxis (chronic maintenance therapy).[6,100,101] In

Brazil, a relapse rate of 28.6% of patients with HIV-cutaneous leishmaniasis was reported, regardless of viral load and adherence to ART.[35] Therefore, secondary prophylaxis with an effective antileishmanial drug administered at least every 4 weeks is recommended, particularly for patients with visceral leishmaniasis and CD4 counts <200 cells/mm^3 **(AII).**[6,26,100,102]

The only published, randomized trial of secondary prophylaxis compared amphotericin B lipid complex (3 mg/kg every 21 days) in eight patients with no prophylaxis in nine patients; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up.[102] In retrospective observational studies, monthly pentavalent antimony or lipid formulations of amphotericin every 2 to 4 weeks were also associated with decreased relapse rates.[26,100] With a 2 year follow-up, 74 people with HIV-visceral leishmaniasis coinfection were given monthly intravenous pentamidine isethionate (4 mg/kg with a maximal dose 300 mg) and 71% were relapse-free after 12 months.[103] In 54 persons followed for 390 days stratified for CD4 above and below 200, there was a reported overall relapse-free survival of 50% and 53% if CD4 ≥200 cells/µL.[104]

Liposomal amphotericin B (4 mg/kg every 2–4 weeks) **(AII)** is the preferred regimen for secondary prophylaxis. Amphotericin B lipid complex (3 mg/kg every 21 days) **(BII)** and pentavalent antimony (meglumine antimoniate, 20 mg/kg IV or IM every 4 weeks) are alternatives **(BII).** Although pentamidine isethionate is no longer recommended to treat primary visceral leishmaniasis, a dosage of 4 mg/kg IV (300 mg for adult) every 2 to 4 weeks has been suggested as another alternative for secondary prophylaxis **(BII).**[105-107] Allopurinol, used for maintenance therapy, is less effective than monthly pentavalent antimony and **is not recommended (BII).**[100] Although no published data on efficacy are available, maintenance therapy may be indicated for immunocompromised patients with cutaneous leishmaniasis who have multiple relapses after adequate treatment **(CIII).**

When to Stop Secondary Prophylaxis

Some investigations suggest that secondary antileishmanial prophylaxis can be discontinued in patients whose CD4 count is >200 to 350 cells/mm^3 in response to ART.[105,108] Others, however, suggest that secondary prophylaxis should be maintained indefinitely. Among 74 patients in Ethiopia with HIV-visceral leishmaniasis coinfection, who received monthly intravenous pentamidine for 12 to 18 months, a 36.9% relapse rate was identified over a 2-year follow-up, mainly among those with a low baseline CD4 count of ≤100 cells/mm^3. All with CD4 count >200 cells/mm^3 at Month 12 were relapse-free.[105] In one study, a positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse.[96] Therefore, the Panel recommends considering cessation of secondary prophylaxis when CD4 count is >350 cell/mm^3 and HIV viral load has been undetectable for 6 months and there is no clinical evidence of visceral leishmaniasis relapse **(CIII).**

Special Considerations During Pregnancy

During pregnancy, diagnostic considerations are the same as for other people with HIV. Retrospective analyses suggest that rates of preterm birth and spontaneous abortion may be increased in women with visceral leishmaniasis during pregnancy, especially in the first trimester and when antimonial drugs are used.[109,110] Because visceral leishmaniasis is a potentially lethal disease, postponing treatment until after delivery is not an option. Several small published series of pregnant women treated with amphotericin B deoxycholate or liposomal amphotericin B have demonstrated good clinical outcomes.[111-115] Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy **(AIII).**[111] Amphotericin B deoxycholate, which has demonstrated positive

clinical and pregnancy outcomes in a small group of pregnant women, can be given as an alternative therapy **(AIII).**[111]

There are concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy; labels for pentavalent antimony compounds state that these drugs are contraindicated for use in pregnancy, although various antimonial compounds were found to not be teratogenic in chickens, rats, or sheep.[116-118] Therefore, pentavalent antimonial drugs are not recommended in pregnancy **(BIII).** Miltefosine is teratogenic and pentamidine is embryotoxic; therefore, both drugs **are not recommended** in pregnancy **(AII).**[63,119] In a systematic review including 346 pregnant women with visceral leishmaniasis, 176 pregnant women treated with liposomal amphotericin were reported to have 4 (2.3%) maternal deaths, 5 (2.8%) miscarriages, and 2 (1.1%) fetal deaths/stillbirths versus 88 pregnant women receiving pentavalent antimonial drugs, where reported outcomes included 4 (4.5%) maternal deaths, 24 (27.3%) spontaneous abortions, and 2 (2.3%) miscarriages.[115]

In contrast to visceral leishmaniasis, the Panel recommends deferring treatment of cutaneous leishmaniasis until the postpartum period for most individuals with HIV-cutaneous leishmaniasis **(CIII).** One study suggests that lesions of cutaneous leishmaniasis may be larger and are more likely to be exophytic in pregnancy, and that untreated cutaneous leishmaniasis may be associated with an increased risk of preterm delivery and stillbirth.[120] This is presumed to be related to transient modulation of maternal immune responses during pregnancy.[121] In cases of severe cutaneous leishmaniasis with multiple and/or very large lesions, the Panel recommends shared decision making with the patient to discuss the potential risks and benefits of deferring treatment until after pregnancy, treating with systemic therapy, or using local therapy as a temporizing approach (followed by systemic therapy to be given after pregnancy if the lesions do not resolve) **(CIII).** Systemic therapy is recommended in most cases of mucosal leishmaniasis in patients with HIV **(CIII).** During pregnancy, when systemic therapy is chosen for mucosal leishmaniasis or cutaneous leishmaniasis, the treatment of choice is liposomal amphotericin B **(CIII).**

Perinatal transmission of *Leishmania spp*. is rare. In a systematic review of suspected cases of vertical transmission, 26 were reported after 6 months postbirth.[109,115,122-124] A case report described a woman with HIV who experienced visceral leishmaniasis relapse during pregnancy and was treated with 40 mg/kg liposomal amphotericin; the infant likely acquired leishmaniasis from amastigotes seen in the placenta.[125]

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis*. 2004;27(5):305-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15225981.

2. Ruiz-Postigo JA, Saurabh J, Madjou S, et al. Global leishmaniasis surveillance, 2022: assessing trends over the past 10 years. *Weekly Epidemiological Record*. 2023;98:471-487. Available at: https://www.who.int/publications/i/item/who-wer9840-471-487.

3. Curtin JM, Aronson NE. Leishmaniasis in the United States: emerging issues in a region of low endemicity. *Microorganisms*. 2021;9(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33799892.

4. World Health Organization. Leishmaniasis fact sheet. 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.

5. Kantzanou M, Karalexi MA, Theodoridou K, et al. Prevalence of visceral leishmaniasis among people with HIV: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2023;42(1):1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36427170.

6. Alvar J, Canavate C, Gutierrez-Solar B, et al. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev*. 1997;10(2):298-319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9105756.

7. Rosenthal E, Marty P, del Giudice P, et al. HIV and *Leishmania* coinfection: a review of 91 cases with focus on atypical locations of *Leishmania*. *Clin Infect Dis*. 2000;31(4):1093-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11049794.

8. Tortajada C, Perez-Cuevas B, Moreno A, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2002;30(3):364-366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12131576.

9. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging leishmania/HIV co-infection in Africa. *Med Microbiol Immunol*. 2001;190(1-2):65-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11770113.

10. Mathur P, Samantaray JC, Vajpayee M, Samanta P. Visceral leishmaniasis/human immunodeficiency virus co-infection in India: the focus of two epidemics. *J Med Microbiol*. 2006;55(Pt 7):919-922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16772420.

11. Charoensakulchai S, Bualert L, Manomat J, et al. Risk factors of *Leishmania* infection among HIV-infected patients in Trang Province, southern Thailand: a study on three prevalent species. *Am J Trop Med Hyg*. 2020;103(4):1502-1509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32700674.

12. Leelayoova S, Siripattanapipong S, Manomat J, et al. Leishmaniasis in Thailand: a review of causative agents and situations. *Am J Trop Med Hyg*. 2017;96(3):534-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28093539.

13. Manomat J, Leelayoova S, Bualert L, et al. Prevalence and risk factors associated with *Leishmania* infection in Trang Province, southern Thailand. *PLoS Negl Trop Dis*. 2017;11(11):e0006095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29155831.

14. Jimenez-Marco T, Fisa R, Girona-Llobera E, et al. Transfusion-transmitted leishmaniasis: a practical review. *Transfusion*. 2016;56 Suppl 1:S45-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27001361.

15. Rodrigues WF, Mendes NS, de Carvalho Ribeiro P, et al. A critical review of the applicability of serological screening for leishmaniasis in blood banks in Brazil. *J Parasit Dis*. 2021;45(1):109-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33746394.

16. Chicharro C, Morales MA, Serra T, Ares M, Salas A, Alvar J. Molecular epidemiology of *Leishmania infantum* on the island of Majorca: a comparison of phenotypic and genotypic tools. *Trans R Soc Trop Med Hyg*. 2002;96 Suppl 1:S93-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12055859.

17. Cruz I, Morales MA, Noguer I, Rodriguez A, Alvar J. *Leishmania* in discarded syringes from intravenous drug users. *Lancet*. 2002;359(9312):1124-1125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11943264.

18. Aronson N, Copeland, N. Leishmania species: visceral (kala-azar), cutaneous, and mucosal leishmaniasis. In: Blaser M, Cohen J, Holland S, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 10th ed. Elsevier; 2023.

19. Rabello A, Orsini M, Disch J. *Leishmania*/HIV co-infection in Brazil: an appraisal. *Ann Trop Med Parasitol*. 2003;97 Suppl 1:17-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14678630.

20. Marty P, Le Fichoux Y, Giordana D, Brugnetti A. Leishmanin reaction in the human population of a highly endemic focus of canine leishmaniasis in Alpes-Maritimes, France. *Trans R Soc Trop Med Hyg*. 1992;86(3):249-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1412644.

21. Moral L, Rubio EM, Moya M. A leishmanin skin test survey in the human population of l'Alacanti region (Spain): implications for the epidemiology of Leishmania infantum infection in southern Europe. *Trans R Soc Trop Med Hyg*. 2002;96(2):129-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12055798.

22. Werneck GL, Rodrigues L, Santos MV, et al. The burden of *Leishmania chagasi* infection during an urban outbreak of visceral leishmaniasis in Brazil. *Acta Trop*. 2002;83(1):13-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12062788.

23. Zijlstra EE. PKDL and other dermal lesions in HIV co-infected patients with leishmaniasis: review of clinical presentation in relation to immune responses. *PLoS Negl Trop Dis*. 2014;8(11):e3258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25412435.

24. Abdoli A, Maspi N, Ghaffarifar F, Nasiri V. Viscerotropic leishmaniasis: a systematic review of the case reports to highlight spectrum of the infection in endemic countries. *Parasitology Open*. 2018;4(E11):1-14. Available at:

https://www.cambridge.org/core/journals/parasitology-open/article/viscerotropic-leishmaniasis-a-systematic-review-of-the-case-reports-to-highlight-spectrum-of-the-infection-in-endemic-countries/096BDC88EEA424B04E4536C8CA423268.

25. Lopez-Velez R, Perez-Molina JA, Guerrero A, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfected with human immunodeficiency virus and *Leishmania* in an area of Madrid, Spain. *Am J Trop Med Hyg*. 1998;58(4):436-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9574788.

26. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. *Medicine (Baltimore)*. 2001;80(1):54-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11204503.

27. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, Switzerland: 2007. Available at: https://apps.who.int/iris/bitstream/handle/10665/43699/9789241595629_eng.pdf?sequence=1&isAllowed=y.

28. Mota Sasaki M, Matsumo Carvalho M, Schmitz Ferreira ML, Machado MP. Cutaneous leishmaniasis coinfection in AIDS patients: case report and literature review. *Braz J Infect Dis*. 1997;1(3):142-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11105130.

29. Diro E, van Griensven J, Mohammed R, et al. Atypical manifestations of visceral leishmaniasis in patients with HIV in north Ethiopia: a gap in guidelines for the management of opportunistic infections in resource poor settings. *Lancet Infect Dis*. 2015;15(1):122-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25300862.

30. Gonzalez-Beato MJ, Moyano B, Sanchez C, et al. Kaposi's sarcoma-like lesions and other nodules as cutaneous involvement in AIDS-related visceral leishmaniasis. *Br J Dermatol*. 2000;143(6):1316-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11122042.

31. Carnauba D, Jr., Konishi CT, Petri V, Martinez IC, Shimizu L, Pereira-Chioccola VL. Atypical disseminated leishmaniasis similar to post-kala-azar dermal leishmaniasis in a Brazilian AIDS patient infected with *Leishmania (Leishmania) infantum chagasi*: a case report. *Int J Infect Dis*. 2009;13(6):e504-507. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19447660.

32. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. *Br J Dermatol*. 2009;160(2):311-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19187345.

33. Albrecht H, Stellbrink HJ, Gross G, Berg B, Helmchen U, Mensing H. Treatment of atypical leishmaniasis with interferon gamma resulting in progression of Kaposi's sarcoma in an AIDS patient. *Clin Investig*. 1994;72(12):1041-1047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7711412.

34. Bosch RJ, Rodrigo AB, Sanchez P, de Galvez MV, Herrera E. Presence of *Leishmania* organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral

leishmaniasis. *Int J Dermatol*. 2002;41(10):670-675. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12390190.

35. Araujo CF, Oliveira IBN, Silva MVT, et al. New world *Leishmania spp*. infection in people living with HIV: concerns about relapses and secondary prophylaxis. *Acta Trop*. 2021;224:106146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34562423.

36. Couppie P, Clyti E, Sobesky M, et al. Comparative study of cutaneous leishmaniasis in human immunodeficiency virus (HIV)-infected patients and non-HIV-infected patients in French Guiana. *Br J Dermatol*. 2004;151(6):1165-1171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15606511.

37. Alvar J, Aparicio P, Aseffa A, et al. The relationship between leishmaniasis and AIDS: the second 10 years. *Clin Microbiol Rev*. 2008;21(2):334-359, table of contents. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18400800.

38. Guerra JA, Coelho LI, Pereira FR, et al. American tegumentary leishmaniasis and HIV-AIDS association in a tertiary care center in the Brazilian Amazon. *Am J Trop Med Hyg*. 2011;85(3):524-527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21896816.

39. Choi CM, Lerner EA. Leishmaniasis: recognition and management with a focus on the immunocompromised patient. *Am J Clin Dermatol*. 2002;3(2):91-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11893221.

40. Puig L, Pradinaud R. Leishmania and HIV co-infection: dermatological manifestations. *Ann Trop Med Parasitol*. 2003;97 Suppl 1:107-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14678638.

41. Postigo C, Llamas R, Zarco C, et al. Cutaneous lesions in patients with visceral leishmaniasis and HIV infection. *J Infect*. 1997;35(3):265-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9459400.

42. Aliaga L, Cobo F, Mediavilla JD, et al. Localized mucosal leishmaniasis due to *Leishmania (Leishmania) infantum*: clinical and microbiologic findings in 31 patients. *Medicine (Baltimore)*. 2003;82(3):147-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12792301.

43. Torrico F, Parrado R, Castro R, et al. Co-infection of *Leishmania (Viannia) braziliensis* and HIV: report of a case of mucosal leishmaniasis in Cochabamba, Bolivia. *Am J Trop Med Hyg*. 2009;81(4):555-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19815865.

44. De Godoy NS, Vera Demarchi A, Regina Maia S, Thelma O, Lucia Maria Almeida B. Unusual clinical manifestations of *Leishmania (L.) infantum chagasi* in an HIV-coinfected patient and the relevance of ITS1-PCR-RFLP: a case report. *Iran J Parasitol*. 2018;13(4):655-660. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30697322.

45. Bains A, Vedant D, Gupta P, Tegta GR. Unusual presentation of mucocutaneous leishmaniasis in HIV-infected patient. *Indian J Sex Transm Dis AIDS*. 2016;37(2):193-196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27890957.

46. da Silva GA, Sugui D, Nunes RF, et al. Mucocutaneous leishmaniasis/HIV coinfection presented as a diffuse desquamative rash. *Case Rep Infect Dis*. 2014;2014:293761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25548691.

47. Amato VS, Nicodemo AC, Amato JG, Boulos M, Neto VA. Mucocutaneous leishmaniasis associated with HIV infection treated successfully with liposomal amphotericin B (AmBisome). *J Antimicrob Chemother*. 2000;46(2):341-342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10933674.

48. Miralles ES, Nunez M, Hilara Y, Harto A, Moreno R, Ledo A. Mucocutaneous leishmaniasis and HIV. *Dermatology*. 1994;189(3):275-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7949483.

49. Canovas DL, Carbonell J, Torres J, Altes J, Buades J. Laryngeal leishmaniasis as initial opportunistic disease in HIV infection. *J Laryngol Otol*. 1994;108(12):1089-1092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7861090.

50. Lindoso JA, Cunha MA, Queiroz IT, Moreira CH. Leishmaniasis-HIV coinfection: current challenges. *HIV AIDS (Auckl)*. 2016;8:147-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27785103.

51. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. *Clin Diagn Lab Immunol*. 2002;9(5):951-958. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12204943.

52. Medrano FJ, Canavate C, Leal M, Rey C, Lissen E, Alvar J. The role of serology in the diagnosis and prognosis of visceral leishmaniasis in patients coinfected with human immunodeficiency virus type-1. *Am J Trop Med Hyg*. 1998;59(1):155-162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9684645.

53. Houghton RL, Petrescu M, Benson DR, et al. A cloned antigen (recombinant K39) of *Leishmania chagasi* diagnostic for visceral leishmaniasis in human immunodeficiency virus type 1 patients and a prognostic indicator for monitoring patients undergoing drug therapy. *J Infect Dis*. 1998;177(5):1339-1344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9593022.

54. Gonzalez U, Pinart M, Sinclair D, et al. Vector and reservoir control for preventing leishmaniasis. *Cochrane Database Syst Rev*. 2015;2015(8):CD008736. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26246011.

55. Stockdale L, Newton R. A review of preventative methods against human leishmaniasis infection. *PLoS Negl Trop Dis*. 2013;7(6):e2278. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23818997.

56. Davidson RN, Di Martino L, Gradoni L, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med*. 1994;87(2):75-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8153291.

57. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect*. 1996;32(2):133-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8708370.

58. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. *AIDS*. 1999;13(9):1063-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10397536.

59. Lazanas MC, Tsekes GA, Papandreou S, et al. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimonium compounds. *AIDS*. 1993;7(7):1018-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8357549.

60. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis*. 2004;38(3):377-383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14727208.

61. Torre-Cisneros J, Villanueva JL, Kindelan JM, Jurado R, Sanchez-Guijo P. Successful treatment of antimony-resistant visceral leishmaniasis with liposomal amphotericin B in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1993;17(4):625-627. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8268341.

62. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. *Clin Infect Dis*. 2006;43(7):917-924. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16941377.

63. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. *Adv Parasitol*. 2006;61:223-274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16735166.

64. Laguna F, Torre-Cisneros J, Moreno V, Villanueva JL, Valencia E. Efficacy of intermittent liposomal amphotericin B in the treatment of visceral leishmaniasis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21(3):711-712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8527591.

65. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clin Infect Dis*. 1999;28(1):42-48; discussion 49-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10028069.

66. Laguna F, Videla S, Jimenez-Mejias ME, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. *J Antimicrob Chemother*. 2003;52(3):464-468. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12888588.

67. Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis*. 2016;63(12):e202-e264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27941151.

68. Sundar S, Jha TK, Thakur CP, Bhattacharya SK, Rai M. Oral miltefosine for the treatment of Indian visceral leishmaniasis. *Trans R Soc Trop Med Hyg*. 2006;100 Suppl 1:S26-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16730038.

69. Dorlo TP, Rijal S, Ostyn B, et al. Failure of miltefosine in visceral leishmaniasis is associated with low drug exposure. *J Infect Dis*. 2014;210(1):146-153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24443541.

70. Sindermann H, Engel KR, Fischer C, Bommer W, Miltefosine Compassionate Use Program. Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis*. 2004;39(10):1520-1523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15546090.

71. Ramesh V, Dixit KK, Sharma N, Singh R, Salotra P. Assessing the efficacy and safety of liposomal amphotericin B and miltefosine in combination for treatment of post kala-azar dermal leishmaniasis. *J Infect Dis*. 2020;221(4):608-617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31854451.

72. Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis*. 2006;43(3):357-364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16804852.

73. Diro E, Blesson S, Edwards T, et al. A randomized trial of AmBisome monotherapy and AmBisome and miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients in Ethiopia. *PLoS Negl Trop Dis*. 2019;13(1):e0006988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30653490.

74. Burza S, Mahajan R, Kazmi S, et al. AmBisome monotherapy and combination AmBisome - miltefosine therapy for the treatment of visceral leishmaniasis in patients co-infected with HIV in India: a randomised open label, parallel arm, phase 3 trial. *Clin Infect Dis*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35147680.

75. World Health Organization. WHO guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. In: WHO guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. Geneva: 2022. https://www.ncbi.nlm.nih.gov/pubmed/35763584.

76. Pan American Health Organization. Guideline for the treatment of leishmaniasis in the Americas. 2nd ed. 2022. Available at: https://iris.paho.org/handle/10665.2/56120.

77. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg*. 1992;46(3):296-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1313656.

78. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis*. 2007;7(9):581-596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17714672.

79. Christen JR, Bourreau E, Demar M, et al. Use of the intramuscular route to administer pentamidine isethionate in *Leishmania guyanensis* cutaneous leishmaniasis increases the risk of treatment failure. *Travel Med Infect Dis*. 2018;24:31-36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29482012.

80. Piccica M, Lagi F, Bartoloni A, Zammarchi L. Efficacy and safety of pentamidine isethionate for tegumentary and visceral human leishmaniasis: a systematic review. *J Travel Med*. 2021;28(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33890115.

81. Belay AD, Asafa Y, Mesure J, Davidson RN. Successful miltefosine treatment of post-kala-azar dermal leishmaniasis occurring during antiretroviral therapy. *Ann Trop Med Parasitol*. 2006;100(3):223-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16630379.

82. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clin Infect Dis*. 2005;40(8):1148-1155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15791515.

83. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis*. 2004;38(9):1266-1272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15127339.

84. Aronson NE, Billick K. Intralesional antimonial drug treatment for *Leishmania braziliensis* cutaneous leishmaniasis: the knowns and the unknowns. *Clin Infect Dis*. 2023;77(4):583-588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37185765.

85. de la Rosa R, Pineda JA, Delgado J, et al. Influence of highly active antiretroviral therapy on the outcome of subclinical visceral leishmaniasis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 2001;32(4):633-635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11181128.

86. Delgado J, Macias J, Pineda JA, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. *Am J Trop Med Hyg*. 1999;61(5):766-769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10586909.

87. Berry A, Abraham B, Dereure J, Pinzani V, Bastien P, Reynes J. Two case reports of symptomatic visceral leishmaniasis in AIDS patients concomitant with immune reconstitution due to antiretroviral therapy. *Scand J Infect Dis*. 2004;36(3):225-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15119371.

88. Posada-Vergara MP, Lindoso JA, Tolezano JE, Pereira-Chioccola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. *J Infect Dis*. 2005;192(10):1819-1822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16235183.

89. Lee GL, Woods KL, Clark L, Peters S, Wong HK, McGwire BS. Short communication: mucocutaneous leishmaniasis in HIV-related immune reconstitution syndrome. *AIDS Res Hum Retroviruses*. 2015;31(9):889-892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26154873.

90. Gois L, Badaro R, Schooley R, Grassi MF. Immune response to *Leishmania* antigens in an AIDS patient with mucocutaneous leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome (IRIS): a case report. *BMC Infect Dis*. 2015;15:38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25645330.

91. Chrusciak-Talhari A, Ribeiro-Rodrigues R, Talhari C, et al. Tegumentary leishmaniasis as the cause of immune reconstitution inflammatory syndrome in a patient co-infected with human immunodeficiency virus and Leishmania guyanensis. *Am J Trop Med Hyg*. 2009;81(4):559-564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19815866.

92. Sinha S, Fernandez G, Kapila R, Lambert WC, Schwartz RA. Diffuse cutaneous leishmaniasis associated with the immune reconstitution inflammatory syndrome. *Int J Dermatol*. 2008;47(12):1263-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19126013.

93. Tadesse A, Hurissa Z. Leishmaniasis (PKDL) as a case of immune reconstitution inflammatory syndrome (IRIS) in HIV-positive patient after initiation of anti-retroviral therapy (ART). *Ethiop Med J*. 2009;47(1):77-79. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19743785.

94. Antinori S, Longhi E, Bestetti G, et al. Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome. *Br J Dermatol*. 2007;157(5):1032-1036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17854365.

95. Rousset S, Zenou M, Saunier A, et al. Immune recovery-related patterns of post kala-azar dermal and ocular leishmaniasis in people living with HIV. *AIDS*. 2022;36(13):1819-1827. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35848585.

96. Bourgeois N, Bastien P, Reynes J, Makinson A, Rouanet I, Lachaud L. 'Active chronic visceral leishmaniasis' in HIV-1-infected patients demonstrated by biological and clinical long-term follow-up of 10 patients. *HIV Med*. 2010;11(10):670-673. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20500233.

97. Monge-Maillo B, Lopez-Velez R. Treatment options for visceral leishmaniasis and HIV coinfection. *AIDS Rev*. 2016;18(1):32-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26936761.

98. Kip AE, Blesson S, Alves F, et al. Low antileishmanial drug exposure in HIV-positive visceral leishmaniasis patients on antiretrovirals: an Ethiopian cohort study. *J Antimicrob Chemother*. 2021;76(5):1258-1268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33677546.

99. Cota GF, de Sousa MR, Rabello A. Predictors of visceral leishmaniasis relapse in HIV-infected patients: a systematic review. *PLoS Negl Trop Dis*. 2011;5(6):e1153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21666786.

100. Ribera E, Ocana I, de Otero J, Cortes E, Gasser I, Pahissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. *Am J Med*. 1996;100(5):496-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8644760.

101. ter Horst R, Collin SM, Ritmeijer K, Bogale A, Davidson RN. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome. *Clin Infect Dis*. 2008;46(11):1702-1709. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18419422.

102. Lopez-Velez R, Videla S, Marquez M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother*. 2004;53(3):540-543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14739148.

103. Diro E, Ritmeijer K, Boelaert M, et al. Use of pentamidine as secondary prophylaxis to prevent visceral leishmaniasis relapse in HIV infected patients, the first twelve months of a prospective cohort study. *PLoS Negl Trop Dis*. 2015;9(10):e0004087. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26431253.

104. Diro E, Edwards T, Ritmeijer K, et al. Long term outcomes and prognostics of visceral leishmaniasis in HIV infected patients with use of pentamidine as secondary prophylaxis based on CD4 level: a prospective cohort study in Ethiopia. *PLoS Negl Trop Dis*. 2019;13(2):e0007132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30789910.

105. Diro E, Ritmeijer K, Boelaert M, et al. Long-term clinical outcomes in visceral leishmaniasis/human immunodeficiency virus-coinfected patients during and after pentamidine secondary prophylaxis in Ethiopia: a single-arm clinical trial. *Clin Infect Dis*. 2018;66(3):444-451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29020217.

106. Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. *Trop Med Int Health*. 2009;14(9):1064-1070. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19552658.

107. Dorlo TP, Kager PA. Pentamidine dosage: a base/salt confusion. *PLoS Negl Trop Dis*. 2008;2(5):e225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18509543.

108. Berenguer J, Cosin J, Miralles P, Lopez JC, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. *AIDS*. 2000;14(18):2946-2948. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11153679.

109. Adam GK, Abdulla MA, Ahmed AA, Adam I. Maternal and perinatal outcomes of visceral leishmaniasis (kala-azar) treated with sodium stibogluconate in eastern Sudan. *Int J Gynaecol Obstet*. 2009;107(3):208-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19766208.

110. Mueller M, Balasegaram M, Koummuki Y, Ritmeijer K, Santana MR, Davidson R. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother*. 2006;58(4):811-815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16916865.

111. Pagliano P, Carannante N, Rossi M, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother*. 2005;55(2):229-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15649998.

112. Gradoni L, Gaeta GB, Pellizzer G, Maisto A, Scalone A. Mediterranean visceral leishmaniasis in pregnancy. *Scand J Infect Dis*. 1994;26(5):627-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7855563.

113. Topno RK, Pandey K, Das VN, et al. Visceral leishmaniasis in pregnancy - the role of amphotericin B. *Ann Trop Med Parasitol*. 2008;102(3):267-270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18348781.

114. Pekelharing JE, Gatluak F, Harrison T, Maldonado F, Siddiqui MR, Ritmeijer K. Outcomes of visceral leishmaniasis in pregnancy: a retrospective cohort study from South Sudan. *PLoS Negl Trop Dis*. 2020;14(1):e0007992. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31978116.

115. Dahal P, Singh-Phulgenda S, Maguire BJ, et al. Visceral leishmaniasis in pregnancy and vertical transmission: a systematic literature review on the therapeutic orphans. *PLoS Negl Trop Dis*. 2021;15(8):e0009650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34375339.

116. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. *Am J Vet Res*. 1966;27(116):132-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/5913019.

117. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. *Ann N Y Acad Sci*. 1952;55(2):203-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12977037.

118. Rossi F, Acampora R, Vacca C, et al. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. *Teratog Carcinog Mutagen*. 1987;7(5):491-496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2893463.

119. Ito S, Koren G. Estimation of fetal risk from aerosolized pentamidine in pregnant healthcare workers. *Chest*. 1994;106(5):1460-1462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7956402.

120. Morgan DJ, Guimaraes LH, Machado PR, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis*. 2007;45(4):478-482. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17638198.

121. Conceicao-Silva F, Morgado FN, Pimentel MI, et al. Two women presenting worsening cutaneous ulcers during pregnancy: diagnosis, immune response, and follow-up. *PLoS Negl Trop Dis*. 2013;7(12):e2472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24349585.

122. Boehme CC, Hain U, Novosel A, Eichenlaub S, Fleischmann E, Loscher T. Congenital visceral leishmaniasis. *Emerg Infect Dis*. 2006;12(2):359-360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17080586.

123. Meinecke CK, Schottelius J, Oskam L, Fleischer B. Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. *Pediatrics*. 1999;104(5):e65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10545591.

124. Zinchuk A, Nadraga A. Congenital visceral leishmaniasis in Ukraine: case report. *Ann Trop Paediatr*. 2010;30(2):161-164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20522305.

125. Argy N, Lariven S, Rideau A, et al. Congenital leishmaniasis in a newborn infant whose mother was coinfected with leishmaniasis and HIV. *J Pediatric Infect Dis Soc*. 2020;9(2):277-280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31589299.

Malaria

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Epidemiology

Malaria continues to contribute disproportionately to the global burden of infectious diseases, especially in sub-Saharan Africa and Southeast Asia. In 2015, the World Health Organization estimated that 97 countries had ongoing malaria transmission, and almost half the world's population, approximately 3.2 billion people, lived in areas with some risk of malaria transmission.[1] Of the nearly 214 million cases of malaria worldwide in 2015 (based on reports and models), approximately 88% (188 million) occurred in Africa, the area of the world with the highest HIV prevalence.[1] Approximately 438,000 deaths were attributable to malaria in 2015, with ~90% occurring in Africa and 74% of those deaths in children younger than 5 years of age. Fifteen countries, mainly in sub-Saharan Africa, account for 80% of malaria cases and 78% of deaths worldwide.[1] Current attributable morbidity and mortality are likely underestimated, given our limited understanding, surveillance, and reporting of non-falciparum infections.

Malaria typically is transmitted by the bite of an infected female *Anopheles sp*. mosquito. Reports of vertical transmission and infection after blood transfusion do exist, but these routes of transmission are uncommon in non-endemic areas.[2-5]

Malaria in humans can be caused by any one of five species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi* (a zoonotic species that also infects macaques in Southeast Asia).[4] Although *P. vivax* infections are more common and occur in a far wider geographic distribution,[6] *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections. *P. vivax*, however, should not be discounted as a risk for travelers in many parts of the world.

Malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa. Given this substantial overlap, even modest interactions between them have public health importance.[7,8] Malaria influences the natural history of HIV infection, and HIV infection alters the natural history and severity of malaria.[9]

Many foreign-born individuals develop malaria in the United States because of distant exposure before their arrival, or as a result of more recent travel for business or family reasons. Similarly, U.S.-born individuals can develop malaria during travel to endemic areas.[10-13] Failure to take appropriate chemoprophylaxis is a common problem for both groups of individuals.[14,15] People who formerly lived in malarious areas may believe that they are immune, and therefore do not need to take prophylaxis.[16] Such patients are at high risk of infection, however, because they likely have lost partial immunity within 6 months after leaving endemic regions.

Consideration of malaria in returning travelers who are febrile is important: Of the nearly 50 million individuals who travel to developing countries each year, between 5% and 11% develop a fever during or after travel.[17-20] Malaria is a surprisingly common cause of these fevers.[21]

Clinical Manifestations

The clinical syndromes caused by *Plasmodium* species depend on prior exposure.[22] While many native U.S. travelers have no prior immunity, clinical manifestations in those who have resided in malarious areas depend

on whether they lived in an area with stable endemic malaria transmission (year round) or unstable (seasonal, infrequent or very low) transmission.[23]

In stable endemic areas, children younger than age 5 years may experience chronic infections with recurrent parasitemia, resulting in severe anemia and death. Children who survive these infections usually acquire partial immunity by age 5 years, and if they remain in the area where malaria is endemic, they maintain this immunity into adulthood. In stable endemic areas, adults usually experience asymptomatic or milder infections as a result of this acquired immune response. However, as noted previously, patients who leave endemic areas and subsequently return may be at high risk of disease because they likely have lost partial immunity 6 months after leaving endemic regions.

In unstable transmission areas, protective immunity is not acquired. For populations in these areas, the overwhelming clinical manifestation is acute febrile disease that can be complicated by cerebral malaria, affecting persons of all ages.

When pregnant women in areas of unstable transmission develop acute malaria, the consequences may include spontaneous abortion and stillbirth. In more stable transmission areas, pregnant women, particularly primigravidas, may lose some acquired immunity. Although infections may continue to be asymptomatic, infected pregnant women may acquire placental malaria that contributes to intrauterine growth retardation, low birth weight, and increased infant mortality.

Patients with malaria can exhibit various symptoms and a broad spectrum of severity, depending upon factors such as the infecting species and level of acquired immunity in the host. HIV-immunosuppressed patients in endemic areas may lose acquired malarial immunity, and HIV-immunosuppressed adults with little or no previous malaria exposure (such as travelers) appear to be at increased risk of severe outcomes.[24]

The incubation period for *P. falciparum* is from a week to several months, but most often less than 60 days. Patients can present much later (>1 year), but this pattern is more common with other species, especially *P. vivax*. In non-immune patients, typical symptoms of malaria include fever, chills, myalgias and arthralgias, headache, diarrhea, vomiting, and other non-specific signs. Splenomegaly, anemia, thrombocytopenia, pulmonary or renal dysfunction, and neurologic findings also may be present. Classically, paroxysmal fevers occur every 48 hours for *P. falciparum, P. vivax,* and *P. ovale* malaria; those with *P. malariae* occur every 72 hours. This classic presentation is highly variable, however, and may not be present. *P. knowlesi*, known to cause human infection in Southeast Asia in travelers to jungle/forested areas, is clinically indistinguishable from other species of malaria, and the overwhelming majority of patients present with uncomplicated disease (~90%).[25]

Uncomplicated malaria infection can progress to severe disease or death within hours. Malaria with central nervous system symptoms can be particularly ominous. Cerebral malaria refers to unarousable coma not attributable to any other cause in patients infected with *P. falciparum*; in Africa, case fatality rates with cerebral malaria approach 40%.[26-28] The risk of severe and complicated illness is increased in patients with high levels of parasitemia and without partial immunity. Metabolic acidosis is an important manifestation of severe malaria and an indicator of poor prognosis.[29] Other acute complications include renal failure, hypoglycemia, disseminated intravascular coagulation, shock, and acute pulmonary edema.[30] *P. falciparum* is the species most commonly responsible for severe disease and death, although the other species can cause severe disease and death as well.[25,31]

Effect of HIV on Parasitemia and Clinical Severity

HIV infection impairs acquired immunity to malaria that is present in older children and adults in stable endemic areas. Large cohort studies have demonstrated the increased frequency (with rates one- to two-fold higher) of both parasitemia and clinical malaria in HIV-infected adults, with increasing risk and higher-density parasitemia associated with more advanced immunosuppression, particularly among those with CD4 T-lymphocyte (CD4) cell counts <350 cells/mm^3.[32-34] Increased rates of malaria among individuals with HIV do not appear to be as great as the rates observed with classic opportunistic infections such as tuberculosis and *Pneumocystis jirovecii* pneumonia.[35]

In a prospective cohort study in an area with unstable malaria transmission, HIV-infected non-immune adults were found to be at increased risk of severe malaria, and the risk was associated with a low CD4 cell count.[36] Non-immune HIV-infected patients were substantially more likely to have severe clinical malaria than were non-immune patients without HIV. In KwaZulu Natal, an area of unstable malaria transmission, HIV-infected adults hospitalized for malaria were substantially more likely to die or require an intensive care unit admission than those who were not HIV-infected.[37] In contrast, HIV infection did not confer an increased risk of poor outcomes among partially immune adults in areas with more stable transmission.[32] In a cross-sectional study of travelers returning to France from malaria-endemic areas between 2000 and 2003, HIV-infected individuals with CD4 counts <350 cells/mm^3 were at significantly higher risk of developing severe malaria, compared with those who were HIV-negative.[34]

Effects of Malaria on Mother-to-Child HIV Transmission

Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages[38] and increased viral load,[39] raising the possibility of placental malaria leading to increased mother-to-child transmission (MTCT) of HIV. In addition, fetal immune activation by malaria antigens may increase susceptibility to HIV infection.[40] Data are conflicting concerning the effect of malaria during pregnancy on risk of MTCT in the pre-ART era and are limited since the widespread use of ART for prevention of MTCT.[41-43]

Diagnosis

A malaria diagnosis must be considered in all febrile patients who have traveled to or lived in malaria-endemic areas or who have received blood products, tissues, or organs from individuals who have been to such areas.

Several diagnostic methods are available, including microscopic diagnosis, antigen detection tests, polymerase chain reaction-based assays, and serologic tests, though serologic tests which detect host antibody are inappropriate for the diagnosis of acute malaria.

Direct microscopic examination of intracellular parasites on stained blood films is the standard for definitive diagnosis in nearly all settings because it allows for identification of the species and provides a measure of parasite density. Microscopic diagnosis of *P. knowlesi* is difficult because it is commonly misidentified as *P. malariae*, which tends to follow a more benign course. Providers should have a high index of suspicion for *P. knowlesi* in travelers returning from Southeast Asia.[31]

In non-immune patients with all types of malaria, symptoms may develop before detectable levels of parasitemia are evident. For this reason, several blood smear examinations taken at 12- to 24-hour intervals may be needed to positively rule out a diagnosis of malaria in symptomatic patients. Guidelines for laboratory diagnosis are summarized elsewhere and are available at the Centers for Disease Control and Prevention

(CDC)'s malaria website (https://www.cdc.gov/malaria). Rapid diagnostic tests, particularly for the diagnosis of *P. falciparum*, can be used depending on the local expertise and practice and can facilitate prompt diagnosis and treatment of infected patients, but must be followed by microscopy.

Preventing Exposure

Pre-travel evaluation by a travel medicine specialist can provide specific education about risk of exposure in various geographic locales, the utility of insecticide-impregnated bed nets in the setting where the individual will be traveling or residing, and the use of DEET (N,N-diethyl-3-methyl-benzamide)-containing repellants.

Infection with *P. falciparum* can be more severe in HIV-infected patients with low CD4 cell counts and in pregnant women regardless of HIV infection than in other individuals. Because no chemoprophylactic regimen is completely effective, HIV-infected patients with low CD4 cell counts and women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible **(AIII).** If travel to an endemic area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

Preventing Disease

For United States travelers (including HIV-infected patients) to endemic areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. Recommendations for prophylaxis are the same for HIV-infected patients as for those who are not HIV-infected and are available at CDC's malaria website **(AIII)** (https://www.cdc.gov/malaria).

Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.[44] A recent study of HIV-infected patients in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, and then reduced another 50% when antiretroviral (ARV) drugs were provided, and finally reduced another 50% with provision of insecticide-treated nets.[45] However, cotrimoxazole is not as effective an antimalarial prophylactic regimen as the recommended antimalarials. Therefore, HIV-infected travelers should not rely on prophylaxis with cotrimoxazole for chemoprophylaxis against malaria **(AIII).**

Treating Disease

Because *P. falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment **(AIII).** Diagnosis prior to treatment should always be pursued; however, treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed **(AIII).**

Choice of treatment is guided by the degree of parasitemia, the species of *Plasmodium*, a patient's clinical status, and the likely drug susceptibility of the infecting species (as determined by where the infection was acquired).

For HIV-infected patients who do acquire *Plasmodium* infection, treatment recommendations are the same as for HIV-uninfected patients **(AIII).** CDC posts current treatment recommendations on its website (https://www.cdc.gov/malaria) and has clinicians on call 24 hours to provide advice to clinicians on diagnosing and treating malaria (CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours).

Special Considerations with Regard to Starting Antiretroviral Therapy (ART)

There is no reason to defer ART initiation after patients have recovered from acute malaria.

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Careful monitoring of patients (especially those with *P. falciparum* malaria) is necessary, including measurement of peripheral parasitemia and hemoglobin and blood glucose levels, as well as assessment of cerebral, pulmonary, and renal function. Frequency of monitoring depends on severity of disease, a patient's immune status, and the species of *Plasmodium*.

Chemoprophylaxis or treatment for malaria in patients receiving ARV agents requires attention to potential drug interactions. Several potential drug interactions can occur between antimalarial and HIV drugs as well as other medications used to treat HIV-associated opportunistic infections (see Table 4).[46] Providers are also encouraged to check for drug-drug interactions by using an interactive web-based resource from the University of Liverpool at https://www.hiv-druginteractions.org. Mefloquine in repeated doses has been observed to reduce area under the concentration-time curve and maximal plasma concentrations of ritonavir by 31% and 36%, respectively. Insufficient data are available to suggest that dose adjustments are needed.

Quinine levels may be increased by ritonavir-containing regimens or cobicistat; conversely, nevirapine and efavirenz can reduce plasma quinine levels. Potential interactions can occur between ritonavir or cobicistat and chloroquine, but their clinical significance is unclear, and until further data are available, no dose adjustments are recommended.

Artemether-lumefantrine is now approved in the United States for treatment of uncomplicated *P. falciparum* infection. Data in children suggest that this combination is well tolerated and safe in HIV-infected children,[47] however, efficacy data are conflicting in HIV-infected adults. An open-label trial in Tanzania demonstrated excellent efficacy (97.6%) of artemether-lumefantrine for treating uncomplicated *P. falciparum* malaria in HIV-infected adults on nevirapine-based ART.[48] Conversely, 28-day clinical and parasitologic response was sub-optimal in the efavirenz-based ART group, with efficacy of 82.5%, and a 19-fold increased risk of recurrent parasitemia compared to the control group of HIV-infected adults not on ART.[48] Artesunate is available for treatment of severe malaria through a compassionate use Investigational New Drug application. A trial in Uganda demonstrated the effectiveness of artesunate plus amodiaquine in HIV-infected children, but treatment was associated with increased risk of neutropenia in those on ART, particularly zidovudine, which was attributed to the amodiaquine component of therapy.[49]

Ritonavir or cobicistat-boosted ARV regimens and non-nucleoside reverse transcriptase inhibitors have the potential to affect metabolism of artemisinin-containing drugs,[50] but the overall effect and clinical significance remain unclear. No dose alterations currently are recommended.

No immune reconstitution inflammatory syndrome (IRIS) has been described in association with malaria.

Managing Treatment Failure

HIV-infected individuals are at increased risk of malaria treatment failure.[51] Management of treatment failure is the same in HIV-infected and HIV-uninfected patients, except for considerations about drug interactions between ART and antimalarial drugs. Drug-resistant malaria and possible concomitant infections should be considered in HIV-infected patients whose malaria fails to respond to therapy.

Preventing Recurrence

If the species of malaria identified is *P. vivax* or *P. ovale*, which can cause recurrence due to hepatic phase of infection, then treatment with primaquine in addition to standard treatment is recommended to prevent recurrence **(AI).** Guidelines for primaquine treatment do not differ in HIV-infected individuals.

Special Considerations During Pregnancy

Malaria in pregnancy affects both mother and fetus. Infection with *P. falciparum* during pregnancy can increase maternal risk of severe disease and anemia and risk for stillbirth, preterm birth, and low birth weight.[52] The diagnosis of malaria in pregnant women is the same as in women who are not pregnant.

For pregnant women with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended.[53] For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with mefloquine for 7 days is recommended. For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with mefloquine or quinine and clindamycin is recommended as per CDC guidelines.[54]

On the basis of extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria in pregnancy. Although quinine at high doses has been associated with an increased risk of birth defects (especially deafness) in some animal species and humans (usually during attempted abortion), use of therapeutic doses in pregnancy is considered safe.[53,55] Because of the potential for hypoglycemia, glucose levels should be monitored in pregnant women treated with quinine and their neonates. Clindamycin use has not been associated with birth defects. Animal and human data on use of prophylactic and treatment doses of mefloquine do not suggest teratogenicity and the drug can be used safely during all trimesters.[56] One randomized trial of mefloquine used in addition to daily cotrimoxazole for malaria prophylaxis in pregnant women living with HIV demonstrated an increased risk of transmission of HIV to the infant in the mefloquine arm, potentially because of drug interactions.[57] Although experience is limited, available data on artemether-lumefantrine during pregnancy suggest that use is not associated with increased adverse events or birth defects.[58] A pharmacokinetic study in HIV-uninfected women found no difference in levels between pregnant and non-pregnant subjects except for small differences in elimination half-life of lumefantrine.[59] Data on pharmacokinetics in HIV-infected pregnant women were not included. Because of limited data, atovaquone-proguanil is not recommended for treatment in pregnancy and should be used only if quinine plus clindamycin, quinine monotherapy, or mefloquine are unavailable or not tolerated.[55] Tetracyclines are not recommended in pregnancy because of increased risk of maternal hepatotoxicity and staining of fetal teeth and bones. Primaquine use during pregnancy is not recommended because of limited experience with its use and the potential for fetal glucose-6-phosphate dehydrogenase (G6PD) deficiency. After treatment, all pregnant women with *P. vivax* and *P. ovale* should receive chloroquine prophylaxis for the duration of pregnancy to avoid relapses. Once-weekly mefloquine can be used for prophylaxis in pregnant women with *P. vivax* acquired in an area with chloroquine-resistant strains. Women who have normal G6PD screening tests can be treated with primaquine after delivery.

Recommendations for Preventing and Treating Malaria

Preventing Malaria in Patients Traveling to Endemic Areas:

- Recommendations are the same for HIV-infected and HIV-uninfected patients.
- Specific recommendations are based on region of travel, malaria risks, and drug susceptibility in the region.
- Clinicians should refer to the following website for the most up-to-date recommendations: https://www.cdc.gov/malaria
- TMP-SMX has been shown to reduce malaria in HIV-infected adults in Africa. However, it is not as effective as antimalarial prophylactic regimens. Therefore, HIV-infected travelers should not rely on TMP-SMX for prophylaxis against malaria (AIII).

Treating Malaria

- Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infection should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to therapy (AIII).
- When suspicion of malaria is low, antimalarial treatment should not be initiated until the diagnosis has been confirmed by laboratory investigations.
- Treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed (AIII).
- When malaria is strongly suspected, but not yet confirmed, clinicians are advised to consider and initiate treatment for other possible diagnoses in addition to malaria.
- Treatment recommendations for HIV-infected patients are the same as HIV-uninfected patients (AIII).
- Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, and the likely drug susceptibility of the infected species.
- For treatment recommendations for specific region, clinicians should refer to
  - The CDC malaria website: https://www.cdc.gov/malaria
  - The CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours.

Key: CDC = the Centers for Disease Control and Prevention; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. World Health Organization. World Malaria Report 2015. 2015.Available at: https://www.who.int/publications/i/item/9789241565158. Accessed: April 5, 2016.

2. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med*. 2001;344(26):1973-1978. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11430326.

3. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis. Modern parallels. *JAMA*. 1992;268(4):516-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1619744.

4. Mali S, Steele S, Slutsker L, Arguin PM, Centers for Disease Control and Prevention. Malaria surveillance - United States, 2008. *MMWR Surveill Summ*. 2010;59(7):1-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20577158.

5. Centers for Disease Control and Prevention. Update: self-induced malaria associated with malariotherapy for Lyme disease--Texas. *MMWR Morb Mortal Wkly Rep*. 1991;40(39):665-666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1896006.

6. Guerra CA, Howes RE, Patil AP, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. *PLoS Negl Trop Dis*. 2010;4(8):e774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20689816.

7. Korenromp EL, Williams BG, de Vlas SJ, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. *Emerg Infect Dis*. 2005;11(9):1410-1419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16229771.

8. Van Geertruyden JP, Menten J, Colebunders R, Korenromp E, D'Alessandro U. The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance. *Malar J*. 2008;7:134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18647387.

9. Slutsker L, Marston BJ. HIV and malaria: interactions and implications. *Curr Opin Infect Dis*. 2007;20(1):3-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17197875.

10. Kemper CA, Linett A, Kane C, Deresinski SC. Frequency of Travel of Adults Infected with HIV. *J Travel Med*. 1995;2(2):85-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9815367.

11. Simons FM, Cobelens FG, Danner SA. Common health problems in HIV-infected travelers to the (sub)tropics. *J Travel Med*. 1999;6(2):71-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10381957.

12. Castelli F, Patroni A. The human immunodeficiency virus-infected traveler. *Clin Infect Dis*. 2000;31(6):1403-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11096010.

13. Bhadelia N, Klotman M, Caplivski D. The HIV-positive traveler. *Am J Med*. 2007;120(7):574-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17602926.

14. Smego RA, Jr. Effectiveness of antimalarial drugs. *N Engl J Med*. 2005;353(4):420-422; author reply 420-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16050053.

15. Suh KN, Mileno MD. Challenging scenarios in a travel clinic: advising the complex traveler. *Infect Dis Clin North Am*. 2005;19(1):15-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15701545.

16. Sherrard AW, McCarthy AE. Travel patterns and health risks for patients infected with HIV. *Travel Med Infect Dis*. 2009;7(5):291-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19747664.

17. Ryan ET, Wilson ME, Kain KC. Illness after international travel. *N Engl J Med*. 2002;347(7):505-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181406.

18. Spira AM. Assessment of travellers who return home ill. *Lancet*. 2003;361(9367):1459-1469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12727414.

19. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis*. 1987;156(1):84-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3598228.

20. Winer L, Alkan M. Incidence and precipitating factors of morbidity among Israeli travelers abroad. *J Travel Med*. 2002;9(5):227-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12962594.

21. Wilson ME, Weld LH, Boggild A, et al. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis*. 2007;44(12):1560-1568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17516399.

22. Mackinnon MJ, Marsh K. The selection landscape of malaria parasites. *Science*. 2010;328(5980):866-871. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20466925.

23. Snow RW, Marsh K. The consequences of reducing transmission of Plasmodium falciparum in Africa. *Adv Parasitol*. 2002;52:235-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12521262.

24. Matteelli A, Casalini C, Bussi G, et al. Imported malaria in an HIV-positive traveler: a case report with a fatal outcome. *J Travel Med*. 2005;12(4):222-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16086898.

25. Daneshvar C, Davis TM, Cox-Singh J, et al. Clinical and laboratory features of human Plasmodium knowlesi infection. *Clin Infect Dis*. 2009;49(6):852-860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19635025.

26. Severe and complicated malaria. World Health Organization, Division of Control of Tropical Diseases. *Trans R Soc Trop Med Hyg*. 1990;84 Suppl 2(Suppl 2):1-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2219249.

27. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. *Bull World Health Organ*. 1989;67(2):189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2743538.

28. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med*. 1989;71(265):441-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2690177.

29. English M, Sauerwein R, Waruiru C, et al. Acidosis in severe childhood malaria. *QJM*. 1997;90(4):263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9307760.

30. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med*. 1995;332(21):1399-1404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7723795.

31. Cox-Singh J, Davis TM, Lee KS, et al. Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis*. 2008;46(2):165-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18171245.

32. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet*. 2000;356(9235):1051-1056. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11009139.

33. Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis*. 2005;192(6):984-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16107950.

34. Mouala C, Guiguet M, Houze S, et al. Impact of HIV infection on severity of imported malaria is restricted to patients with CD4 cell counts < 350 cells/microl. *AIDS*. 2009;23(15):1997-2004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19654499.

35. Laufer MK, van Oosterhout JJ, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi. *J Infect Dis*. 2006;193(6):872-878. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16479522.

36. Cohen C, Karstaedt A, Frean J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis*. 2005;41(11):1631-1637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16267737.

37. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS*. 2004;18(3):547-554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15090809.

38. Tkachuk AN, Moormann AM, Poore JA, et al. Malaria enhances expression of CC chemokine receptor 5 on placental macrophages. *J Infect Dis*. 2001;183(6):967-972. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11237815.

39. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of Plasmodium falciparum malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. *AIDS*. 2004;18(7):1051-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15096809.

40. Steiner K, Myrie L, Malhotra I, et al. Fetal immune activation to malaria antigens enhances susceptibility to in vitro HIV infection in cord blood mononuclear cells. *J Infect Dis*. 2010;202(6):899-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20687848.

41. Msamanga GI, Taha TE, Young AM, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. *Am J Trop Med Hyg*. 2009;80(4):508-515. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19346367.

42. Bulterys PL, Chao A, Dalai SC, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1 in rural Rwanda. *Am J Trop Med Hyg*. 2011;85(2):202-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21813835.

43. Ezeamama AE, Duggan C, Manji KP, et al. Clinical malaria diagnosis in pregnancy in relation to early perinatal mother-to-child transmission of HIV: a prospective cohort study. *HIV Med*. 2014;15(5):276-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24215465.

44. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. 1999;353(9163):1463-1468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10232311.

45. Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. *Lancet*. 2006;367(9518):1256-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16631881.

46. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. *AIDS*. 2005;19(10):995-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15958830.

47. Katrak S, Gasasira A, Arinaitwe E, et al. Safety and tolerability of artemether-lumefantrine versus dihydroartemisinin-piperaquine for malaria in young HIV-infected and uninfected children. *Malar J*. 2009;8:272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19948038.

48. Maganda BA, Minzi OM, Kamuhabwa AA, Ngasala B, Sasi PG. Outcome of artemether-lumefantrine treatment for uncomplicated malaria in HIV-infected adult patients on anti-retroviral therapy. *Malar J*. 2014;13:205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24885714.

49. Gasasira AF, Kamya MR, Achan J, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis*. 2008;46(7):985-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18444813.

50. Parikh S, Gut J, Istvan E, Goldberg DE, Havlir DV, Rosenthal PJ. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. *Antimicrob Agents Chemother*. 2005;49(7):2983-2985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15980379.

51. Van Geertruyden JP, Mulenga M, Mwananyanda L, et al. HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria. *J Infect Dis*. 2006;194(7):917-925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16960779.

52. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. 2007;7(2):93-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17251080.

53. Griffith KS, Lewis LS, Mali S, Parise ME. Treatment of malaria in the United States: a systematic review. *JAMA*. 2007;297(20):2264-2277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17519416.

54. Centers for Disease Control and Prevention. Part 3: Alternatives for Pregnant Women and Treatment of Severe Malaria. In: Secondary Centers for Disease Control and Prevention, ed^eds. Subsidiary Centers for Disease Control and Prevention, trans. Secondary Part 3: Alternatives for Pregnant Women and Treatment of Severe Malaria. Vol. ed.: 2013.

55. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. *Trans R Soc Trop Med Hyg*. 2002;96(2):180-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12055810.

56. Centers for Disease Control and Prevention. Update: New Recommendations for Mefloquine Use in Pregnancy. 2011. Available at: http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html.

57. Gonzalez R, Desai M, Macete E, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. *PLoS Med*. 2014;11(9):e1001735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25247995.

58. Manyando C, Kayentao K, D'Alessandro U, Okafor HU, Juma E, Hamed K. A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated Plasmodium falciparum malaria during pregnancy. *Malar J*. 2012;11:141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22548983.

59. Nyunt MM, Nguyen VK, Kajubi R, et al. Artemether-Lumefantrine Pharmacokinetics and Clinical Response Are Minimally Altered in Pregnant Ugandan Women Treated for Uncomplicated Falciparum Malaria. *Antimicrob Agents Chemother*. 2015;60(3):1274-1282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26666942.

Microsporidiosis

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Epidemiology

Microsporidia are protists related to fungi, defined by the presence of a unique invasive organelle consisting of a single polar tube that coils around the interior of the spore. They are ubiquitous organisms and are likely zoonotic and/or waterborne in origin. Phylogenetic studies now place microsporidia with the Cryptomycota as the basal branch of the fungal kingdom (or alternatively as a sister phylum).[1] The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon* (syn *Septata*) *intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* species, *Pleistophora ronneafiei*, *Vittaforma* (syn *Nosema*) *corneae*, *Tubulonosema acridophagus*, *Endoreticulatus* sp., *Nosema ocularum*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, *Anncaliia* (syns *Brachiola/Nosema*) *algerae*, and *Microsporidium* sp.[2-8] In the pre-antiretroviral therapy (ART) era, reported prevalence rates of microsporidiosis varied between 2% and 70% among people with HIV/AIDS with diarrhea, depending on the diagnostic techniques employed and the population described.[3-5,8] The incidence of microsporidiosis has declined with the widespread use of effective ART, but it continues to occur among people with HIV who are unable to obtain ART or to remain on it.[9] Microsporidiosis is increasingly recognized among people without HIV, including children, travelers, organ transplant recipients, contact lens wearers, and the elderly. In people with immune suppression, clinical signs related to microsporidiosis[3-5,8] are most commonly observed when CD4 T lymphocyte (CD4) cell counts are <100 cells/mm^3.

Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection have also been described.[3-5,8]

Clinical syndromes can vary by infecting species. *E. bieneusi* is associated with malabsorption, diarrhea, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Anncaliia*, *Vittaforma*, and *Trachipleistophora* are associated with keratoconjunctivitis. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

Diagnosis

Effective morphologic demonstration of microsporidia by light microscopy can be accomplished with staining methods that produce differential contrast between the spores of the microsporidia and the cells and debris in clinical samples, such as stool. In addition, because of the small size of the spores (1–5 mm), magnification up to 1,000 times is required for visualization. Chromotrope 2R and

the fluorescent brighteners calcofluor white and Uvitex 2B are useful as selective stains for microsporidia in stool and other body fluids.[7]

In biopsy specimens, microsporidia can be visualized with Giemsa, tissue Gram stains (Brown-Hopps Gram stain), calcofluor white or Uvitex 2B (fluorescent brighteners) staining, Warthin-Starry silver staining, or Chromotrope 2A.[7] In gastrointestinal disease, examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool examination is negative and microsporidiosis is suspected, a small bowel biopsy may be useful. If the etiologic agent is *Encephalitozoon* or *Trachipleistophora* sp., examination of urine often also reveals the organism. Determination of the species of microsporidia causing disease can be made by the morphology of the organism demonstrated by transmission electron microscopy, by staining with species-specific antibodies, or by polymerase chain reaction using species- or genus-specific primers.[7,10] The assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

People with HIV who have CD4 counts <200 cells/mm^3 should avoid untreated water sources **(AIII).** Additional recommendations include increasing attention to hand washing and personal hygiene, avoiding eating undercooked meat or seafood, and limiting exposure to animals known to be infected with microsporidia **(BIII).**[11] The precautions described in the section on cryptosporidiosis also are applicable to microsporidiosis.

Preventing Disease

Preventing Chronic Microsporidiosis
• Because chronic microsporidiosis occurs primarily in people with advanced immunodeficiency, initiate ART before severe immunosuppression occurs (AII).

Key: ART = antiretroviral therapy

Because chronic microsporidiosis occurs primarily in people with advanced immunodeficiency, appropriate initiation of ART before severe immunosuppression should prevent this disease **(AII).** No specific chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treating Disease

Managing Microsporidiosis
• Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 (AII).
• Manage severe dehydration, malnutrition, and wasting with fluid support (AII) and nutritional supplements (AIII).
• Antimotility agents can be used for diarrhea control, if required (BIII).
GI Infections Caused by Enterocytozoon bieneusi
• The best treatment option is ART and fluid support (AII).
• No specific therapeutic agent is available for this infection.
• Fumagillin 60 mg PO daily (BII) and TNP-470 (BIII) (unavailable in the United States)

- Nitazoxanide 500 mg twice daily for at least 14 days may resolve chronic diarrhea and is a reasonable alternative if fumagillin is not available (CIII), but the effect appeared to be minimal in people with low CD4 counts.

Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than E. bieneusi and Vittaforma corneae

- Albendazole is recommended only for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* (AII). Albendazole 400 mg PO twice daily (AII) for at least 14 days; continue therapy until the CD4 count is >200 cells/mm^3 after initiation of ART (BIII).

Disseminated Disease Caused by Trachipleistophora or Anncaliia

- Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily (CIII)

Ocular Infection

- Topical fumagillin bicylohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops four times daily (investigational use only in the United States; needs to be prepared by a compounding pharmacy) (BII), *and*
- Albendazole 400 mg PO twice daily for management of systemic infection (BIII)
- For people with CD4 count >200 cells/mm^3, therapy can be discontinued after ocular infection resolves (CIII).
- For people with CD4 count ≤200 cells/mm^3, therapy should be continued indefinitely as recurrence or relapse may occur when therapy is discontinued (BIII).

Discontinuation of Chronic Maintenance Therapy for Non-Ocular Manifestations (BIII)

- No longer have signs and symptoms of microsporidiosis, *and*
- Sustained increase in CD4 count >200 cells/mm^3 for ≥3 months after ART

Pregnancy Considerations

- Albendazole is not recommended for use during the first trimester (BIII); use in later pregnancy should be considered only if benefits outweigh potential risks (CIII).
- Fumagillin has an antiangiogenic effect and should not be used systemically during pregnancy (AIII). Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate (CIII).
- Nitazoxanide has not been associated with adverse outcomes in pregnancy; however, data are very limited on its use during pregnancy (CIII).
- Azole antifungals should be avoided during the first trimester (BIII).
- Loperamide should be avoided in the first trimester unless benefits outweigh potential risks of congenital malformations (CIII). Loperamide is the preferred antimotility agent in late pregnancy (CIII).
- Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium is not recommended in late pregnancy (AIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; GI = gastrointestinal; PO = orally

Data suggest that treatment with ART enables a person's own defenses to eradicate microsporidia,[12,13] and administration of ART with immune restoration (an increase in CD4 count to >100 cells/mm^3) is associated with resolution of symptoms of enteric microsporidiosis, including illness caused by *E. bieneusi*.[12-15] Everyone, therefore, should be offered ART as part of the initial management of microsporidial infection **(AII),** and they should be given fluid support if they have signs of diarrhea and dehydration **(AII).** People with malnutrition and wasting should be treated with nutritional supplementation **(AIII).** Antimotility agents can be used if required for diarrhea control **(BIII).**

No specific therapeutic agent is available for *E. bieneusi* infection. Based on results from a controlled clinical trial, oral fumagillin (60 mg/day), a water-insoluble antibiotic made from *Aspergillus fumigatus* **(BII),**[16,17] or to its synthetic analog, TNP-470 can be administered **(BIII).**[18] Fumagillin and TNP-470 are not commercially available for systemic use in the United States, and Sanofi in France no longer produces FLISINT (fumagillin). One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART;[19] however, the effect appeared to be minimal among people with low CD4 counts. Based on the professional experience of several experts who have treated diarrhea caused by *E. bieneusi* with nitazoxanide in organ transplant recipients, nitazoxanide is a reasonable alternative for the treatment of diarrhea due to *E. bieneusi* if fumagillin is not available **(CIII).**[20]

Albendazole, a benzimidazole that binds to β-tubulin, has activity against many species of microsporidia, but it is not effective against *E. bieneusi* or *V. corneae* infections. The tubulin genes of both *E. bieneusi*[21] and *V. corneae*[22] have amino acid residues associated with albendazole resistance. Albendazole is recommended only for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII).**[23-25]

Itraconazole may be useful in disseminated disease when combined with albendazole, especially in infections caused by *Trachipleistophora* or *Anncaliia* **(CIII).** Treatment with furazolidone (an agent that is not currently available in the United States) combined with albendazole was reported to improve clinical signs in four people with HIV with persistent diarrhea and *E. bieneusi* infection **(CIII)**[26]; however, furazolidone has not been demonstrated to be active in other case reports. Metronidazole and atovaquone are not active *in vitro* or in animal models and **should not be used** to treat microsporidiosis **(AII).**

People with ocular infections caused by microsporidia should be administered topical Fumidil B (fumagillin bicylohexylammonium) in saline (to achieve a concentration of 70 µg/mL of fumagillin) **(BII).**[23] Topical fumagillin solution needs to be made by a compounding pharmacy because it is not commercially available in the United States and is investigational. Although clearance of microsporidia from the eye can be demonstrated, the organism often is still present systemically and can be detected in urine or in nasal smears; therefore, the use of albendazole as a companion systemic agent to fumagillin is recommended in ocular infections **(BIII).**

Special Considerations with Regard to Starting ART

As noted above, people with HIV should be offered ART as part of the initial management of microsporidial infection, as well as fluid support if they have signs of diarrhea and dehydration **(AII).** Data suggest that treatment with ART, which results in immune reconstitution, enables a person's own defenses to eradicate microsporidia.[12,13]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Although side effects with albendazole are rare, hepatic enzymes should be monitored because elevations have been reported. Albendazole is not known to be carcinogenic or mutagenic. Topical fumagillin has not been associated with substantial side effects. Oral fumagillin has been associated with thrombocytopenia, which is reversible after stopping the drug.

One report of immune reconstitution inflammatory syndrome (IRIS) has been described in a person with HIV treated with ART in the setting of *E. bieneusi* infection;[27] however, no IRIS reactions have

been reported with other species of microsporidia or with other cases of *E. bieneusi*. Concerns about IRIS should not alter therapy or the use of ART **(AIII).**

Managing Treatment Failure

Supportive treatment and optimization of ART to attempt to achieve full virologic suppression are the only currently feasible approaches to managing treatment failure **(AIII).**

Preventing Recurrence

In individuals with relatively competent immune systems (>200 CD4 cells/mm^3), treatment should be discontinued after ocular infection resolves **(CIII);** treatment should be continued indefinitely if CD4 counts fall below 200 cells/mm^3 because recurrence or relapse may occur after treatment discontinuation **(BIII).** Whether it is safe to discontinue treatment for other manifestations after immune restoration with ART is unknown. Based on experience with discontinuation of secondary prophylaxis for other opportunistic infections, it is reasonable to discontinue chronic maintenance therapy in those who no longer have signs and symptoms of microsporidiosis and have a sustained increase in their CD4 counts to >200 cells/mm^3 for 3 to 6 months after ART **(BIII).**[13]

Special Considerations During Pregnancy

During pregnancy, rehydration and initiation of ART are the preferred initial treatment of microsporidiosis as for all people with HIV **(AII).** In rats and rabbits, albendazole is embryotoxic and teratogenic at exposure levels less than those estimated with therapeutic human dosing. There are no adequate and well-controlled studies of albendazole exposure in early human pregnancy. A recent randomized trial in which albendazole was used for second-trimester treatment of soil-transmitted helminth infections found no evidence of teratogenicity or other adverse pregnancy effects.[28]

Based on these data, albendazole **is not recommended** for use during the first trimester **(BIII);** use in later pregnancy should be considered only if benefits outweigh potential risks **(CIII).** Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, because of the antiangiogenic effect of fumagillin, this drug **should not be used** systemically during pregnancy **(AIII).** Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate **(CIII).** Furazolidone is not teratogenic in animal studies, but human data are limited to a case series that found no association between first-trimester use of furazolidone and birth defects in 132 furazolidone-exposed pregnancies.[29] Nitazoxanide has not been associated with adverse outcomes in pregnancy; however, data are very limited on its use during pregnancy **(CIII).** Case reports exist of birth defects in infants exposed to itraconazole, but prospective cohort studies of >300 women with first-trimester exposure did not show an increased risk of malformation.[30,31] In general, however, azole antifungals should be avoided during the first trimester **(BIII).** Loperamide is poorly absorbed and has not been associated with birth defects in animal studies; however, a recent study identified an increased risk of congenital malformations, specifically hypospadias, among 683 women with exposure to loperamide in early pregnancy.[32] Therefore, loperamide should be avoided in the first trimester unless benefits outweigh potential risks **(CIII).** Loperamide is the preferred antimotility agent in late pregnancy **(CIII).** Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium **is not recommended** in late pregnancy **(AIII).**

References

1. James TY, Pelin A, Bonen L, et al. Shared signatures of parasitism and phylogenomics unite Cryptomycota and microsporidia. *Curr Biol*. 2013;23(16):1548-1553. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23932404.

2. Beauvais B, Sarfati C, Molina JM, Lesourd A, Lariviere M, Derouin F. Comparative evaluation of five diagnostic methods for demonstrating microsporidia in stool and intestinal biopsy specimens. *Ann Trop Med Parasitol*. 1993;87(1):99-102. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8346996.

3. Deplazes P, Mathis A, Weber R. Epidemiology and zoonotic aspects of microsporidia of mammals and birds. *Contrib Microbiol*. 2000;6:236-260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10943515.

4. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. *Adv Parasitol*. 1998;40:321-349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9554078.

5. Mathis A. Microsporidia: emerging advances in understanding the basic biology of these unique organisms. *Int J Parasitol*. 2000;30(7):795-804. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10899524.

6. Weber R, Bryan RT, Owen RL, Wilcox CM, Gorelkin L, Visvesvara GS. Improved light-microscopical detection of microsporidia spores in stool and duodenal aspirates. The Enteric Opportunistic Infections Working Group. *N Engl J Med*. 1992;326(3):161-166. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1370122.

7. Weiss LM, Vossbrinck CR. Microsporidiosis: molecular and diagnostic aspects. *Adv Parasitol*. 1998;40:351-395. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9554079.

8. Wittner M, Weiss L. The microsporidia and microsporidiosis. Washington D.C.: ASM Press; 1999.

9. Stark D, Barratt JL, van Hal S, Marriott D, Harkness J, Ellis JT. Clinical significance of enteric protozoa in the immunosuppressed human population. *Clin Microbiol Rev*. 2009;22(4):634-650. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19822892.

10. Sheoran AS, Feng X, Singh I, et al. Monoclonal antibodies against Enterocytozoon bieneusi of human origin. *Clin Diagn Lab Immunol*. 2005;12(9):1109-1113. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16148179.

11. Didier ES, Weiss LM. Microsporidiosis: current status. *Curr Opin Infect Dis*. 2006;19(5):485-492. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16940873.

12. Goguel J, Katlama C, Sarfati C, Maslo C, Leport C, Molina JM. Remission of AIDS-associated intestinal microsporidiosis with highly active antiretroviral therapy. *AIDS*. 1997;11(13):1658-1659. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9365777.

13. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2000;25(2):124-129. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11103042.

14. Conteas CN, Berlin OG, Speck CE, Pandhumas SS, Lariviere MJ, Fu C. Modification of the clinical course of intestinal microsporidiosis in acquired immunodeficiency syndrome patients by immune status and anti-human immunodeficiency virus therapy. *Am J Trop Med Hyg*. 1998;58(5):555-558. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9598440.

15. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. 2000;19(3):213-217. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10795595.

16. Molina JM, Goguel J, Sarfati C, et al. Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. ANRS 054 Study Group. Agence Nationale de Recherche sur le SIDA. *AIDS*. 2000;14(10):1341-1348. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10930148.

17. Molina JM, Tourneur M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med*. 2002;346(25):1963-1969. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12075057.

18. Didier PJ, Phillips JN, Kuebler DJ, et al. Antimicrosporidial activities of fumagillin, TNP-470, ovalicin, and ovalicin derivatives in vitro and in vivo. *Antimicrob Agents Chemother*. 2006;50(6):2146-2155. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16723577.

19. Bicart-See A, Massip P, Linas MD, Datry A. Successful treatment with nitazoxanide of Enterocytozoon bieneusi microsporidiosis in a patient with AIDS. *Antimicrob Agents Chemother*. 2000;44(1):167-168. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10602740.

20. Saffo Z, Mirza N. Successful treatment of Enterocytozoon bieneusi gastrointestinal infection with nitazoxanide in a immunocompetent patient. *IDCases*. 2019;18:e00586. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31388488.

21. Akiyoshi DE, Weiss LM, Feng X, et al. Analysis of the beta-tubulin genes from Enterocytozoon bieneusi isolates from a human and rhesus macaque. *J Eukaryot Microbiol*. 2007;54(1):38-41. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17300517.

22. Franzen C, Salzberger B. Analysis of the beta-tubulin gene from Vittaforma corneae suggests benzimidazole resistance. *Antimicrob Agents Chemother*. 2008;52(2):790-793. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18056284.

23. Diesenhouse MC, Wilson LA, Corrent GF, Visvesvara GS, Grossniklaus HE, Bryan RT. Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol*. 1993;115(3):293-298. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8117342.

24. Dieterich DT, Lew EA, Kotler DP, Poles MA, Orenstein JM. Treatment with albendazole for intestinal disease due to Enterocytozoon bieneusi in patients with AIDS. *J Infect Dis*. 1994;169(1):178-183. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8277179.

25. Molina JM, Chastang C, Goguel J, et al. Albendazole for treatment and prophylaxis of microsporidiosis due to Encephalitozoon intestinalis in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis*. 1998;177(5):1373-1377. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9593027.

26. Dionisio D, Manneschi LI, Di Lollo S, et al. Persistent damage to Enterocytozoon bieneusi, with persistent symptomatic relief, after combined furazolidone and albendazole in AIDS patients. *J Clin Pathol*. 1998;51(10):731-736. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10023334.

27. Sriaroon C, Mayer CA, Chen L, Accurso C, Greene JN, Vincent AL. Diffuse intra-abdominal granulomatous seeding as a manifestation of immune reconstitution inflammatory syndrome associated with microsporidiosis in a patient with HIV. *AIDS Patient Care STDS*. 2008;22(8):611-612. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18627278.

28. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. *Am J Trop Med Hyg*. 2008;79(6):856-863. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19052293.

29. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton: Publishing Sciences Group; 1977.

30. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19338381.

31. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. 2000;183(3):617-620. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10992182.

32. Kallen B, Nilsson E, Otterblad Olausson P. Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatr*. 2008;97(5):541-545. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18394096.

Mpox

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Epidemiology

Mpox (formerly monkeypox) is a zoonotic viral disease caused by monkeypox virus (MPXV), an enveloped double-stranded DNA virus that belongs to the *Orthopoxvirus* genus of the Poxviridae family, which also includes the causative agent of smallpox. MPXV circulates among certain small mammals found in the forested regions of western and central Africa, creating a reservoir of disease in the animal population that is believed to have been the source of the first human case in 1970.[1] Infections remained limited to western and central Africa, with rare travel-related cases outside this region until 2022. Two main clades of MPXV have been described in different geographic regions of Africa; clade I (previously called Congo Basin clade) has historically been associated with more severe disease and more human-to-human transmission than clade II (previously called West African clade).[2-4] Each clade has two distinct subclades: clades Ia and Ib, and clades IIa and IIb.[5]

During May 2022, a multinational outbreak of clade II (subclade IIb) mpox emerged, causing more than 100,000 illnesses in over 120 countries as of November 2024.[6] This outbreak was largely controlled by 2023; however, in the United States, clade IIb MPXV continues to circulate at low levels.[6] The majority of infections have been transmitted sexually through intimate contact with one or more mpox lesions on the skin or mucosal surfaces of people with mpox.[7] Transmission has also rarely occurred through occupational exposure through injuries via contaminated sharps. In the United States, infections have disproportionately affected gay, bisexual, and other men who have sex with men (MSM). Infections in women and children have been reported.[8-16] Among MSM, coinfection with HIV and other sexually transmitted infections (STIs) has been common.[8] Across reports, around 40 to 50% of cases have been in people with HIV, and around 15 to 30% of cases have been diagnosed concomitantly with gonorrhea, syphilis, chlamydia, or other STIs.[8,9,17,18] Severe and fatal cases have disproportionately been reported in people with HIV, especially among people with advanced or uncontrolled HIV.[19-30] Although the overall mortality rate for clade II infection is low (<1%), mortality risk is higher among people with HIV that is advanced or not virologically suppressed.[26-33]

During January 2024, a separate outbreak of clade I mpox emerged in the Democratic Republic of Congo and spread to parts of eastern and southern Africa. Cases of clade I mpox outside of Africa have been rare and, as of this writing, are limited to individual travelers returning from Africa and their immediate household contacts.[6,34,35]

Clinical Manifestations

In outbreaks prior to 2022, mpox cases had been characterized by prodromal symptoms of fever, headache, lymphadenopathy, myalgias, or fatigue followed by a distinctive rash that progressed synchronously from macules to papules, vesicles, pustules, and, ultimately, crusted lesions. People with advanced HIV experienced longer duration of illness, larger sized lesions, more frequent secondary bacterial infections, and the presence of genital ulcers.[29,31]

During the 2022 multinational mpox outbreak and among ongoing cases in the United States, the clinical manifestations associated with clade II infection are distinct in several respects.[9,36] Prodromal symptoms have been mild or absent and have not always preceded the rash.[36] Rash commonly occurs as anogenital or oropharyngeal/perioral lesions but has also involved the limbs, face, and trunk.[9,36] Lesions can be single or multiple, limited to a single body site, and can progress in varying stages asynchronously.[9,36] Inguinal, cervical, and/or axillary lymphadenopathy can be present but not as reliably as with classic presentations.[36]

People with well-controlled HIV typically experience self-limiting disease and recover with supportive care alone.[37] Nonetheless, mpox can cause significant pain, especially in sensitive anatomic sites, including the oropharynx, genitals, and anorectum, where it can lead to other complications. Pharyngeal involvement can result in tonsillitis or pharyngitis associated with odynophagia or dysphagia.[9] Inflammation from genital lesions can produce dysuria, occasionally complicated by significant paraphimosis/phimosis or urethritis that limits the ability to urinate.[30,38,39] Anorectal involvement can cause tenesmus, proctitis, and rectal bleeding.[9,40] Gastrointestinal manifestations, such as enteritis or colitis, and anogenital involvement can necessitate hospitalization for enhanced symptom control or pain management.[9,30,39] Lesions have led to stricture and scar formation, causing urethral or bowel obstruction.[30,39] Ocular involvement from autoinoculation can result in conjunctivitis, blepharitis, keratitis, corneal ulcer with possible scarring, and, in rare cases, loss of vision.[41-43] Bacterial superinfections (e.g., staphylococcal skin and soft tissue infections) can also occur.[30] Other reported manifestations have included necrotizing digestive tract lesions, diffuse nodular pulmonary disease with infarcts and bronchopneumonia, encephalitis and transverse myelitis, myocarditis and pericarditis, septic arthritis, viral cold abscesses, and genital necrosis.[30,44-46]

People with HIV and significant immunocompromise (i.e., unsuppressed viral load or CD4 T lymphocyte [CD4] cell count <200 cells/mm^3 and especially <50 cells/mm^3) are more likely to experience prolonged and progressive illness leading to hospitalization or death.[19-30,37,47,48] Illness can include coalescing or necrotic lesions of the skin and mucosa that require surgical debridement. These lesions can continue to enlarge and deepen, despite initiation of medical treatment for mpox (see Treating Disease below).[49-51]

Cases among pregnant women have been less common and not yet been associated with severe disease.[52,53]

Although the clinical presentation of clade I infection overlaps closely with that of clade II (i.e., fever, lymphadenopathy, malaise, and a centrifugal rash with classic lesions), overall, the severity of these signs and symptoms are typically greater with clade I illness.[2,54-58] Historically, illness from clade I infection has exhibited a greater case fatality rate than clade II in Africa; however, access to robust supportive care is expected to substantially decrease clade I fatalities.[2,54-58]

Diagnosis

A high index of suspicion is warranted for mpox. Clinical presentation with symptoms such as a characteristic rash is strongly suggestive of mpox.[59] However, diagnosis of mpox based solely on clinical presentation can be challenging. Illness can be atypical, with isolated proctitis or rectal bleeding, or a small number of lesions. Skin and mucosal lesions can mimic lesions seen in other infections, such as herpes zoster, herpes simplex, syphilis, and molluscum contagiosum. For these reasons, and due to the high frequency of coinfection with STIs seen during the multinational 2022 clade II mpox outbreak, a broad differential diagnosis is encouraged for all people undergoing

evaluation for mpox. Screening for STIs, including HIV, is recommended where sexual exposure to mpox might have occurred.[8]

Mpox can be confirmed by the presence of viral DNA in a clinical specimen using polymerase chain reaction (PCR).[7,59] The recommended specimen is skin lesion material, which can include swabs of a lesion's surface, lesion exudate, or lesion crusts. In the absence of a lesion on epithelialized skin, specimens from mucosal (e.g., oropharynx, anorectum) lesions or tissues can support diagnosis of mpox.[9,60-62] Unroofing or aspirating lesions is neither required nor recommended and has led to occupational infections from injuries with contaminated sharps; vigorous swabbing of lesion surfaces alone is sufficient.[13,14,63] Testing is available through state public health laboratories and multiple commercial laboratories. Check with your local institution or public health department for instructions on specimen collection and transport.

Mpox diagnosis can also be established by serologic testing that demonstrates detectable levels of anti-*Orthopoxvirus* immune globulin M antibody within 4 to 56 days after rash onset in the absence of recent mpox vaccination.[59] If there is high clinical suspicion for mpox and inconclusive or negative testing via PCR or antibody testing, additional testing can be used to confirm diagnosis. Options include next-generation sequencing, viral culture to demonstrate the presence of replication-competent virus, biopsy with immunohistochemical staining to demonstrate the presence of viral antigen, or electron microscopy to demonstrate the presence of characteristic viral particles; however, these diagnostic technologies have varying availability.[59]

Clade I infection outside of Africa remains rare and limited mostly to travelers. Thus, the Centers of Disease Control and Prevention (CDC) recommends that patients with suspected mpox undergo clade-specific testing if they have traveled to affected areas of cental and eastern Africa within 21 days of illness onset.[64] See CDC's Clade I Mpox Outbreak Originating in Central Africa webpage for a list of such countries afected by mpox. Clinicians pursuing clade-specific testing should consult with their state health departments for details about specimen collection and transport.[65,66]

Preventing Exposure

Strategies to prevent mpox exposure are similar for people with and without HIV.[67] Regardless of vaccination status, people with HIV should avoid direct contact (including sex) with people who may have symptoms of mpox, avoid surfaces or objects that may have been used by someone with mpox, and frequently wash hands after contact with rash material or contaminated surfaces **(AIII).** Condoms or other barrier methods might provide additional protection during sex or other intimate activity. During active mpox outbreaks when rates of community transmission are elevated, it is recommended that all people (including people with HIV) be counseled about the value of temporarily reducing their number of sexual partners and limiting visits to venues where group sex or other prolonged skin-to-skin contact is possible **(CIII).**

For clinicians managing patients with confirmed or suspected mpox, the recommended personal protective equipment includes gowns, gloves, eye protection, and N95 masks. Procedures that could cause the spread of oral secretions should be performed in an airborne infection isolation room. Self-inoculation with sharps contaminated with monkeypox virus has been the leading cause of health care-associated infections.[13-16,68,69] Thus, as noted above (see Diagnosis section), it is neither necessary nor recommended that lesions be unroofed using sharps when collecting diagnostic samples. See CDC's Mpox Infection Prevention and Control in Healthcare Settings webpage for additional infection control recommendations.

Preventing Disease

Vaccination is the principal biomedical means of preventing mpox, regardless of clade. Mpox vaccination should be offered to all people with HIV who have not had prior mpox and who have or anticipate potential exposure to mpox, regardless of CD4 count, per CDC's interim clinical considerations **(BII).**[70]

For unvaccinated people with HIV who experience a known or presumed exposure, post-exposure vaccination is recommended as soon as possible, per CDC's interim clinical considerations.[71]

On a case-by-case basis and in consultation with an infectious disease expert and the CDC, drugs used to treat mpox (i.e., tecovirimat, vaccinia immune globulin intravenous [VIGIV]) can be considered for mpox post-exposure prophylaxis for people with HIV who have advanced immunosuppression or a contraindication to vaccination. Currently, clinical data are incomplete regarding the effectiveness of mpox post-exposure prophylaxis with these agents.

For additional details on mpox immunizations for pre- and post-exposure prophylaxis, see the Mpox vaccine section of the Immunization chapter.

Treating Disease

Recommendations for Treating Mpox
General Considerations • Mpox is typically a self-limiting illness that resolves spontaneously in people with well-controlled HIV. People with mild to moderate mpox who are not at high risk for severe disease should be managed with supportive care, including adequate pain control (BIII), and be offered referral to clinical trials of mpox treatment, if available (CIII). • People with HIV who have severe mpox* or are at high risk for severe mpox** should receive directed mpox antiviral treatment (BIII). The Panel recommends early consultation with the CDC or an expert in mpox treatment and prompt use of combination therapy, ideally at the time of the first medical encounter and after considering the risks and benefits (CIII). Providers can reach CDC's clinical consultation service via email (poxvirus@cdc.gov) or by calling the CDC Emergency Operations Center at 770-488-7100. • People with severe immunocompromise might benefit from extended treatment (i.e., >14 days) if new confirmed mpox lesions occur or existing lesions or symptoms worsen despite treatment (CIII). • People with HIV not taking effective ART at the time of mpox diagnosis should initiate an effective antiretroviral regimen as soon as possible (AIII). Preferred Therapy for Severe Disease* or People at Risk for Severe Disease** • Tecovirimat is available via an EA-IND protocol and can be considered for patients who meet the EA-IND criteria. For patients who do not meet inclusion criteria, supportive care is recommended (AII). See text for details. • Tecovirimat 600 mg PO every 12 hours (for weight 40 kg to <120 kg) or every 8 hours (for weight ≥120 kg) for 14 days; each dose should be taken within 30 minutes of a high-fat meal (BIII); *or* • Tecovirimat 200 mg IV every 12 hours for 14 days (for weight 35 kg to <120 kg) or 300 mg IV every 12 hours (for weight ≥120 kg) infused over 6 hours (BIII) • IV therapy is indicated if concern exists regarding altered gastrointestinal absorption, inability to take PO medications, or severity of illness. Adjunctive Therapy for Severe Disease or People at Risk for Severe Disease*

Prompt use of combination therapy, in consultation with the CDC or an expert in mpox treatment and after considering risks and benefits, is recommended (CIII). Cidofovir or brincidofovir can be used as adjunctive therapy in people with or at risk for severe disease or in people who experience clinically significant progression while receiving tecovirimat, develop recrudescence of disease after an initial period of improvement while receiving tecovirimat, or are otherwise ineligible to receive oral or IV tecovirimat (BIII). VIGIV can be used in severe cases where the development of a robust antibody response may be impaired (BIII).

- Cidofovir 5 mg/kg IV once weekly for 2 weeks. Each dose should be given with saline hydration before and after therapy plus probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose and 1 g PO 8 hours after the dose (total of 4 g) (BIII).

  or

- Brincidofovir 200 mg PO once weekly for two doses (BIII)
  - Brincidofovir is available via a single-patient emergency use IND authorization for treatment of mpox.
  - Male patients should be counseled on the risk for irreversible effects of brincidofovir on male fertility (AII).
  - Women of childbearing potential should use effective contraception and/or condoms during treatment and for at least 4 months after the last dose (AIII).

  or

- VIGIV 6,000–9,000 units/kg IV single dose (BIII)
  - VIGIV is available via an expanded access IND.
  - Repeat doses may be considered on a case-by-case basis in consultation with the CDC (BIII).
  - Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration (CIII). People who received VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin (CIII).

Preferred Therapy for Ocular Mpox

- Tecovirimat 600 mg PO every 12 hours (for weight 40 to <120 kg) or every 8 hours (for weight ≥120 kg) for 14 days within 30 minutes of a fatty meal (BIII), *plus*
- Trifluridine (Viroptic) 1 drop into affected eye(s) every 2 hours when awake (max: 9 drops/day) until reepithelialization, then every 4 hours (min: 5 drops/day) for 7 days, or until all periocular lesions have healed (BIII)
  - Trifluridine should be used in consultation with an ophthalmologist (BIII).
  - Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided (AII).

Pregnancy Considerations

- Pregnant, recently pregnant, or breastfeeding women should be offered treatment for mpox (AIII).
- Tecovirimat is available through CDC-sponsored EA-IND for women who are pregnant or breastfeeding (BIII).
- In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are not recommended for use during pregnancy (AIII).

* Severe mpox might manifest as hemorrhagic disease; lesions affecting 25% or more of body surface that may be confluent, necrotic, and/or hemorrhagic in appearance or cause sepsis; disease resulting in airway compromise or affecting the nervous system; cardiac and/or neurologic disease; ocular or periorbital infections; or other conditions requiring hospitalization.

** People with HIV at risk for severe mpox include people who are not virologically suppressed, have CD4 counts <200 cells/mm^3, have another immunocompromising condition, have atopic dermatitis or other conditions affecting skin integrity, or are children, pregnant, or breastfeeding. Consult CDC's Tecovirimat webpage for more details.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; EA-IND = expanded access investigational new drug; IND = investigational new drug; IV = intravenous; the Panel = Panel on

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV; PO = orally; VIGIV = vaccinia immune globulin intravenous

Mpox is typically a self-limiting illness that resolves spontaneously in people with well-controlled HIV. People with mild to moderate mpox and who are not at high risk for severe disease should be managed with supportive care, including adequate pain control **(BIII),** and be offered referral to clinical trials of mpox treatment, if available **(CIII).** The CDC offers a clinical consultation service (email poxvirus@cdc.gov), or health care providers may contact the CDC Emergency Operations Center at 770-488-7100, where the CDC can provide additional guidance to clinicians with patient management questions.

People with HIV experiencing or at high risk of developing more severe, prolonged, and potentially life-threating mpox (e.g., have CD4 counts <200 cells/mm^3 or are otherwise severely immunocompromised) should receive directed mpox antiviral treatment **(BIII).**[37] The Panel recommends early consultation with the CDC or an expert in mpox treatment and the prompt use of combination therapy, ideally at the time of the first medical encounter and after considering the risks and benefits **(CIII).** People with severe immunocompromise might benefit from extended treatment (i.e., >14 days) if new confirmed mpox lesions occur or existing lesions or symptoms worsen despite treatment **(CIII).**

Clinicians can request and obtain tecovirimat for non-research single-patient use through a CDC-sponsored expanded access investigational new drug (EA-IND) protocol, and it might also be available through clinical trials. At this time, tecovirimat under the EA-IND is available for people with HIV who have a CD4 count <200 cells/mm^3 or are experiencing certain immunocompromising illnesses or undergoing certain immunocompromising treatments, are experiencing atopic dermatitis or other conditions affecting skin integrity, are children, are pregnant, or are breastfeeding. For patients who do not meet inclusion criteria, supportive care is recommended **(AII).**

Tecovirimat, which inhibits the *Orthopoxvirus* VP37 envelope-wrapping protein, is available as an oral capsule or intravenous (IV) injection. Clinical trials have demonstrated the drug has an acceptable safety profile,[72-74] and observational data have suggested that tecovirimat might hasten subjective symptomatic improvement in patients with severe mpox.[75] However, two randomized, placebo-controlled double-blind trials found tecovirimat provided no efficacy against mpox. Specifically, the PALM007 trial conducted in the Democratic Republic of Congo[76] demonstrated no difference in the time to mpox lesion resolution[77] in people with clade I infection, and the international STOMP trial[78] was stopped early for futility because it neither improved time to lesion resolution nor improved self-reported pain scores or pain duration in patients with mild to moderate illness from clade II infection.[77] As a result, in the United States, non-research access to tecovirimat for people with HIV is currently limited to patients who have a CD4 count <200 cells/mm^3 or are severely immunocompromised, have atopic dermatitis or other conditions affecting skin integrity, are children, are pregnant, or are breastfeeding **(BIII).**

The decision to use oral or IV tecovirimat should be based on the severity of illness (e.g., extent of other organ systems affected by mpox, presence of coalescing nonhealing lesions), other comorbidities that could contribute to greater severity of illness, expected adherence to the oral formulation, and gastrointestinal absorption capacity.[37] Oral tecovirimat requires intact gastrointestinal absorption and the ability to consume a high-fat meal (600 calories and 25 g fat) when dosed to support absorption.[79]

IV cidofovir or oral brincidofovir can be used as adjunctive therapy in people with or at risk for severe disease or in people who experience clinically significant progression while receiving tecovirimat, develop recrudescence of disease after an initial period of improvement while receiving tecovirimat, or are otherwise ineligible to receive oral or IV tecovirimat **(BIII).** Cidofovir, which acts via competitive inhibition of DNA polymerase to block DNA synthesis of many DNA viruses, is an U.S. Food and Drug Administration–approved antiviral medication for the treatment of cytomegalovirus retinitis in people with advanced HIV. Brincidofovir is a prodrug of cidofovir that acts similarly and is associated with less nephrotoxicity. There are insufficient clinical trial data on the effectiveness of cidofovir or brincidofovir in treating human mpox, including in people with HIV. However, *in vitro* and animal studies have demonstrated that these drugs are effective against other *Orthopoxviruses*.[80-85] Data from animal models suggest that the combination of tecovirimat and brincidofovir might act synergistically to improve outcomes and could be considered for patients with disseminated infection **(CIII).**[86] A randomized, placebo-controlled trial to assess safety and efficacy of brincidofovir for mpox treatment is ongoing in Africa.[87] Presently, brincidofovir is only available from federal partners to clinicians who request and obtain a single-patient emergency use IND authorization for treatment of mpox. Clinicians should consider the side effect profiles of both medications when deciding on their use (see Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections for more information).

VIGIV can be used in severe cases where the development of a robust antibody response may be impaired **(BIII).** Data are not available on the effectiveness of VIGIV to treat human mpox, including in people with HIV. In animal models using non-human primates, vaccine-induced vaccinia antibodies were protective against the lethal challenges of monkeypox virus. The benefit of VIGIV for treatment of severe mpox is unknown. VIGIV is administered under a specific CDC protocol. Subsequent dosing (i.e., redosing) decisions should be made on a case-by-case basis in consultation with the CDC and can be considered when mpox lesions affect a large percentage of a person's body surface at the time of diagnosis (e.g., 25%), new lesions emerge or borders on existing lesions enlarge several days after administration of VIGIV, lesions affect mobility or are concerning for long-term sequelae (such as sexual dysfunction), or adverse events or contraindications preclude maximal use of other medical countermeasures **(BIII).**[37]

For people for whom VIGIV might be considered as pre-exposure prophylaxis, VIGIV might theoretically impair the efficacy of live attenuated replicating virus vaccines; however, the extent to which VIGIV might affect live attenuated nonreplicating vaccines, such as JYNNEOS, is unclear.[88] Thus, vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration **(CIII).**[88] People who receive VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin **(CIII).**[88]

The role of topical therapy in the treatment of mpox remains unknown. Topical cidofovir has been used for skin lesions with mixed success.[89,90] For ocular involvement, trifluridine, in addition to systemic therapy, can be used in cases of MPXV conjunctivitis and is recommended in cases of MPXV keratitis, in consultation with an ophthalmologist **(BIII).**[41,91,92] Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided **(AII).**[93]

Treatments for mpox have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. See Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for recommendations regarding therapeutic drug monitoring and dosage adjustments, where feasible.

Vaccines and therapeutics active against clade II mpox are expected to be equally active against clade I.

Special Considerations With Regard to Starting Antiretroviral Therapy

People with HIV not presently taking effective antiretroviral therapy (ART) when diagnosed with mpox should initiate an effective antiretroviral regimen as soon as possible to improve T and B cell function, which have key roles in modulating mpox disease severity and preventing mortality **(AIII).**[37,94-96]

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome)

As with other opportunistic infections in people with advanced HIV, concerns have been raised about possible dysregulated immune responses, such as immune reconstitution inflammatory syndrome (IRIS), following initiation of ART.[26] IRIS could lead to paradoxical worsening or a protracted course of mpox disease. Data are insufficient to inform recommendations on the identification and management of dysregulated immune responses in the setting of mpox infection in people with advanced HIV. Providing passive immunity with the use of VIGIV and extending the duration of antivirals such as tecovirimat should be considered pending immune recovery **(CIII).** VIGIV has an estimated half-life of up to 3 weeks. If immune reconstitution is slow, repeat VIGIV dosing should be considered on a case-by-case basis, as noted above **(BIII).**

Monitoring is recommended during and after treatment of mpox to detect drug toxicity, as well as persistence or recurrence of mpox. The most common adverse effects of tecovirimat are headache and nausea.[79] For patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min), the IV formulation of tecovirimat should not be used due to the accumulation of an excipient (hydroxypropyl-beta-cyclodextrin) that has shown potential for nephrotoxicity at very high exposure levels **(BIII).** Exceptions may be considered in consultation with the CDC. Renal function should be closely monitored if the IV formulation is used; if renal toxicity is suspected, consult with the CDC on switching to oral tecovirimat (if possible) or using an alternative agent **(BIII).** See Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections that Require Dosage Adjustment in Adults With Renal Insufficiency for renal dosing information.

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and hypotony (low intraocular pressure).[97] The risk of severe renal injury from IV cidofovir can be reduced by prehydration and oral probenecid before and after cidofovir administration. In people receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion.[97] Cidofovir administration is **contraindicated** if renal dysfunction or substantial proteinuria is detected (a serum creatinine >1.5 mg/dL, CrCl ≤55 mL/min, or a urine protein ≥100 mg/dL [equivalent to ≥2+ proteinuria]).[97] Particular attention is needed for patients receiving other potentially nephrotoxic medications, including tenofovir disoproxil fumarate.[97] Periodic (e.g., weekly) ophthalmologic examinations are recommended to monitor for cidofovir-associated uveitis or hypotony.[97]

Adverse effects of brincidofovir include diarrhea, nausea, and other gastrointestinal adverse events, such as elevations in both hepatic enzymes (e.g., alanine transaminase, aspartate aminotransferase) and bilirubin.[98] Brincidofovir-induced diarrhea may impair absorption of oral tecovirimat. Screening for liver test abnormalities should be performed before starting therapy with repeat testing during

follow-up as clinically indicated.[98] Since brincidofovir is usually given only in two doses 1 week apart, monitoring of liver function parameters is generally done before the second dose (Day 8).[98] If serum aminotransferases are elevated and persist above 10 times the upper limit of normal, consider not giving the second dose of brincidofovir.[98] Do not give the second dose of brincidofovir on Day 8 if elevation of serum aminotransferases is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or international normalized ratio.[98] Male patients should be counseled on the risk for irreversible effects on male fertility based on testicular toxicity observed in animal studies **(AII).**[98] Women of childbearing potential should use effective contraception and/or condoms during treatment and for at least 4 months after the last dose due to the teratogenic effect of brincidofovir **(AIII).**[98]

Managing Treatment Failure

Clinical failure of therapy for mpox is more likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART or who are otherwise severely immunocompromised. Treatment failure can also result from inadequate therapeutic drug levels secondary to inadequate gastrointestinal absorption, nonadherence, or drug resistance.

Tecovirimat has a relatively low barrier to viral resistance. Single amino acid substitutions at various locations in the F13L gene coding the viral VP37 drug target confer substantial reductions in tecovirimat's antiviral activity.[79] Genotypic and phenotypic resistance to tecovirimat has been documented in patients with severe immunocompromising conditions who have disseminated and progressive mpox infection and have received or are undergoing prolonged tecovirimat treatment.[99] Community transmission of a tecovirimat resistance-associated mutation has also been reported.[100]

For people with documented or suspected tecovirimat resistance (e.g., new lesions form after the first 7 days of the 14-day regimen), additional therapeutics can be considered, including cidofovir or brincidofovir and VIGIV. Efforts should be made to ensure adherence and gastrointestinal absorption, and to maximize immune function by ensuring receipt of effective ART and limiting the use of immunocompromising therapies.[37]

If new lesions occur or existing lesions worsen or other clinical manifestations do not improve during the initial 14-days of antivirals, extending treatment might be beneficial. IV tecovirimat should be initiated if not already being used, particularly if there are concerns about gastrointestinal absorption **(BIII).** The addition of other therapeutics, including brincidofovir or cidofovir and VIGIV, should also be assessed if they are not already being used. Extending the duration of tecovirimat treatment should be done carefully, through short increments of time (e.g., an additional 3 to 7 days), while monitoring for clinical improvement or lack of response and adverse events to assess continuing or stopping treatment accordingly **(BIII).** Tecovirimat resistance has also been detected in a small number of patients with advanced HIV who received tecovirimat for durations of weeks to months.[101,102]

Clinicians can send repeat sample swabs to the CDC to assess for the continued presence of MPXV and for evidence of potential viral resistance based on genetic sequencing **(CIII).** Formal tecovirimat sensitivity testing results cannot be used to guide treatment decisions for individual patients for two reasons: first, they require culture-based resistance testing techniques that take weeks to perform (i.e., results cannot be returned in a timely manner); and second, reporting of these results is not permitted under Clinical Laboratory Improvement Amendments. However, the results of tecovirimat

susceptibility testing are helpful to public health efforts to monitor for the emergence of tecovirimat resistance.

Persistently positive PCR test results are expected until lesions resolve; therefore, subsequent testing of lesion specimens may not be informative unless new lesions or progressive lesions occur after 14 days of tecovirimat treatment. Evaluating trends in MPXV PCR cycle threshold (Ct) values may be informative; Ct values ≥35 are generally accepted evidence that replication-competent virus is not present in clinically relevant concentration.[103] Certain laboratories can test for the presence of viable virus with culture techniques, but these results might not be available in a clinically relevant timeframe.

Other possible reasons for treatment failure include a dysregulated immune response with associated inflammation or the presence of another opportunistic infection. If viable MPXV is still detected by culture, then viral replication and ongoing infection might be driving the disease process and antiviral medications should be continued. Biopsy of the affected tissue can be performed in cases with new or atypical lesions where it is unclear if the lesions are primarily due to mpox or another infectious cause, including secondary bacterial or fungal infections, and in cases with significant complications (e.g., mucosal or bowel lesions, severe lymphadenopathy, pulmonary nodular lesions, severe conjunctivitis). Consultation with infectious disease specialists and the CDC is encouraged.

The use of topical or ablative therapies for progressive hypertrophic lesions has been reported, but their role still remains under exploration.[104] Consultation with an infectious disease specialist, dermatologist, and wound care specialist (or facility) should be sought. The CDC offers a clinical consultation service (email poxvirus@cdc.gov), or health care providers may contact the CDC Emergency Operations Center at 770-488-7100, where the CDC can provide additional guidance to clinicians with patient management questions.

Preventing Recurrence and Reinfection

The durability of immunity after either infection with mpox or vaccination is unknown, including among people with HIV. No clinical correlates of immunity have yet been established to guide when additional vaccination might be needed following infection. Reinfection with mpox remains very rare. Observational data indicate people with acquired immunity after initial infection tend to have a self-limited illness with a lower burden of lesions that can be managed in outpatient settings.[105,106] Per CDC clinical considerations, people who have recovered from mpox are **not recommended** to receive JYNNEOS vaccine doses.[70] At this time, additional vaccinations for people with prior mpox and with advanced HIV (CD4 <200 cells/mm^3) following immune reconstitution are **not recommended (CIII).**

Special Considerations During Pregnancy

Data regarding mpox infection in pregnancy are scant and largely limited to case reports and case series.[5,52,107-112] Whether pregnant women are more susceptible to mpox or experience more severe disease remains unknown.[107,113] For considerations related to immunization during pregnancy, please refer to the Mpox Vaccine section of the Immunization chapter.

Adverse pregnancy outcomes of mpox historically associated with maternal infection include spontaneous pregnancy loss, stillbirth, and preterm delivery.[5] One meta-analysis synthesized available data from four studies with seven mpox-affected pregnancies prior to 2019 and estimated

the risk for miscarriage was 39% (three pregnancies with 95% confidence interval [CI], 0.00–0.89) and for intrauterine fetal demise 23% (two pregnancies; 95% CI, 0.00–0.74).[109] A subsequent meta-analysis that synthesized data from six studies (two new studies in addition to the four analyzed in the prior meta-analysis) with 12 mpox-affected pregnancies, including pregnancies from the recent outbreak, estimated the risk for fetal death was 50% (95% CI, 27–79).[110] Adverse outcomes might differ by MPXV clade, but the data remain sparse. A recent report of eight pregnant women with confirmed clade I mpox infection in the Democratic Republic of the Congo (DRC) found miscarriage in all four women infected during the first trimester.[114] *In utero* transmission of clade I mpox infection has also been reported. A 21-week stillborn fetus born to a woman with confirmed clade I mpox infection from the DRC showed cutaneous maculopapular lesions, with viral DNA identified in both fetal and placental tissues, confirming *in utero* transmission.[5]

In contrast, during the 2022 to 2023 clade II mpox outbreak, there were no reports of maternal death or intrauterine infection, and adverse pregnancy outcomes (e.g., pregnancy loss) were less common.[52,111,112] These findings suggest that the clade II infection might be associated with a lower risk of adverse perinatal outcomes than the clade I infection.

The signs and symptoms of mpox infection in pregnant women appear similar to those in nonpregnant women, including prodromal symptoms and rash. The approach to diagnosis of mpox in pregnant women is the same as in nonpregnant women.

Because pregnancy represents an immunosuppressed state and vertical transmission of mpox has been documented, treatment for mpox should be offered to women who are pregnant, recently pregnant, or breastfeeding **(AIII).** Tecovirimat is available through CDC-sponsored EA-IND for women who are pregnant or breastfeeding. No adverse reactions were reported in a small series of pregnant women who received tecovirimat.[111] Information about the impact of tecovirimat on reproductive development is limited to animal studies in which no specific fetal effects were observed.[79] It is not known if treatment with tecovirimat during pregnancy prevents congenital mpox, and reports of its use during 12 human pregnancies described no harmful effects.[115] Animal reproduction studies have not been conducted with VIGIV; therefore, it is not known whether VIGIV can cause fetal harm when administered during pregnancy or can affect future fertility.[88] However, other immune globulins have been widely used during pregnancy for many years without any apparent negative reproductive effects. In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are **not recommended** for use in pregnancy **(AIII).**[97,98]

Considerations for mpox and breastfeeding are complex and should be discussed with the patient using shared decision-making. For additional information, see Mpox Clinical Care and Treatment During Pregnancy.

References

1. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ*. 1972;46(5):593-597. Available at: https://www.pubmed.ncbi.nlm.nih.gov/4340218.

2. Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology*. 2005;340(1):46-63. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16023693.

3. Likos AM, Sammons SA, Olson VA, et al. A tale of two clades: monkeypox viruses. *J Gen Virol*. 2005;86(Pt 10):2661-2672. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16186219.

4. McQuiston JH, Luce R, Kazadi DM, et al. U.S. Preparedness and response to increasing clade I mpox cases in the Democratic Republic of the Congo - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73(19):435-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38753567.

5. Mbala PK, Huggins JW, Riu-Rovira T, et al. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo. *J Infect Dis*. 2017;216(7):824-828. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29029147.

6. Centers for Disease Control and Prevention. Mpox in the United States and around the World: current situation. 2025. Available at: https://www.cdc.gov/mpox/situation-summary/index.html

7. Centers for Disease Control and Prevention. Science brief: detection and transmission of monkeypox virus. Available at: https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html

8. Curran KG, Eberly K, Russell OO, et al. HIV and sexually transmitted infections among persons with monkeypox - eight U.S. jurisdictions, May 17–July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(36):1141-1147. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36074735.

9. Thornhill JP, Barkati S, Walmsley S, et al. Monkeypox virus infection in humans across 16 countries - April-June 2022. *N Engl J Med*. 2022;387(8):679-691. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35866746.

10. Saunders KE, Van Horn AN, Medlin HK, et al. Monkeypox in a young infant - Florida, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(38):1220-1221. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36136958.

11. Aguilera-Alonso D, Alonso-Cadenas JA, Roguera-Sopena M, Lorusso N, Miguel LGS, Calvo C. Monkeypox virus infections in children in Spain during the first months of the 2022 outbreak. *Lancet Child Adolesc Health*. 2022;6(11):e22-e23. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36058226.

12. Alonso-Cadenas JA, Andina-Martinez D, Garcia-Garcia CJ, Gaitero-Tristan J, Garcia-Ascaso MT, Torrelo A. monkeypox disease in a breastfeeding infant. *Pediatr Dermatol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36180382.

13. Carvalho LB, Casadio LVB, Polly M, et al. Monkeypox virus transmission to healthcare worker through needlestick injury, Brazil. *Emerg Infect Dis*. 2022;28(11):2334-2336. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36121391.

14. Mendoza R, Petras JK, Jenkins P, et al. Monkeypox virus infection resulting from an occupational needlestick - Florida, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1348-1349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36264845.

15. Choi Y, Jeon EB, Kim T, et al. Case report and literature review of occupational transmission of monkeypox virus to healthcare workers, South Korea. *Emerg Infect Dis*. 2023;29(5):997-1001. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36856759.

16. Caldas JP, Valdoleiros SR, Rebelo S, Tavares M. Monkeypox after occupational needlestick injury from pustule. *Emerg Infect Dis*. 2022;28(12):2516-2519. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36252152.

17. Tarin-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet*. 2022;400(10353):661-669. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35952705.

18. Philpott D, Hughes CM, Alroy KA, et al. Epidemiologic and clinical characteristics of monkeypox cases - United States, May 17–July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1018-1022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35951487.

19. Philpott D, Bonacci R, Weidle P, et al. CD4 count <350 cells/mm3 increases risk of hospitalization with mpox in PWH. Presented at: Conference on Retroviruses and Opportunistic Infections; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/HIV_gdph_croi_poster-133209603871672583.pdf.

20. Cholli PA, Miller MJ, Paromita P, et al. Characteristics of patients hospitalized with mpox during the 2022 U.S. outbreak. Presented at: Conference on Retroviruses and Opportunistic Infections; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Poster_-_Mpox_in_Hospitalized_Patien_(1)-133199180923744122.pdf.

21. Corma-Gómez A, Santos M, Cabello A, et al. Mpox virus infection is more severe in patients with uncontrolled HIV infection. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Mpox-133211828530842872.pdf.

22. Garcia EA, Lash MK, McPherson TD, et al. Severe mpox among people living with HIV receiving tecovirimat in New York City. Presented at: Conference on Retroviruses and Opportunistic Infections; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/NYCDOHMH_SevereMpox-HIV_CROI2023_0735-133205427984584752.pdf.

23. Garneau WM, Jones JL, Dashler G, et al. Clinical outcomes among in- and outpatients with mpox in an urban health system. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/mpox_outcomes_-_garneau-133207198771747332.pdf.

24. Silva M, Coutinho C, Torres T, et al. Impact of HIV infection on mpox-related hospitalizations in Brazil. Presented at: Conference on Retroviruses and Opportunistic Infections; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_Poster_MpoxHospitalizationsHIV_0905_vers%C3%A3o_final-133209759446392218.pdf.

25. Vo C, Zomorodi R, Silvera R, et al. Demographic and clinical characteristics of mpox within a New York City health system. Presented at: Conference on Retroviruses and Opportunistic Infections; 2023. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2023/CROI_poster_v21_final_-_Chris_Vo-133211560201291269.pdf.

26. Mitja O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36828001.

27. World Health Organization. Multi-country outbreak of mpox, external situation report #12 - 14 December 2022. 2022. Available at: https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-12--14-december-2022

28. Nigeria Centre for Disease Control. Weekly epidemiological report week 51: 16th–22nd December 2019. Nigeria: Nigeria Centre for Disease Control and Prevention; 2020.Available at: https://reliefweb.int/report/nigeria/ncdc-weekly-epidemiological-report-volume-9-no-51-16th-22nd-december-2019. Accessed.

29. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. *Clin Infect Dis*. 2020;71(8):e210-e214. Available at: https://www.pubmed.ncbi.nlm.nih.gov/32052029.

30. Miller MJ, Cash-Goldwasser S, Marx GE, et al. Severe monkeypox in hospitalized patients - United States, August 10–October 10, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1412-1417. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36327164.

31. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017–18: a clinical and epidemiological report. *Lancet Infect Dis*. 2019;19(8):872-879. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31285143.

32. Kibungu EM, Vakaniaki EH, Kinganda-Lusamaki E, et al. Clade I-associated mpox cases associated with sexual contact, the Democratic Republic of the Congo. *Emerg Infect Dis*. 2024;30(1):172-176. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38019211.

33. Riser AP, Hanley A, Cima M, et al. Epidemiologic and clinical features of mpox-associated deaths-United States, May 10, 2022-March 7, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(15):404-410. Available at: https://pubmed.ncbi.nlm.nih.gov/37053126/.

34. UK Health Security Agency. Clade I mpox: affected countries. 2024. Available at: https://www.gov.uk/guidance/clade-i-mpox-affected-countries

35. World Health Organization. Mpox.Multi-country external situation report no. 45, published 2025. Available at: https://cdn.who.int/media/docs/default-source/documents/emergencies/mpox-sitrep_-45.pdf?sfvrsn=67f9f699_1&download=true

36. Centers for Disease Control and Prevention. Monkeypox Virus Infection in the United States and Other Non-endemic Countries. 2022. Available at: https://archive.cdc.gov/#/details?url=https://www.cdc.gov/han/2022/han00466.html

37. Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations for severe manifestations of mpox - United States, February 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(9):232-243. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36862595.

38. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. 2022;378:e072410. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35902115.

39. Centers for Disease Control and Prevention. Health Alert Network (HAN) No. 475: severe manifestations of monkeypox among people who are immunocompromised due to HIV or other conditions. 2022. Available at: https://emergency.cdc.gov/han/2022/han00475.asp

40. Lucar J, Roberts A, Saardi KM, Yee R, Siegel MO, Palmore TN. Monkeypox virus-associated severe proctitis treated with oral tecovirimat: a report of two cases. *Ann Intern Med*. 2022;175(11):1626-1627. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35981225.

41. Cash-Goldwasser S, Labuda SM, McCormick DW, et al. Ocular monkeypox - United States, July–September 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1343-1347. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36264836.

42. Nogueira Filho PA, Lazari CDS, Granato CFH, et al. Ocular manifestations of monkeypox: a case report. *Arq Bras Oftalmol*. 2022;85(6):632-635. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36350927.

43. Kaufman AR, Chodosh J, Pineda R, 2nd. Monkeypox virus and ophthalmology-a primer on the 2022 monkeypox outbreak and monkeypox-related ophthalmic disease. *JAMA Ophthalmol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36326768.

44. Pastula DM, Copeland MJ, Hannan MC, et al. Two cases of monkeypox-associated encephalomyelitis - Colorado and the District of Columbia, July–August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(38):1212-1215. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36136957.

45. Fonti M, Mader T, Burmester-Kiang J, et al. Monkeypox associated acute arthritis. *Lancet Rheumatol*. 2022;4(11):e804. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36247685.

46. Ritter JM, Martines RB, Bhatnagar J, et al. Pathology and monkeypox virus localization in tissues from immunocompromised patients with severe or fatal mpox. *J Infect Dis*. 2024;229(Supplement_2):S219-S228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38243606.

47. Pinnetti C, Cimini E, Mazzotta V, et al. Mpox as AIDS-defining event with a severe and protracted course: clinical, immunological, and virological implications. *Lancet Infect Dis*. 2024;24(2):e127-e135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37778364.

48. O'Shea J, Zucker J, Stampfer S, et al. Prolonged mpox disease in people with advanced HIV: characterization of Mpox skin lesions. *J Infect Dis*. 2024;229(Supplement_2):S243-S248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38019806.

49. Carrubba S, Geevarghese A, Solli E, et al. Novel severe oculocutaneous manifestations of human monkeypox virus infection and their historical analogues. *Lancet Infect Dis*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36702137.

50. Govind A, Lazarte SM, Kitchell E, et al. Severe mpox infections in people with uncontrolled human immunodeficiency virus. *Clin Infect Dis*. 2023;76(10):1843-1846. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36718662.

51. Filippov E, Duhan S, Lehman L, Keisham B, Sethi V. Treatment failure in patient with severe mpox and untreated HIV, Maryland, USA. *Emerg Infect Dis*. 2023;29(6):1262-1265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37172298.

52. Khalil A, Samara A, O'Brien P, et al. Monkeypox in pregnancy: update on current outbreak. *Lancet Infect Dis*. 2022;22(11):1534-1535. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36115375.

53. Hennessee I, Shelus V, McArdle CE, et al. Epidemiologic and clinical features of children and adolescents aged <18 years with monkeypox - United States, May 17–September 24, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1407-1411. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36331124.

54. Lansiaux E, Jain N, Laivacuma S, Reinis A. The virology of human monkeypox virus (hMPXV): A brief overview. *Virus Res*. 2022;322:198932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36165924.

55. Jezek Z, Szczeniowski M, Paluku KM, Mutombo M. Human monkeypox: clinical features of 282 patients. *J Infect Dis*. 1987;156(2):293-298. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3036967.

56. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16(2):e0010141. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35148313.

57. Gessain A, Nakoune E, Yazdanpanah Y. Monkeypox. *N Engl J Med*. 2022;387(19):1783-1793. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36286263.

58. Saijo M, Ami Y, Suzaki Y, et al. Virulence and pathophysiology of the Congo Basin and West African strains of monkeypox virus in non-human primates. *J Gen Virol*. 2009;90(Pt 9):2266-2271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19474247.

59. Centers for Disease Control and Prevention. Mpox Case Definitions. 2024. Available at: https://www.cdc.gov/mpox/hcp/case-definitions/?CDC_AAref_Val=https://www.cdc.gov/poxvirus/mpox/clinicians/case-definition.html

60. Golden MR, Soge OO, Mills M, et al. Asymptomatic and subclinical mpox: an association with modified vaccinia ankara vaccine. *Sex Transm Dis*. 2024;51(5):342-347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38301634.

61. Pestana M, Brito Caldeira M, Aparicio Martins I, Valente C, Neves JM, Fernandes C. Monkeypox infection with primarily mucosal involvement. *Sex Transm Dis*. 2023;50(4):241-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36729940.

62. Ciccarese G, Brucci G, Di Biagio A, et al. Two cases of monkeypox virus infection without detectable cutaneous/mucosal lesions. *Travel Med Infect Dis*. 2023;54:102605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37302775.

63. Centers for Disease Control and Prevention. Mpox Infection Prevention and Control in Healthcare Settings. 2025. Available at: https://www.cdc.gov/mpox/hcp/infection-control/healthcare-settings.html?CDC_AAref_Val=https://www.cdc.gov/poxvirus/mpox/clinicians/infection-control-healthcare.html

64. Centers for Disease Control and Prevention. Mpox caused by human-to-human transmission of monkeypox virus with geographic spread in the Democratic Republic of the Congo. 2023. Available at: https://emergency.cdc.gov/han/2023/han00501.asp

65. Centers for Disease Control and Prevention. Mpox caused by human-to-human transmission of monkeypox virus in the Democratic Republic of the Congo with spread to neighboring countries. 2024. Available at: https://emergency.cdc.gov/han/2024/han00513.asp

66. Centers for Disease Control and Prevention. Health Alert Network (HAN) No. 513: mpox caused by human-to-human transmission of monkeypox virus in the Democratic Republic of the Congo with spread to neighboring countries. 2024. Available at: https://www.cdc.gov/han/2024/han00513.html

67. O'Shea J, Filardo TD, Morris SB, Weiser J, Petersen B, Brooks JT. Interim guidance for prevention and treatment of monkeypox in persons with HIV infection - United States, August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1023-1028. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35951495.

68. Migaud P, Hosmann K, Drauz D, Mueller M, Haumann J, Stocker H. A case of occupational transmission of mpox. *Infection*. 2023;51(4):1169-1173. Available at: https://pubmed.ncbi.nlm.nih.gov/36735196/.

69. Safir A, Safir M, Henig O, et al. Nosocomial transmission of MPOX virus to health care workers -an emerging occupational hazard: A case report and review of the literature. *Am J Infect Control*. 2023;51(9):1072-1076. Available at: https://pubmed.ncbi.nlm.nih.gov/36736902/.

70. Centers for Disease Control and Prevention. Vaccine for mpox prevention in the United States. 2024. Available at: https://www.cdc.gov/mpox/hcp/vaccine-considerations/index.html

71. Centers for Disease Control and Prevention. Preventing Mpox. 2024. Available at: https://www.cdc.gov/mpox/prevention/index.html

72. Desai AN, Thompson GR, 3rd, Neumeister SM, Arutyunova AM, Trigg K, Cohen SH. Compassionate use of tecovirimat for the treatment of monkeypox infection. *JAMA*. 2022;328(13):1348-1350. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35994281.

73. O'Laughlin K, Tobolowsky FA, Elmor R, et al. Clinical use of tecovirimat (TPOXX) for treatment of monkeypox under an investigational new drug protocol - United States, May–August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(37):1190-1195. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36107794.

74. Grosenbach DW, Honeychurch K, Rose EA, et al. Oral tecovirimat for the treatment of smallpox. *N Engl J Med*. 2018;379(1):44-53. Available at: https://www.pubmed.ncbi.nlm.nih.gov/29972742.

75. Karmarkar EN, Golden MR, Kerani RP, et al. Association of tecovirimat therapy with mpox symptom improvement: a cross-sectional study-King County, Washington, May-October 2022. *Open Forum Infect Dis*. 2024;11(3):ofae029. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38456195.

76. National Institutes of Health. Tecovirimat for treatment of monkeypox virus. 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05559099

77. National Institute for Health. NIH study finds tecovirimat was safe but did not improve Mpox resolution or pain. 2024. Available at: https://www.nih.gov/news-events/news-releases/nih-study-finds-tecovirimat-was-safe-did-not-improve-mpox-resolution-or-pain

78. National Institutes of Health. Study of tecovirimat for human monkeypox virus (STOMP). 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05534984

79. ^TPOXX (tecovirimat) [package insert]. Food and Drug Administration. Food and Drug Administration. 2018. https://www.fda.gov/media/75792/download

80. Rice AD, Adams MM, Wallace G, et al. Efficacy of CMX001 as a post exposure antiviral in New Zealand white rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. *Viruses*. 2011;3(1):47-62. Available at: https://www.pubmed.ncbi.nlm.nih.gov/21373379.

81. Parker S, Chen NG, Foster S, et al. Evaluation of disease and viral biomarkers as triggers for therapeutic intervention in respiratory mousepox - an animal model of smallpox. *Antiviral Res*. 2012;94(1):44-53. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22381921.

82. Baker RO, Bray M, Huggins JW. Potential antiviral therapeutics for smallpox, monkeypox and other orthopoxvirus infections. *Antiviral Res*. 2003;57(1-2):13-23. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12615299.

83. Smee DF. Progress in the discovery of compounds inhibiting orthopoxviruses in animal models. *Antivir Chem Chemother*. 2008;19(3):115-124. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19024628.

84. Stittelaar KJ, Neyts J, Naesens L, et al. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. *Nature*. 2006;439(7077):745-748. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16341204.

85. Hutson CL, Kondas AV, Mauldin MR, et al. Pharmacokinetics and efficacy of a potential smallpox therapeutic, brincidofovir, in a lethal monkeypox virus animal model. *mSphere*. 2021;6(1). Available at: https://www.pubmed.ncbi.nlm.nih.gov/33536322.

86. Quenelle DC, Prichard MN, Keith KA, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. *Antimicrob Agents Chemother*. 2007;51(11):4118-4124. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17724153.

87. BioSolutions E. Emergent BioSolutions supports new clinical trial evaluating the safety and efficacy of brincidofovir in treating mpox virus across africa. 2024. Available at: https://www.globenewswire.com/en/news-release/2024/11/06/2976160/33240/en/Emergent-BioSolutions-Supports-New-Clinical-Trial-Evaluating-the-Safety-and-Efficacy-of-Brincidofovir-in-Treating-Mpox-Virus-Across-Africa.html

88. ^Vaccinia Immune Globulin Intravenous [package insert]. Food and Drug Administration. Food and Drug Administration. 2005. https://www.fda.gov/media/78174/download

89. Sobral-Costas TG, Escudero-Tornero R, Servera-Negre G, et al. Human monkeypox outbreak: epidemiological data and therapeutic potential of topical cidofovir in a prospective cohort study. *J Am Acad Dermatol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36455826.

90. Rubio-Muniz CA, Montero-Menárguez J, López-Valle A, et al. Monkeypox: is topical cidofovir a good idea? *Clinical and Experimental Dermatology*. 2022. Available at: https://doi.org/10.1093/ced/llac038.

91. Parkhurst JR, Danenberg PV, Heidelberger C. Growth inhibition of cells in cultures and of vaccinia virus infected HeLa cells by derivatives of trifluorothymidine. *Chemotherapy*. 1976;22(3-4):221-231. Available at: https://www.pubmed.ncbi.nlm.nih.gov/178485.

92. Hyndiuk RA, Seideman S, Leibsohn JM. Treatment of vaccinial keratitis with trifluorothymidine. *Arch Ophthalmol*. 1976;94(10):1785-1786. Available at: https://www.pubmed.ncbi.nlm.nih.gov/823931.

93. Maudgal PC, Van Damme B, Missotten L. Corneal epithelial dysplasia after trifluridine use. *Graefes Arch Clin Exp Ophthalmol*. 1983;220(1):6-12. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6403411.

94. Agrati C, Cossarizza A, Mazzotta V, et al. Immunological signature in human cases of monkeypox infection in 2022 outbreak: an observational study. *Lancet Infect Dis*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36356606.

95. Lum FM, Torres-Ruesta A, Tay MZ, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. *Nat Rev Immunol*. 2022;22(10):597-613. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36064780.

96. Hermanussen L, Grewe I, Tang HT, et al. Tecovirimat therapy for severe monkeypox infection: longitudinal assessment of viral titers and clinical response pattern-A first case-series experience. *J Med Virol*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36177717.

97. ^Cidofovir [package insert]. Food and Drug Administration. Food and Drug Administration. 2000. https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf)

98. ^Brincidofovir [package insert]. Food and Drug Administration. Food and Drug Administration. 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf

99. Centers for Disease Control and Prevention. Update on Managing Monkeypox in Patients Receiving Therapeutics. 2022. Available at: https://archive.cdc.gov/#/details?url=https://www.cdc.gov/han/2022/han00481.html

100. Garrigues JM, Hemarajata P, Espinosa A, et al. Community spread of a human monkeypox virus variant with a tecovirimat resistance-associated mutation. *Antimicrob Agents Chemother*. 2023;67(11):e0097223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37823631.

101. Smith TG, Gigante CM, Wynn NT, et al. Tecovirimat resistance in mpox patients, United States, 2022-2023. *Emerg Infect Dis*. 2023;29(12):2426-2432. Available at: https://pubmed.ncbi.nlm.nih.gov/37856204/.

102. Garrigues JM, Hemarajata P, Karan A, et al. Identification of tecovirimat resistance-associated mutations in human Monkeypox virus - Los Angeles County. *Antimicrob Agents Chemother*. 2023;67(7):e0056823. Available at: https://pubmed.ncbi.nlm.nih.gov/37338408/.

103. Paran N, Yahalom-Ronen Y, Shifman O, et al. Monkeypox DNA levels correlate with virus infectivity in clinical samples, Israel, 2022. *Euro Surveill*. 2022;27(35). Available at: https://www.pubmed.ncbi.nlm.nih.gov/36052723.

104. Scotti B, Piraccini BM, Gaspari V. Hypertrophic verrucous lesions after monkeypox virus infection. *Lancet Infect Dis*. 2022. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36309035.

105. Faherty EAG, Holly T, Ogale YP, et al. Notes from the field: emergence of an mpox cluster primarily affecting persons previously vaccinated against mpox - Chicago, Illinois, March 18-June 12, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(25):696-698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37347713.

106. Hazra A, Zucker J, Bell E, et al. Mpox in people with past infection or a complete vaccination course: a global case series. *Lancet Infect Dis*. 2024;24(1):57-64. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37678309.

107. Jamieson DJ, Cono J, Richards CL, Treadwell TA. The role of the obstetrician-gynecologist in emerging infectious diseases: monkeypox and pregnancy. *Obstet Gynecol*. 2004;103(4):754-756. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15051569.

108. Bragazzi NL, Woldegerima WA, Wu J, et al. Epidemiological and clinical characteristics of mpox in cisgender and transgender women and non-binary individuals assigned to the female sex at birth: A comprehensive, critical global perspective. *Viruses*. 2024;16(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/38543691.

109. D'Antonio F, Pagani G, Buca D, Khalil A. Monkeypox infection in pregnancy: a systematic review and metaanalysis. *Am J Obstet Gynecol MFM*. 2023;5(1):100747. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36096413.

110. Sanchez Clemente N, Coles C, Paixao ES, et al. Paediatric, maternal, and congenital mpox: a systematic review and meta-analysis. *Lancet Glob Health*. 2024;12(4):e572-e588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38401556.

111. Oakley LP, Hufstetler K, O'Shea J, et al. Mpox cases among cisgender women and pregnant persons - United States, May 11-November 7, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(1):9-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36602932.

112. Schwartz DA, Pittman PR. Mpox (Monkeypox) in Pregnancy: Viral clade differences and their associations with varying obstetrical and fetal outcomes. *Viruses*. 2023;15(8). Available at: https://www.ncbi.nlm.nih.gov/pubmed/37631992.

113. Meaney-Delman DM, Galang RR, Petersen BW, Jamieson DJ. A primer on monkeypox virus for obstetrician-gynecologists: diagnosis, prevention, and treatment. *Obstet Gynecol*. 2022;140(3):391-397. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36356237.

114. Masirika LM, Nieuwenhuijse DF, Ndishimye P, et al. Mapping the distribution and describing the first cases from an ongoing outbreak of a New Strain of mpox in South Kivu, Eastern Democratic Republic of Congo between September 2023 to April 2024. *BMJ*. 2024:1-20. Available at: https://www.medrxiv.org/content/10.1101/2024.05.10.24307057v1.

115. Sampson MM, Magee G, Schrader EA, et al. Mpox (Monkeypox) infection during pregnancy. *Obstet Gynecol*. 2023;141(5):1007-1010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36928418.

Disseminated *Mycobacterium avium* Complex Disease

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Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.[1-6] In the era before effective antiretroviral therapy (ART) was available, *M. avium* was the etiologic agent in >95% of people with HIV with advanced immunosuppression who acquired disseminated MAC disease.[4,7-12] Newer bacterial typing technology suggests organisms causing bacteremia in people with HIV represent a diversity of species, including the *M. avium* subspecies *hominissuis* and *M. colombiense* and other non-MAC species, including *M. genavense*, *M. kansasii*, *M. simiae*, *M. mycogenicum*, and others.[13-16] These comprise what was historically referred to as disseminated MAC. An estimated 7% to 12% of adults with HIV have been previously infected with MAC, although rates of disease vary in different geographic locations.[2,4,8,11,12] In particular, disseminated MAC in people with HIV has been described more frequently in the United States and Europe than in resource-limited settings.[17]

Although epidemiologic associations with infection have been identified, no singular environmental exposure or behavior has been consistently linked to subsequent increased risk of developing MAC disease. The mode of MAC infection is thought to be through repeated inhalation or ingestion of MAC bacteria via the respiratory or gastrointestinal (GI) tract, likely from environmental exposure.[1,18] Household or close contacts of those with MAC disease do not appear to be at increased risk of disease, and person-to-person transmission is unlikely.[19]

MAC disease typically occurs in people with HIV with CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. The previously reported incidence of disseminated MAC disease ranged from 20% to 40% in people with HIV with advanced immunosuppression in the absence of effective ART or chemoprophylaxis.[20,21] However, the overall incidence of MAC disease among people with HIV has declined substantially in the modern ART era to current levels of <2 cases of MAC as the first opportunistic infection [OI] per 1,000 person-years for individuals in care, even among those not receiving effective ART.[22-26] In addition to a CD4 count <50 cells/mm^3, factors associated with increased risk for MAC disease are ongoing HIV viral replication despite ART, previous or concurrent OIs, reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens (possibly reflecting defects in T-cell repertoire), and genetic predisposition in some populations.[24-27] While effective ART has clearly been associated with dramatic reductions in risk of developing MAC disease, MAC disease still can occur in people with HIV on suppressive ART, and the clinical presentation may differ from what is seen in people with untreated HIV. In one retrospective case series following people with HIV mostly on ART, nontuberculous mycobacterial (NTM) disease occurred in nine people who were virologically suppressed on ART at the time of their diagnosis—seven with pulmonary NTM only and two with extrapulmonary disease. MAC was the most common NTM pathogen, isolated in 19 of the 34 cases.[13] Those with extrapulmonary disease were younger and had higher viral loads and lower CD4 counts at diagnosis.

Clinical Manifestations

In people with HIV with advanced immunosuppression who are not on ART, MAC disease generally presents as a disseminated, multi-organ infection, although localized disease may also be seen.[28-32] Early symptoms may be minimal and can precede mycobacteremia or positive tissue cultures by several weeks. Symptoms are nonspecific and include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.[8,13-15]

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase levels.[4,5,7-12,20,21,33,34] Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) may be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities may occur with localized disease.

Localized MAC disease occurs more often in people with HIV on suppressive ART with increased CD4 counts than in people with HIV not on ART, suggesting improved immune function is associated with more localized disease. Localized syndromes include cervical, intraabdominal, or mediastinal lymphadenitis; pneumonia; pericarditis; osteomyelitis; skin or soft-tissue abscesses; bursitis; genital ulcers; and central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), as discussed below.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph fluid, bone marrow, or other normally sterile tissue or body fluids, although data suggest that bone marrow cultures have low yield for detection of MAC in this setting, particularly if blood cultures are negative.[21,31,32,35-40] Species identification should be performed using molecular techniques, polymerase chain reaction-based assays, whole-genome sequencing, high-performance liquid chromatography, or biochemical tests.

Other ancillary studies provide supportive diagnostic information, including acid-fast bacilli smear and culture of tissue, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

Although isolated pulmonary MAC disease is not often observed in people with advanced HIV-associated immunosuppression, occasionally MAC disease may be limited to the lung in people with HIV who are virologically suppressed on ART. Diagnostic criteria for disease limited to the lung in this setting should follow those established by the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the Infectious Disease Society of America (IDSA) joint guideline on Treatment of Nontuberculous Mycobacterial Pulmonary Disease, which include pulmonary clinical signs and symptoms, exclusion of other alternative diagnoses, nodular or cavitary disease on lung imaging, and a positive culture for MAC from at least two sputum specimens or at least one bronchoalveolar lavage or biopsy sample.[41]

Detection of MAC organisms in the respiratory or GI tract may represent colonization of these sites and may be a harbinger of disseminated MAC infection. However, no data are available regarding

efficacy of treatment for asymptomatic colonization with MAC organisms at these sites. Therefore, routine screening of respiratory or GI specimens and preemptive treatment for MAC **is not recommended.**

Preventing Exposure

MAC organisms commonly contaminate environmental sources of infection, such as food and water. Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Recommendations for Preventing Disseminated *Mycobacterium avium* Complex Disease

Preventing First Episode of Disseminated MAC Disease (Primary Prophylaxis)
• Primary prophylaxis **is not recommended** for adults and adolescents who immediately initiate ART (AII). Indications for Primary Prophylaxis • CD4 count <50 cells/mm^3 AND not receiving ART or remains viremic on ART or has no options for a fully suppressive ART regimen (AI) • Before primary prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, and if appropriate, by obtaining a blood culture for MAC (AI). If blood culture is obtained, prophylaxis should be delayed until results are available to avoid exposing patients to monotherapy and the attendant risk of drug resistance (AI). Preferred Therapy • Azithromycin 1,200 mg PO once weekly (AI), *or* • Clarithromycin 500 mg PO twice daily (AI), *or* • Azithromycin 600 mg PO twice weekly (BIII) Alternative Therapy • Rifabutin 300 mg PO daily (BI) in people who cannot tolerate azithromycin or clarithromycin o Dose adjustment of rifabutin may be necessary based on drug–drug interactions, please refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendation when used with certain ARV drugs. o Active TB should be ruled out before starting rifabutin to avoid monotherapy in the setting of active TB. Indication for Discontinuing Primary Prophylaxis • If previously initiated, primary prophylaxis should be discontinued if the patient is continuing on a fully suppressive ART regimen (AI).
Pregnancy Considerations
• During pregnancy, if ART is immediately initiated, then primary prophylaxis for MAC disease **is not recommended** (AIII). • When primary prophylaxis is required because of the absence of effective ART, azithromycin is the preferred agent (BIII).

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; MAC = *Mycobacterium avium* complex; PO = orally; TB = tuberculosis

Indication for Primary Prophylaxis

Primary prophylaxis against disseminated MAC disease **is not recommended** for adults and adolescents with HIV who immediately initiate ART, regardless of CD4 count **(AII).** People with HIV who have CD4 counts <50 cells/mm^3 and who are not receiving ART, remain viremic on ART, or have no options for a fully suppressive ART regimen should receive chemoprophylaxis against disseminated MAC **(AI).** Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment and, if appropriate based on that assessment, by obtaining a blood culture for MAC. MAC prophylaxis should be delayed until results are available to avoid exposing patients to monotherapy and the attendant risk of drug resistance **(AI).**

When to Stop Primary Prophylaxis

Primary MAC prophylaxis, if previously initiated, should be discontinued in adults and adolescents who are continuing on a fully suppressive ART regimen **(AI).** Two randomized, placebo-controlled trials and several large observational cohort studies have demonstrated that people with HIV taking ART can discontinue primary prophylaxis with minimal risk of developing MAC disease, particularly if they are virologically suppressed.[42-47] Conclusions from these studies indicate that the overall incidence of disseminated MAC within 6 to 12 months after stopping primary prophylaxis in these circumstances, regardless of CD4 count, was 0.6 to 0.8 per 100 person-years. In each of these studies, plasma HIV RNA level >1,000 copies/mL was the principal risk factor for developing MAC disease regardless of MAC prophylaxis. However, in a study from the TREAT Asia HIV Observational Database, which evaluated the impact of MAC prophylaxis on AIDS-defining conditions and HIV-associated mortality in people with HIV on ART from September 2015 onward, macrolide use within 3 months of starting ART for those with a CD4 count <50 at ART initiation was associated with a decreased risk of HIV-associated mortality (HR 0.10; 95% CI, 0.01–0.80; P = 0.031) but not with the combined outcome of developing an AIDS-defining condition or death.[48] Despite this finding, only 10.6% of the 1,345 participants in the cohort eligible for MAC prophylaxis received it. The authors concluded that there may be an additive protective effect of macrolide prophylaxis in reducing overall HIV-related mortality among Asians with HIV and CD4 counts <50 even though they received effective ART. Despite some differences among these published data, for most individuals, particularly in higher resourced settings, the preponderance of current data suggest that primary MAC prophylaxis provides no additional benefit in people started on effective ART that results in viral suppression. Additional arguments against primary MAC prophylaxis while prioritizing effective ART to achieve viral suppression include (1) the potential for adding additional cost and adverse effects of the drugs used for prophylaxis; (2) the likelihood that only a small number of people with HIV will develop "unmasking MAC IRIS" (i.e., active MAC disease after starting ART); (3) the potential for acquired drug resistance if people fail monotherapy for MAC prophylaxis; and (4) limiting polypharmacy to assist with adherence to ART.[49-51]

Preferred and Alternative Drugs for Prophylaxis

As previously stated, primary prophylaxis for MAC is not recommended for people on effective ART, but for those for whom prophylaxis is being considered, azithromycin[52] and clarithromycin[5,53] are the preferred prophylactic agents **(AI).**[1,54] The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and **should not be used (AI).**[5] The combination of azithromycin and rifabutin is more effective than azithromycin alone in preventing MAC disease.[52] However, based on the additional cost, increased occurrence of adverse effects, potential for drug

interactions, and lack of greater survival benefit than with azithromycin alone, the combination regimen of azithromycin and rifabutin **is not recommended (AI).** In people with HIV who cannot tolerate azithromycin or clarithromycin, rifabutin can be used as a prophylactic agent for MAC disease **(BI),** although drug interactions may complicate use of this agent. Moreover, tuberculosis (TB) should be excluded before rifabutin is used to avoid monotherapy in the setting of active TB, which could result in acquired rifamycin resistance.

Treating Disease

Recommendations for Treating Disseminated *Mycobacterium avium* Complex Disease

Treating Disseminated MAC Disease

Preferred Therapy
• At least two drugs as initial therapy to prevent or delay emergence of resistance (AI)
  o Clarithromycin 500 mg PO twice daily (AI) plus ethambutol 15 mg/kg PO daily (AI), *or*
  o Azithromycin 500–600 mg (AII) plus ethambutol 15 mg/kg PO daily (AI) when drug interactions or intolerance precludes the use of clarithromycin (AII)
  o Note: Testing of susceptibility to clarithromycin or azithromycin is recommended.
• Some experts would add rifabutin when more severe disease manifestations are present.
  o Rifabutin 300 mg PO daily (CI). Dose adjustment of rifabutin may be necessary based on drug–drug interactions. Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for more information.
• Some experts would also add a fourth drug if more severe disease is present, the risk of mortality is high, emergence of drug resistance is likely (e.g., after failure of MAC prophylaxis), CD4 count is <50 cells/mm^3, mycobacterial loads are high (>2 $\log_{10}$ CFU/mL of blood), or effective ART is absent (CIII). Fourth drug options may include:
  o A fluoroquinolone (CIII) (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), *or*
  o An injectable aminoglycoside (CIII) (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily) (generally avoided unless in the setting of refractory disease when other alternatives are not available or tolerated)
  o Bedaquiline, tedizolid, linezolid, and omadacycline have demonstrated *in vitro* activity against clinical isolates of MAC; these might also be considered in people with refractory MAC disease.
Duration of Therapy
• At least 12 months (AII)
• Shorter duration may be considered depending on the degree of immunologic recovery following initiation of ART. CD4 count should be >100 cells/mm^3 for ≥6 months before discontinuation of therapy (CIII).
Chronic Maintenance Therapy (Secondary Prophylaxis)
• Same as treatment regimens
• If ART does not result in immune reconstitution, people with HIV and disseminated MAC disease should continue chronic maintenance therapy (AII).
Criteria for Discontinuing Chronic Maintenance Therapy (Secondary Prophylaxis) (AI)
• Completed at least 12 months of therapy, *and*

- No signs or symptoms of MAC disease, *and*
- Have sustained (≥6 months) CD4 count >100 cells/mm^3 in response to ART

Indication for Restarting Chronic Maintenance Therapy (Secondary Prophylaxis)

- If a fully suppressive ART regimen is not possible and CD4 is consistently <100 cells/mm^3 (BIII)

Pregnancy Considerations

- For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination (BIII).

Other Considerations

- NSAIDs may be used for people with HIV who experience moderate to severe symptoms attributed to IRIS (BIII).
- If IRIS symptoms persist, a short-term course (4–8 weeks) of systemic corticosteroid therapy (equivalent to prednisone 20–40 mg/day) can be used (BII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CFU = colony-forming units; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; MAC = *Mycobacterium avium* complex; NSAID = nonsteroidal anti-inflammatory drug; PO = orally

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance **(AI).**[1,6,11,12,18,55-63] Clarithromycin **(AI)** or azithromycin **(AII)** are preferred first agents; published data are more extensive for clarithromycin than for azithromycin in people with advanced HIV disease, and clarithromycin appears to be associated with more rapid clearance of MAC from the blood.[6,55,57,61,62,64] However, azithromycin is acceptable when drug interactions or intolerance preclude the use of clarithromycin **(AII).** Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI).**[65] Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all people with HIV, particularly those who developed MAC disease while receiving prophylaxis with one of these agents.[66,67] In three randomized clinical trials, clarithromycin-resistant isolates were reported in 29% and 58% of people with HIV who developed MAC bacteremia during prophylaxis with clarithromycin, and azithromycin-resistant isolates were recovered from 11% of those who developed bacteremia while on azithromycin prophylaxis.[5,52,53,68] More advanced immunosuppression at prophylaxis initiation and longer duration of MAC prophylaxis are associated with higher rates of clarithromycin resistance at the time of MAC prophylaxis failure.[68]

Ethambutol is the recommended second drug for the initial treatment of MAC disease **(AI)** based on randomized trials of MAC therapy that indicate its use in the regimen is associated with lower rates of relapse.[56,58,64,69] Rifabutin can be used as a third drug **(CI)** with or without a fluoroquinolone (levofloxacin or moxifloxacin) (**CIII),** or an injectable aminoglycoside (amikacin or streptomycin) **(CIII)** can be used as a fourth drug if more severe disease is present; the risk of mortality is high; emergence of drug resistance is likely (e.g., after failure of MAC prophylaxis); or in the setting of advanced immunosuppression (CD4 count <50 cells/mm^3), high mycobacterial loads (>2 $\log_{10}$ colony-forming units/mL of blood), or the absence of effective ART **(CIII).** One randomized clinical trial demonstrated that adding rifabutin to the combination of clarithromycin and ethambutol improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance[6,57] in individuals with advanced HIV and disseminated MAC disease. These studies were completed before the availability of effective ART. It has not been established whether similar results would be observed for people with HIV receiving effective ART. The fluoroquinolones levofloxacin and moxifloxacin and amikacin have *in vitro* and animal model

activity against MAC, although randomized trials evaluating the efficacy of adding a fluoroquinolone or injectable aminoglycoside as part of a multidrug regimen for treatment of MAC have not been done. Injectable aminoglycosides should generally be avoided except in the setting of refractory disease when other alternative agents are not available or tolerated.[66,70] Additional drugs with *in vitro* activity against clinical isolates of MAC include bedaquiline, tedizolid, linezolid, and omadacycline; these might also be considered in people with refractory MAC disease.[71-75]

While not specifically applicable to people with HIV (who more often have disseminated MAC disease than isolated pulmonary disease), in 2020, the ATS/ERS/ESCMID/IDSA updated their jointly sponsored clinical guideline for treatment of nontuberculous mycobacterial pulmonary disease, including pulmonary MAC.[41] People with HIV fully suppressed on ART with higher CD4 counts may present with localized pulmonary or other local organ system MAC disease that may clinically resemble such disease in people without HIV. Following the ATS/ERS/ESCMID/IDSA guidelines would be reasonable in such settings. The recommended treatment includes an initial three-drug regimen containing a macrolide and ethambutol for those with macrolide-susceptible pulmonary MAC disease. Addition of an aminoglycoside, which in refractory cases can be given as inhalation suspension, is recommended if cavitary or severe bronchiectatic disease is present or if macrolide resistance is suspected.[76]

People with HIV and disseminated MAC disease should be treated for a minimum duration of 12 months **(AII).** Shorter duration of treatment may be considered depending on the degree of immunologic recovery following initiation of ART **(CIII);** the CD4 count should be maintained above 100 cells/mm^3 for at least 6 months before discontinuing MAC treatment.[77-79]

Special Considerations Regarding Antiretroviral Therapy Initiation

ART should be started as soon as possible after the diagnosis of MAC disease, preferably at the same time as initiation of antimycobacterial therapy in people with HIV and disseminated MAC disease who are not receiving effective ART **(BIII).** ART is recommended as soon as possible to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression **(BIII).** If ART has already been initiated, it should be continued. The regimens should be modified when there is any potential for an adverse drug–drug interaction(s) between the antiretroviral (ARV) and antimycobacterial drugs **(BIII).** Information on drug–drug interactions can be found in the Adult and Adolescent Antiretroviral Guidelines. People with HIV will need continuous antimycobacterial treatment until ART results in sustained immune reconstitution, as indicated above (CD4 count maintained above 100 cells/mm^3 for at least 6 months).

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiating antimycobacterial therapy in people with HIV who do not have a clinical response to their initial treatment regimens. Improvement in fever and other systemic symptoms and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 to 4 weeks after initiation of appropriate therapy; clinical response may be delayed, however, in those with more extensive MAC disease or advanced immunosuppression.

Adverse effects of clarithromycin and azithromycin include GI upset, metallic taste, elevations in liver transaminase levels, and hypersensitivity reactions. Clarithromycin's adverse effects may be exacerbated when drug levels are increased due to drug interactions associated with some ARV

drugs. Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI).**[65] Protease inhibitors (PIs) can increase clarithromycin levels; clarithromycin dose adjustment or switching clarithromycin to azithromycin may be necessary. Azithromycin metabolism is not affected by the cytochrome P450 (CYP) system; azithromycin can be used safely in the presence of PIs, non-nucleoside reverse transcriptase inhibitors, or integrase inhibitors without concerns about drug interactions.

When used with clarithromycin or other drugs that inhibit CYP isoenzyme 3A4, rifabutin has been associated with a higher risk of adverse drug interactions, in particular sight-threatening uveitis and neutropenia.[80-82] Rifabutin adverse effects are concentration related; therapeutic drug level monitoring may be considered to reduce the potential for adverse effects. Rifabutin must be dose adjusted in people with HIV receiving PIs or efavirenz. Rifabutin should not be coadministered with cobicistat-boosted PIs, long-acting injectable cabotegravir/rilpivirine, bictegravir, elvitegravir/cobicistat, fostemsavir, or lenacapavir.[82-86] Rilpivirine and doravirine must be dose adjusted if either is coadministered with rifabutin. No dose adjustment for rifabutin or the integrase inhibitors dolutegravir or raltegravir or injectable cabotegravir alone is currently recommended, although at least one study suggested that compared with people without TB or MAC, lower trough concentrations were observed when once daily dolutegravir was used together with rifabutin.[87-89] The most updated drug–drug interaction information can be found in the Adult and Adolescent Antiretroviral Guidelines. Therapeutic drug monitoring may be helpful for optimizing drug dosing in the context of complex drug–drug interactions.[90]

IRIS associated with MAC disease is recognized as a systemic inflammatory syndrome, with signs and symptoms clinically indistinguishable from active MAC infection, although bacteremia is generally absent. Similar to TB, MAC-associated IRIS can occur as "unmasking" IRIS in people with HIV with subclinical (undiagnosed) MAC or "paradoxical" IRIS in those with previously established MAC disease.[91-95] Both variants occur primarily in those with advanced immunosuppression who begin ART and have a rapid and marked reduction in plasma HIV RNA.[95,96] Elevated alkaline phosphatase levels may be a predictor of MAC-associated IRIS.[97] The syndrome may be benign and self-limited or may result in severe, unremitting symptoms that improve with the use of systemic anti-inflammatory therapy or corticosteroids.

People with HIV on ART who develop moderate to severe symptoms typical of IRIS should receive initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) **(BIII).** If IRIS symptoms do not improve, short-term (4–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, can be used to reduce symptoms and morbidity **(BII).**[92,98] Severe forms of MAC IRIS with a hemophagocytic lymphohistiocytosis (HLH) phenotype may occur, and a lower hemoglobin prior to ART may help predict this more severe form of IRIS.[97,99] Patients with this more severe form may have a genetic predisposition, and cases of MAC IRIS and other NTM IRIS requiring additional immunosuppression in addition to corticosteroids have been reported.[99,100]

Managing Treatment Failure

MAC treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia (or persistently positive tissue cultures from other sites) after 4 to 8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for people with HIV whose disease relapses after an initial response to treatment.

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multidrug regimen. The regimen should consist of at least two new drugs (i.e., not previously used) to which the isolate is susceptible. Drugs from which to choose include rifabutin, fluoroquinolone (levofloxacin or moxifloxacin), an injectable aminoglycoside (amikacin or streptomycin), or possibly bedaquiline, tedizolid, linezolid, or omadacycline, although data supporting a survival or microbiologic benefit when these agents are added are limited.[11,12,41,56-60,64,69,72-75,101-104] Continuing clarithromycin or azithromycin despite resistance **is not recommended (BIII),** as there is likely to be no additional benefit and may have added toxicity. Clofazimine **should generally not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality **(AI).**[56,58,69] Optimization of ART is an important adjunct to second-line or salvage therapy for MAC disease in people with HIV for whom initial treatment is unsuccessful or who have disease that is resistant to antimycobacterial drugs **(AIII).**

Although anecdotal data and individual case reports suggest potential benefit, adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for routine use, except in the setting of familial immunodeficiencies associated with increased risk of MAC disease.[105]

Preventing Recurrence

As indicated above, people with HIV and disseminated MAC disease should be treated for a minimum duration of 12 months **(AII).** Shorter duration of treatment may be considered depending on the degree of immunologic recovery following initiation of ART; the CD4 count should be maintained above 100 cells/mm^3 for at least 6 months before discontinuing MAC treatment. If ART initiation does not result in immune reconstitution, people with HIV and disseminated MAC disease should continue chronic maintenance therapy **(AII).**[77-79]

When to Stop Secondary Prophylaxis or Chronic Maintenance Therapy

The risk of MAC recurrence is low in people with HIV who have completed at least a 12-month MAC treatment course, remain asymptomatic with respect to MAC signs and symptoms, and sustain an increase in CD4 count to >100 cells/mm^3 for ≥6 months after initiation of ART. In this setting, it is reasonable to discontinue maintenance therapy based on data from studies in people with HIV and inferences from more extensive study data that indicate the safety of discontinuing secondary prophylaxis for other OIs **(AI).**[44,60,77-79,106-108] Reintroducing chronic maintenance therapy or secondary prophylaxis for people with HIV for whom a fully suppressive ART regimen is not possible and who have a decline in their CD4 count to levels consistently below 100 cells/mm^3 may be indicated **(BIII).**

Special Considerations During Pregnancy

During pregnancy, if ART is being immediately initiated, then primary prophylaxis for MAC disease **is not recommended (AIII).** When primary prophylaxis is required because of the absence of effective ART, azithromycin is the preferred agent **(BIII).** For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination **(BIII).** Because clarithromycin is associated with an increased risk of birth defects based on evidence from certain animal studies, it **is not recommended** as the first-line agent for prophylaxis or treatment of MAC in pregnancy **(BIII).** Two studies, each with slightly more than 100 women with first-trimester

exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk of spontaneous abortion was noted in one study.[109,110]

Azithromycin did not produce defects in animal studies, but experience with use in humans during the first trimester is limited. A nested case-control study conducted within the large Quebec Pregnancy cohort found an association between azithromycin use and spontaneous miscarriage[111]; however the authors were not able to adjust for severity of infection, an important confounder. Multiple studies, including large cohort studies, have found no association between the use of azithromycin in the first trimester and major congenital malformations, including heart defects.[112-114] A systematic review of pregnancy outcomes following macrolide use found no significant increased risks for major congenital malformations or congenital heart defects following all macrolide use in the first trimester, but a small but significant increased rate of major congenital malformations with azithromycin though maternal confounders could not be excluded. In a Cochrane systematic review of *Chlamydia trachomatis* infection treatment in pregnancy, there was no apparent difference between azithromycin and other agents in terms of efficacy and pregnancy complications.[115]

References

1. Karakousis PC, Moore RD, Chaisson RE. *Mycobacterium avium* complex in patients with HIV infection in the era of highly active antiretroviral therapy. *Lancet Infect Dis*. 2004;4(9):557-565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15336223.

2. Hoefsloot W, van Ingen J, Andrejak C, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J*. 2013;42(6):1604-1613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23598956.

3. Reed C, von Reyn CF, Chamblee S, et al. Environmental risk factors for infection with *Mycobacterium avium* complex. *Am J Epidemiol*. 2006;164(1):32-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16675537.

4. Inderlied CB. Microbiology and minimum inhibitory concentration testing for *Mycobacterium avium* complex prophylaxis. *Am J Med*. 1997;102(5):2-10. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0002934397000375?showall=true.

5. Benson CA, Williams PL, Cohn DL, et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of *Mycobacterium avium* complex disease in patients with AIDS: a randomized, double-blind, placebo-controlled trial. The AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team. *J Infect Dis*. 2000;181(4):1289-1297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10762562.

6. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2003;37(9):1234-1243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14557969.

7. Kemper CA, Havlir D, Bartok AE, et al. Transient bacteremia due to *Mycobacterium avium* complex in patients with AIDS. *J Infect Dis*. 1994;170(2):488-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8035044.

8. Gordin FM, Cohn DL, Sullam PM, Schoenfelder JR, Wynne BA, Horsburgh CR, Jr. Early manifestations of disseminated *Mycobacterium avium* complex disease: a prospective evaluation. *J Infect Dis*. 1997;176(1):126-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9207358.

9. Benson CA, Ellner JJ. *Mycobacterium avium* complex infection and AIDS: advances in theory and practice. *Clin Infect Dis*. 1993;17(1):7-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8353249.

10. Havlik JA, Jr., Horsburgh CR, Jr., Metchock B, Williams PP, Fann SA, Thompson SE, 3rd. Disseminated *Mycobacterium avium* complex infection: clinical identification and epidemiologic trends. *J Infect Dis*. 1992;165(3):577-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1347060.

11. Benson CA. Treatment of disseminated disease due to the *Mycobacterium avium* complex in patients with AIDS. *Clin Infect Dis*. 1994;18 Suppl 3:S237-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8204776.

12. Benson CA. Disease due to the *Mycobacterium avium* complex in patients with AIDS: epidemiology and clinical syndrome. *Clin Infect Dis*. 1994;18 Suppl 3:S218-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8204773.

13. Lee EH, Chin B, Kim YK, et al. Clinical characteristics of nontuberculous mycobacterial disease in people living with HIV/AIDS in South Korea: a multi-center, retrospective study. *PLoS One*. 2022;17(11):e0276484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36355915.

14. Ricotta EE, Adjemian J, Blakney RA, Lai YL, Kadri SS, Prevots DR. Extrapulmonary nontuberculous mycobacteria infections in hospitalized patients, United States, 2009–2014. *Emerg Infect Dis*. 2021;27(3):845-852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33622461.

15. Wetzstein N, Geil A, Kann G, et al. Disseminated disease due to non-tuberculous mycobacteria in HIV positive patients: a retrospective case control study. *PLoS One*. 2021;16(7):e0254607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34255788.

16. Lee MR, Chien JY, Huang YT, et al. Clinical features of patients with bacteraemia caused by *Mycobacterium avium* complex species and antimicrobial susceptibility of the isolates at a medical centre in Taiwan, 2008-2014. *Int J Antimicrob Agents*. 2017;50(1):35-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28478210.

17. Heidary M, Nasiri MJ, Mirsaeidi M, et al. *Mycobacterium avium* complex infection in patients with human immunodeficiency virus: a systematic review and meta-analysis. *J Cell Physiol*. 2019;234(7):9994-10001. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30548598.

18. Corti M, Palmero D. *Mycobacterium avium* complex infection in HIV/AIDS patients. *Expert Rev Anti Infect Ther*. 2008;6(3):351-363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18588499.

19. Carbonne A, Lemaitre N, Bochet M, et al. *Mycobacterium avium* complex common-source or cross-infection in AIDS patients attending the same day-care facility. *Infect Control Hosp Epidemiol*. 1998;19(10):784-786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9801289.

20. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of *Mycobacterium avium-intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. *J Infect Dis*. 1992;165(6):1082-1085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1349906.

21. Chaisson RE, Moore RD, Richman DD, Keruly J, Creagh T. Incidence and natural history of *Mycobacterium avium*-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology

Study Group. *Am Rev Respir Dis*. 1992;146(2):285-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1362634.

22. Marochi-Telles JP, Muniz R, Jr., Sztajnbok J, Cosme-de Oliveira A. Disseminated *Mycobacterium avium* on HIV/AIDS: historical and current literature review. *AIDS Rev*. 2020;22(1):9-15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167509.

23. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. *AIDS*. 2010;24(10):1549-1559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20502317.

24. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort snalysis of HIV-infected persons in the United States and Canada, 2000–2010. *J Infect Dis*. 2016;214(6):862-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27559122.

25. Collins LF, Clement ME, Stout JE. Incidence, long-term outcomes, and healthcare utilization of patients with human immunodeficiency virus/acquired immune deficiency syndrome and disseminated *Mycobacterium avium* complex from 1992-2015. *Open Forum Infect Dis*. 2017;4(3):ofx120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28748197.

26. Jung Y, Song KH, Choe PG, et al. Incidence of disseminated *Mycobacterium avium*-complex infection in HIV patients receiving antiretroviral therapy with use of *Mycobacterium avium*-complex prophylaxis. *Int J STD AIDS*. 2017;28(14):1426-1432. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28592210.

27. Hsu DC, Breglio KF, Pei L, et al. Emergence of polyfunctional cytotoxic CD4+ T cells in *Mycobacterium avium* immune reconstitution inflammatory syndrome in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 2018;67(3):437-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29538651.

28. Barbaro DJ, Orcutt VL, Coldiron BM. *Mycobacterium avium-Mycobacterium intracellulare* infection limited to the skin and lymph nodes in patients with AIDS. *Rev Infect Dis*. 1989;11(4):625-628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2772468.

29. Hellyer TJ, Brown IN, Taylor MB, Allen BW, Easmon CS. Gastro-intestinal involvement in *Mycobacterium avium-intracellulare* infection of patients with HIV. *J Infect*. 1993;26(1):55-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8454889.

30. Torriani FJ, McCutchan JA, Bozzette SA, Grafe MR, Havlir DV. Autopsy findings in AIDS patients with *Mycobacterium avium* complex bacteremia. *J Infect Dis*. 1994;170(6):1601-1605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7996004.

31. Roth RI, Owen RL, Keren DF, Volberding PA. Intestinal infection with *Mycobacterium avium* in acquired immune deficiency syndrome (AIDS): histological and clinical comparison with Whipple's disease. *Dig Dis Sci*. 1985;30(5):497-504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2580679.

32. Gillin JS, Urmacher C, West R, Shike M. Disseminated *Mycobacterium avium-intracellulare* infection in acquired immunodeficiency syndrome mimicking Whipple's disease.

Gastroenterology. 1983;85(5):1187-1191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6194041.

33. Inderlied CB, Kemper CA, Bermudez LE. The *Mycobacterium avium* complex. *Clin Microbiol Rev*. 1993;6(3):266-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8358707.

34. Packer SJ, Cesario T, Williams JH, Jr. *Mycobacterium avium* complex infection presenting as endobronchial lesions in immunosuppressed patients. *Ann Intern Med*. 1988;109(5):389-393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3165608.

35. Shanson DC, Dryden MS. Comparison of methods for isolating *Mycobacterium avium-intracellulare* from blood of patients with AIDS. *J Clin Pathol*. 1988;41(6):687-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3385000.

36. Hafner R, Inderlied CB, Peterson DM, et al. Correlation of quantitative bone marrow and blood cultures in AIDS patients with disseminated *Mycobacterium avium* complex infection. *J Infect Dis*. 1999;180(2):438-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10395860.

37. Cornejo-Juárez P, Islas-Muñoz B, Ramírez-Ibarguen AF, et al. Bone marrow culture yield for the diagnosis of opportunistic diseases in patients with AIDS and disseminated Kaposi sarcoma. *Curr HIV Res*. 2020;18(4):277-282. Available at: https://pubmed.ncbi.nlm.nih.gov/32493198.

38. Prabhu V, Coelho S, Achappa B, Baliga S, Sharon L, Shah J. Role of fluorescence in situ hybridization in detecting *Mycobacterium avium* complex presenting as fever in treatment failure HIV. *J Clin Tuberc Other Mycobact Dis*. 2020;21:100188. Available at: https://pubmed.ncbi.nlm.nih.gov/32995570.

39. Sharma S, Latawa R, Wanchu A, Verma I. Differential diagnosis of disseminated *Mycobacterium avium* and *Mycobacterium tuberculosis* infection in HIV patients using duplex PCR. *Future Microbiol*. 2021;16(3):159-173. Available at: https://pubmed.ncbi.nlm.nih.gov/33528278.

40. Sharvit G, Schwartz D, Heering G, et al. Evaluation of the clinical impact of bone marrow cultures in current medical practice. *Sci Rep*. 2022;12(1):9664. Available at: https://pubmed.ncbi.nlm.nih.gov/35690634/.

41. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis*. 2020;71(4):e1-e36. Available at: https://pubmed.ncbi.nlm.nih.gov/32628747.

42. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10915098.

43. El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to

antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. 2000;342(15):1085-1092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10766581.

44. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count: a randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. *Ann Intern Med*. 2000;133(7):493-503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11015162.

45. Furrer H, Telenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against *Mycobacterium avium* in patients on successful antiretroviral combination therapy. The Swiss HIV Cohort Study. *AIDS*. 2000;14(10):1409-1412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10930156.

46. Brooks JT, Song R, Hanson DL, et al. Discontinuation of primary prophylaxis against *Mycobacterium avium* complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992–2002. *Clin Infect Dis*. 2005;41(4):549-553. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16028167.

47. Chene G, Phillips A, Costagliola D, et al. Cohort profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. *Int J Epidemiol*. 2017;46(3):797-797n. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27864413.

48. Pasayan MKU, ML SM, Boettiger D, et al. Effect of macrolide prophylactic therapy on AIDS-defining conditions and HIV-associated mortality. *J Acquir Immune Defic Syndr*. 2019;80(4):436-443. Available at: https://pubmed.ncbi.nlm.nih.gov/30550488.

49. Lange CG, Woolley IJ, Brodt RH. Disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection in the era of effective antiretroviral therapy: is prophylaxis still indicated? *Drugs*. 2004;64(7):679-692. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15025543.

50. Sax PE. "Choosing wisely" in HIV medicine — should we stop giving MAC prophylaxis? *HIV and ID Observations*. 2016;2018(3/20/2016). Available at: https://blogs.jwatch.org/hiv-id-observations/index.php/choosing-wisely-in-hiv-medicine-should-we-stop-giving-mac-prophylaxis/2016/03/20.

51. Vervoort SC, Borleffs JC, Hoepelman AI, Grypdonck MH. Adherence in antiretroviral therapy: a review of qualitative studies. *AIDS*. 2007;21(3):271-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17255734.

52. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med*. 1996;335(6):392-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8676932.

53. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced

acquired immunodeficiency syndrome. *N Engl J Med*. 1996;335(6):384-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8663871.

54. Uthman MM, Uthman OA, Yahaya I. Interventions for the prevention of *Mycobacterium avium* complex in adults and children with HIV. *Cochrane Database Syst Rev*. 2013(4):CD007191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23633339.

55. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. *Ann Intern Med*. 1994;121(12):905-911. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7978715.

56. May T, Brel F, Beuscart C, et al. Comparison of combination therapy regimens for treatment of human immunodeficiency virus-infected patients with disseminated bacteremia due to *Mycobacterium avium*. ANRS Trial 033 Curavium Group. Agence Nationale de Recherche sur le Sida. *Clin Infect Dis*. 1997;25(3):621-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9314450.

57. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. *Clin Infect Dis*. 1999;28(5):1080-1085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10452638.

58. Dube MP, Sattler FR, Torriani FJ, et al. A randomized evaluation of ethambutol for prevention of relapse and drug resistance during treatment of *Mycobacterium avium* complex bacteremia with clarithromycin-based combination therapy. California Collaborative Treatment Group. *J Infect Dis*. 1997;176(5):1225-1232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9359722.

59. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Terry Beirn Community Programs for Clinical Research on AIDS. *Clin Infect Dis*. 1999;29(1):125-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10433575.

60. Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated *Mycobacterium avium* complex infection after 12 months of antimycobacterial therapy combined with highly active antiretroviral therapy. *J Infect Dis*. 1998;178(5):1446-1449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9780266.

61. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. Veterans Affairs HIV Research Consortium. *Clin Infect Dis*. 1998;27(5):1278-1285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9827282.

62. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. *Clin Infect Dis*. 2000;31(5):1245-1252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11073759.

63. Xu HB, Jiang RH, Li L. Treatment outcomes for *Mycobacterium avium* complex: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2014;33(3):347-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23979729.

64. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group. *N Engl J Med*. 1996;335(6):377-383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8676931.

65. Food and Drug Administration. Clarithromycin [package insert]. 2017. Accessed May 25. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050662s058,050698s038,050775s026lbl.pdf.

66. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175(4):367-416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17277290.

67. Gardner EM, Burman WJ, DeGroote MA, Hildred G, Pace NR. Conventional and molecular epidemiology of macrolide resistance among new *Mycobacterium avium* complex isolates recovered from HIV-infected patients. *Clin Infect Dis*. 2005;41(7):1041-1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16142672.

68. Craft JC, Notario GF, Grosset JH, Heifets LB. Clarithromycin resistance and susceptibility patterns of *Mycobacterium avium* strains isolated during prophylaxis for disseminated infection in patients with AIDS. *Clin Infect Dis*. 1998;27(4):807-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9798037.

69. Chaisson RE, Keiser P, Pierce M, et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic *Mycobacterium avium* complex disease in patients with HIV infection. *AIDS*. 1997;11(3):311-317. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9147422.

70. Koh WJ, Hong G, Kim SY, et al. Treatment of refractory *Mycobacterium avium* complex lung disease with a moxifloxacin-containing regimen. *Antimicrob Agents Chemother*. 2013;57(5):2281-2285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23478956.

71. Chapagain M, Pasipanodya JG, Athale S, et al. Omadacycline efficacy in the hollow fibre system model of pulmonary *Mycobacterium avium* complex and potency at clinically attainable doses. *J Antimicrob Chemother*. 2022;77(6):1694-1705. Available at: https://pubmed.ncbi.nlm.nih.gov/35257162.

72. Litvinov V, Makarova M, Kudlay D, Nikolenko N, Mikhailova J. In vitro activity of bedaquiline against *Mycobacterium avium* complex. *J Med Microbiol*. 2021;70(10). Available at: https://pubmed.ncbi.nlm.nih.gov/34668850.

73. Lin S, Hua W, Wang S, et al. In vitro assessment of 17 antimicrobial agents against clinical *Mycobacterium avium* complex isolates. *BMC Microbiol*. 2022;22(1):175. Available at: https://pubmed.ncbi.nlm.nih.gov/35804298.

74. Gil E, Sweeney N, Barrett V, et al. Bedaquiline as treatment for disseminated nontuberculous mycobacteria infection in 2 patients co-infected with HIV. *Emerg Infect Dis*. 2021;27(3):944-948. Available at: https://pubmed.ncbi.nlm.nih.gov/33622490.

75. Philley JV, Wallace RJ, Jr., Benwill JL, et al. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. *Chest*. 2015;148(2):499-506. Available at: https://pubmed.ncbi.nlm.nih.gov/25675393.

76. Shirley M. Amikacin liposome inhalation suspension: a review in *Mycobacterium avium* complex lung disease. *Drugs*. 2019;79(5):555-562. Available at: https://pubmed.ncbi.nlm.nih.gov/30877642.

77. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex: AIDS Clinical Trial Group 393 Study Team. *J Infect Dis*. 2003;187(7):1046-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12660918.

78. Shafran SD, Mashinter LD, Phillips P, et al. Successful discontinuation of therapy for disseminated *Mycobacterium avium* complex infection after effective antiretroviral therapy. *Ann Intern Med*. 2002;137(9):734-737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12416943.

79. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med*. 2002;137(4):239-250. Available at: https://pubmed.ncbi.nlm.nih.gov/12186514.

80. Shafran SD, Deschenes J, Miller M, Phillips P, Toma E. Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. MAC Study Group of the Canadian HIV Trials Network. *N Engl J Med*. 1994;330(6):438-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8284019.

81. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother*. 1998;42(3):631-639. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9517944.

82. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2023. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-overview?view=full.

83. Hennig S, Svensson EM, Niebecker R, et al. Population pharmacokinetic drug-drug interaction pooled analysis of existing data for rifabutin and HIV PIs. *J Antimicrob Chemother*. 2016;71(5):1330-1340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26832753.

84. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV-infected tuberculosis patients on lopinavir/ritonavir-based

antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25406657.

85. Kakuda TN, Woodfall B, De Marez T, et al. Pharmacokinetic evaluation of the interaction between etravirine and rifabutin or clarithromycin in HIV-negative, healthy volunteers: results from two phase 1 studies. *J Antimicrob Chemother*. 2014;69(3):728-734. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24155058.

86. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet*. 2011;50(4):229-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21348537.

87. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23075918.

88. Brainard DM, Kassahun K, Wenning LA, et al. Lack of a clinically meaningful pharmacokinetic effect of rifabutin on raltegravir: *in vitro/in vivo* correlation. *J Clin Pharmacol*. 2011;51(6):943-950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20852006.

89. Le X, Guo X, Sun J, et al. Pharmacokinetic features of dolutegravir with rifampicin and rifabutin among patients coinfected with human immunodeficiency virus and tuberculosis/*Mycobacterium avium* complex. *Int J Infect Dis*. 2022;116:147-150. Available at: https://pubmed.ncbi.nlm.nih.gov/34999246.

90. Alffenaar JW, Martson AG, Heysell SK, et al. Therapeutic drug monitoring in non-tuberculosis mycobacteria infections. *Clin Pharmacokinet*. 2021;60(6):711-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33751415.

91. Phillips P, Kwiatkowski MB, Copland M, Craib K, Montaner J. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr*. 1999;20(2):122-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10048898.

92. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. 2005;41(10):1483-1497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16231262.

93. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. 1998;351(9098):252-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9457095.

94. Cabie A, Abel S, Brebion A, Desbois N, Sobesky G. Mycobacterial lymphadenitis after initiation of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis*. 1998;17(11):812-813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9923530.

95. Smibert OC, Trubiano JA, Cross GB, Hoy JF. Short communication: *Mycobacterium avium* complex infection and immune reconstitution inflammatory syndrome remain a challenge in

the era of effective antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2017;33(12):1202-1204. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28791872.

96. Barber DL, Andrade BB, McBerry C, Sereti I, Sher A. Role of IL-6 in *Mycobacterium avium*—associated immune reconstitution inflammatory syndrome. *J Immunol*. 2014;192(2):676-682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24337386.

97. Breglio KF, Vinhaes CL, Arriaga MB, et al. Clinical and immunologic predictors of *Mycobacterium avium* complex immune reconstitution inflammatory syndrome in a contemporary cohort of patients with human immunodeficiency virus. *J Infect Dis*. 2021;223(12):2124-2135. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205640.

98. Wormser GP, Horowitz H, Dworkin B. Low-dose dexamethasone as adjunctive therapy for disseminated *Mycobacterium avium* complex infections in AIDS patients. *Antimicrob Agents Chemother*. 1994;38(9):2215-2217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7811052.

99. Rocco JM, Laidlaw E, Galindo F, et al. Severe mycobacterial immune reconstitution inflammatory syndrome (IRIS) in advanced human immunodeficiency virus (HIV) has features of hemophagocytic lymphohistiocytosis and requires prolonged immune suppression. *Clin Infect Dis*. 2023;76(3):e561-e570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36048425.

100. Rocco JM, Laidlaw E, Galindo F, et al. Mycobacterial immune reconstitution inflammatory syndrome in HIV is associated with protein-altering variants in hemophagocytic lymphohistiocytosis-related genes. *J Infect Dis*. 2023;228(2):111-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37040388.

101. Masur H. Recommendations on prophylaxis and therapy for disseminated Mycobacterium avium complex disease in patients infected with the human immunodeficiency virus. Public Health Service Task Force on Prophylaxis and Therapy for Mycobacterium avium Complex. *N Engl J Med*. 1993;329(12):898-904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8395019.

102. Kemper CA, Meng TC, Nussbaum J, et al. Treatment of *Mycobacterium avium* complex bacteremia in AIDS with a four-drug oral regimen: rifampin, ethambutol, clofazimine, and ciprofloxacin. The California Collaborative Treatment Group. *Ann Intern Med*. 1992;116(6):466-472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1739237.

103. Chiu J, Nussbaum J, Bozzette S, et al. Treatment of disseminated *Mycobacterium avium* complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. California Collaborative Treatment Group. *Ann Intern Med*. 1990;113(5):358-361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2382918.

104. Rodriguez Diaz JC, Lopez M, Ruiz M, Royo G. *In vitro* activity of new fluoroquinolones and linezolid against non-tuberculous mycobacteria. *Int J Antimicrob Agents*. 2003;21(6):585-588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12791475.

105. Liu L, Song Z, Xun J, et al. PD-1 inhibitor for disseminated Mycobacterium avium infection in a person with HIV. *Open Forum Infect Dis*. 2023;10(1):ofac700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36686637.

106. Aberg J, Powderly W. HIV: primary and secondary prophylaxis for opportunistic infections. *BMJ Clin Evid*. 2010;2010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21418688.

107. Green H, Hay P, Dunn DT, McCormack S, Investigators S. A prospective multicentre study of discontinuing prophylaxis for opportunistic infections after effective antiretroviral therapy. *HIV Med*. 2004;5(4):278-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15236617.

108. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9862944.

109. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *Am J Perinatol*. 1998;15(9):523-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9890248.

110. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiol Drug Saf*. 2000;9(7):549-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11338912.

111. Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ*. 2017;189(17):E625-E633. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28461374.

112. Berard A, Sheehy O, Zhao JP, Nordeng H. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. *Pharmacoepidemiol Drug Saf*. 2015;24(12):1241-1248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26513406.

113. Lin KJ, Mitchell AA, Yau WP, Louik C, Hernandez-Diaz S. Safety of macrolides during pregnancy. *Am J Obstet Gynecol*. 2013;208(3):221 e221-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23254249.

114. Bahat Dinur A, Koren G, Matok I, et al. Fetal safety of macrolides. *Antimicrob Agents Chemother*. 2013;57(7):3307-3311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23650169.

115. Cluver C, Novikova N, Eriksson DO, Bengtsson K, Lingman GK. Interventions for treating genital chlamydia trachomatis infection in pregnancy. *Cochrane Database Syst Rev*. 2017;9(9):CD010485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28937705.

Mycobacterium tuberculosis Infection and Disease

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Epidemiology

Tuberculosis (TB) is the leading cause of morbidity and mortality among people with HIV worldwide. In 2020 and 2021, progress towards reducing TB morbidity and mortality slowed amidst the widespread disruption of health services from the COVID-19 pandemic. Globally, the annual number of estimated TB deaths increased in 2020 and 2021, to 1.5 million and 1.6 million, respectively.[1,2] Among people with HIV, there were an estimated 703,000 people who had TB, but only 52% were diagnosed and reported. A total of 187,000 deaths among people with HIV were attributed to TB in 2021, the first time there has been an increase in HIV-associated TB deaths since 2006.[2] People with HIV still account for a disproportionate number of TB deaths worldwide (11.8% of deaths vs. 6.7% of TB cases); however, a 47% reduction in deaths has occurred since 2010.[2]

In the United States, more than two-thirds (5,456; 71.4%) of people newly reported with TB in 2021 were born outside the United States, similar to 2019 and 2020 proportions.[3] The incidence of HIV-related TB in the United States has declined substantially, in part because of the widespread use of antiretroviral therapy (ART).[4,5] Among all people reported with TB with known HIV status in the United States in 2021, 293 people (4.2%) were coinfected with HIV (6.3% among people with TB aged 25–44 years vs. 5.6% among those aged 45–64 years).[6] Overall, the proportion of reported people with TB and HIV co-infection has been steadily declining over the past decade (7.4% in 2011).

Latent TB Infection

TB infection occurs when a person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms. Usually within 2 to 12 weeks after infection, the immune response limits the multiplication of tubercle bacilli. However, viable bacilli can persist for years, a condition referred to as latent TB infection (LTBI). People with LTBI are asymptomatic and are not infectious. TB disease (defined as clinically active disease, often with positive smears and cultures) can develop soon after exposure to *M. tuberculosis* organisms (primary disease) or after reactivation of latent infection.[7,8] The risk of TB disease due to reactivation of LTBI for people with untreated HIV has been estimated as 3% to 16% per year, which approximates the lifetime risk of TB disease for people with LTBI who do not have HIV (approximately 5%).[9-14] The risk of TB disease begins in the first year following HIV infection.[15] TB disease can occur at any CD4 T lymphocyte (CD4) cell count, although the risk increases with progressive immunodeficiency.[15,16] The estimated annual risk of developing TB disease among people with LTBI (diagnosed by a positive tuberculin skin test [TST] or interferon-gamma release assay [IGRA] in the absence of a TB disease diagnosis) is 3 to 12 times greater for people with untreated HIV than for those without HIV.[17] Even with effective ART, the risk of TB disease among people with HIV remains greater than that among the general population.[18] Since 2006, the TB incidence rate in people with HIV has been lower than in previous years, but the TB risk is still substantially higher than among people without HIV.[19] In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.[20]

The risk of progression from LTBI to TB disease in people with HIV is reduced both by ART and by the treatment of LTBI.[18,21-24] In combination with ART, isoniazid preventive therapy decreased the risk of TB disease by 76% among people with HIV in Brazil.[25] Furthermore, isoniazid preventive therapy and ART independently and additively decreased the risk of death and severe HIV-related illness.[21,23]

Diagnosing Latent TB Infection

All people with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure**.** In programmatic settings in the United States, TB screening has been suboptimal, with only 47% to 69% of people with HIV presenting to care completing initial screening, and 42% of those with LTBI initiating therapy.[26-30] The two current diagnostics available for the detection of *M. tuberculosis* infection in the United States, IGRA and TST, help differentiate those with and without TB infection. However, the diagnostic accuracy of TST and IGRA is limited; a negative test does not exclude the diagnosis of LTBI or TB disease, and a positive test does not, by itself, mean LTBI therapy is warranted. Decisions about medical and public health management should include epidemiological risk factors, medical history, and other clinical information when interpreting IGRA or TST results.

People with advanced HIV (CD4 count <200 cells/mm^3) and negative diagnostic tests for LTBI, and no indications for initiating empiric LTBI treatment (i.e., no recent exposure to a culture-confirmed TB case) should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3 to ensure that the initial test result was a true negative result.[31-33] Annual testing for LTBI using TST or IGRA is recommended only for people with HIV who have a history of a negative test for infection and are at high risk for repeated or ongoing exposure to people with active TB disease (e.g., during incarceration, travel to a high-TB incidence country, homelessness, living in a congregate setting).[34]

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48–72 hours in people with HIV) in people with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among people with HIV, the test has several disadvantages: the requirement for two visits to place and read the test, decreased specificity (false positive results) among people who received Bacillus Calmette-Guérin (BCG) vaccination, and decreased sensitivity (false negative results) among people with advanced immunodeficiency.[33,35] The first two limitations of the TST have led to broader use of IGRAs for the detection of LTBI.

IGRAs include the T-SPOT.TB and QFT-TB Gold Plus (QFT-Plus). Systematic reviews and meta-analyses, as well as a large study in the United States, have found that IGRAs generally have higher specificity than the TST, may correlate better with exposure to *M. tuberculosis*, and are less likely to cross-react with BCG vaccination or exposure to nontuberculous mycobacteria.[19,36,37] A systematic review among people with HIV did not find robust evidence that IGRAs were superior to TST in diagnosing either active TB or LTBI.[33] However, in a prospective study of 1,510 people with HIV in the United States (median CD4 count of 532 cells/mm^3), T.SPOT.TB was significantly more specific (99.7%) and had a significantly higher positive predictive value (PPV; 90.0%) than the older QuantiFERON Gold In-Tube (QFT-GIT) (96.5% specificity, 50.7% PPV) and TST (96.8% specificity, 45.4% PPV). QFT-GIT was significantly more sensitive (72.2%) than TST (54.2%) and T.SPOT.TB (51.9%).[38]

As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.[39] In addition, the reproducibility of positive results of IGRAs may be limited. Among 46 people with HIV who had initial positive tests with the QFT-GIT assay, 33 (72%) had negative repeat tests, particularly those whose responses were at the lower range of the manufacturer's suggested range of positive results.[40] Similar to recommendations for healthcare workers, annual testing for people with HIV is no longer recommended unless high risk exists for repeated or ongoing exposure to people with active TB disease.[41]

Among people with HIV, the correlation between the TST and IGRA test results is poor to moderate.[42,43] In prospective studies not limited to people with HIV, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease.[19,44-46] In some studies (again not limited to people with HIV), patients with a positive IGRA were at a higher risk of subsequently developing TB disease than those with a positive TST.[19,47,48] Despite its limitations, a positive TST result strongly predicts that the treatment of LTBI will decrease the risk of TB progression among people with HIV.[18] Studies are underway to formally evaluate if IGRAs are similarly predictive.[49]

Although no definitive comparisons of the TST and IGRAs for screening people with HIV in low-burden settings have been published, both the TST and the approved IGRAs are considered appropriate for TB screening among people with HIV in the United States.[17,38] Some experts have suggested using both the TST and an IGRA in a stepwise or sequential manner to screen for LTBI, but the predictive value of this approach is not clear, and it may be challenging to implement. The routine use of both TST and IGRAs in a single patient to screen for LTBI is not recommended in the United States.[50]

As tests of immune reactivity against *M. tuberculosis*, TST and IGRAs are often positive among people with TB disease. Therefore, all people with a positive TST or IGRA should be evaluated for the possibility of active TB disease.[17] Most, but not all, people with HIV and TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); the absence of these symptoms had a 98% negative predictive value for culture-positive TB in low-resource settings, although this varied depending on pretest probability.[51] The addition of a chest radiograph improved the sensitivity of this screening algorithm but decreased specificity.[52] It is important to note that in a symptomatic patient with clinical suspicion of TB disease, a negative TST or IGRA does not rule out TB disease, particularly in those with CD4 count <200 cells/mm^3.

Obtaining a sputum specimen for *M. tuberculosis* identification is the gold standard for diagnosing pulmonary TB disease, but it is not high yield in screening people with HIV without pulmonary symptoms, particularly in low-prevalence settings. Therefore, a negative symptom screen (including absent cough of *any* duration) coupled with a normal chest radiograph is usually sufficient to exclude TB disease in a patient with a positive TST or IGRA in low TB incidence settings.[17] Sub-clinical TB among people with HIV is of greater concern in high TB burden settings.[53]

Treating Latent TB Infection

Recommendations for Treating LTBI to Prevent TB Disease in People with HIV

Indications

- Positive screening test[a] for LTBI (≥5 mm of induration at 48–72 hours in people with HIV or positive IGRA) regardless of BCG status, no evidence of active TB disease, and no prior history of treatment for active disease or latent TB infection (AI).
- Close contact with a person with infectious TB (such as someone who has shared air space, such as in a household or close congregate setting, with a person with active pulmonary TB according to the Centers for Disease Control and Prevention Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis) regardless of screening test result and CD4 count (AII).

Preferred Therapy

- Isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus rifapentine (see weight-based dosing below) PO once weekly plus pyridoxine 50 mg PO once weekly (3HP) for 12 weeks (AI). Note: 3HP is recommended only for virally-suppressed patients receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen (AII).
  - Rifapentine Weekly Dose (maximum 900 mg)
    - *Weighing 25.1–32 kg:* 600 mg
    - *Weighing 32.1–49.9 kg*: 750 mg
    - *Weighing ≥50.0 kg*: 900 mg
- Isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25–50 mg PO daily (AI) for 3 months (3HR). See the Dosing Recommendations for use of ARV and Anti-TB Drugs When Treating Latent TB table for the list of ARV drugs not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc).

Alternative Therapy

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6–9 months (AII) *or*
- Rifampin 600 mg PO daily for 4 months (BI) (4R)
  - Consult the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for the list of ARV drugs not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (e.g., raltegravir, dolutegravir, or maraviroc).
- Isoniazid 300 mg PO daily plus rifapentine (see weight-based dosing below) PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks (BI) (1HP) Note: 1HP is recommended only for patients receiving an efavirenz-based ARV regimen (AI).
  - Rifapentine Daily Dose (maximum 600 mg)
    - *Weighing <35 kg*: 300 mg
    - *Weighing 35–45 kg*: 450 mg
    - *Weighing >45 kg*: 600 mg
- For people exposed to drug-resistant TB, select drugs for prevention of TB after consultation with experts and with public health authorities (AIII).

Pregnancy Considerations

- During pregnancy, 4R and 3HR are acceptable alternative regimens (BIII).
- For pregnant women receiving effective ART and without close household contact with infectious TB or recent test for TB infection (TST or IGRA) conversion from negative to positive, therapy for LTBI may be deferred until after delivery (BIII).

- Although rifampin generally is considered safe in pregnancy, data on the use of rifapentine are extremely limited and its use in pregnancy is not currently recommended (BIII).

Additional Considerations

- Deferring ART until after completion of treatment for LTBI is not recommended (AI).
- Given the important drug–drug interactions between rifamycins and several antiretroviral (ARV) agents, selection of an LTBI regimen will depend on a patient's current or planned ARV regimen.

[a] Screening tests for LTBI include a tuberculin skin test (TST) or interferon-gamma release assay (IGRA); see text for details regarding these tests.

Key: H = Isoniazid; P = Rifapentine; R = Rifampin; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; CD4 = CD4 T lymphocyte; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; IPT = isoniazid preventive therapy; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally; TB = tuberculosis

Once active TB disease is excluded and in the absence of other medical contraindications, people with HIV with a positive TB screening test should receive LTBI treatment **(AI),** unless there is documentation of prior treatment for active TB or LTBI.[54] Additionally, people with HIV who are in close contact with anyone with infectious TB should receive LTBI treatment, regardless of their TB screening test results and CD4 count **(AII).** Selection of an LTBI regimen may depend on the potential for drug interactions, toxicity concerns, as well as medication availability and/or cost (see Recommendations for Treating LTBI to Prevent TB Disease in People with HIV table above). People with HIV who have been treated successfully for LTBI should not have repeat testing with TST or IGRA; a previously positive test result generally will not revert to negative.

People with HIV in the United States who have a negative TST or IGRA and no recent contact with a person with infectious TB likely will not benefit from the treatment of LTBI, and preventive therapy is not generally recommended **(AIII);** this is in contrast to high TB prevalence countries where isoniazid (i.e., isoniazid preventive therapy; IPT) decreased TB risk and mortality in people with HIV, regardless of TST or IGRA result.[24]

LTBI treatment and ART act independently to decrease the risk of TB disease.[22,23,25,55,56] Therefore, the use of both interventions is recommended for people with LTBI and HIV **(AI).** Given the important drug–drug interactions between rifamycins and several antiretroviral (ARV) agents, selection of an LTBI regimen will depend on a patient's current or planned ARV regimen. Deferring ART until after completion of treatment for LTBI is not recommended **(AI).**[23]

Preferred Drugs for Treatment of Latent TB Infection

3HP

- Rifapentine (weight-based dosing) orally (PO) once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks is one of two preferred regimens for the treatment of LTBI **(AI).**[54]

In two randomized controlled trials, rifapentine plus isoniazid once weekly for 12 weeks (3HP) was as effective and well-tolerated as 6 to 9 months of daily isoniazid, including in people with HIV whose CD4 counts were generally >350 cells/mm^3 and who were not yet on ART.[57,58] 3HP treatment completion rates with self-administered therapy were inferior to those with directly observed therapy (DOT) but non-inferior among study participants enrolled in the United States—and generally high overall.[59]

Although individuals taking ART were not included in the Phase 3 trial of 3HP,[57] the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.[60,61] Raltegravir concentrations were modestly increased when it was given with once-weekly rifapentine in healthy volunteers.[62] In a Phase 1/2 single-arm study of people with HIV treated with dolutegravir and 3HP, rifapentine decreased dolutegravir exposure by 26%. However, trough concentrations remained above the 90% maximum inhibitory concentration for all but one participant, and all participants maintained an undetectable viral load throughout the study period.[63] Based on these PK data and limited outcome data, 3HP is recommended in virally suppressed people receiving efavirenz, raltegravir, or once-daily dolutegravir without dose adjustment of rifapentine, isoniazid, or ART **(AII).**[64] A trial is currently underway examining the use of 3HP in ART-naive participants who are initiating therapy with a dolutegravir-based regimen.[65] 3HP has not been studied in patients receiving twice-daily dolutegravir and is therefore not recommended **(AIII)**.

3HR

- Daily isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25 mg to 50 mg PO daily for 3 months is also a preferred option for the treatment of LTBI in people with HIV **(AI).**

In studies of adults and children without HIV who had a positive TST, those who received 3HR had a similar decreased risk of TB disease, hepatotoxicity, and adverse effects requiring treatment discontinuation compared with those who received ≥6 months of daily isoniazid.[66-70] Among people with HIV, several studies found no difference in the incidence of TB disease between those who received 3HR and those who received ≥6 months of daily isoniazid, regardless of TST status;[71-74] hepatotoxicity was less frequent among those receiving 3HR, but treatment-limiting adverse effects were more common.[54] When using rifampin for LTBI treatment, either dose adjustment or substitution of many commonly used ARVs may be needed (see Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB table).

Alternative Drugs for Treatment of Latent TB Infection

Isoniazid

- Isoniazid 300 mg PO daily plus pyridoxine 25 mg to 50 mg PO daily for 6 to 9 months is an alternative regimen for the treatment of LTBI, particularly when drug–drug interactions between rifamycins and ARV regimens limit the use of rifamycin-containing LTBI therapies **(AII).**

Daily isoniazid for 6 to 9 months is effective and reasonably well-tolerated; severe toxicity is infrequent.[23,74-78] However, treatment completion rates are suboptimal, decreasing its effectiveness.[79] Longer courses of isoniazid (e.g., 12 months) are more effective at preventing TB but carry a higher risk of toxicity[80,81] and patients are more likely to complete shorter regimens.[57,59,79,82-85] Peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or some ARV drugs. Isoniazid, when used, should be supplemented with pyridoxine at a dose of 25 to 50 mg per day to prevent peripheral neuropathy **(AIII).**

4R

- Rifampin 600 mg PO daily for 4 months (4R) is an alternative regimen for the treatment of LTBI in people with HIV **(BI).**

A large trial compared 4 months of daily rifampin (4R) to 9 months of daily isoniazid (9H) in more than 6,000 participants who were predominantly HIV-seronegative.[77] Although rates of incident active TB were low in both arms, the 4R regimen was non-inferior to 9H. Treatment completion rates were significantly higher and adverse events were less common in the 4R arm than in the 9H arm (78.8% vs. 63.2%; $P < 0.001$ and 1.5% vs. 2.6%; $P = 0.003$, respectively). However, only 255 participants were people with HIV, which limits the generalizability of the findings for this population. Although the National Tuberculosis Controllers Association (NTCA)/CDC guidelines recommend 4R as a preferred treatment for LTBI in people without HIV,[54] given the lack of trial data in people with HIV, the 4R regimen is recommended only as an alternative to 3HP, 3HR, and 6 or 9 months of isoniazid in people with HIV **(BI).** When using rifampin for LTBI treatment, either dose adjustment or substitution of key ARVs may be needed. Given the theoretical but unproven risk of selecting for drug-resistant TB with rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in people with HIV on ART,[86,87] some clinicians would obtain a specimen for *M. tuberculosis* testing before starting 4R for LTBI. Due to limited data on 4R in people with HIV, concerns about using this regimen in people with low CD4 cell counts, and an absence of data on the use of 4 months of rifabutin either in people with or without HIV, rifabutin monotherapy is not recommended **(AIII).**[88-90]

1HP

- Isoniazid 300 mg PO daily plus rifapentine (weight-based dosing to a maximum of 600 mg) PO daily plus pyridoxine 25 mg to 50 mg PO daily for 4 weeks (1HP) is an alternative therapy for the treatment of LTBI in people with HIV treated with efavirenz **(BI).**

The BRIEF-TB study (AIDS Clinical Trials Group [ACTG] 5279) evaluated 1 month of daily rifapentine plus isoniazid (1HP) versus 9 months of daily isoniazid (9H) in people with HIV residing in mostly high TB burden settings (TB incidence >60 per 100,000 population).[83] The median CD4 count of study participants was 470 cells/mm^3, 50% of the study population was on efavirenz or nevirapine-based ART regimens at study entry, and 21% of the study population was TST positive. 1HP was non-inferior to 9H when comparing the composite outcome of confirmed or probable TB, death due to TB, and death due to unknown cause. Treatment completion rates (by self-report) were 97% in the 1HP arm and 90% in the 9H arm. Of note, although the population of people with HIV enrolled was at increased risk for LTBI due to high endemic exposure, the number of participants with documented LTBI based on TST or IGRA testing was low (23%), and the overall event rate (i.e., the number of participants who developed active TB in either arm) was also low (0.56/100 person-years) after more than 3 years of follow-up. Based on these data, 1HP is recommended as an alternative regimen for treatment of LTBI in people with HIV **(BI).** The NTCA/CDC guidelines do not include 1HP as a preferred or alternative regimen given that the BRIEF-TB study was performed largely in people with HIV living in high TB burden settings, most of whom did not have positive tests for LTBI.[54] In light of the strengths of the study results and the convenience and safety of the regimen, some clinicians may choose to use 1HP for treatment of LTBI as an alternative option to those recommended in the current NTCA/CDC guidelines. If ART is administered together with 1HP, an efavirenz-based regimen should be used **(AI).**[60,91] A study evaluating co-administration of 1HP with dolutegravir is in progress; the use of dolutegravir-based ART should await results from this trial.[92]

Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB Infection

TB Drug	ARV Drugs	Dose of TB Drug
Isoniazid (INH)	• All ARVs • Note: for information on coadministration of ARVs with rifampin or rifapentine, see entries below	Use INH with pyridoxine 25–50 mg PO daily (50 mg once weekly if used with 3HP) *For 3HP (weekly INH + rifapentine x 12 weeks)* • 15 mg/kg PO once weekly (900 mg maximum) *For 3HR (daily INH + rifampin x 3 months), or 1HP (daily INH + rifapentine x 4 weeks), or INH alone (daily INH x 6–9 months)* • 300 mg PO daily
Rifampin[a]	• NRTIs (TAF with caution[b]) • EFV 600 mg • DTG, RAL (twice daily), and MVC without a strong CYP3A4 inhibitor (note: doses of these ARV drugs need to be adjusted when used with rifampin) • IBA, T-20	*For 3HR (daily rifampin + INH x 3 months), or 4R (daily rifampin x 4 months)* • 600 mg PO daily
	• All other ARVs	Not recommended
Rifapentine[a] 3HP *Weekly rifapentine + INH x 12 weeks*	• EFV 600 mg, RAL or once daily DTG • NRTIs (TAF with caution[b]) • IBA, T-20	• Weighing 32.1–49.9 kg: 750 mg PO weekly • Weighing ≥50.0 kg: 900 mg PO weekly
	• All other ARVs	Not recommended
Rifapentine[a] 1HP *Daily rifapentine + INH x 4 weeks*	• NRTIs (TAF with caution[b]) • EFV 600 mg • IBA, T-20	• Weighing <35 kg: 300 mg PO daily • Weighing 35–45 kg: 450 mg PO daily • Weighing >45 kg: 600 mg PO daily
	• All other ARVs	Not Recommended

[a] For additional drug—drug interaction information between antiretrovirals and anti-TB drugs, see Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines.

[b] If TAF and rifamycins are coadministered, monitor for HIV treatment efficacy. Note that FDA labeling recommends not to coadminister. See Drug-Drug Interactions in the Treatment of HIV-Related TB below and Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections table for more information.

Key: ARV = antiretroviral; BIC = bictegravir; DTG = dolutegravir; EFV = efavirenz; IBA = ibalizumab; IM = intramuscular; INH = isoniazid; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PO = oral; RAL = raltegravir; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TB = tuberculosis

Treatment of LTBI Following Exposure to Drug-Resistant TB

For people exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities **(AIII).**[93] A large randomized clinical trial of 26 weeks of either isoniazid or delamanid for people at high risk for TB, including people with HIV, following household exposure to drug-resistant TB is in progress.[94]

Monitoring for Adverse Events Related to Treating Latent TB Infection

Individuals receiving TB-preventive therapy should be evaluated by a clinician monthly to assess adherence and evaluate for possible drug toxicity. Although people with HIV may not have a higher risk of hepatitis from isoniazid than people without HIV, people with HIV should have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin levels measured before starting LTBI treatment and repeated if abnormal.[54] People with concomitant chronic viral hepatitis and older individuals have an increased risk of isoniazid-related hepatotoxicity, and such people should be monitored closely when being treated for LTBI.[95,96]

Following initiation of isoniazid, ALT and AST levels often increase during the first 3 months of treatment but return to normal despite continued therapy. Hepatotoxicity also can occur with rifamycins, although it is less common than with isoniazid.[78,83] Factors that increase the risk of drug-induced clinical hepatitis include daily alcohol consumption, underlying liver disease, pregnancy and early postpartum, and concurrent treatment with other hepatotoxic drugs.[97] At each visit, patients should be asked about adherence, new medications, and alcohol use and should be screened for potential adverse effects of treatment for LTBI (e.g., unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesia of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness, easy bruising or bleeding, arthralgia) and told to stop medications immediately and return to the clinic for an assessment should any of these occur **(AIII).**

If the serum ALT or AST levels increase to (1) greater than five times the upper limit of normal without symptoms or (2) greater than three times the upper limit of normal AND total bilirubin greater than two times the upper limit of normal without symptoms or (3) greater than three times the upper limit of normal with symptoms (or greater than two times the baseline value for patients with baseline abnormal transaminases), LTBI treatment should be stopped **(AIII).**

The ultimate decision regarding resumption of therapy with the same or different agents for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease,[97] and ideally in consultation with an expert in treating LTBI in people with HIV. If a local expert is not available through the public health department, clinicians and TB programs can contact the CDC (tbinfo@cdc.gov) and utilize remote TB medical consultation services available through the CDC-funded TB Center of Excellence that serves their region.

Clinical Manifestations of TB Disease

Similar to people without HIV, people with HIV and TB disease may be asymptomatic but have positive sputum cultures with or without abnormal findings on chest radiograph (subclinical TB).[98,99] In ambulatory people with HIV, the presence of any one of the classic symptoms of TB disease (i.e., cough, fever, night sweats, weight loss) has high sensitivity but low specificity for diagnosing TB as assessed in resource-limited settings.[51] Compared to treatment-naive patients with HIV, the sensitivity of classic TB symptoms is lower in people with HIV on ART.[86]

The presentation of TB disease is influenced by the degree of immunodeficiency.[100-102] In people with HIV and CD4 counts >200 cells/mm^3, HIV-related TB generally resembles TB among people without HIV. Most people with or without HIV have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.[103]

In people with HIV and CD4 counts <200 cells/mm^3, the chest radiographic findings of pulmonary TB are markedly different, with infiltrates showing no predilection for the upper lobes, and cavitation uncommon.[100,103,104] Normal chest radiographs can be seen in some people with respiratory symptoms and positive sputum cultures. Thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.[105]

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. In people with HIV who are markedly immune-suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.[106] Clinical manifestations of extrapulmonary TB in people with HIV are not substantially different from those described in people without HIV. TB must be considered in disease processes involving any site in the body,[107] especially in those with central nervous system (CNS) disease, when early TB treatment is essential to improve outcomes.[108-111]

After initiation of ART, immune reconstitution can unmask subclinical TB disease, resulting in pronounced inflammatory reactions at the sites of infection (see Unmasking TB-IRIS below).

Diagnosis

Initial diagnostic testing for TB disease should be directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid).[17] Pulmonary involvement is common at all CD4 counts.[99,112] The initial evaluation of a person suspected of having HIV-related TB should always include chest imaging, even in the absence of pulmonary symptoms or signs. However, chest radiography is an imperfect screen for pulmonary TB, particularly among individuals with advanced immunodeficiency who can have TB culture-positive sputum despite normal chest radiographs.[113,114] Therefore, sputum acid-fast bacilli (AFB) smear, nucleic acid amplification (NAA) testing, and AFB culture should be performed in people with HIV with symptoms of TB disease who have a normal chest radiograph, as well as in those with no pulmonary symptoms but evidence of TB disease elsewhere in the body.[17]

Sputum culture yield is not affected by HIV or the degree of immunodeficiency. Sputum smear-negative, culture-positive TB disease is common among people with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.[115,116] NAA tests have a higher sensitivity for culture-positive disease than smear.[17,117] Smear and culture of three sputum specimens is recommended based on a large study in people with HIV that showed a 10% incremental yield for broth culture between the second and third specimens.[118] Additionally, up-front NAA testing for *M. tuberculosis* can expedite diagnosis.[17]

Lymph node involvement is common in HIV-related TB, and the combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes is quite high.[119,120] While NAA testing on specimens other than sputum is an off-label use of the test, a positive NAA test result can be useful as evidence of extrapulmonary TB and for clinical decision-making.[121] Histopathologic findings also are affected by the degree of immunodeficiency. People with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or can be completely absent.[101,122]

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if there is clinical evidence of involvement. Polymerase chain reaction (PCR) testing to aid with molecular identification of *M. tuberculosis* on formalin-fixed tissue is available through reference laboratories

and, in special situations, through the CDC. Clinical providers and pathologists should contact their state or local health department for consultation with the CDC (tbinfo@cdc.gov) and the CDC-funded TB Center of Excellence for assistance with referring specimens for evaluation. The yield of mycobacterial urine and blood cultures depends on the clinical setting; among people with HIV and advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high[101,107] and may allow definitive diagnosis and be the only source of an isolate for drug-susceptibility testing (DST).[123]

Nucleic-Acid Amplification Testing

NAA tests provide rapid diagnosis of TB, and some assays also provide rapid detection of drug resistance. NAA assays, if positive, are highly predictive of TB disease when performed on Acid-Fast Bacillus (AFB) smear-positive specimens. However, because nontuberculous mycobacterial infections (NTM) may occur in people with HIV with advanced immunodeficiency, negative NAA results in the setting of smear-positive specimens may indicate NTM infection and can be used to direct further workup and guide decisions about the need for respiratory isolation.

NAA tests are more sensitive than AFB smears, being positive in 50% to 80% of smear-negative, culture-positive sputum specimens[124,125] and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, an NAA test be performed on at least one sputum specimen.[17,126] NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.[17] Importantly, a smear-negative specimen with a negative NAA test result does not rule out active TB disease.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations in the *rpoB* gene associated with rifampin resistance. It has been implemented widely in resource-limited settings with high TB prevalence and as a frontline TB diagnostic test in people with HIV.[127] This assay combines simple processing requirements in the laboratory and rapid turnaround (results within 2 hours). In a meta-analysis, the overall sensitivity and specificity of the Xpert MTB/RIF assay were 88% (95% confidence interval [CI], 83% to 92%) and 98% (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among people with HIV overall,[128] however, this may be, in part, attributed to a higher prevalence of smear-negative disease in people with HIV.[129] In one key study from South Africa, the sensitivity of Xpert MTB/RIF a relationship with CD4 count was demonstrated, indicating higher sensitivity among people with HIV as the CD4 count declined below 500 cells/mm^3.[130] Importantly, patients in this study with the lowest CD4 count (<100 cells/mm^3) actually had higher rates of smear-positivity and higher markers of severe TB disease (C-reactive protein, anemia, and WHO symptom screen).

Xpert MTB/RIF sensitivity in extrapulmonary specimens is up to 95% in smear-positive specimens and 69% in smear-negative specimens.[131] Median sensitivity varied by specimen type, with higher yield from lymph nodes (96%), cerebrospinal fluid (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%). Xpert MTB/RIF also has been applied with excellent diagnostic accuracy to stool specimens in people with pulmonary TB,[132] which may provide an alternative for people with HIV who are being evaluated for TB and unable to expectorate.

The next-generation Xpert MTB/RIF Ultra improved the sensitivity of the existing test platform, but it is not currently approved by the U.S. Food and Drug Administration (FDA) or available in the

United States. Similarly, the Xpert MTB/XDR cartridge incorporates other drug-resistance targets that may be relevant for constructing a treatment regimen for drug-resistant TB, particularly in settings without access to conventional growth-based or sequencing-based DST, but is also not currently approved by the U.S. FDA and is unavailable in the United States (see Drug-Resistance Testing, below).[133]

Lipoarabinomannan (LAM)

LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of people with TB.[134-137] LAM has been shown to be more sensitive and specific as an adjunct diagnostic test in people with HIV with advanced immunosuppression. The Alere Determine TB LAM is a lateral flow strip applied to a urine sample and recommended by the WHO as an additional diagnostic test for TB among people with HIV.[138] Newer generation LAM assays have increased sensitivity and may be particularly useful in paucibacillary clinical specimens such as cerebrospinal fluid. In a study of 101 patients with suspected TB meningitis, 95 of whom were people with HIV, the SILVAMP TB LAM (Fujifilm) sensitivity from cerebrospinal fluid was 52% for definite or probable TB meningitis (with specificity of 98%), which compared favorably to the sensitivity of 55% for Xpert Ultra. LAM assays are not commercially available in the United States at this time.[139]

Drug-Resistance Testing

Evaluation for TB drug resistance should be considered in all people with HIV, especially those who meet any of the following criteria:

- Known exposure to a person with drug-resistant TB,
- Residence in a setting with high rates of primary drug-resistant TB,
- Persistently positive smear or culture results at or after 4 months of treatment, *or*
- Previous TB treatment, particularly if it was not directly observed or was interrupted for any reason.

Rapid molecular DST for rifampin (and isoniazid, if available) should be performed on the initial isolates from all patients suspected of having TB, because resistance to rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[140,141]

The presence of multidrug-resistant TB (MDR TB; defined as resistance to at least isoniazid and rifampin) or extensively drug-resistant TB (XDR TB; defined as MDR TB with additional resistance to a fluoroquinolone and either bedaquiline or linezolid) is associated with a markedly increased risk of death.[142-144] Therefore, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on both full molecular and conventional DST results, is critical to the successful treatment of TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.[17]

For all patients with TB disease, phenotypic DST to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. Given the alternative of a shorter drug-susceptible TB regimen containing moxifloxacin (see Treating TB Disease), public health laboratories in the U.S. may add routine moxifloxacin susceptibility testing as well. Molecular resistance testing should be performed, and resistance testing should be repeated if

sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive again 1 month or longer after culture conversion to negative. Resistance testing for second-line TB medications (including bedaquiline, linezolid, clofazimine, pretomanid, cycloserine, ethionamide, and others) should be limited to specimens with resistance to first-line TB medications and should be performed in reference laboratories with substantial experience in these techniques.[126]

Conventional Growth-Based Drug-Susceptibility Testing

Conventional DST is used widely and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turnaround time of a conventional broth or agar-based culture followed by DST may be as long as 8 weeks,[145] due to the slow growth of *M. tuberculosis*. During this time, people with drug-resistant TB may be receiving ineffective, empiric first-line TB therapy, which could allow ongoing transmission, further clinical deterioration, acquisition of additional drug resistance, and death, particularly in individuals with HIV.[144] Yet, for many second-line drugs used to treat MDR and XDR TB, conventional DST remains either the gold standard or the only available technique because molecular correlates of phenotypic drug resistance are incomplete.

Molecular Tests for Drug Resistance

Genotypic testing to identify mutations that confer drug resistance allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied for a number of TB medications.[146,147] Commercial NAA tests—such as Xpert MTB/RIF—identify resistance mutations associated with rifampin, and commercially available line probe assays (LPAs) identify genotypic resistance to other drugs.[129,148] All probe-based assays, including Xpert MTB/RIF and LPAs, should be confirmed with sequence-based tests and growth-based DST. For initial evaluation of drug resistance or confirmation of drug resistance identified by the aforementioned assays, the CDC Division of Tuberculosis Elimination has a Molecular Detection of Drug Resistance (MDDR) service that offers rapid sequencing-based testing for first-and second-line TB medications at no charge for providers evaluating people for drug-resistant TB. State TB programs and state laboratories also should be consulted for resistance testing options. Several assays can be performed on cultured isolates or directly on sputum specimens. Molecular resistance testing also can be performed on extrapulmonary specimens that are NAA-positive; if unable to be performed by local or state public health laboratories, this testing can be arranged through the CDC's Division of TB Elimination Laboratory (TBLab@cdc.gov).

In low TB prevalence settings—such as the United States—the positive predictive value for NAA tests of rifampin resistance is low.[149] False-positive rifampin resistance on Xpert MTB/RIF is associated with lower sputum bacillary burden (i.e., high cycle thresholds on Xpert).[150] Therefore, isolates with an initial reading of rifampin resistance by commercial NAA test should always undergo confirmatory testing (*rpoB* gene sequencing and phenotypic DST), with results taken into consideration for treatment decisions. Clinicians who suspect drug-resistant TB in a patient with HIV should make every effort to expedite a diagnosis and consult with their state TB program and then the CDC as needed.

Treating TB Disease

Treating Active TB Disease in People with HIV

- After collecting a specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in people with HIV with clinical and radiographic presentation suggestive of HIV-related TB (AIII).
- DOT is recommended for all patients requiring treatment for HIV-related TB (AII).
- Please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB (below) for specific TB drug dosing recommendations and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations of ARV drugs when used with rifampin or rifabutin.
- Recommendations for monitoring during TB treatment and when to start ART in the context of TB treatment are described in the text.

For Drug-Susceptible TB

Preferred Therapy

Intensive Phase (8 weeks)

- Isoniazid plus (rifampin or rifabutin) plus pyrazinamide plus ethambutol plus pyridoxine 25–50 mg PO daily (AI)
- If molecular or phenotypic drug susceptibility reports show sensitivity to isoniazid and rifampin, then ethambutol may be discontinued before the end of 8 weeks (AI).

Continuation Phase (for Drug-Susceptible TB)

- Isoniazid plus (rifampin or rifabutin) plus pyridoxine 25–50 mg PO daily (AII)

Total Duration of Therapy

- Pulmonary, drug-susceptible, uncomplicated TB: 6 months (BII)
- Pulmonary TB and positive culture at 8 weeks of TB treatment, severe cavitary disease or disseminated extrapulmonary TB: 9 months (BII)
- Extrapulmonary TB with TB meningitis: 9–12 months (BII)
- Extrapulmonary TB in other sites: 6 months (BII)

Alternative Therapy (only for patients receiving an efavirenz-based ARV regimen; not recommended for extrapulmonary TB)

Intensive Phase (8 weeks)

- Isoniazid plus rifapentine 1,200 mg plus moxifloxacin 400 mg plus pyrazinamide plus pyridoxine 25–50 mg PO daily (AI).[a]

Continuation Phase (9 weeks)

- Isoniazid plus rifapentine 1,200 mg plus moxifloxacin 400 mg plus pyridoxine 25–50 mg PO daily (AI).

For Drug-Resistant TB

Empiric Therapy for Suspected Resistance to Rifamycin With or Without Resistance to Other Drugs

- Isoniazid[b] plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin[c]) (BII)

Resistant to Isoniazid

- (Moxifloxacin or levofloxacin) plus (rifampin or rifabutin) plus ethambutol plus pyrazinamide for 6 months (BII)

Resistant to Rifamycins With or Without Other Antimycobacterial Agents

Preferred Therapy

- For 14 days: pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg plus bedaquiline 400 PO daily, *followed by*
- For 24 weeks: pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily, *and* bedaquiline 200 mg PO three times per week
- Note: Omit moxifloxacin if resistant to fluoroquinolones (AI).

Alternative Therapy

- An individualized regimen including based on drug susceptibility test results and clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists (BIII).

Duration

- 6–24 months (see Managing Drug-Resistant TB section below for discussion of treatment duration)

Treatment of TB During Pregnancy

- TB therapy should not be withheld because of pregnancy (AIII).
- Treatment of TB disease during pregnancy should be the same as for any other patient with HIV, but with attention to the following considerations (AIII):
  - Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended (BIII).
  - If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB (AII). The decision regarding whether to include pyrazinamide in treatment regimens during a pregnancy should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.
  - Fluoroquinolones are typically not recommended during pregnancy because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero* (CIII). Fluoroquinolones can, however, be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing (BII).
  - Based on data derived from studies of streptomycin and kanamycin, and the theoretical risk of ototoxicity with *in utero* exposure to amikacin, aminoglycosides should be avoided during pregnancy, if possible (AIII).

TB-Associated IRIS

Preventing Paradoxical TB-IRIS

- In high-risk patients (i.e., starting ART within 30 days after TB treatment initiation and a CD4 count ≤100/mm^3) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (BI): prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks

Managing Paradoxical TB-IRIS

- Paradoxical reaction/IRIS that is not severe may be treated symptomatically (CIII).
- For moderately severe paradoxical TB-IRIS, use of prednisone is recommended (AI).
- In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks
- In patients on a rifabutin plus boosted PI-based regimen: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks
- Taper over 4 weeks (or longer) based on clinical symptoms; a more gradual tapering schedule over 2 to 3 months is recommended for patients whose signs and symptoms have not improved or have worsened due to tapering (BIII).

Other Considerations in TB Management
• Adjunctive corticosteroid is recommended for patients with HIV-related TB involving the CNS (AII). • Dexamethasone has been used for CNS disease with the following dosing schedule: 0.3–0.4 mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks[d] • Despite the potential of drug–drug interactions, rifamycins remain the most potent TB drug and should remain as part of the TB regimen, unless a rifamycin-resistant isolate is detected or the patient has a severe adverse effect that is likely due to the rifamycin (please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB below and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations involving concomitant use of rifampin or rifabutin and different ARV drugs). • Intermittent rifamycin use can result in the development of resistance in patients with HIV and is not recommended (AI).

[a] This regimen was not studied and is not recommended for people who are pregnant, breastfeeding, <40kg, or who have most types of extrapulmonary TB (other than pleural TB or lymphadenitis).

[b] Many patients with rifampin resistance also have resistance to isoniazid. Susceptibility should be confirmed in any patient with rifampin resistance to determine if isoniazid can be included in the treatment regimen.

[c] Given the risk of ototoxicity and nephrotoxicity with aminoglycosides, use of amikacin should generally be restricted to bridging regimens, while awaiting availability of less toxic medications and/or results of drug-susceptibility testing.

[d] At doses above 16 mg, dexamethasone is a CYP3A4 inducer and can decrease certain ARVs that are substrates of CYP3A4 (e.g., DOR, RPV, and protease inhibitors). Consultation with a pharmacist is recommended.

Key: ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally

TB among people with advanced immunodeficiency can be a rapidly progressive and fatal illness if treatment is delayed. Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is recommended in patients with clinical and radiographic findings suggestive of HIV-related TB **(AIII).**

Treatment of TB for people with HIV is the same as for individuals without HIV[151] although the current standard of care continues to evolve as new data emerge from clinical trials. Recommended dosing of drugs for treating active TB disease is summarized in the following table.

Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB

TB Drug	ARV Drugs	Daily Dose of TB Drug
Isoniazid	• All ARVs	5 mg/kg (usual dose 300 mg) Use INH with pyridoxine 25–50 mg PO daily
Rifampin[a,b]	• NRTIs (use TAF with caution[c]) • EFV 600 mg • DTG, RAL (twice daily), MVC without a strong CYP3A4 inhibitor (note: doses of these ARVs need to be adjusted when used with rifampin) • IBA, T-20	10 mg/kg (usual dose 600 mg)
	• DOR, ETR, EFV 400 mg, NVP, RPV (PO) • BIC, EVG/c, RAL (daily) • CAB/RPV (IM/PO) • HIV PIs	Not recommended

TB Drug	ARV Drugs	Daily Dose of TB Drug
	• LEN (SC/PO), FTR, MVC with a strong CYP3A4 inhibitor	
Rifabutin[a]	• NRTIs (use TAF with caution[c]) • ETR without boosted PIs • DOR and RPV (PO) (note: doses need to be adjusted when used with rifabutin) • DTG, RAL • MVC without a strong CYP3A4 inhibitor • IBA, T-20, FTR	5 mg/kg (usual dose 300 mg)
	• PIs with RTV • MVC with a strong CYP3A4 inhibitor	150 mg daily[e]
	• EFV	450–600 mg
	• ETR with boosted PIs • BIC, EVG/c • CAB/RPV (IM/PO) • PIs with COBI • LEN (SC/PO)	Not recommended
Rifapentine	• EFV • NRTIs (use TAF with caution[c])	1,200 mg/day for people weighing ≥40 kg
	• All other ARVs	Not recommended
Pyrazinamide	• All ARVs	Weight-based dosing • *40–55 kg*: 1,000 mg • *56–75 kg*: 1,500 mg • *76–90 kg*: 2,000 mg • *>90 kg*: 2,000 mg[f]
Ethambutol	• All ARVs	Weight-based dosing • *40–55 kg*: 800 mg • *56–75 kg*: 1,200 mg • *76–90 kg*: 1,600 mg • *>90 kg*: 1,600 mg[f]
Moxifloxacin	• All ARVs	• 400 mg daily for those weighing ≥40 kg

[a] For more detailed guidelines on use of different ARV drugs with rifamycin, clinicians should refer to the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines.

[b] Higher doses may be needed in the treatment of TB meningitis. Expert consultation is advised.

[c] If TAF and rifamycins are coadministered, monitor for HIV treatment efficacy. Note that FDA labeling recommends not to coadminister. See text below and Table 4 for more information.

[e] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg three times per week dosing together with RTV-boosted PIs. May consider therapeutic drug monitoring (TDM) when rifabutin is used with an RTV-boosted PI and adjust dose accordingly.

[f] Monitor for therapeutic response and consider TDM to assure dosage adequacy in patients weighing >90 kg.

Note: For drug-drug interaction information between antiretrovirals and anti-TB drugs for treatment of drug-resistant TB, see the Adult and Adolescent Antiretroviral Guidelines.

Key: ARV = antiretroviral; BIC = bictegravir; BID = twice a day; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; IBA = ibalizumab; IM = intramuscular; INH = isoniazid; LEN = lenacapavir; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SC = subcutaneous; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TB = tuberculosis; TDM = Therapeutic Drug Monitoring

The preferred regimen for drug-susceptible TB includes a 2-month (8-week) intensive phase of isoniazid, rifampin, ethambutol, and pyrazinamide **(AI).** Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy, generally recommended as an additional 4 months (18 weeks) of treatment for uncomplicated TB **(AI).**[151] Extension of therapy to 9 months is recommended for patients who have a positive sputum culture after 2 months of treatment or severe cavitary or disseminated extrapulmonary disease **(BII).**

A recently completed large, randomized clinical trial that enrolled 2,516 participants at 34 clinical sites in 13 countries established that a 4-month regimen of 2 months (8 weeks) of rifapentine, moxifloxacin, isoniazid, and pyrazinamide followed by 2 months (9 weeks) of rifapentine, moxifloxacin, and isoniazid was as effective as the standard 6-month regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampin for an additional four months.[152] In this study, the four-month regimen was non-inferior to the control regimen in both the microbiologically eligible and the assessable populations, with unfavorable outcome rates of 15.5% vs. 14.6% (95% CI, -2.6 to 4.5) and 11.6% vs. 9.6% (95% CI, -1.1 to 5.1) respectively. Additionally, the four-month regimen had slightly lower rates of grade 3 or higher adverse events than the control arm. While participants with HIV were included in the trial, the only antiretroviral therapy regimen allowed during the study was efavirenz-containing.[153] This four-month regimen is now recommended as an alternative option for people with and without HIV who are 12 years of age or older **(AI).** It is not recommended for children under 12 years of age, pregnant women, people with extrapulmonary TB, or people with HIV who are taking a non-efavirenz-based antiretroviral regimen **(AI)**.[154] The trial also evaluated a four-month regimen with the same high dose of rifapentine but without moxifloxacin, which was found to be inferior to the control arm.

If rapid DST results indicate resistance to rifampin, with or without resistance to other drugs, an initial MDR TB regimen, as indicated below, should be used **(BIII)** and adjusted as molecular sequencing and conventional DST results become available.

Directly Observed Therapy (DOT)

DOT monitored by trained health care workers, who can be community-based or clinic-based, is recommended for all people with HIV-related TB **(AII).** Digital technology—such as video-DOT and pill sensors—may be useful alternatives to clinic-based or health care worker–based DOT.[155-160] The likelihood of treatment success is further enhanced with comprehensive case management; assistance with housing and other social support; and, if needed, assistance to help people establish or re-engage with HIV care.[151]

Dosing and Duration of Therapy

Although intermittent dosing (administration less often than daily) facilitates DOT, regimens that included twice- or thrice-weekly dosing during the intensive or continuation phase have been

associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in people with HIV.[161-169] Intermittent rifamycin use can result in the development of resistance in patients with HIV and is not recommended **(AI).** Therefore, daily therapy is recommended during both the intensive and continuation treatment phases **(AII).**[151,167,168,170]

Earlier recommendations[171] for TB treatment in people without HIV indicated that therapy should be based on the number of doses received rather than the duration of therapy. However, no data substantiate the minimum number of doses needed within a specified time interval in people with HIV.[151] Every effort should be made to ensure that people with HIV receive daily therapy as previously described.

The optimal duration of TB treatment for people with HIV and drug-susceptible TB disease has not been fully established. In general, the outcomes of 6-month regimens given as DOT to people with HIV have been favorable.[2,151] A 1998 randomized but underpowered trial in the United States showed excellent and comparable outcomes of TB therapy among people with HIV assigned to 6 months or 9 months of therapy.[172]

Two trials in high-burden settings showed a higher risk of recurrent TB among people treated with 6 months of therapy than among those assigned to 9-month[161] or 12-month regimens.[173] However, the applicability of these two trials to low-burden settings—such as the United States—and in the context of universal ART is uncertain. In people with HIV receiving an efavirenz-based ART regimen, the 4-month alternative regimen of rifapentine, moxifloxacin, isoniazid, and pyrazinamide previously described was not associated with a higher rate of recurrent TB compared to the standard of care arm after follow-up out to at least 18 months post-TB treatment initiation.[152,154] Whether outcomes with this 4-month regimen will be similar to standard 6-month anti-TB therapy in people with HIV treated with non-efavirenz-based ART is not known. Additional TB treatment shortening trials using alternative strategies in participants with HIV and TB coinfection are ongoing.

Treatment of TB Meningitis

With regard to the treatment of tuberculous meningitis, data regarding optimal drugs and doses to use are sparse. Many experts suggest that TB meningitis should be treated for an extended period of 9 to 12 months, but there is no evidence to support this recommended treatment duration.[174] Recent clinical trials have suggested that the use of higher rifampin doses (up to 30–35 mg/kg/day) or the addition of fluoroquinolones or linezolid to initial treatment for TB meningitis may be beneficial, but the data are limited, particularly in people with HIV, and are insufficient to support a clear recommendation at this time.[175-183] Adjunctive corticosteroid therapy is recommended for all individuals who have TB involving the CNS **(AII)** including those with HIV, as indicated below.

Adjunctive Corticosteroid Use in TB Treatment

Several clinical trials have demonstrated that adjunctive corticosteroid therapy increases survival overall for people with TB meningitis, improves treatment effectiveness, and reduces adverse event rates. These trials, however, either excluded people with HIV or were underpowered for detecting statistically significant outcome benefits in that group.[111,184,185] A recent clinical trial compared adjunctive corticosteroids to placebo in people with HIV—the majority of whom had advanced HIV (52% of participants had a CD4 ≤50 cells/mm^3)—and failed to find a statistically significant benefit (HR for death 0.85 [95% CI, 0.66–1.10]).[186] The trial was powered to detect a 31% improvement in

survival and it is possible that corticosteroids have a more modest effect. Importantly, the study found no evidence of harm with corticosteroids and, given the high morbidity and mortality associated with TB meningitis, adjunctive corticosteroids are still recommended in people with HIV and TB meningitis. Dexamethasone should be administered in a dose of 0.3 mg/kg/day to 0.4 mg/kg/day for 2 to 4 weeks, then tapered by 0.1 mg/kg per week until a dose of 0.1 mg/kg is reached, then 4 mg per day and tapered by 1 mg/week) for a total duration of 12 weeks **(BII).**[111,151]

TB involving the CNS is currently the only organ system manifestation for which corticosteroids are recommended.[151] Adjunctive corticosteroid therapy is **not recommended** in the treatment of TB pericarditis **(AI).** In a randomized trial that compared adjunctive prednisolone with placebo—each administered for 6 weeks in individuals with tuberculous pericarditis, with and without HIV—prednisolone was not associated with a significant reduction in the composite endpoint of death, cardiac tamponade, or constrictive pericarditis. Those receiving prednisolone also had a higher incidence of some cancers.[187] A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a nonsignificant reduction in constrictive pericarditis. Notably, however, <20% of people with HIV in the trials analyzed were receiving ART.[188] No trials have been conducted comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations Regarding ART Initiation

The preponderance of data from several large randomized trials in people with HIV and TB, as well as subsequent systematic reviews and meta-analyses, supports the recommendation that ART should not be withheld until completion of TB treatment **(AI).**[108,189-196] ART is recommended for all people with HIV and TB **(AI).** For ART-naive patients, ART should be started within 2 weeks after TB treatment initiation in those with CD4 count <50 cells/mm^3 when TB meningitis is not suspected **(AI).** For ART-naive patients with higher CD4 cell counts, ART should be started within 2-8 weeks of starting anti-TB treatment when TB meningitis is not suspected **(AI).** For ART-naïve patients with TB meningitis, ART should be started once the TB meningitis is under control—with either clinical improvement or improvement in CSF parameters—after at least 2 weeks of anti-TB treatment, to reduce the risk of immune reconstitution causing life-threatening inflammation in a closed space **(AIII).** Rifamycin-associated drug interactions should be considered when selecting the ARV drug regimen. Preemptive prednisone therapy should be offered to patients starting ART within 30 days after TB treatment initiation, have a CD4 count ≤100/mm^3, are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B **(BI)** (see TB-Associated IRIS below for details).[197]

American Thoracic Society (ATS)/CDC/Infectious Diseases Society of America (IDSA) guidelines recommend that people with TB meningitis should not start ART before 8 weeks of TB treatment is completed, regardless of CD4 count, based primarily on a randomized trial in 253 people with HIV and TB meningitis conducted in Vietnam. This trial compared immediate ART within 7 days of starting TB treatment with delayed ART started two months after starting TB treatment.[151,193] The study showed no difference in mortality or TB outcomes, but those receiving immediate ART had a higher rate of severe adverse events. It is unclear whether the study's findings are generalizable to higher-resourced settings with access to frequent monitoring and adjustment of dosing. We recommend that for ART-naive people with HIV and TB meningitis, ART should be started once the TB meningitis is under control, after at least 2 weeks of anti-TB treatment **(AIII).** The greatest risk of early ART is the occurrence of intracerebral TB-IRIS after starting ART, which has been reported in up to 50% of people with HIV and TB meningitis and may increase morbidity and mortality[198] (although mortality was similar in both early and delayed ART arms in the only randomized trial

completed to date).[193] However, adjunctive corticosteroid therapy is recommended for all people with HIV and TB meningitis **(AII)** and precludes the need for pre-emptive use of prednisone to prevent IRIS. Whether the corticosteroid regimen recommended as adjunctive therapy for TB meningitis also further reduces the risk of TB IRIS and its consequences has not been evaluated.

In summary, early ART initiation requires close collaboration between HIV and TB care clinics, expertise in the management of ARV regimen selection, close monitoring, potential adjunctive corticosteroid therapy, and support and adherence services. The prevention and management of IRIS are discussed in detail below (see TB-Associated IRIS, below).

When TB occurs in people already on ART, treatment for TB must be started immediately **(AIII),** and ART should be modified to reduce the risk of drug interactions and to maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed, and intensified adherence counseling should be provided. A new ARV regimen may be required to achieve virologic suppression and minimize drug interactions with the anti-TB regimen.

Drug–Drug Interactions in the Treatment of HIV-Related TB

Dolutegravir in combination with two nucleoside(tide) reverse transcriptase inhibitors, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), abacavir, emtricitabine, or lamivudine, is the preferred regimen for co-treatment of HIV in most ART-naive people with TB **(AI).** This regimen can be managed with rifamycin-based anti-TB treatment (see Integrase Inhibitor section below for recommendations about dolutegravir dose adjustment if coadministered with rifampin). The following text summarizes the most important drug-drug interactions for antiretroviral drugs and anti-TB drugs to guide choices if other ART regimens are considered.

The rifamycin class of antibiotics is the cornerstone of effective and shorter-course first-line treatments for drug-sensitive TB. The currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with several ARV drugs. Most of these result from the rifamycin's potent induction of genes involved in the metabolism and transport of ARV agents, and these interactions should be taken into consideration before initiating therapy (see Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB above, and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines). Every effort should be made to include a rifamycin in the TB treatment regimen. Rifamycins remain the most potent drug class for TB treatment. Older regimens that included only 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among people with HIV-related TB.[199,200] If a rifamycin cannot be used, TB treatment duration must be extended, and treatment complexity increases substantially. Thus, individuals with rifamycin-susceptible *M. tuberculosis* isolates should be treated with a regimen that includes a rifamycin unless a serious adverse event is highly likely due to a rifamycin **(AIII).**

No clinical trial has specifically compared rifampin- and rifabutin-containing anti-TB regimens among people with HIV and TB taking ART. Rifabutin is generally regarded as a reasonable substitute for rifampin for the treatment of active TB disease in people with HIV who concurrently receive ARVs that have adverse drug interactions with rifamycins, because rifabutin is a less potent inducer of CYP3A4 than rifampin.[201] Although clinical trial data among people with HIV are limited to one small study, observational data among people with HIV, and several trials among people without HIV have found similar outcomes between those treated with rifampin or rifabutin.[202-205]

Nucleoside Reverse Transcriptase Inhibitor Backbone

Nucleoside(tide) backbone drugs—including tenofovir disoproxil fumarate (TDF), abacavir, emtricitabine, and lamivudine—can be given together with rifampin-containing TB treatment without dose adjustment. Tenofovir alafenamide (TAF), a substrate of drug transporters including P-glycoprotein, may be more likely to have drug–drug interactions than TDF. A study conducted among healthy volunteers without HIV showed that concentrations of intracellular tenofovir-diphosphate (TFV-DP) were higher with TAF/emtricitabine given with rifampin than with TDF given alone, suggesting that TAF may be given together with rifampin-containing TB treatment without dose adjustment.[206] Neither TDF nor TAF has been fully evaluated with rifabutin. In one small study, though, HIV virologic suppression was sustained during TAF-rifabutin co-administration.[207] In one study of TAF (as part of Biktarvy™) taken with daily high-dose rifapentine and isoniazid (1HP) for the treatment of LTBI, plasma tenofovir concentration was similar when TAF was taken alone versus together with 1HP, suggesting that TAF can be taken with rifapentine for short periods of time for prevention of TB.[208]

Non-Nucleoside Reverse Transcriptase Inhibitors—Efavirenz, Nevirapine, Etravirine, Doravirine, and Rilpivirine

One alternative co-treatment regimen for HIV-related TB disease is rifampin-based TB therapy with an ARV regimen of efavirenz (600 mg daily) plus two nucleoside(tide) analogues **(AII).** Studies in people with HIV and TB (including patients with higher body weight) have not shown a significant effect of rifampin-containing TB treatment on efavirenz plasma concentrations when used at the standard 600 mg per day dose in the majority of patients.[209-211] Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[212,213] the 600 mg daily dose of efavirenz is recommended **(AII).** A small study among people with HIV found similar efavirenz concentrations when the 400 mg dose was taken with isoniazid and rifampicin versus when it was taken alone,[214] suggesting that, while not recommended, rifampicin-based TB treatment could be given with efavirenz without a need for efavirenz dose adjustment. Pharmacokinetic studies also support the use of the 600mg efavirenz dose with the new 4-month rifapentine-moxifloxacin-isoniazid-pyrazinamide regimen.[215]

Nevirapine is **not recommended** for HIV and TB co-treatment **(AII).**[216] The use of rifampin or rifapentine with doravirine, etravirine, or rilpivirine **is not recommended (AIII)** (see Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB, above, and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines).

Some experts might consider substitution of rifabutin for rifampin with an appropriate dose adjustment of rifabutin (e.g., increasing to 450–600 mg daily when given with efavirenz) or of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., increasing doravirine dosing to 100 mg twice daily and increasing oral rilpivirine to 50 mg daily), where appropriate,[217,218] for patients who require one of these NNRTIs;[219] however, IM rilpivirine, as used in long-acting ARV combinations, is **not recommended (AIII).** Rifabutin has not been evaluated in combination with rilpivirine, doravirine, or etravirine in people with HIV requiring treatment for active TB disease.

Integrase Inhibitors—Bictegravir, Dolutegravir, Elvitegravir, Raltegravir, and Cabotegravir

As indicated above, dolutegravir in combination with nucleoside reverse transcriptase inhibitors is the preferred option for co-treatment of HIV in most patients with TB **(AI).** A PK study in healthy volunteers showed that increasing the dose of dolutegravir to 50 mg twice a day with rifampin resulted in similar exposure to dolutegravir dosed 50 mg daily without rifampin, and that rifabutin 300 mg daily did not significantly reduce the area under the concentration curve of dolutegravir.[220] A Phase 2 trial in people with HIV and TB (INSPIRING) demonstrated that PK targets and virologic suppression were favorable at 24 and 48 weeks when dolutegravir 50 mg twice daily was administered with rifampin-containing TB treatment.[221] Dolutegravir is currently recommended at a dose of 50 mg twice daily when used together with a rifampin-containing TB regimen **(AI)** (and for two weeks following the completion of TB therapy), though randomized trials evaluating standard once-daily dosing are underway.[222] Dolutegravir should be used at a standard 50 mg once-daily dose when used with rifabutin **(AII).**

Another alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 800 mg twice daily, with standard rifampin dosing **(BI).**[223] Raltegravir concentrations are decreased significantly when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[224] No PK or clinical data exist regarding the use of rifampin with the once-daily, extended-release 600 mg formulation of raltegravir, and co-administration **is not recommended (AIII).** Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without a dose adjustment of either drug **(BII).**[225]

At this time, bictegravir **should not be used** together with rifamycin-containing TB treatment (rifampin, rifabutin, or rifapentine) **(AII).** A trial conducted among healthy participants without HIV evaluated bictegravir concentrations when given twice daily together with rifampin versus once daily alone.[226] Bictegravir trough concentrations, with the dose adjustment, were reduced by 80%. Although studied only with rifabutin, elvitegravir/cobicistat **is not recommended** with TB treatment that contains rifamycins **(AII).**[227,228] When given at steady-state with oral cabotegravir, rifampin decreased cabotegravir AUC by 59% in healthy volunteers.[229] The long-acting injectable formulation of cabotegravir has not been studied with rifamycins, but a pharmacokinetic model of long-acting, injectable, co-formulated cabotegravir-rilpivirine predicted that concurrent rifampin would decrease cabotegravir AUC by 41% to 46%.[230] As a result, oral and long-acting injectable cabotegravir **is not recommended for use** with rifampin or rifapentine **(AII).**[229] Oral and long-acting injectable cabotegravir may be coadministered with rifabutin **(AIII)**; however, long-acting injectable cabotegravir plus rilpivirine is not recommended for use with rifabutin due to the rilpivirine component **(AIII)**.

Protease Inhibitors with Rifampin or Rifabutin

Rifampin decreases the plasma concentrations and exposure of co-administered PIs by >75%.[231-234] One trial tested adjusted doses of ritonavir-boosted darunavir (1600/200 mg once daily and 800/100 mg twice daily) with rifampicin in people with HIV without TB.[235] The trial was stopped early because of high rates of hepatotoxicity, and trough concentrations in the once-daily group were reduced substantially. Thus, boosted darunavir **is not recommended for use** together with rifampin, even with dose adjustment **(AI).**

The effects of rifampin on lopinavir/ritonavir PK may be overcome by doubling the dose of lopinavir/ritonavir.[233,236] In a study of 71 people with HIV and TB, double doses of lopinavir/ritonavir were reasonably well tolerated in those on rifampin-based TB treatment.[205] Some experts would consider this an alternative when a PI-based ART regimen is required during TB treatment **(BI).** Regular monitoring of transaminases and HIV RNA is recommended when double-dose lopinavir/ritonavir is used (e.g., more frequently initially, then monthly once transaminase levels are stable on full dose).

Use of rifabutin with a boosted PI is preferred to the use of rifampin with double-dose PI in settings where rifabutin is readily available. Co-administered rifabutin has little effect on ritonavir-boosted lopinavir[205,237] or atazanavir[238] and only moderately increases concentrations of ritonavir-boosted darunavir[239] and fosamprenavir.[240] However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal active metabolites, 25-O-desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased from 300 mg to 150 mg daily with all ritonavir-boosted PIs to avoid dose-related toxicity, such as uveitis and neutropenia **(AI).**[205,241] Coadministration of cobicistat-boosted PIs with rifabutin is not recommended **(AII)**.

In studies in people with HIV, rifabutin exposures were significantly lower when rifabutin was dosed at 150 mg three times weekly (with lopinavir/ritonavir) than when dosed at 300 mg daily without a PI, but concentrations of the active desacetyl metabolite were high.[242,243] Among people with HIV and TB, cases have been reported of acquired rifamycin resistance when doses of rifabutin of 150 mg three times weekly were co-administered with a boosted PI-based ARV regimen.[244,245] Based on available PK data, it is generally recommended that rifabutin be dosed 150 mg daily in patients who are on a ritonavir-boosted PI-containing ARV regimen **(AI).** However, given the potential risk of adverse events related to high levels of rifabutin's metabolite with this dosing strategy, close monitoring for toxicity (especially neutropenia and uveitis) is required.[205] Close monitoring of adherence to ART is essential because these reduced doses of rifabutin would be inadequate if the patient stopped taking the PI, putting the patient at risk of rifamycin-resistant TB.

Monitoring the Response to Therapy

Patients with pulmonary TB should have at least monthly sputum smears and cultures performed to document culture conversion on therapy (defined as two consecutive negative cultures) **(AII).** Sputum cultures from patients with susceptible TB typically convert to negative within 2 months of first-line TB therapy, although sputum culture conversion to negative may take longer for people with cavitary TB disease.[246-248] Sputum cultures that do not convert to negative at or after 4 months of therapy indicate treatment failure and should prompt further evaluation, including drug-resistance testing of available specimens.

In patients with extrapulmonary TB, obtaining follow-up specimens can be challenging, making it difficult to assess a bacteriologic response to therapy. Instead, the response typically is measured by an improvement in clinical and radiographic findings, but the frequency of such evaluations will depend on the infected sites, the severity of disease, and the ease with which specimens can be obtained.

Managing Suspected Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, incorrect or inadequate prescribed regimen, subtherapeutic drug levels due to malabsorption

or drug interactions, reinfection or mixed infection with drug-resistant *M. tuberculosis*, and acquired drug resistance.

People with suspected treatment failure should be evaluated with a medical history, physical exam, and chest radiograph to determine whether a clinical response to therapy has occurred despite the absence of sputum culture conversion. The initial culture results and drug-resistance tests, treatment regimen, and adherence to the regimen also should be reviewed. Some experts would perform therapeutic drug monitoring to determine if serum concentrations of the TB drugs are within expected ranges and adjust dosage as necessary.[151,249] In addition, samples from all available sites (e.g., sputum, blood, urine) should be collected for repeat culture and DST, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or mixed infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, broadening empiric TB treatment to include at least two additional second-line TB drugs should be considered in consultation with an expert in the field **(BIII).**

Adverse Drug Reactions in TB Patients on Antiretroviral Therapy

Retrospective observational studies reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy. Many of these studies, however, included patients receiving older antiretrovirals which carried more frequent side effects.[250] Three later randomized controlled trials reported similar rates of adverse events during anti-TB therapy with and without concomitant ART, suggesting no significant additive toxicity when ART is co-administered with anti-TB therapy.[153,189,191] Nevertheless, managing suspected adverse drug reactions in this setting is complex because assigning causality to individual drugs in patients on anti-TB drugs, ART, and other agents is very difficult.

Because first-line anti-TB drugs are more effective and have fewer toxicities than alternative drugs, first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently, unless strong evidence exists that a severe drug reaction was caused by a specific anti-TB drug **(AIII).** In such situations, decisions regarding rechallenge with first-line drugs and/or substitution of second-line drugs may be made in consultation with a specialist in treating TB disease in people with HIV.

Liver transaminases should be monitored at baseline and monthly for those with underlying risk factors for hepatotoxicity.[151] Drug-induced liver injury (DILI) can be caused by isoniazid, rifamycins, pyrazinamide, some ARV drugs, and trimethoprim-sulfamethoxazole (TMP-SMX). Anti-TB DILI is defined as an ALT elevation ≥3 times the upper limit of normal (ULN) in the presence of symptoms (e.g., fever, rash, fatigue, nausea, anorexia, jaundice); ALT ≥3 times the ULN plus total bilirubin 2 times the ULN in the absence of symptoms; or ALT ≥5 times the ULN alone in the absence of symptoms. An increase in ALT concentration occurs in approximately 5% to 30% of people treated with the standard four-drug anti-TB regimen,[97,251] but many of these have only transient, mild elevations of ALT.[97]

If the criteria for anti-TB DILI are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately **(AIII)**. Serologic testing for syphilis and hepatitis A, B, and C should be performed, and the patient should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins. At least three anti-TB drugs not

associated with hepatoxicity should be started (e.g., ethambutol, linezolid, and moxifloxacin or levofloxacin)[252] as a "bridging regimen" until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed **(BIII)**.

After the ALT level returns to <2.5 times the ULN (or to near baseline for those with preexisting abnormalities), rechallenge with the hepatotoxic first-line anti-TB medications can be started by adding each drug individually to the bridging regimen at 7-day intervals. During the rechallenge, ALT levels should be monitored frequently.

Rechallenge was successful in almost 90% of people without HIV in one randomized controlled trial of different rechallenge regimens.[252] Because the rifamycins are a critical part of the TB regimen, they should be restarted first. Rechallenge with pyrazinamide is controversial because some studies have reported high rates of recurrent ALT elevations with reintroduction of the drug. Other studies, however, have demonstrated successful reintroduction of pyrazinamide,[253,254] and some experts would therefore recommend rechallenge with pyrazinamide in people with severe forms of TB (e.g., meningitis or disseminated TB).

Bridging drugs can be stopped once three active nonbridging drugs are reinstated successfully. Depending on the outcome of the rechallenge, the anti-TB therapy regimen and duration may need to be altered, in which case, expert consultation is advised. After successful anti-TB drug rechallenge (i.e., if appropriate), relevant ARV drugs and TMP-SMX may be restarted.

Cutaneous adverse drug reactions may occur with all anti-TB drugs, notably rifampin and isoniazid[255]; some ARV drugs, notably the NNRTIs; and TMP-SMX. If the rash is minor, affects a limited area, and causes pruritus, antihistamines should be administered for symptomatic relief and all anti-TB medications should be continued. If the rash is generalized or associated with fever or DILI or involves mucous membrane or desquamation, all anti-TB medications, relevant ARVs, and TMP-SMX should be stopped. When the rash improves substantially, the TB drugs should be restarted as described in the section on DILI above. If the rash recurs, the last drug that had been added should be stopped and the TB regimen modified. Thereafter, if appropriate, relevant ARV drugs and TMP-SMX may be restarted.

Managing Drug-Resistant TB

Although drug-resistant TB represents a small fraction of the TB cases in the United States, the increasing number of people with drug-resistant TB globally plus the high proportion of TB cases in the United States in people who are from TB-endemic areas make it increasingly likely that local TB programs will be faced with this complex disease. The most active and effective TB drugs are those used in first-line TB treatment regimens. When resistance to these medications develops, alternative combinations of TB medications must be used, but clinical trial data on their optimal use are limited, and most recent studies have been conducted primarily in TB-endemic resource-constrained settings.

In the United States, approximately 7% of people with TB have baseline isoniazid mono-resistance.[256] Growing evidence demonstrates an increased risk of treatment failure associated with isoniazid monoresistance,[257] particularly in people with HIV and TB.[258] For people with isoniazid monoresistance, it is recommended that a fluoroquinolone (levofloxacin or moxifloxacin) be substituted for isoniazid and given together with rifampin or rifabutin, pyrazinamide, and ethambutol for 6 months **(BII).**[93,259-261] Though rifampin reduces concentrations of moxifloxacin by 20% to 40%, there is no clinical evidence that a moxifloxacin dose adjustment improves outcomes.[262-264]

The treatment of rifampin-resistant (RR) and MDR TB (resistance to both isoniazid and rifampin) is an area of active investigation and is evolving rapidly. Historically, RR/MDR TB has been treated with individualized regimens taking into account the results of drug resistance testing and prior treatment exposure. In 2019, ATS, CDC, IDSA, and the European Respiratory Society (ERS) issued MDR TB treatment guidelines recommending a fully oral regimen consisting of at least 5 active drugs for most patients with drug-resistant TB, including people with HIV.[93]

Since the publication of the 2019 guidelines, however, several clinical trials have examined the efficacy and safety of a 6-month, all-oral regimen comprised of bedaquiline, pretomanid, and linezolid ("BPaL"). Pretomanid is a novel oral antimycobacterial agent that was approved by the FDA in 2019 exclusively as part of the BPaL regimen. The initial study ("Nix-TB") on which approval was based, was a single-arm study in 109 patients, of whom 51% were people with HIV.[265] Although the study had no control arm, 90% of participants had a favorable outcome. High rates of peripheral neuropathy were seen in Nix-TB study participants, and this was attributed to the high dose of linezolid used (1200 mg daily). The follow-up ZeNix study (n=181) compared outcomes of patients receiving the BPaL regimen at different linezolid doses and showed similarly favorable outcomes with a lower dose of 600 mg daily.[266] The TB-PRACTECAL study compared a regimen in which moxifloxacin was added to BPaL (aka "BPaLM") to longer injectable-based regimens, which were the standard of care at the time.[267,268] In modified intention-to-treat analyses, 121 of 138 (88%) participants in the BPaLM arm achieved treatment success compared with 81 of 137 (59%) of those receiving standard of care. Disease recurrence occurred in one participant in the BPaLM group (n=151) and four in the BPaL group (n=123); new resistance to bedaquiline was observed in the BPaL group in isolates from three of four recurrences, with no new resistance to other drugs in the regimens.[267]

The BPaL and BPaLM regimens have been used in the United States, and treatment outcomes thus far have been very successful among 152 patients with culture-positive pulmonary TB, most of whom received the 600 mg daily dose of linezolid.[269,270] Three recurrences after treatment completion were reported among 116 who received BPaL and none among 36 patients who received BPaLM.

Based on these data, **BPaLM is recommended as the preferred therapy for people with HIV with pulmonary RR-TB and without known resistance to the component medications (AI).**[271] Patients with RR-TB with fluoroquinolone resistance should receive BPaL without moxifloxacin **(AI)**. This recommendation is similar to that of WHO, which conditionally recommends both the BPaL and BPaLM regimens to patients ≥15 years of age with RR-TB who have not had previous exposure or resistance to the drugs in the regimen.[272] BPaLM and BPaL regimens should be given for a total of 26 weeks (6 months) **(AI).** Treatment should be extended up to a total of 39 weeks (9 months) if sputum cultures are positive between months 4 and 6 **(AI)**.

For patients who have not been included in BPaL or BPaLM studies—such as those with extrapulmonary TB or those with known or suspected resistance to bedaquiline, pretomanid, or linezolid—we recommend an individualized regimen consisting of at least 5 active drugs, based on the results of resistance testing and prior treatment exposure **(AI)**. Component medications should be selected using the ranking outlined in the ATS/CDC/IDSA/ERS guidelines.[93] When possible, an initial individualized regimen should contain bedaquiline, linezolid, a fluoroquinolone (levofloxacin or moxifloxacin), clofazimine, and a D-alanine analog (cycloserine or terizidone). All remaining drugs should be used to complete the regimen only when the recommended drugs cannot be used. Kanamycin and capreomycin are no longer recommended due to the increased risk of treatment

failure and relapse with their use.[273] Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used. The duration of therapy with such a regimen will depend on the component drugs and the patient's response to therapy. The ATS/CDC/IDSA/ERS guidelines currently recommend a treatment duration of 15 to 24 months *after culture conversion* when using an individualized regimen, although these guidelines are currently undergoing revision.[93] Several clinical trials have examined different regimens with total durations as short as 9 months and show TB treatment success rates comparable to or better than longer duration therapy.[274-278] Consultation with an expert who has experience managing drug-resistant TB is advised.

An important concern regarding BPaL(M) regimens is the growing prevalence of bedaquiline resistance and the lack of widespread availability of phenotypic second-line TB drug susceptibility testing.[279,280] Rapid molecular testing with confirmatory sequencing for fluoroquinolones and first-line drugs should ideally be performed prior to the initiation of treatment for RR/MDR TB; phenotypic testing should also be undertaken. This testing, as well as susceptibility testing for second-line agents, is available at many local or state public health laboratories or through the CDC's Molecular Detection of Drug Resistance (MDDR) service. To submit a sample for the MDDR service, complete the CDC's MDDR Request Form.

Importantly, as with all TB drugs, there is incomplete concordance between purported bedaquiline resistance-conferring mutations and phenotypic resistance.[281] If bedaquiline is being used, then bedaquiline phenotypic testing should be pursued, if available. Treatment with BPaLM need not be delayed, however, while awaiting the results of bedaquiline susceptibility testing. Of note, pretomanid resistance testing is not currently available.

For people with HIV with RR-TB, several important drug–drug interactions occur between bedaquiline and some ARV drugs. Specifically, efavirenz decreases bedaquiline plasma concentrations.[282] For people with HIV with RR-TB, efavirenz **should not be used** concurrently with bedaquiline **(AI).** Lopinavir/ritonavir increases bedaquiline plasma concentrations approximately twofold when given at steady-state,[283,284] but this has not been associated with additional prolongation of the QT-interval or other adverse events.[285]

Given the options for regimen choice and individual drug dosing within regimens, as well as variations in local drug susceptibilities, the treatment of RR-TB should involve an expert with experience in treating drug-resistant TB.[267,269] If a local expert is not available through the public health department, clinicians and TB programs can contact the CDC (tbinfo@cdc.gov) and one of the CDC's TB Centers of Excellence for Training, Education, and Medical Consultation.

TB-Associated IRIS

TB-IRIS is a frequent, early complication of ART in people with HIV with active TB. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[286-288] TB-IRIS is characterized by excessive local or systemic inflammation. Two forms of TB-IRIS are recognized: paradoxical TB-IRIS and unmasking TB-IRIS. Proposed clinical case definitions for these syndromes have been published.[289]

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in people who are diagnosed with active TB disease before starting ART. Typically, people experiencing paradoxical TB-IRIS have had clinical improvement on TB

treatment before starting ART, and within the first 1 to 4 weeks of ART (though sometimes later), they develop new or recurrent symptoms and worsening or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include fevers, new or enlarging lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality due to paradoxical TB-IRIS is uncommon,[287,290] but life-threatening manifestations include enlarging cerebral tuberculomas, meningitis, enlargement of pericardial effusions causing cardiac tamponade, extensive pulmonary involvement with respiratory failure, nodal enlargement causing airway obstruction, and splenic rupture due to rapid enlargement.[287,291,292] In people with disseminated TB, hepatic TB-IRIS is common, manifesting with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.[288,293] A liver biopsy often reveals granulomatous hepatitis.[294] Hepatic TB-IRIS may be difficult to differentiate from drug-induced liver injury.

Paradoxical TB-IRIS is relatively common among patients starting ART while on TB treatment. A meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18% in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2% of the cases.[295] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[296-301] The syndrome lasts for 2 to 3 months on average,[300,302] but in some cases, symptoms may continue for several more months, and in rare cases, local manifestations may persist or recur over a year after onset.[289,302,303] In such cases of prolonged TB-IRIS, manifestations usually include suppurative lymphadenitis and abscess formation.

The most consistently identified risk factors for paradoxical TB-IRIS are a low CD4 count at the start of ART, especially a CD4 count[239,244] <100 cells/mm^3;[299,304] high HIV viral load before ART[305,306]; disseminated or extrapulmonary TB[291,298,300,304]; and a short interval between starting TB treatment and initiating ART, particularly if ART is started within the first 1 to 2 months of TB treatment.[291,297,299] Although early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in patients with CD4 counts <50 cells/mm^3 and within 2 to 8 weeks of TB diagnosis in those with higher CD4 counts, as previously discussed, to reduce the risk of HIV progression and death (see Special Considerations Regarding ART Initiation, above) **(AI)**.[295]

The diagnosis of paradoxical TB-IRIS may be challenging, and no definitive confirmatory test exists. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms with treatment before ART, deterioration with inflammatory features of TB soon after starting ART, or demonstration of a response to ART (CD4 rise and/or HIV viral load reduction). In addition, diagnosis of paradoxical TB-IRIS requires investigations to exclude alternative causes for deterioration, particularly another opportunistic infection, undetected TB drug resistance, or other cause of treatment failure (see Managing Suspected Treatment Failure, above).[307]

Prevention of Paradoxical TB-IRIS

Pre-emptive treatment with prednisone may prevent or reduce the consequences of TB-IRIS. A randomized, double-blind, placebo-controlled trial of prednisone (40 mg/day for 2 weeks, then 20 mg/day for 2 weeks) versus placebo in 240 ART-naive adults at high risk of developing IRIS at the time of ART initiation demonstrated that preemptive prednisone treatment was effective in reducing the risk of paradoxical TB-IRIS.[197] The incidence of TB-IRIS was 47% in the placebo arm and 33% in the prednisone arm (RR = 0.70; 95% CI, 0.51–0.96). No excess risk was observed for malignancy, severe infections, or other complications. Based on these study findings, preemptive prednisone therapy should be offered for high-risk patients as defined in this study (i.e., starting ART

within 30 days after TB treatment initiation and a CD4 count ≤100/mm^3) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (**BI)**.

Managing Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many people require symptomatic therapy (e.g., analgesia, anti-emetics), and if symptoms are significant, anti-inflammatory therapy is appropriate. Clinicians may use non-steroidal anti-inflammatory drugs to provide symptomatic relief in patients with mild TB-IRIS **(CIII)**. Needle aspiration of enlarging serous effusions, large tuberculous abscesses, or suppurative lymphadenitis may also provide symptom relief **(CIII)**. Repeated aspirations may be required as abscesses and effusions often re-accumulate.[291]

In people with moderately severe paradoxical TB-IRIS, treatment with prednisone is recommended **(AI)**. One randomized, placebo-controlled trial among patients with moderately severe paradoxical TB-IRIS showed that treatment with prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) resulted in a reduction in a combined endpoint of days hospitalized plus outpatient therapeutic procedures.[308] In that study, however, 4 weeks of prednisone treatment was insufficient in a subset of participants. If clinical assessment indicates that signs and symptoms have not improved or have worsened as corticosteroids are tapered, a more gradual tapering of steroids over 2 to 3 months is recommended **(BIII)**.[308] Patients on prednisone experienced more rapid symptoms and radiographic improvement. No reduction in mortality was demonstrated, but immediately life-threatening cases (e.g., those with neurological involvement) were excluded from this study.[111,292,308] Rifampin increases the clearance of prednisolone (the active metabolite of prednisone),[309] but no such effect is expected with rifabutin; dosing of prednisone should therefore be adjusted in patients receiving rifampin or rifabutin-containing regimens (See the Treating TB-Associated IRIS section of the Treating TB Disease table). Corticosteroids should be avoided in people with Kaposi sarcoma because life-threatening exacerbations can occur. Case reports have been published of patients with steroid-refractory and prolonged IRIS or paradoxical reactions responding to TNF-blockers, IL-1 inhibitors, JAK inhibitors, or thalidomide.[310-317]

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in people who have unrecognized TB (because TB is either symptomatic or it has eluded diagnosis) at the start of ART. These people may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[289] A common presentation is pulmonary TB with rapid symptom onset and clinical features similar to bacterial pneumonia with high fever, respiratory distress, sepsis syndrome, and consolidation on chest radiograph.[289,308,318-320] Focal inflammatory manifestations—such as abscesses and lymphadenitis— also may develop.[321] In cases of unmasking TB-IRIS, the treatment should be standard TB treatment and, if the manifestations are life-threatening, adjunctive corticosteroid therapy is recommended, although steroid use in this setting has not been studied in a clinical trial **(BIII).**

Prevention of Recurrent TB

Among patients receiving the same TB treatment regimen in the same setting, the risk of recurrent TB appears to be higher among those with HIV than among those without HIV.[322,323] In TB-endemic settings, much of the increased risk of recurrent TB appears to be due to the higher risk of re-infection with a new strain of *M. tuberculosis*, with subsequent rapid progression to TB disease.[324,325]

In settings with low rates of TB—such as the United States—recurrent TB due to re-infection is uncommon, even among people with HIV.[326]

Several interventions may decrease the risk of recurrent TB among people with HIV: longer TB treatment regimens, administering therapy daily throughout the course of the intensive and continuation phases, post-treatment isoniazid therapy, and use of ART. None of these interventions has been adequately evaluated in randomized trials in settings with low TB burdens. Post-treatment isoniazid (6–9 months of daily isoniazid therapy after the completion of standard multidrug therapy) has been shown to be effective in high-burden settings in which the risk of re-exposure is high,[327,328] suggesting that this intervention decreases the risk of re-infection. Post-treatment isoniazid **is not recommended** for patients in the United States or other low-burden settings due to a lack of evidence of effectiveness supporting a reduced risk of re-infection for these settings **(AIII).** Given that ART reduces the risk of initially developing TB disease, it is likely that ART also decreases the risk of re-infection with TB.

Special Considerations During Pregnancy

During pregnancy, if there is no documentation of a prior negative TB screening test result or there is a high risk for repeated or ongoing exposure to people with active TB disease, then test for TB **(AIII).** TB rates in pregnant and postpartum women are higher than in other people with HIV, after adjusting for age,[329] and this is likely due to pregnancy-related immunologic shifts.[330-334] Several studies have examined the performance of IGRAs for diagnosis of LTBI in pregnant women. In pregnant women with or without HIV, the test appears to perform well.[335,336] Longitudinal studies conducted in high-burden countries, however, suggest that test performance may be compromised in late pregnancy versus postpartum, especially at delivery.[337-343]

A clinical trial of isoniazid preventive therapy (IPT) among women with HIV in high TB prevalence settings (TB APPRISE) found increased adverse pregnancy outcomes in women treated with isoniazid during pregnancy compared to postpartum initiation of isoniazid.[344] Importantly, however, none of the women were close household TB contacts, and most of the women in the trial were IGRA-negative and were receiving efavirenz-based ART. Two smaller observational studies of isoniazid given to pregnant women with HIV in South Africa did not find an increased risk of adverse pregnancy outcomes with isoniazid.[345,346] Similarly, a study of participants in Botswana who became pregnant in a trial of 36 months of isoniazid for people with HIV also did not report increased adverse pregnancy outcomes.[347] A subsequent systematic review of the association of adverse pregnancy outcomes and isoniazid found inconsistent associations.[348] Among women enrolled in the BRIEF-TB study who became pregnant while taking isoniazid for TB prevention, first-trimester IPT exposure was associated with increased risk of fetal demise, though this association was attenuated when adjusted for covariates proximal to pregnancy outcome including ART use.[349]

Studies in individuals with HIV who are not receiving ART have shown a high risk of progression from LTBI to active TB disease (10% per year), and a high risk exists for maternal and infant mortality in pregnant women with HIV who have active TB disease.[350,351] Although the risk of progression from LTBI to active TB disease in individuals on ART is decreased significantly, risk in these individuals with HIV appears higher than in pregnant and postpartum women without HIV.[337,352] Pregnant women with HIV should be receiving ART both for their own health and for prevention of perinatal transmission **(AI).** In the United States, isoniazid preventive therapy is recommended for pregnant women with HIV whose close household contacts include a person with

active TB disease **(AI).** For those receiving effective ART and without recent TST or IGRA conversion or close household contacts with infectious TB, therapy for LTBI may be deferred until after delivery **(BIII).** The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy and in the first 2 to 3 months post-partum.[344] Therefore, if isoniazid is prescribed, frequent monitoring is needed.[34] Pregnant women receiving isoniazid should receive daily pyridoxine supplementation **(AII)** because they are at risk of isoniazid-associated peripheral neuropathy.[151,353] Limited data exist on alternatives to isoniazid for LTBI therapy in pregnant women with HIV. In the IMPAACT 2001 study, pregnant women with and without HIV received 3HP and no serious adverse pregnancy outcomes were observed. Drug exposures were similar to non-pregnant populations, suggesting this regimen does not require dose adjustment in pregnancy.[354] Despite these promising data and although rifampin generally is considered safe in pregnancy, data on the use of rifapentine remain extremely limited and the use of rifapentine during pregnancy is not currently recommended **(BIII).**[355-357] The DOLPHIN Moms trial (NCT05122026) currently underway is examining the pharmacokinetics and safety of 3HP and 1HP in pregnant women with HIV who are virally suppressed on a dolutegravir-based regimen.

During pregnancy, the diagnostic evaluation for TB disease is the same as for other adults with HIV. It is important to recognize that standard symptom screens have lower sensitivity in pregnant women than in non-pregnant populations, and that some TB symptoms may be masked by common symptoms of pregnancy (e.g. poor appetite).[358-360] In addition to standard sputum testing, chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure.[361] An increase in pregnancy complications—including preterm birth, low birthweight, and fetal growth restriction—can be seen among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when TB treatment is delayed until late in pregnancy.[34,330,333,335,336,339,344,351,362-366] Congenital TB infection has been reported, although it appears relatively uncommon; history of maternal infertility and acid-fast bacilli from placenta or endometrial biopsy may be found with this rare diagnosis.[367-372] While rare, congenital TB might be more common among children born to mothers with TB/HIV coinfection, especially when those children also have perinatally acquired HIV.[373,374]

TB therapy should not be withheld because of pregnancy **(AIII).** Treatment of TB disease during pregnancy should be the same as for any other patient with HIV, but with attention to the following considerations **(AIII):**

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently during pregnancy and the postpartum period.[375] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(BIII).**
- Rifampin is not teratogenic in humans.
- Ethambutol is teratogenic in rodents and rabbits at doses that are much higher than those used in humans. No evidence of teratogenicity has been observed in humans. Ocular toxicity has been reported in adults taking ethambutol but changes in visual acuity have not been detected in infants exposed to ethambutol *in utero*.
- Pyrazinamide is not teratogenic in animals. The WHO and the International Union Against Tuberculosis and Lung Diseases have made recommendations for the routine use of pyrazinamide in pregnant women.[272,376] Pyrazinamide has been recommended for use during pregnancy in the United States, although data characterizing its safety in this setting are limited and the CDC guidance suggests that clinicians consider the use of this agent based on individual

patient considerations weighing benefit and risks.[151,377] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB **(AII).** The decision regarding whether to include pyrazinamide in treatment regimens during a pregnancy should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.

Experience using the majority of the second-line drugs for TB during pregnancy is limited.[378-381] MDR TB in pregnancy should be managed in consultation with a specialist. In a small prospective study of pregnant women who received second-line MDR/RR-TB regimens that contained bedaquiline or delamanid (including linezolid, clofazimine, amikacin, capreomycin, and kanamycin) 98% had successful treatment outcomes, and at least 81% of continued pregnancies resulted in live births with 68% normal birthweight neonates.[378] The following concerns should be considered when selecting second-line anti-TB drugs for use during pregnancy:

- **Bedaquiline:** Data on the use of bedaquiline in pregnancy are limited, but a study of 108 pregnant women from South Africa found an increased frequency of low birthweight (<2,500 g) among children exposed to bedaquiline *in utero* compared to those who were not exposed (45% vs. 26%; $P = 0.034$).[382] The median birthweight between the two groups, however, was not statistically significant (2690 vs. 2900 grams [$P = 0.18$]) and after 1 year, most children exposed to bedaquiline had gained weight and were doing well. Bedaquiline concentrations in breast milk may be as high or higher than concentrations in maternal plasma, which may have implications for the infant.[383,384]
- **Cycloserine:** No data are available from animal studies or reports of cycloserine use in humans during pregnancy.
- **Ethionamide** has been associated with an increased risk for several anomalies in rats after high-dose exposure, but not in mice or rabbits.[385-387] Case reports have documented cases of CNS defects in humans and hypothyroidism, but overall experience is limited with use during human pregnancy.[388] Ethionamide is likely present in the breast milk, which could be associated with thyroid issues in the infant. Thus, ethionamide should be avoided, unless its use is required on the basis of susceptibility testing **(CIII).**
- **Fluoroquinolones:** Because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero*, quinolones are typically not recommended during pregnancy or for children aged <18 years **(CIII).** However, studies evaluating fluoroquinolone use in pregnant women did not find an increased risk of birth defects or congenital musculoskeletal abnormalities.[389-393] Furthermore, fluoroquinolones were used in a larger South African case series of MDR TB treatment in pregnancy with generally good outcomes.[382] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(BII).**[394]
- **Linezolid:** Animal studies of linezolid in pregnancy report decreased fetal body weight and increased fusion of costal cartilage.[395] There are few studies in human pregnancy, but linezolid has been used for the treatment of DR-TB in some high-burden countries.[378,382] In these case studies, monitoring complete blood counts for anemia and thrombocytopenia and advising iron supplementation has been recommended.[384,396]
- **Delamanid:** Delamanid appears to be safe in animal reproductive toxicity studies. It has been used in small cohorts of pregnant women for DR-TB with favorable outcomes.[378,397]

- **Pretomanid**: Animal studies of pretomanid do not indicate direct or indirect harmful effects with respect to embryo-fetal development. However, pretomanid has been associated with reproductive toxicity in animal models; specifically, reduced fertility in male rats.[398] There has been very limited use in human pregnancies. Therefore, pretomanid should be avoided in pregnancy until more data is available **(AIII)**.
- **Para-aminosalicylic acid** is not teratogenic in rats or rabbits.[377] In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed to para-aminosalicylic acid during the first trimester of pregnancy.[399] No specific pattern of defects and no increase in the rate of defects have been detected in other human studies, indicating that this agent can be used with caution, if needed **(CIII).**
- **Aminoglycosides/polypeptides:** Streptomycin use has been associated with a 10% rate of vestibulocochlear nerve toxicity in infants exposed to the drug *in utero*; its use during pregnancy should be avoided, if possible **(AIII).** Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided, if possible **(AIII).** The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented. Capreomycin is no longer recommended, but amikacin might be used as an alternative when an aminoglycoside is required for the treatment of MDR TB **(CIII).**

References

1. World Health Organization. Global tuberculosis report 2021. 2021. Available at: https://www.who.int/publications/i/item/9789240037021.

2. World Health Organization. Global tuberculosis report 2022. 2022. Available at: https://www.who.int/publications/i/item/9789240061729.

3. Filardo TD, Feng PJ, Pratt RH, Price SF, Self JL. Tuberculosis - United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(12):441-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35324877.

4. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000;30 Suppl 1:S5-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10770911.

5. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000-2010. *J Infect Dis*. 2016;214(6):862-872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27559122.

6. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2021. 2021. Available at: https://www.cdc.gov/tb/statistics/reports/2021/table19.htm.

7. Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clin Microbiol Rev*. 2018;31(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30021818.

8. Pai M, Behr MA, Dowdy D, et al. Tuberculosis. *Nat Rev Dis Primers*. 2016;2(16076). Available at: https://www.nature.com/articles/nrdp201676.

9. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320(9):545-550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2915665.

10. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA*. 1992;268(4):504-509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1619742.

11. Moreno S, Baraia-Etxaburu J, Bouza E, et al. Risk for developing tuberculosis among anergic patients infected with HIV. *Ann Intern Med*. 1993;119(3):194-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8100693.

12. Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS

(GISTA). *JAMA*. 1995;274(2):143-148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7596002.

13. Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1997;126(2):123-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9005746.

14. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol*. 1974;99(2):131-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4810628.

15. Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis*. 2005;191(2):150-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15609223.

16. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. 2000;23(1):75-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10708059.

17. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. 2017;64(2):111-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28052967.

18. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20091503.

19. Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. *BMJ*. 2020;368:m549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32156698.

20. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. *PLoS One*. 2015;10(11):e0140881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26536035.

21. Badje A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health*. 2017;5(11):e1080-e1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29025631.

22. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. 2014;384(9944):682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24835842.

23. Temprano ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26193126.

24. Ross JM, Badje A, Rangaka MX, et al. Isoniazid preventive therapy plus antiretroviral therapy for the prevention of tuberculosis: a systematic review and meta-analysis of individual participant data. *Lancet HIV*. 2021;8(1):e8-e15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33387480.

25. Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2007;21(11):1441-1448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17589190.

26. Holzman SB, Perry A, Saleeb P, et al. Evaluation of the latent tuberculosis care cascade among public health clinics in the United States. *Clin Infect Dis*. 2022;75(10):1792-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35363249.

27. Wilson IB, Landon BE, Hirschhorn LR, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med*. 2005;143(10):729-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16287794.

28. Backus LI, Boothroyd DB, Phillips BR, et al. National quality forum performance measures for HIV/AIDS care: the Department of Veterans Affairs' experience. *Arch Intern Med*. 2010;170(14):1239-1246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660844.

29. Lee LM, Lobato MN, Buskin SE, Morse A, Costa OS. Low adherence to guidelines for preventing TB among persons with newly diagnosed HIV infection, United States. *Int J Tuberc Lung Dis*. 2006;10(2):209-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16499263.

30. Reaves EJ, Shah NS, France AM, et al. Latent tuberculous infection testing among HIV-infected persons in clinical care, United States, 2010-2012. *Int J Tuberc Lung Dis*. 2017;21(10):1118-1126. Available at: https://pubmed.ncbi.nlm.nih.gov/28911355/.

31. Fisk TL, Hon HM, Lennox JL, Fordham von Reyn C, Horsburgh CR, Jr. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *AIDS*. 2003;17(7):1102-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12700468.

32. Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS*. 2002;16(14):1976-1979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12351964.

33. Overton K, Varma R, Post JJ. Comparison of interferon-gamma release assays and the tuberculin skin test for diagnosis of tuberculosis in human immunodeficiency virus: a systematic review. *Tuberc Respir Dis (Seoul)*. 2018;81(1):59-72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29256218.

34. Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. 2020. Available at: https://www.cdc.gov/tb/hcp/education/latent-tb-infection-guide-primary-care-providers.html?CDC_AAref_Val=https://www.cdc.gov/tb/publications/ltbi/default.htm.

35. Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1993;119(3):185-193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8100692.

36. Auguste P, Tsertsvadze A, Pink J, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. *BMC Infect Dis*. 2017;17(1):200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28274215.

37. Ho CS, Feng PI, Narita M, et al. Comparison of three tests for latent tuberculosis infection in high-risk people in the USA: an observational cohort study. *Lancet Infect Dis*. 2022;22(1):85-96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34499863.

38. Pettit AC, Stout JE, Belknap R, et al. Optimal testing choice and diagnostic strategies for latent tuberculosis infection among US-born people living with human immunodeficiency virus (HIV). *Clin Infect Dis*. 2021;73(7):e2278-e2284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761083.

39. Cattamanchi A, Smith R, Steingart KR, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2011;56(3):230-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239993.

40. Gray J, Reves R, Johnson S, Belknap R. Identification of false-positive QuantiFERON-TB Gold In-Tube assays by repeat testing in HIV-infected patients at low risk for tuberculosis. *Clin Infect Dis*. 2012;54(3):e20-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22057704.

41. Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis screening, testing, and treatment of U.S. health care personnel: recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(19):439-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31099768.

42. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med*. 2007;175(7):737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17218620.

43. Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis*. 2009;9:15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19208218.

44. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21846592.

45. Hill PC, Jackson-Sillah DJ, Fox A, et al. Incidence of tuberculosis and the predictive value of ELISPOT and Mantoux tests in Gambian case contacts. *PLoS One*. 2008;3(1):e1379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18167540.

46. Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis*. 2009;48(7):954-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245343.

47. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med*. 2008;177(10):1164-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18276940.

48. Leung CC, Yam WC, Yew WW, et al. T-Spot.TB outperforms tuberculin skin test in predicting tuberculosis disease. *Am J Respir Crit Care Med*. 2010;182(6):834-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20508217.

49. Ledesma JR, Ma J, Zheng P, Ross JM, Vos T, Kyu HH. Interferon-gamma release assay levels and risk of progression to active tuberculosis: a systematic review and dose-response meta-regression analysis. *BMC Infect Dis*. 2021;21(1):467. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34022827.

50. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR Recomm Rep*. 2010;59(RR-5):1-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20577159.

51. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011;8(1):e1000391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21267059.

52. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. *Lancet HIV*. 2018;5(9):e515-e523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30139576.

53. Stuck L, van Haaster AC, Kapata-Chanda P, Klinkenberg E, Kapata N, Cobelens F. How "subclinical" is subclinical tuberculosis? An analysis of National Prevalence Survey data from Zambia. *Clin Infect Dis*. 2022;75(5):842-848. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34984431.

54. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep*. 2020;69(1):1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32053584.

55. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009;23(5):631-636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19525621.

56. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9777):1588-1598. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21492926.

57. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV co-infected persons. *AIDS*. 2016;30(10):1607-1615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26990624.

58. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365(1):11-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21732833.

59. Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2017;167(10):689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29114781.

60. Podany AT, Bao Y, Swindells S, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving rifapentine and isoniazid for tuberculosis prevention. *Clin Infect Dis*. 2015;61(8):1322-1327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26082504.

61. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine once-weekly dosing effect on efavirenz emtricitabine and tenofovir PKs. Presented at: Conference on Retroviruses and Opportunistic Infections; 2014. Boston, MA. Available at: https://www.croiconference.org/abstract/rifapentine-once-weekly-dosing-effect-efavirenz-emtricitabine-and-tenofovir-pks.

62. Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. 2014;69(4):1079-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24343893.

63. Dooley KE, Savic R, Gupte A, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial.

Lancet HIV. 2020;7(6):e401-e409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32240629.

64. Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2018;67(25):723-726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29953429.

65. U.S. National Library of Medicine. Safety tolerability DDI short course treatment of LTBI infection with high-dose rifapentine and isoniazid or standard isoniazid preventive therapy in HIV+ patients (DOLPHIN & DOLPHIN TOO) (IMPAACT4TB). 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT03435146.

66. Hong Kong Chest Service/Tuberculosis Research Centre; Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *Am Rev Respir Dis*. 1992;145(1):36-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1731596.

67. Geijo MP, Herranz CR, Vano D, Garcia AJ, Garcia M, Dimas JF. [Short-course isoniazid and rifampin compared with isoniazid for latent tuberculosis infection: a randomized clinical trial]. *Enferm Infecc Microbiol Clin*. 2007;25(5):300-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504682.

68. Jimenez-Fuentes MA, de Souza-Galvao ML, Mila Auge C, Solsona Peiro J, Altet-Gomez MN. Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population. *Int J Tuberc Lung Dis*. 2013;17(3):326-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23407221.

69. Martinez Alfaro E, Solera J, Serna E, et al. [Compliance, tolerance and effectiveness of a short chemoprophylaxis regimen for the treatment of tuberculosis]. *Med Clin (Barc)*. 1998;111(11):401-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9834911.

70. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis*. 2005;40(5):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15714411.

71. Fitzgerald DW, Severe P, Joseph P, et al. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV-infected adults living in a country with endemic tuberculosis: results of a randomized trial. *J Acquir Immune Defic Syndr*. 2001;28(3):305-307. Available at: https://pubmed.ncbi.nlm.nih.gov/11694842/.

72. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*. 2001;15(16):2137-2147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11684933.

73. Rivero A, Lopez-Cortes L, Castillo R, et al. [Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients]. *Enferm Infecc Microbiol Clin*. 2007;25(5):305-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504683.

74. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*. 1997;337(12):801-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9295239.

75. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. 1997;337(5):315-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9233868.

76. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *AIDS*. 1997;11(7):875-882. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9189212.

77. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379(5):440-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30067931.

78. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22150035.

79. Horsburgh CR, Jr., Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*. 2010;137(2):401-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19793865.

80. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis*. 1999;3(10):847-850. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10524579.

81. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bull World Health Organ*. 1982;60(4):555-564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6754120.

82. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA*. 2000;283(11):1445-1450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10732934.

83. Swindells S, Ramchandani R, Gupta A, et al. One Month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380(11):1001-1011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865794.

84. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2008;149(10):689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19017587.

85. Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *Int J Infect Dis*. 2010;14(4):e292-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19656705.

86. Rangaka MX, Wilkinson RJ, Glynn JR, et al. Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic. *Clin Infect Dis*. 2012;55(12):1698-1706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22955441.

87. den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2016;20(8):1065-1071. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27393541.

88. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberc Lung Dis*. 2002;6(11):995-1000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12475146.

89. McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. *Chest*. 2003;123(1):102-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12527609.

90. Centers for Disease Control and Prevention. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC Recommendations--United States, 2001. *MMWR*. 2001. Available at: https://www.cdc.gov/mmwr/PDF/wk/mm5034.pdf.

91. Podany AT, Leon-Cruz J, Hakim J, et al. Nevirapine pharmacokinetics in HIV-infected persons receiving rifapentine and isoniazid for TB prevention. *J Antimicrob Chemother*. 2021;76(3):718-721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33241266.

92. U.S. National Library of Medicine. Drug-drug interactions between rifapentine and dolutegravir in HIV/LTBI co-infected individuals. 2023. Available at: https://clinicaltrials.gov/study/NCT04272242.

93. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200(10). Available at: https://www.atsjournals.org/doi/ref/10.1164/rccm.201909-1874ST.

94. U.S. National Library of Medicine. Protecting households on exposure to newly diagnosed index multidrug-resistant tuberculosis patients (PHOENIx MDR-TB). 2023. Available at: https://clinicaltrials.gov/study/NCT03568383?cond=NCT03568383&rank=1.

95. Bliven-Sizemore EE, Sterling TR, Shang N, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. *Int J Tuberc Lung Dis*. 2015;19(9):1039-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26260821.

96. Ngongondo M, Miyahara S, Hughes MD, et al. Hepatotoxicity during isoniazid preventive therapy and antiretroviral therapy in people living with HIV with severe immunosuppression: a secondary analysis of a multi-country open-label randomized controlled clinical trial. *J Acquir Immune Defic Syndr*. 2018;78(1):54-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29406428.

97. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174(8):935-952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17021358.

98. Kendall EA, Shrestha S, Dowdy DW. The epidemiological importance of subclinical tuberculosis. A critical reappraisal. *Am J Respir Crit Care Med*. 2021;203(2):168-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33197210.

99. Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med*. 2010;362(8):707-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20181972.

100. Batungwanayo J, Taelman H, Dhote R, Bogaerts J, Allen S, Van de Perre P. Pulmonary tuberculosis in Kigali, Rwanda. Impact of human immunodeficiency virus infection on clinical and radiographic presentation. *Am Rev Respir Dis*. 1992;146(1):53-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1626814.

101. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis*. 1993;148(5):1292-1297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7902049.

102. Dhana A, Hamada Y, Kengne AP, et al. Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis. *Lancet Infect Dis*. 2022;22(4):507-518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34800394.

103. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25(2):242-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9332519.

104. Post F, Wood R, Pillay G. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tuber Lung Dis*. 1995;76:518-21. Available at https://pubmed.ncbi.nlm.nih.gov/8593372.

105. Pepper T, Joseph P, Mwenya C, et al. Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. *Int J Tuberc Lung Dis*. 2008;12(4):397-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18371265.

106. Ahuja SS, Ahuja SK, Phelps KR, Thelmo W, Hill AR. Hemodynamic confirmation of septic shock in disseminated tuberculosis. *Crit Care Med*. 1992;20(6):901-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1597048.

107. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine*. 1991;70(6):384-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1956280.

108. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010913.

109. Whalen C, Horsburgh CR, Jr., Hom D, Lahart C, Simberkoff M, Ellner J. Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. *AIDS*. 1997;11(4):455-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9084792.

110. Kourbatova EV, Leonard MK, Jr., Romero J, Kraft C, del Rio C, Blumberg HM. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. *Eur J Epidemiol*. 2006;21(9):715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072539.

111. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351(17):1741-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15496623.

112. Lewis JJ, Charalambous S, Day JH, et al. HIV infection does not affect active case finding of tuberculosis in South African gold miners. *Am J Respir Crit Care Med*. 2009;180(12):1271-1278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19745207.

113. Cavanaugh JS, Modi S, Musau S, et al. Comparative yield of different diagnostic tests for tuberculosis among people living with HIV in western Kenya. *PLoS One*. 2016;11(3):e0152364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27023213.

114. Henostroza G, Harris JB, Chitambi R, et al. High prevalence of tuberculosis in newly enrolled HIV patients in Zambia: need for enhanced screening approach. *Int J Tuberc Lung Dis*. 2016;20(8):1033-1039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27393536.

115. Arpagaus A, Franzeck FC, Sikalengo G, et al. Extrapulmonary tuberculosis in HIV-infected patients in rural Tanzania: The prospective Kilombero and Ulanga antiretroviral cohort. *PLoS One*. 2020;15(3):e0229875. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130279.

116. Elliott AM, Halwiindi B, Hayes RJ, et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. *J Trop Med Hyg*. 1993;96(1):1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8429569.

117. Reid MJ, Shah NS. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *Lancet Infect Dis*. 2009;9(3):173-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19246021.

118. Monkongdee P, McCarthy KD, Cain KP, et al. Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. *Am J Respir Crit Care Med*. 2009;180(9):903-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19628775.

119. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis*. 1992;15(4):601-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1420673.

120. Razack R, Louw M, Wright CA. Diagnostic yield of fine needle aspiration biopsy in HIV-infected adults with suspected mycobacterial lymphadenitis. *S Afr Med J*. 2013;104(1):27-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24388082.

121. Cheng VC, Yew WW, Yuen KY. Molecular diagnostics in tuberculosis. *Eur J Clin Microbiol Infect Dis*. 2005;24(11):711-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16283213.

122. Diedrich CR, O'Hern J, Gutierrez MG, et al. Relationship between HIV coinfection, interleukin 10 production, and *Mycobacterium tuberculosis* in human lymph node granulomas. *J Infect Dis*. 2016;214(9):1309-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27462092.

123. Heysell SK, Moll AP, Gandhi NR, et al. Extensively drug-resistant *Mycobacterium tuberculosis* from aspirates, rural South Africa. *Emerg Infect Dis*. 2010;16(3):557-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20202446.

124. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363(11):1005-1015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20825313.

125. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess*. 2007;11(3):1-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17266837.

126. Forbes BA, Hall GS, Miller MB, et al. Practice guidelines for clinical microbiology laboratories: mycobacteria. *Clin Microbiol Rev*. 2018. Available at: https://cmr.asm.org/content/cmr/31/2/e00038-17.full.pdf.

127. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. 2011. Available at: https://www.who.int/publications/i/item/9789241501545.

128. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;1:CD009593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24448973.

129. Luetkemeyer AF, Kendall MA, Wu X, et al. Evaluation of two line probe assays for rapid detection of *Mycobacterium tuberculosis*, tuberculosis (TB) drug resistance, and non-TB mycobacteria in HIV-infected individuals with suspected TB. *J Clin Microbiol*. 2014;52(4):1052-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24430455.

130. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. *BMC Med*. 2013;11:231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24168211.

131. Maynard-Smith L, Larke N, Peters JA, Lawn SD. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis*. 2014;14:709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25599808.

132. Rahman SMM, Maliha UT, Ahmed S, et al. Evaluation of Xpert MTB/RIF assay for detection of *Mycobacterium tuberculosis* in stool samples of adults with pulmonary tuberculosis. *PLoS One*. 2018;13(9):e0203063. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30212505.

133. Xie YL, Chakravorty S, Armstrong DT, et al. Evaluation of a rapid molecular drug-susceptibility test for tuberculosis. *N Engl J Med*. 2017;377(11):1043-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902596.

134. Drain PK, Losina E, Coleman SM, et al. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study. *BMC Infect Dis*. 2014;14:110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24571362.

135. Drain PK, Losina E, Coleman SM, et al. Value of urine lipoarabinomannan grade and second test for optimizing clinic-based screening for HIV-associated pulmonary tuberculosis. *J Acquir Immune Defic Syndr*. 2015;68(3):274-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25415288.

136. Lawn SD, Dheda K, Kerkhoff AD, et al. Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. *BMC Infect Dis*. 2013;13:407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24004840.

137. Broger T, Moyoyeta M, Kerkhoff AD, Denkinger CM, Moreau E. Tuberculosis test results using fresh versus biobanked urine samples with FujiLAM. *The Lancet: Infectious Diseases*. 2020;20(1):22-23. Available at: https://pubmed.ncbi.nlm.nih.gov/31876492.

138. World Health Organization. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV, 2019 Update. 2019. Available at: https://www.who.int/publications/i/item/9789241550604.

139. Quinn CM, Kagimu E, Okirworth M, et al. Fujifilm SILVAMP TB LAM assay on cerebrospinal fluid for the detection of tuberculous meningitis in adults with Human Immunodeficiency Virus. *Clin Infect Dis*. 2021;73(9):e3428-e3434. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33388751.

140. Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28344011.

141. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. 2008;149(2):123-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626051.

142. Centers for Disease Control and Prevention. Surveillance definitions for extensively drug resistant (XDR) and pre-XDR tuberculosis. 2022. Available at: https://archive.cdc.gov/#/details?url=https://www.cdc.gov/tb/php/dear-colleague-letters/2022-xdr-surveillance-definitions.html.

143. Viney K, Linh NN, Gegia M, et al. New definitions of pre-extensively and extensively drug-resistant tuberculosis: update from the World Health Organization. *Eur Respir J*. 2021;57(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33833074.

144. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. 2010;181(1):80-86. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19833824.

145. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med*. 2006;355(15):1539-1550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17035648.

146. Walker TM, Miotto P, Koser CU, et al. The 2021 WHO catalogue of *Mycobacterium tuberculosis* complex mutations associated with drug resistance: A genotypic analysis. *Lancet Microbe*. 2022;3(4):e265-e273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35373160.

147. Heysell SK, Houpt ER. The future of molecular diagnostics for drug-resistant tuberculosis. *Expert Rev Mol Diagn*. 2012;12(4):395-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22616704.

148. Barnard M, Warren R, Gey Van Pittius N, et al. Genotype MTBDRsl line probe assay shortens time to diagnosis of extensively drug-resistant tuberculosis in a high-throughput diagnostic laboratory. *Am J Respir Crit Care Med*. 2012;186(12):1298-1305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23087027.

149. Rice JP, Seifert M, Moser KS, Rodwell TC. Performance of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis and rifampin resistance in a low-incidence, high-resource setting. *PLoS One*. 2017;12(10):e0186139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29016684.

150. Ocheretina O, Byrt E, Mabou MM, et al. False-positive rifampin resistant results with Xpert MTB/RIF version 4 assay in clinical samples with a low bacterial load. *Diagn Microbiol Infect Dis*. 2016;85(1):53-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26915638.

151. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63(7):e147-e195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27516382.

152. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med*. 2021;384(18):1705-1718. Available at: https://pubmed.ncbi.nlm.nih.gov/33951360/.

153. Pettit AC, Phillips PPJ, Kurbatova E, et al. Rifapentine with and without moxifloxacin for pulmonary tuberculosis in people with human immunodeficiency virus (S31/A5349). *Clin Infect Dis*. 2023;76(3):e580-e589. Available at: https://pubmed.ncbi.nlm.nih.gov/36041016/.

154. Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim guidance: 4-month rifapentine-moxifloxacin regimen for the treatment of drug-susceptible pulmonary tuberculosis - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(8):285-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35202353.

155. Mangan JM, Woodruff RS, Winston CA, et al. Recommendations for use of video directly observed therapy during tuberculosis treatment - United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(12):313-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36952279.

156. Burzynski J, Mangan JM, Lam CK, et al. In-person vs electronic directly observed therapy for tuberculosis treatment adherence: a randomized noninferiority trial. *JAMA Netw Open*. 2022;5(1):e2144210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35050357.

157. Alipanah N, Jarlsberg L, Miller C, et al. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLoS Med*. 2018;15(7):e1002595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29969463.

158. Story A, Aldridge RW, Smith C, Garber E, Hall J, Ferenando G. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicenter, analyst-blinded

randomized, controlled superiority trial. *Lancet*. 2019;393(10177):1216-1224. Available at: https://pubmed.ncbi.nlm.nih.gov/30799062.

159. Browne SH, Umlauf A, Tucker AJ, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. *PLoS Med*. 2019;16(10):e1002891. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31584944.

160. Centers for Disease Control and Prevention. Implementing an electronic directly observed therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs. 2017. Available at: https://www.cdc.gov/tb-programs/php/edot-toolkit/?CDC_AAref_Val=https://www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm.

161. Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med*. 2010;181(7):743-751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19965813.

162. Nettles RE, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis*. 2004;38(5):731-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14986259.

163. Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. *Clin Infect Dis*. 2005;41(1):83-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937767.

164. Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2010;50(9):1288-1299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20353364.

165. Vashishtha R, Mohan K, Singh B, et al. Efficacy and safety of thrice weekly DOTS in tuberculosis patients with and without HIV co-infection: an observational study. *BMC Infect Dis*. 2013;13:468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24099345.

166. Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. *Clin Infect Dis*. 2014;59(12):1798-1804. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25156114.

167. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*. 1999;353(9167):1843-1847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10359410.

168. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med*. 2006;173(3):350-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16109981.

169. Gopalan N, Santhanakrishnan RK, Palaniappan AN, et al. Daily vs intermittent antituberculosis therapy for pulmonary tuberculosis in patients with HIV: a randomized clinical trial. *JAMA Intern Med*. 2018;178(4):485-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29507938.

170. Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med*. 2018;24(11):1708-1715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30397355.

171. Centers for Disease Control and Prevention. Treatment of tuberculosis. *MMWR Recomm Rep*. 2003;52(RR11):1-77. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

172. el-Sadr WM, Perlman DC, Matts JP, et al. Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1998;26(5):1148-1158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9597244.

173. Perriens JH, St Louis ME, Mukadi YB, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment for either 6 or 12 months. *N Engl J Med*. 1995;332(12):779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7862181.

174. Jullien S, Ryan H, Modi M, Bhatia R. Six months therapy for tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;9(9):CD012091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27581996.

175. Cresswell FV, Meya DB, Kagimu E, et al. High-dose oral and intravenous rifampicin for the treatment of tuberculous meningitis in predominantly human immunodeficiency virus (HIV)-positive Ugandan adults: a Phase II open-label randomized controlled trial. *Clin Infect Dis*. 2021;73(5):876-884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33693537.

176. Smith AGC, Gujabidze M, Avaliani T, et al. Clinical outcomes among patients with tuberculous meningitis receiving intensified treatment regimens. *Int J Tuberc Lung Dis*. 2021;25(8):632-639. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34330348.

177. Huynh J, Donovan J, Phu NH, Nghia HDT, Thuong NTT, Thwaites GE. Tuberculous meningitis: progress and remaining questions. *Lancet Neurol*. 2022;21(5):450-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35429482.

178. Dian S, Yunivita V, Ganiem AR, et al. Double-blind, randomized, placebo-controlled phase II dose-finding study to evaluate high-dose rifampin for tuberculous meningitis. *Antimicrob Agents Chemother*. 2018;62(12). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30224533.

179. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374(2):124-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26760084.

180. Te Brake L, Dian S, Ganiem AR, et al. Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis. *Int J Antimicrob Agents*. 2015;45(5):496-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25703312.

181. Yunivita V, Dian S, Ganiem AR, et al. Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients. *Int J Antimicrob Agents*. 2016;48(4):415-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27526979.

182. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis*. 2017;17(1):39-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28100438.

183. Ruslami R, Ganiem AR, Aarnoutse RE, van Crevel R, study t. Rifampicin and moxifloxacin for tuberculous meningitis--authors' reply. *Lancet Infect Dis*. 2013;13(7):570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23809224.

184. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4:CD002244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27121755.

185. Wang W, Gao J, Liu J, Qi J, Zhang Q. Clinical efficacy of dexamethasone in the treatment of patients with tuberculous meningitis: a meta-analysis. *Contrast Media Mol Imaging*. 2022;2022:2180374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35418812.

186. Donovan J, Bang ND, Imran D, et al. Adjunctive dexamethasone for tuberculous meningitis in HIV-positive adults. *N Engl J Med*. 2023;389(15):1357-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37819954.

187. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371(12):1121-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25178809.

188. Wiysonge CS, Ntsekhe M, Thabane L, et al. Interventions for treating tuberculous pericarditis. *Cochrane Database Syst Rev*. 2017;9:CD000526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28902412.

189. Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis*. 2014;14(7):563-571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24810491.

190. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010914.

191. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20181971.

192. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med*. 2007;175(11):1199-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17290042.

193. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. 2011;52(11):1374-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21596680.

194. Li L, Li J, Chai C, et al. Association of CD4 T cell count and optimal timing of antiretroviral therapy initiation with immune reconstitution inflammatory syndrome and all-cause mortality for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis. *Int J Clin Exp Pathol*. 2021;14(6):670-679. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34239668.

195. Chelkeba L, Fekadu G, Tesfaye G, Belayneh F, Melaku T, Mekonnen Z. Effects of time of initiation of antiretroviral therapy in the treatment of patients with HIV/TB co-infection: A systemic review and meta-analysis. *Ann Med Surg (Lond)*. 2020;55:148-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32477514.

196. Burke RM, Rickman HM, Singh V, et al. What is the optimum time to start antiretroviral therapy in people with HIV and tuberculosis coinfection? A systematic review and meta-analysis. *J Int AIDS Soc*. 2021;24(7):e25772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34289243.

197. Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. *N Engl J Med*. 2018;379(20):1915-1925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30428290.

198. Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis*. 2013;56(3):450-460. Available at: https://pubmed.ncbi.nlm.nih.gov/23097584/.

199. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet*. 2004;364(9441):1244-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15464185.

200. Johnson JL, Okwera A, Nsubuga P, et al. Efficacy of an unsupervised 8-month rifampicin-containing regimen for the treatment of pulmonary tuberculosis in HIV-infected adults. Uganda-

Case Western Reserve University Research Collaboration. *Int J Tuberc Lung Dis*. 2000;4(11):1032-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11092715.

201. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin Infect Dis*. 1996;22 Suppl 1:S15-21; discussion S21-12. Available at: https://pubmed.ncbi.nlm.nih.gov/8785251/.

202. Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev*. 2007(4):CD005159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17943842.

203. Singh R, Marshall N, Smith CJ, et al. No impact of rifamycin selection on tuberculosis treatment outcome in HIV coinfected patients. *AIDS*. 2013;27(3):481-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23014518.

204. McGregor MM, Olliaro P, Wolmarans L, et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J Respir Crit Care Med*. 1996;154(5):1462-1467. Available at: https://pubmed.ncbi.nlm.nih.gov/8912765/.

205. Kendall MA, Lalloo U, Fletcher CV, et al. Safety and pharmacokinetics of double-dose lopinavir/ritonavir + rifampin versus lopinavir/ritonavir + daily rifabutin for treatment of human immunodeficiency virus-tuberculosis coinfection. *Clin Infect Dis*. 2021;73(4):706-715. Available at: https://pubmed.ncbi.nlm.nih.gov/34398956/.

206. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *J Antimicrob Chemother*. 2019;74(6):1670-1678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30815689.

207. Martin TCS, Hill LA, Tang ME, Balcombe SM. Tenofovir alafenamide and rifabutin co-administration does not lead to loss of HIV-1 suppression: A retrospective observational study. *Int J Infect Dis*. 2020;100:470-472. Available at: https://pubmed.ncbi.nlm.nih.gov/32979587/.

208. Liou BH, Cheng CN, Lin YT, et al. Short-course daily isoniazid and rifapentine for latent tuberculosis infection in people living with HIV who received coformulated bictegravir/emtricitabine/tenofovir alafenamide. *J Int AIDS Soc*. 2021;24(11):e25844. Available at: https://pubmed.ncbi.nlm.nih.gov/34822220/.

209. Cohen K, Grant A, Dandara C, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther*. 2009;14(5):687-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19704172.

210. Ramachandran G, Hemanth Kumar AK, Rajasekaran S, et al. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South India. *Antimicrob Agents Chemother*. 2009;53(3):863-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19124658.

211. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. 2013;57(4):586-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23592830.

212. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS*. 2006;20(1):131-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327334.

213. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. 2008;300(5):530-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18677025.

214. Cerrone M, Wang X, Neary M, et al. Pharmacokinetics of efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus-infected individuals. *Clin Infect Dis*. 2019;68(3):446-452. Available at: https://pubmed.ncbi.nlm.nih.gov/30084943/.

215. Podany AT, Pham M, Sizemore E, et al. Efavirenz pharmacokinetics and human immunodeficiency virus type 1 (HIV-1) viral suppression among patients receiving tuberculosis treatment containing daily high-dose rifapentine. *Clin Infect Dis*. 2022;75(4):560-566. Available at: https://pubmed.ncbi.nlm.nih.gov/34918028/.

216. Yee KL, Khalilieh SG, Sanchez RI, et al. The effect of single and multiple doses of rifampin on the pharmacokinetics of doravirine in healthy subjects. *Clin Drug Investig*. 2017;37(7):659-667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28353169.

217. Khalilieh SG, Yee KL, Sanchez RI, et al. Multiple doses of rifabutin reduce exposure of doravirine in healthy subjects. *J Clin Pharmacol*. 2018;58(8):1044-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29723418.

218. Janssen Therapeutics. Edurant [package insert]. 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf.

219. Kakuda TN, Woodfall B, De Marez T, et al. Pharmacokinetic evaluation of the interaction between etravirine and rifabutin or clarithromycin in HIV-negative, healthy volunteers: results from two Phase 1 studies. *J Antimicrob Chemother*. 2014;69(3):728-734. Available at: https://pubmed.ncbi.nlm.nih.gov/24155058/.

220. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23075918.

221. Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-based antiretroviral therapy for patients coinfected with tuberculosis and human immunodeficiency virus: a multicenter, noncomparative, open-label, randomized trial. *Clin Infect Dis*. 2020;70(4):549-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30918967.

222. Griesel R, Hill A, Meintjes G, Maartens G. Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase 2 non-comparative randomised controlled (RADIANT-TB) trial. *Wellcome Open Res*. 2021;6:1. Available at: https://pubmed.ncbi.nlm.nih.gov/33954265/.

223. Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis*. 2014;14(6):459-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24726095.

224. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother*. 2009;53(7):2852-2856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19433563.

225. Brainard DM, Wenning LA, Stone JA, Wagner JA, Iwamoto M. Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J Clin Pharmacol*. 2011;51(10):1376-1402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21209233.

226. Custodio JM, West SK, Collins S, et al. Pharmacokinetics of bictegravir administered twice daily in combination with rifampin. Presented at: Conference on Retroviruses and Opportunistic Infections; 2018. Boston, MA. Available at: https://www.croiconference.org/abstract/pharmacokinetics-bictegravir-administered-twice-daily-combination-rifampin.

227. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet*. 2011;50(4):229-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21348537.

228. Toomey CB, Lee J, Spencer DB. Rifabutin-cobicistat drug interaction resulting in severe bilateral panuveitis. *Case Rep Ophthalmol*. 2020;11(1):156-160. Available at: https://pubmed.ncbi.nlm.nih.gov/32399018/.

229. Ford SL, Sutton K, Lou Y, et al. Effect of rifampin on the single-dose pharmacokinetics of oral cabotegravir in healthy subjects. *Antimicrob Agents Chemother*. 2017;61(10). Available at: https://pubmed.ncbi.nlm.nih.gov/28739783/.

230. Rajoli RKR, Curley P, Chiong J, et al. Predicting drug-drug interactions between rifampicin and long-acting cabotegravir and rilpivirine using physiologically based pharmacokinetic modeling. *J Infect Dis*. 2019;219(11):1735-1742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30566691.

231. Burger DM, Agarwala S, Child M, Been-Tiktak A, Wang Y, Bertz R. Effect of rifampin on steady-state pharmacokinetics of atazanavir with ritonavir in healthy volunteers. *Antimicrob Agents Chemother*. 2006;50(10):3336-3342. Available at: https://pubmed.ncbi.nlm.nih.gov/17005814/.

232. Justesen US, Andersen AB, Klitgaard NA, Brøsen K, Gerstoft J, Pedersen C. Pharmacokinetic interaction between rifampin and the combination of indinavir and low-dose ritonavir in HIV-infected patients. *Clin Infect Dis*. 2004;38(3):426-429. Available at: https://pubmed.ncbi.nlm.nih.gov/14727216/.

233. la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother*. 2004;48(5):1553-1560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15105105.

234. Regazzi M, Carvalho AC, Villani P, Matteelli A. Treatment optimization in patients co-infected with HIV and *Mycobacterium tuberculosis* infections: focus on drug-drug interactions with rifamycins. *Clin Pharmacokinet*. 2014;53(6):489-507. Available at: https://pubmed.ncbi.nlm.nih.gov/24777631/.

235. Ebrahim I, Maartens G, Wiesner L, Orrell C, Smythe W, McIlleron H. Pharmacokinetic profile and safety of adjusted doses of darunavir/ritonavir with rifampicin in people living with HIV. *J Antimicrob Chemother*. 2020;75(4):1019-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31942627.

236. Decloedt EH, McIlleron H, Smith P, Merry C, Orrell C, Maartens G. Pharmacokinetics of lopinavir in HIV-infected adults receiving rifampin with adjusted doses of lopinavir-ritonavir tablets. *Antimicrob Agents Chemother*. 2011;55(7):3195-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21537021.

237. Food and Drug Adminstration. Kaletra [package insert]. 2020. Available at: https://www.rxabbvie.com/pdf/kaletratabpi.pdf.

238. Bristol-Myers Squibb. Atazanavir [package insert]. 2018. Available at: https://packageinserts.bms.com/pi/pi_reyataz.pdf.

239. Sekar V, Lavreys L, Van de Casteele T, et al. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. *Antimicrob Agents Chemother*. 2010;54(10):4440-4445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660678.

240. Ford SL, Chen YC, Lou Y, et al. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. *Antimicrob Agents Chemother*. 2008;52(2):534-538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18056271.

241. Lin HC, Lu PL, Chang CH. Uveitis associated with concurrent administration of rifabutin and lopinavir/ritonavir (Kaletra). *Eye (Lond)*. 2007;21(12):1540-1541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17962822.

242. Lan NT, Thu NT, Barrail-Tran A, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. *PLoS One*. 2014;9(1):e84866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24465443.

243. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV- infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25406657.

244. Jenny-Avital ER, Joseph K. Rifamycin-resistant *Mycobacterium tuberculosis* in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis*. 2009;48(10):1471-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19368504.

245. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis*. 2009;49(9):1305-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19807276.

246. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360(9332):528-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12241657.

247. Dorman SE, Goldberg S, Stout JE, et al. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the Tuberculosis Trials Consortium. *The Journal of Infectious Diseases*. 2012;206(7):1030-1040. Available at: https://pubmed.ncbi.nlm.nih.gov/22850121.

248. Su WJ, Feng JY, Chiu YC, Huang SF, Lee YC. Role of 2-month sputum smears in predicting culture conversion in pulmonary tuberculosis. *Eur Respir J*. 2011;37(2):376-383. Available at: https://pubmed.ncbi.nlm.nih.gov/20516049/.

249. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs*. 2014;74(8):839-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24846578.

250. McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis*. 2007;196 Suppl 1:S63-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17624828.

251. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. 1991;99(2):465-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1824929.

252. Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity.

Clin Infect Dis. 2010;50(6):833-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20156055.

253. Tahaoglu K, Atac G, Sevim T, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2001;5(1):65-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11263519.

254. Abbara A, Chitty S, Roe JK, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. *BMC Infect Dis*. 2017;17(1):231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28340562.

255. Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis*. 2011;15(12):1649-1657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22118173.

256. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2019. 2019. Available at: https://www.cdc.gov/tb-programs/php/edot-toolkit/?CDC_AAref_Val=https://www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm.

257. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17(2):223-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27865891.

258. van der Heijden YF, Karim F, Mufamadi G, et al. Isoniazid-monoresistant tuberculosis is associated with poor treatment outcomes in Durban, South Africa. *Int J Tuberc Lung Dis*. 2017;21(6):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28482962.

259. Fregonese F, Ahuja SD, Akkerman OW, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med*. 2018;6(4):265-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29595509.

260. World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the WHO treatment guidelines for drug-resistant tuberculosis. 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf.

261. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. Available at: https://www.who.int/publications/i/item/9789241550529.

262. Vogensen VB, Bolhuis MS, Sturkenboom MGG, et al. Clinical relevance of rifampicin-moxifloxacin interaction in isoniazid-resistant/intolerant tuberculosis patients. *Antimicrob Agents Chemother*. 2022;66(2):e0182921. Available at: https://pubmed.ncbi.nlm.nih.gov/34807758/.

263. Weiner M, Burman W, Luo CC, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother*. 2007;51(8):2861-2866. Available at: https://pubmed.ncbi.nlm.nih.gov/17517835/.

264. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis*. 2007;45(8):1001-1007. Available at: https://pubmed.ncbi.nlm.nih.gov/17879915/.

265. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020;382(10):893-902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130813.

266. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med*. 2022;387(9):810-823. Available at: https://pubmed.ncbi.nlm.nih.gov/36053506/.

267. Nyang'wa BT, Berry C, Kazounis E, et al. Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med*. 2024;12(2):117-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37980911.

268. Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med*. 2022;387(25):2331-2343. Available at: https://pubmed.ncbi.nlm.nih.gov/36546625/.

269. Labuda SM, Seaworth B, Dasgupta S, Goswami ND, Team BPAMP. Bedaquiline, pretomanid, and linezolid with or without moxifloxacin for tuberculosis. *Lancet Respir Med*. 2024;12(2):e5-e6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38043563.

270. Haley CA, Schechter MC, Ashkin D, et al. Implementation of BPaL in the United States: experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant TB disease. *Clin Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37249079.

271. Centers for Disease Control and Prevention. Provisional CDC guidance for the use of pretomanid as part of a regimen [bedaquiline, pretomanid, and linezolid (BPaL)] to treat drug-resistant tuberculosis disease. 2024. Accessed February 21. Available at: https://www.cdc.gov/tb/hcp/treatment/bpal.html.

272. World Health Organization. WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. 2022. Accessed May 12. Available at: https://www.who.int/publications/i/item/9789240065116.

273. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821-834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30215381.

274. Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in

South Korea. *Lancet*. 2022;400(10362):1522-1530. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36522208.

275. Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet*. 2022;400(10366):1858-1868. Available at: https://pubmed.ncbi.nlm.nih.gov/36368336/.

276. Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865791.

277. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment - drug-resistant tuberculosis treatment. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32603040.

278. Esmail A, Oelofse S, Lombard C, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT Study). *Am J Respir Crit Care Med*. 2022;205(10):1214-1227. Available at: https://pubmed.ncbi.nlm.nih.gov/35175905/.

279. Barilar I, Fernando T, Utpatel C, et al. Emergence of bedaquiline-resistant tuberculosis and of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* strains with rpoB Ile491Phe mutation not detected by Xpert MTB/RIF in Mozambique: a retrospective observational study. *Lancet Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37956677.

280. Perumal R, Bionghi N, Nimmo C, et al. Baseline and treatment-emergent bedaquiline resistance in drug-resistant tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2023;62(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/37945030.

281. Nimmo C, Bionghi N, Cummings MJ, et al. Opportunities and limitations of genomics for diagnosing bedaquiline-resistant tuberculosis: a systematic review and individual isolate meta-analysis. *Lancet Microbe*. 2024;5(2):e164-e172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38215766.

282. Svensson EM, Aweeka F, Park JG, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. *Antimicrob Agents Chemother*. 2013;57(6):2780-2787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23571542.

283. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58(11):6406-6412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25114140.

284. Pandie M, Wiesner L, McIlleron H, et al. Drug-drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J Antimicrob Chemother*. 2016;71(4):1037-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26747099.

285. Brust JCM, Gandhi NR, Wasserman S, et al. Effectiveness and cardiac safety of bedaquiline-based therapy for drug-resistant tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2021;73(11):2083-2092. Available at: https://pubmed.ncbi.nlm.nih.gov/33882121/.

286. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. 2004;18(12):1615-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15280772.

287. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005;5(6):361-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15919622.

288. Meintjes G, Rabie H, Wilkinson RJ, Cotton MF. Tuberculosis-associated immune reconstitution inflammatory syndrome and unmasking of tuberculosis by antiretroviral therapy. *Clin Chest Med*. 2009;30(4):797-810, x. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19925968.

289. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8(8):516-523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18652998.

290. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(4):251-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20334848.

291. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. *Int J Tuberc Lung Dis*. 2007;11(12):1282-1289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18229435.

292. Pepper DJ, Marais S, Maartens G, et al. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*. 2009;48(11):e96-107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19405867.

293. Lawn SD, Wood R. Hepatic involvement with tuberculosis-associated immune reconstitution disease. *AIDS*. 2007;21(17):2362-2363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18090294.

294. Sonderup MW, Wainwright H, Hall P, Hairwadzi H, Spearman CW. A clinicopathological cohort study of liver pathology in 301 patients with human immunodeficiency virus/acquired immune deficiency syndrome. *Hepatology*. 2015;61(5):1721-1729. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25644940.

295. Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. *Future Microbiol*. 2015;10(6):1077-1099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26059627.

296. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158(1):157-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9655723.

297. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004;59(8):704-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15282393.

298. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis*. 2004;39(11):1709-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15578375.

299. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007;21(3):335-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17255740.

300. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect*. 2006;53(6):357-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16487593.

301. Serra FC, Hadad D, Orofino RL, et al. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. *Braz J Infect Dis*. 2007;11(5):462-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17962870.

302. Olalla J, Pulido F, Rubio R, et al. Paradoxical responses in a cohort of HIV-1-infected patients with mycobacterial disease. *Int J Tuberc Lung Dis*. 2002;6(1):71-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11931404.

303. Huyst V, Lynen L, Bottieau E, Zolfo M, Kestens L, Colebunders R. Immune reconstitution inflammatory syndrome in an HIV/TB co-infected patient four years after starting antiretroviral therapy. *Acta Clin Belg*. 2007;62(2):126-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17547295.

304. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther*. 2005;10(3):417-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15918332.

305. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB

programs. *J Acquir Immune Defic Syndr*. 2014;65(4):423-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24226057.

306. Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS One*. 2013;8(5):e63541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23691062.

307. Meintjes G, Rangaka MX, Maartens G, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis*. 2009;48(5):667-676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19191655.

308. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010;24(15):2381-2390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20808204.

309. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J (Clin Res Ed)*. 1983;286(6369):923-925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6403136.

310. Xie YL, Ita-Nagy F, Chen RY, et al. Neurotuberculosis: control of steroid-refractory paradoxical inflammatory reaction with ruxolitinib. *Open Forum Infect Dis*. 2019;6(10):ofz422. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31687418.

311. Brunel AS, Reynes J, Tuaillon E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS*. 2012;26(16):2110-2112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22874513.

312. Hsu DC, Faldetta KF, Pei L, et al. A paradoxical treatment for a paradoxical condition: infliximab use in three cases of mycobacterial IRIS. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26394669.

313. Fourcade C, Mauboussin JM, Lechiche C, Lavigne JP, Sotto A. Thalidomide in the treatment of immune reconstitution inflammatory syndrome in HIV patients with neurological tuberculosis. *AIDS Patient Care STDS*. 2014;28(11):567-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25285462.

314. Keeley AJ, Parkash V, Tunbridge A, et al. Anakinra in the treatment of protracted paradoxical inflammatory reactions in HIV-associated tuberculosis in the United Kingdom: a report of two cases. *Int J STD AIDS*. 2020;31(8):808-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32631210.

315. Marais BJ, Cheong E, Fernando S, et al. Use of infliximab to treat paradoxical tuberculous meningitis reactions. *Open Forum Infect Dis*. 2021;8(1):ofaa604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33542942.

316. Abo YN, Curtis N, Osowicki J, et al. Infliximab for paradoxical reactions in pediatric central nervous system tuberculosis. *J Pediatric Infect Dis Soc*. 2021;10(12):1087-1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34608937.

317. van Toorn R, Rabie H, Dramowski A, Schoeman JF. Neurological manifestations of TB-IRIS: a report of 4 children. *Eur J Paediatr Neurol*. 2012;16(6):676-682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22658306.

318. John L, Baalwa J, Kalimugogo P, et al. Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?'. *AIDS*. 2005;19(17):2049-2050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260919.

319. Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. *Sex Transm Infect*. 2003;79(4):337-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12902592.

320. Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. *AIDS*. 2009;23(1):143-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19050399.

321. Chen WL, Lin YF, Tsai WC, Tsao YT. Unveiling tuberculous pyomyositis: an emerging role of immune reconstitution inflammatory syndrome. *Am J Emerg Med*. 2009;27(2):251 e251-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19371548.

322. Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis*. 2003;37(1):101-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12830415.

323. Vega V, Rodríguez S, Van der Stuyft P, Seas C, Otero L. Recurrent TB: a systematic review and meta-analysis of the incidence rates and the proportions of relapses and reinfections. *Thorax*. 2021;76(5):494-502. Available at: https://pubmed.ncbi.nlm.nih.gov/33547088/.

324. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet*. 2001;358(9294):1687-1693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11728545.

325. Narayanan S, Swaminathan S, Supply P, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. *J Infect Dis*. 2010;201(5):691-703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20121433.

326. Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med*. 2004;170(12):1360-1366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15477492.

327. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD, Jr., Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet*. 2000;356(9240):1470-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11081529.

328. Haller L, Sossouhounto R, Coulibaly IM, Dosso M, al e. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in Africa: a controlled clinical trial. *Chemotherapy*. 1999;45(6):452-465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10567776.

329. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Glob Health*. 2014;2(12):e710-716. Available at: https://pubmed.ncbi.nlm.nih.gov/25433626/.

330. Mofenson LM, Rodriguez EM, Hershow R, et al. *Mycobacterium tuberculosis* infection in pregnant and nonpregnant women infected with HIV in the Women and Infants Transmission Study. *Arch Intern Med*. 1995;155(10):1066-1072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7748050.

331. Eriksen NL, Helfgott AW. Cutaneous anergy in pregnant and nonpregnant women with human immunodeficiency virus. *Infect Dis Obstet Gynecol*. 1998;6(1):13-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9678142.

332. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. *Int J Gynaecol Obstet*. 1994;44(2):119-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7911094.

333. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. *N Engl J Med*. 1999;341(9):645-649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10460815.

334. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med*. 2014;370(23):2211-2218. Available at: https://pubmed.ncbi.nlm.nih.gov/24897084/.

335. Jonnalagadda S, Lohman Payne B, Brown E, et al. Latent tuberculosis detection by interferon gamma release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1-infected women and their children. *J Infect Dis*. 2010;202(12):1826-1835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21067370.

336. Jonnalagadda SR, Brown E, Lohman-Payne B, et al. Consistency of *Mycobacterium tuberculosis*-specific interferon-gamma responses in HIV-1-infected women during pregnancy and postpartum. *Infect Dis Obstet Gynecol*. 2012;2012:950650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22496602.

337. Bhosale R, Alexander M, Deshpande P, et al. Stages of pregnancy and HIV affect diagnosis of tuberculosis infection and *Mycobacterium tuberculosis* (MTB)-induced immune response:

Findings from PRACHITi, a cohort study in Pune, India. *Int J Infect Dis*. 2021;112:205-211. Available at: https://pubmed.ncbi.nlm.nih.gov/34517050/.

338. Kaplan SR, Escudero JN, Mecha J, et al. Interferon gamma release assay and tuberculin skin test performance in pregnant women living with and without HIV. *J Acquir Immune Defic Syndr*. 2022;89(1):98-107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34629414.

339. Lighter-Fisher J, Surette AM. Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet Gynecol*. 2012;119(6):1088-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22569120.

340. Mathad JS, Bhosale R, Balasubramanian U, et al. Quantitative IFN-γ and IL-2 response associated with latent tuberculosis test discordance in HIV-infected pregnant women. *Am J Respir Crit Care Med*. 2016;193(12):1421-1428. Available at: https://pubmed.ncbi.nlm.nih.gov/26765255/.

341. Mathad JS, Bhosale R, Sangar V, et al. Pregnancy differentially impacts performance of latent tuberculosis diagnostics in a high-burden setting. *PLoS One*. 2014;9(3):e92308. Available at: https://pubmed.ncbi.nlm.nih.gov/24658103/.

342. LaCourse SM, Cranmer LM, Matemo D, et al. Effect of pregnancy on interferon gamma release assay and tuberculin skin test detection of latent TB infection among HIV-infected women in a high burden setting. *J Acquir Immune Defic Syndr*. 2017;75(1):128-136. Available at: https://pubmed.ncbi.nlm.nih.gov/28141782/.

343. Weinberg A, Aaron L, Montepiedra G, et al. Effects of pregnancy and isoniazid preventive therapy on *Mycobacterium tuberculosis* interferon gamma response assays in women with HIV. *Clin Infect Dis*. 2021;73(9):e3555-e3562. Available at: https://pubmed.ncbi.nlm.nih.gov/32720695/.

344. Gupta A, Montepiedra G, Aaron L, Theron G. isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *N Engl J Med*. 2019;381:1333-1346. Available at: https://pubmed.ncbi.nlm.nih.gov/31577875.

345. Salazar-Austin N, Cohn S, Lala S, et al. Isoniazid preventive therapy and pregnancy outcomes in women living with human immunodeficiency virus in the Tshepiso cohort. *Clin Infect Dis*. 2020;71(6):1419-1426. Available at: https://pubmed.ncbi.nlm.nih.gov/31631221/.

346. Kalk E, Heekes A, Mehta U, et al. Safety and effectiveness of isoniazid preventive therapy in pregnant women living with human immunodeficiency virus on antiretroviral therapy: An Observational Study Using Linked Population Data. *Clin Infect Dis*. 2020;71(8):e351-e358. Available at: https://pubmed.ncbi.nlm.nih.gov/31900473/.

347. Taylor AW, Mosimaneotsile B, Mathebula U, et al. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2013;2013:195637. Available at: https://pubmed.ncbi.nlm.nih.gov/23533318/.

348. Hamada Y, Figueroa C, Martín-Sánchez M, Falzon D, Kanchar A. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. *Eur Respir J*. 2020;55(3). Available at: https://pubmed.ncbi.nlm.nih.gov/32217619/.

349. Gupta A, Hughes MD, Cruz JL, et al. Adverse pregnancy outcomes among HIV-infected women taking isoniazid preventive therapy during the first trimester. *Clin Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37768207.

350. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis*. 2010;10(7):489-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610331.

351. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clin Infect Dis*. 2007;45(2):241-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17578786.

352. Middelkoop K, Bekker LG, Myer L, et al. Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township. *Am J Respir Crit Care Med*. 2010;182(8):1080-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20558626.

353. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. *Obstet Gynecol*. 2020;135(6):1444-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459437.

354. Mathad JS, Savic R, Britto P, et al. Pharmacokinetics and safety of 3 months of weekly rifapentine and isoniazid for tuberculosis prevention in pregnant women. *Clin Infect Dis*. 2022;74(9):1604-1613. Available at: https://pubmed.ncbi.nlm.nih.gov/34323955/.

355. Moro RN, Scott NA, Vernon A, et al. Exposure to latent tuberculosis treatment during pregnancy. the PREVENT TB and the iAdhere Trials. *Ann Am Thorac Soc*. 2018;15(5):570-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29393655.

356. Food and Drug Administration. PRIFTIN (rifapentine). 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021024s009lbl.pdf.

357. Mathad JS, Savic R, Britto P, et al. Pharmacokinetics and safety of three months of weekly rifapentine and isoniazid for tuberculosis prevention in pregnant women. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34323955.

358. Hoffmann CJ, Variava E, Rakgokong M, et al. High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa. *PLoS One*. 2013;8(4):e62211. Available at: https://pubmed.ncbi.nlm.nih.gov/23614037/.

359. LaCourse SM, Cranmer LM, Matemo D, et al. Tuberculosis case finding in HIV-infected pregnant women in Kenya reveals poor performance of symptom screening and rapid diagnostic

tests. *J Acquir Immune Defic Syndr*. 2016;71(2):219-227. Available at: https://pubmed.ncbi.nlm.nih.gov/26334736/.

360. Kosgei RJ, Szkwarko D, Callens S, et al. Screening for tuberculosis in pregnancy: do we need more than a symptom screen? Experience from western Kenya. *Public Health Action*. 2013;3(4):294-298. Available at: https://pubmed.ncbi.nlm.nih.gov/26393049/.

361. Committee Opinion. Committee Opinion No. 723: Guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol*. 2017;130(4):e210-e216. Available at https://pubmed.ncbi.nlm.nih.gov/28937575.

362. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *BJOG*. 2011;118(2):226-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21083862.

363. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol Clin North Am*. 1997;24(3):659-673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9266585.

364. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Saf*. 2001;24(7):553-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11444726.

365. Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A population-based case-control study of the safety of oral anti-tuberculosis drug treatment during pregnancy. *Int J Tuberc Lung Dis*. 2001;5(6):564-568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11409585.

366. Efferen LS. Tuberculosis and pregnancy. *Curr Opin Pulm Med*. 2007;13(3):205-211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17414128.

367. Vilarinho LC. Congenital tuberculosis: a case report. *Braz J Infect Dis*. 2006;10(5):368-370. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17293929.

368. Lee LH, LeVea CM, Graman PS. Congenital tuberculosis in a neonatal intensive care unit: case report, epidemiological investigation, and management of exposures. *Clin Infect Dis*. 1998;27(3):474-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9770143.

369. Cantwell MF, Shehab ZM, Costello AM, et al. Brief report: congenital tuberculosis. *N Engl J Med*. 1994;330(15):1051-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8127333.

370. Rinsky JL, Farmer D, Dixon J, et al. Notes from the field: contact investigation for an infant with congenital tuberculosis infection - North Carolina, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(23):670-671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29902167.

371. Chang CW, Wu PW, Yeh CH, Wong KS, Wang CJ, Chang CC. Congenital tuberculosis: case report and review of the literature. *Paediatr Int Child Health*. 2018;38(3):216-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28421876.

372. Stuart RL, Lewis A, Ramsden CA, Doherty RR. Congenital tuberculosis after in-vitro fertilisation. *Med J Aust*. 2009;191(1):41-42. Available at: https://pubmed.ncbi.nlm.nih.gov/19580539/.

373. Pillay T, Sturm AW, Khan M, et al. Vertical transmission of *Mycobacterium tuberculosis* in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis*. 2004;8(1):59-69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14974747.

374. Adhikari M, Pillay T, Pillay DG. Tuberculosis in the newborn: an emerging disease. *Pediatr Infect Dis J*. 1997;16(12):1108-1112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9427454.

375. Franks AL, Binkin NJ, Snider DE, Jr., Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Public Health Rep*. 1989;104(2):151-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2495549.

376. Dlodlo RA, Brigden G, Heldal E, et al. Management of tuberculosis: a guide to essential practice. Paris, France: International Union Against Tuberculosis and Lung Disease; October 2019. Available at: https://theunion.org/sites/default/files/2020-08/TheUnion_Orange_2019.pdf.

377. Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberlostatic drugs. *Diss Pharm Pharmacol*. 1971;23:383-392.

378. Lotia Farrukh I, Lachenal N, Adenov MM, et al. Pregnancy and birth outcomes in patients with multidrug-resistant tuberculosis treated with regimens that include new and repurposed drugs. *Clin Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37606512.

379. Lessnau KD, Qarah S. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. *Chest*. 2003;123(3):953-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12628902.

380. Drobac PC, del Castillo H, Sweetland A, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. *Clin Infect Dis*. 2005;40(11):1689-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15889370.

381. Alene KA, Murray MB, van de Water BJ, et al. Treatment outcomes among pregnant patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(6):e2216527. Available at: https://pubmed.ncbi.nlm.nih.gov/35687333/.

382. Loveday M, Hughes J, Sunkari B, et al. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. *Clinical Infectious Diseases*. 2020;72(7):1158-1168. Available at: https://pubmed.ncbi.nlm.nih.gov/32141495.

383. Court R, Gausi K, Mkhize B, et al. Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis. *Br J Clin Pharmacol*. 2022;88(8):3548-3558. Available at: https://pubmed.ncbi.nlm.nih.gov/35526837/.

384. Jaspard M, Elefant-Amoura E, Melonio I, De Montgolfier I, Veziris N, Caumes E. Bedaquiline and linezolid for extensively drug-resistant tuberculosis in pregnant woman. *Emerg Infect Dis*. 2017;23(10):1731-1732. Available at: https://pubmed.ncbi.nlm.nih.gov/28792382/.

385. Fujimori H, et al. The effect of tuberculostatics on the fetus: an experimental production of congenital anomaly in rats by ethionamide. *Proc Congen Anom Res Assoc Jpn*. 1965;5:34-35.

386. Takekoshi S. Effects of hydroxymethylpyrimidine on isoniazid- and ethionamide-induced teratosis. *Gunma J Med Sci*. 1965;14:233-244.

387. Khan I, Azam A. Study of teratogenic activity of trifluoperazine, amitriptyline, ethionamide and thalidomide in pregnant rabbits and mice. *Proc Eur Soc Study Drug Toxic*. 1969;10:235-242.

388. Potworowska M, Sianoz-Ecka E, Szufladowica R. Treatment with ethionamide in pregnancy. *Pol Med J*. 1966;5(5):1152-1158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/5958801.

389. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European Network of Teratology Information Services (ENTIS). *Eur J Obstet Gynecol Reprod Biol*. 1996;69(2):83-89. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8902438.

390. Yefet E, Schwartz N, Chazan B, Salim R, Romano S, Nachum Z. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis. *BJOG*. 2018;125(9):1069-1076. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29319210.

391. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. *Antimicrob Agents Chemother*. 1998;42(6):1336-1339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9624471.

392. Ziv A, Masarwa R, Perlman A, Ziv D, Matok I. Pregnancy Outcomes Following exposure to quinolone antibiotics - a systematic-review and meta-analysis. *Pharm Res*. 2018;35(5):109. Available at: https://pubmed.ncbi.nlm.nih.gov/29582196/.

393. Acar S, Keskin-Arslan E, Erol-Coskun H, Kaya-Temiz T, Kaplan YC. Pregnancy outcomes following quinolone and fluoroquinolone exposure during pregnancy: A systematic review and meta-analysis. *Reprod Toxicol*. 2019;85:65-74. Available at: https://pubmed.ncbi.nlm.nih.gov/30738954/.

394. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. 2006;107(5):1120-1138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648419.

395. ZYVOX [package insert]. Food and Drug Administration. 2008. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf.

396. Van Kampenhout E, Bolhuis MS, Alffenaar JC, et al. Pharmacokinetics of moxifloxacin and linezolid during and after pregnancy in a patient with multidrug-resistant tuberculosis. *Eur Respir J*. 2017;49(3). Available at: https://pubmed.ncbi.nlm.nih.gov/28331037/.

397. Acquah R, Mohr-Holland E, Daniels J, et al. Outcomes of children born to pregnant women with drug-resistant tuberculosis treated with novel drugs in Khayelitsha, South Africa: A Report of Five Patients. *Pediatr Infect Dis J*. 2021;40(5):e191-e192. Available at: https://pubmed.ncbi.nlm.nih.gov/33847295/.

398. PRETOMANID [package insert]. Food and Drug Administration. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212862s004lbl.pdf.

399. Varpela E. On the effect exerted by first-line tuberculosis medicines on the foetus. *Acta Tuberc Pneumol Scand*. 1964;45:53-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14209270.

Pneumocystis Pneumonia

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Epidemiology

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii*, a ubiquitous fungus. The taxonomy of the organism has been changed; *Pneumocystis carinii* now refers only to the *Pneumocystis* that infects rats, and *P. jirovecii* refers to the distinct species that infects humans. However, the abbreviation PCP is still the preferred acronym to designate the clinical syndrome of *Pneumocystis* pneumonia,[1] although PJP is commonly used. Initial infection with *P. jirovecii* usually occurs in early childhood; two-thirds of healthy children have antibodies to *P. jirovecii* by age 2 years to 4 years.[2]

Rodent studies and case clusters in immunosuppressed patients suggest that *Pneumocystis* spreads by the airborne route. Disease probably occurs by both new acquisition of infection and by reactivation of latent infection.[3-12] Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of people with advanced HIV,[13] with a 20% to 40% mortality rate in individuals despite anti-*Pneumocystis* therapy. Approximately 90% of PCP cases occur in people with HIV with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3.

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; incidence among people with HIV in Western Europe and the United States is <1 case per 100 person-years.[14-16] Most cases of PCP now occur in people with HIV who are unaware of their HIV status or are not receiving ongoing care for HIV,[17] and in those with advanced immunosuppression (i.e., CD4 counts <100 cells/mm^3).[18]

Clinical Manifestations

In people with HIV, the most common manifestations of PCP are subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks. The fulminant pneumonia observed in people who do not have HIV is less common among people with HIV. A more fulminant course can occur particularly after initiation of therapy.[19-21]

In mild cases, pulmonary examination while the patient is at rest usually is normal. With exertion, tachypnea, tachycardia, and diffuse dry (cellophane) rales may be observed.[20] Fever is present in most cases and may be the predominant symptom in some people. Pneumonia limited to the apices and extrapulmonary disease, which can occur in any organ, are rare and have been associated with use of aerosolized pentamidine prophylaxis.[22]

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen partial pressure [PaO_2] ≥70 mmHg or alveolar-arterial gradient [A-a gradient] <35 mmHg) to moderate (A-a gradient ≥35 to <45 mmHg) to severe (A-a gradient ≥45 mmHg). Oxygen desaturation with exercise is often abnormal but is nonspecific.[23] Elevation of lactate dehydrogenase levels to >500 mg/dL is common but also nonspecific.[24] The chest radiograph typically demonstrates diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern[20]; however, in people with HIV with early disease, a chest radiograph may be

normal.[25] Atypical radiographic presentations (such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, intrathoracic adenopathy, and pneumothorax) also occur. Spontaneous pneumothorax in a person with HIV should raise the suspicion of PCP.[26,27] Cavitation and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancies, and their presence may indicate an alternative diagnosis or an additional pathology. People with HIV who have documented PCP may have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma, toxoplasmosis, or fungal or bacterial pneumonia.[28,29]

Thin-section computed tomography (CT) without contrast is a useful adjunctive study, since even in patients with mild-to-moderate symptoms and a normal chest radiograph, a CT scan will be abnormal, demonstrating "ground-glass" attenuation that may be patchy. A normal CT has a high negative predictive value, and alternate diagnoses should be excluded.[30,31]

Diagnosis

Because clinical presentation, blood tests, and chest radiographs are not pathognomonic for PCP (and because the organism cannot be cultivated routinely), histopathologic or cytopathologic demonstration of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or induced sputum samples[19,28,29,32] is required for a definitive diagnosis of PCP. Spontaneously expectorated sputum has low sensitivity for the diagnosis of PCP and should not be submitted to the laboratory to diagnose PCP. Giemsa, Diff-Quik, and Wright stains detect both main life forms of P. *jirovecii*—cysts and trophic forms—but do not stain the cyst wall; Grocott-Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain only the cyst wall. Some laboratories prefer direct immunofluorescent staining, which has higher sensitivity than the colorimetric stains.[33] The sensitivity and specificity of respiratory samples for PCP depend on the stain being used, the experience of the microbiologist or pathologist, the pathogen load, and specimen quality. Studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: <50% to >90% for induced sputum, 90% to 99% for bronchoscopy with BAL, 95% to 100% for transbronchial biopsy, and 95% to 100% for open lung biopsy.[34-40]

Polymerase chain reaction (PCR) is an increasingly utilized method for diagnosing PCP and has replaced staining methods in many laboratories. PCR is highly sensitive and specific for detecting *Pneumocystis*. While PCR cannot reliably distinguish colonization from active disease, quantitative PCR (qPCR) is favored over qualitative assays, as a higher organism load by qPCR is likely to represent clinically significant disease.[41-43] However, the broad range of organism loads in patients with PCP and the lack of commercially available U.S. Food and Drug Administration (FDA)–approved qPCR kits for diagnosis make establishment of cutoffs for colonization versus disease difficult to standardize.

1,3 β-D-glucan (β-glucan), which is a component of the cell wall of *Pneumocystis* cysts, is often elevated in people with HIV who also have PCP. The sensitivity of the β-glucan assay for diagnosis of PCP appears to be high, thus PCP is less likely in people with HIV with a low level of β-glucan (e.g., <80 pg/mL using the Fungitell assay). However, the specificity of β-glucan testing for establishing a PCP diagnosis is low,[44-48] since many other fungal diseases, cellulose membranes used for hemodialysis, and some drugs can elevate β-glucan levels.[47,48]

Because the clinical manifestations of several disease processes are similar, it is important to seek a definitive diagnosis of PCP disease rather than rely on a presumptive diagnosis, especially in patients with moderate-to-severe disease. However, PCP treatment should be initiated before a definitive

diagnosis is established if clinical suspicion is high. *P. jirovecii* persist in clinical specimens for days or weeks after effective therapy is initiated, allowing definitive diagnosis to be established even after initiating therapy.[32]

Preventing Exposure

There are insufficient data to support isolation as standard practice to prevent PCP **(CIII).** *Pneumocystis* can be quantified in the air near people with PCP,[49] and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients as well as other immunosuppressed populations.[6-12,50] Although these findings strongly suggest that isolating people with known PCP from people at high risk for PCP may be beneficial, no study to date has documented the benefit of such an approach.

Preventing Disease

Recommendations for Preventing First Episode of *Pneumocystis* Pneumonia (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis

- CD4 count 100–200 cells/mm^3, if plasma HIV RNA level above detection limits (AI), *or*
- CD4 count <100 cells/mm^3, regardless of plasma HIV RNA level (AIII)
- Note: Patients who are receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).

Preferred Therapy

- TMP-SMX, 1 DS tablet PO daily (AI), *or*
- TMP-SMX, 1 SS tablet PO daily (AI)
- Note: TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections.

Alternative Therapy

- The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*:
  - TMP-SMX 1 DS tablet PO three times weekly (BI), *or*
  - Dapsone[a] 50 mg PO daily with pyrimethamine 50 mg plus leucovorin 25 mg PO weekly (BI), *or*
  - Dapsone[a] 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg PO weekly (BI), *or*
  - Atovaquone 1,500 mg PO daily with food (BI)
- The following regimens should only be used in people who are seronegative for *Toxoplasma gondii*:
  - Dapsone[a] 100 mg PO daily or dapsone 50 mg PO twice a day (BI), *or*
  - Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month (BI), *or*
  - Intravenous pentamidine 300 mg every 28 days (CIII)

Indication for Discontinuing Primary Prophylaxis

- CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months in response to ART (AI)
- Can consider when CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limit of detection of the assay used for ≥3 to 6 months (BII)

Indication for Restarting Primary Prophylaxis
• CD4 count <100 cells/mm^3 regardless of HIV RNA (AIII) • CD4 count 100–200 cells/mm^3 and HIV RNA consistently above detection limit of the assay used (AIII)
Prepregnancy and Pregnancy Considerations
• Clinicians who are providing prepregnancy care for women with HIV receiving PCP prophylaxis can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued with their patients (BIII). • During pregnancy, chemoprophylaxis for PCP should be administered as it would be for other persons with HIV (AIII). TMP-SMX is the recommended prophylactic agent (AIII). For women who are receiving TMP-SMX, clinicians should consider giving supplemental folic acid 4 mg/day if they are capable of becoming pregnant or as soon as possible in their first trimester (BIII). • Given theoretical concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, clinicians may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during the first trimester (CIII) rather than withholding chemoprophylaxis.
Other Considerations/Comments
• For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible. • If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution of therapy should be considered after the reaction has resolved (AII). The dose of TMP-SMX can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII). • TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse reactions including suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for primary PCP prophylaxis.

[a] G6PD levels should be checked before administration of dapsone. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

Indication for Primary Prophylaxis

Chemoprophylaxis against PCP should be given to adults and adolescents with HIV (including during pregnancy) with CD4 counts <100 cells/mm^3 regardless of plasma HIV levels **(AIII)** and those with CD4 counts between 100 and 200 cells/mm^3 with plasma HIV RNA levels above detection limits **(AI).**[13,51] Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP **(AII).**[52]

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent for PCP **(AI).**[51,53-55] One double-strength TMP-SMX tablet daily or one single-strength tablet daily[55] are the preferred regimens **(AI)**; there is greater experience with the double-strength tablet, but the single-strength tablet may be better tolerated. One double-strength TMP-SMX tablet three times weekly is also effective **(BI).**[56] TMP-SMX confers cross-protection against toxoplasmosis[57] and many respiratory bacterial infections.[53,58] TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in people with HIV who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction (e.g., rash without vesicles, bullae, or ulcerations), reinstitution of the drug should be considered after the reaction has resolved **(AII).**[59] Therapy should be permanently discontinued (with no rechallenge) in people with HIV with life-

threatening adverse reactions, including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis **(AIII).** Patients who have experienced adverse events, including fever and rash, may better tolerate reinstitution of TMP-SMX if the dose is gradually increased according to published regimens **(BI)**[60,61] or if the drug is given at a reduced dose or frequency **(CIII).** As many as 70% of people with HIV can tolerate such reinstitution of TMP-SMX therapy.[58]

For people with HIV in whom TMP-SMX use may need to be avoided (e.g., intolerance, severe renal dysfunction, early pregnancy, significant myelosuppression), alternative prophylactic regimens include dapsone **(BI),**[53] dapsone plus pyrimethamine plus leucovorin **(BI),**[62-64] aerosolized pentamidine administered with the Respirgard II nebulizer (manufactured by Marquest; Englewood, Colorado) **(BI),**[54] intravenous (IV) pentamidine **(CIII),**[65-67] and atovaquone **(BI).**[68,69] For people with HIV who are seropositive for *Toxoplasma gondii* and cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin **(BI)**[62-64] or atovaquone **(CIII).** Dapsone alone and pentamidine (aerosol or IV) have not been shown to have activity against toxoplasmosis, and should only be used in people who are seronegative for anti-*Toxoplasma* antibodies.[57,70,71] Glucose-6-phosphate dehydrogenase (G6PD) levels should be checked prior to starting dapsone, and an alternative regimen should be used if G6PD deficiency is present, given the risks of hemolysis and methemoglobinemia in patients with G6PD deficiency.[72]

The utility of IV pentamidine as PCP prophylaxis has been evaluated primarily in retrospective/observational studies in immunosuppressed patients without HIV, especially in pediatric populations; experience in people with HIV is limited. Aerosolized pentamidine should be administered in an appropriately configured negative pressure room.[73] Pyrimethamine has become extremely expensive and can be difficult to obtain in the United States, and atovaquone has variable and unpredictable bioavailability. Atovaquone is as effective as aerosolized pentamidine[68] or dapsone[69] but substantially more expensive than the other regimens, and less preferred by patients due to the taste of the suspension.

The following regimens **are NOT recommended** as alternatives to TMP-SMX for PCP prophylaxis **(AIII):**

- Aerosolized pentamidine administered by nebulization devices other than the Respirgard II nebulizer[74]
- Oral clindamycin plus primaquine, because this regimen has not been studied for PCP prophylaxis, and clindamycin alone was poorly tolerated as a potential prophylactic regimen for toxoplasmosis.[75]

Discontinuing Primary Prophylaxis

Primary *Pneumocystis* prophylaxis should be discontinued in adult and adolescent people with HIV who have responded to ART with an increase in CD4 counts from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months **(AI).** In observational and randomized studies whose findings support this recommendation, most people with HIV had CD4 counts >200 cells/mm^3 for >3 months before discontinuing PCP prophylaxis.[76-85] At discontinuation of prophylaxis, the median CD4 count was >300 cells/mm^3, most participants had a CD4 cell percentage ≥14%, and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 to 19 months.

A combined analysis of European cohorts,[86,87] a small randomized trial,[88] and a case series[89] found a low incidence of PCP in people with HIV with CD4 counts between 100 cells/mm^3 and 200 cells/mm^3, who were receiving ART and had HIV plasma viral loads <50 to <400 copies/mL, and who had stopped or never received PCP prophylaxis; this observation suggests that primary and secondary PCP prophylaxis can be safely discontinued in people with HIV with CD4 counts between 100 cells/mm^3 to 200 cells/mm^3 and HIV plasma RNA levels below the limits of detection of commercial assays. Some clinicians would stop primary prophylaxis in people with HIV with CD4 counts of 100 to 200 cells/mm^3 if HIV plasma RNA levels remain below limits of detection for ≥3 months to 6 months; definitive data for a more precise recommendation are lacking **(BII).** Similar observations have been made with regard to stopping primary prophylaxis for *Toxoplasma* encephalitis.[90]

Prophylaxis should be reintroduced if the patient's CD4 count decreases to 100 to 200 cells/mm^3 in the setting of sustained increases in plasma HIV RNA levels **(AIII)** and in any people with HIV whose CD4 count drops to <100 cells/mm^3 **(AIII).**

Treating Disease

Recommendations for Treating *Pneumocystis* Pneumonia

People with HIV who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (BIII).

If not already started, ART should be initiated in patients within 2 weeks of diagnosis of PCP, if possible (AI).

For Moderate-to-Severe PCP

Preferred Therapy

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) IV given in divided doses every 6 or 8 hours (AI); may switch to PO formulation after clinical improvement (AI)

Alternative Therapy

- Primaquine[a] 30 mg (base) PO once daily plus clindamycin (IV [600 mg every 6 hours or 900 mg every 8 hours] or PO [450 mg every 6 hours or 600 mg every 8 hours]) (AI), *or*
- Pentamidine 4 mg/kg IV once daily infused over ≥60 minutes (AI); may reduce the dose to pentamidine 3 mg/kg IV once daily in the event of toxicities (BI)
- Note: Some clinicians prefer primaquine plus clindamycin because it is more effective and less toxic than pentamidine.

Adjunctive Corticosteroids for Moderate-to-Severe PCP Based on the Following Criteria (AI)

- PaO_2 <70 mmHg at room air, *or*
- A-a gradient ≥35 mmHg

Corticosteroid Dosing Schedule

- Prednisone doses (beginning as soon as possible and ideally within 72 hours of initiating PCP therapy) (AI)
  - Days 1–5: 40 mg PO twice daily
  - Days 6–10: 40 mg PO daily
  - Days 11–21: 20 mg PO daily
- IV methylprednisolone can be given as 80% of prednisone dose.

- Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP (BIII).

For Mild-to-Moderate PCP

Preferred Therapy

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg)/day) PO given in three divided doses (AI), *or*
- TMP-SMX, two DS tablets PO three times daily (AI)

Alternative Therapy

- Dapsone[a] 100 mg PO daily plus TMP 15 mg/kg/day PO given in three divided doses (BI), *or*
- Primaquine[a] 30 mg (base) PO daily plus clindamycin PO (450 mg every 6 hours or 600 mg every 8 hours) (BI), *or*
- Atovaquone 750 mg PO twice daily with food (BI)

Duration of Therapy

- The recommended duration of therapy (irrespective of regimen) is 21 days (AII).
- Secondary prophylaxis should be initiated immediately after completion of treatment (see Recurrence table below).

Pregnancy Considerations

For Moderate-to-Severe PCP

Preferred Therapy

- TMP-SMX, regardless of disease (AIII)
- Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with PCP should be treated with TMP-SMX because of its considerable benefit in reducing morbidity and mortality, which outweighs potential risk (AIII).
- For women who are on TMP-SMX, clinicians should consider giving supplemental folic acid 4 mg/day if they are capable of becoming pregnant or as soon as possible in their first trimester (BIII). Doses of supplemental folic acid of 4 mg/day should be limited to the first trimester during the teratogenic window and can be reduced to 0.4 mg at 12 weeks continuing to 4–6 weeks postpartum or discontinuation of breastfeeding (AIII).
- Whether or not supplemental folic acid is administered during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for follow-up scans subsequently (BIII).

Alternative Therapy

- IV pentamidine (BIII)
- If other alternatives are not available or tolerated, primaquine plus clindamycin (BIII)
    - Because of concerns about hemolytic anemia in exposed fetuses who are G6PD deficient (which cannot be diagnosed antenatally), primaquine (plus clindamycin) should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk (AIII).

For Mild-to-Moderate PCP

Preferred Therapy

- TMP-SMX, regardless of disease (AI)

Alternative Therapy

- Atovaquone suspension (BIII)
- If atovaquone is not available or tolerated, dapsone plus TMX (BIII)

- Because of concerns about hemolytic anemia in exposed fetuses who are G6PD deficient, primaquine or dapsone should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk (AIII).

Note: As with other adults with HIV, G6PD levels should be checked before administration of primaquine or dapsone during pregnancy. While the G6PD level in a fetus generally is unknown during pregnancy, G6PD deficiency is an X-linked inherited condition and primaquine or dapsone can be considered if both the pregnant woman and biologic father have normal G6PD activity.

Adjunctive Corticosteroid Therapy

- During pregnancy, adjunctive corticosteroid therapy should be used to improve treatment outcomes as indicated in any other person with HIV (AIII). Maternal glucose levels and blood pressure should be monitored closely when corticosteroids are used in pregnancy, as well as fetal growth (AIII).
- Patients on chronic steroid therapy during pregnancy for non-hypothalamic-pituitary-adrenal axis disorders do not need stress doses of steroids for vaginal or cesarean delivery but should be continued on their therapeutic dose of steroids without interruption (BIII).

Other Considerations/Comments

- For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution of therapy should be considered after the reaction has resolved (AII). The dose of TMP-SMX can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII).
- TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse reactions including suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for PCP treatment.

[a] G6PD levels should be checked before administration of dapsone or primaquine. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: A-a gradient = alveolar-arterial gradient; ART = antiretroviral therapy; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PaO_2 = room air arterial oxygen partial pressure; PCP = *Pneumocystis* pneumonia; PO = orally; SMX = sulfamethoxazole; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

TMP-SMX is the treatment of choice for PCP **(AI).**[91,92] Standard doses are summarized in the table above; lower doses may also be effective, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable.[93] The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens for PCP treatment.[91,92,94] Adding leucovorin to prevent myelosuppression during acute treatment **is not recommended** because its efficacy in preventing this toxicity is questionable and some evidence suggests adding leucovorin can lead to a higher treatment failure rates. **(AII).**[95] Outpatient therapy with oral TMP-SMX is highly effective in people with HIV with mild-to-moderate PCP **(AI).**[92] TMP-SMX should be permanently discontinued (with no rechallenge) in people with HIV who experience life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis **(AIII).**

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.[96-99] Patients who have PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX **(BIII).**

Patients with documented or suspected PCP and moderate-to-severe disease, defined by room air PaO_2 <70 mmHg or A-a gradient ≥35 mmHg, should receive adjunctive corticosteroids as soon as possible and certainly within 72 hours after starting specific PCP therapy **(AI).**[100-105] The benefits of

starting steroids later are unclear, but most clinicians would administer them even after 72 hours for people with HIV who have moderate-to-severe PCP **(BIII).** Intravenous methylprednisolone at 80% of the corresponding oral prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone plus trimethoprim (TMP) **(BI),**[92,106] which may have efficacy similar to TMP-SMX with fewer side effects, but is less convenient given the number of pills; primaquine plus clindamycin **(BI)**[107-109] (clindamycin can be administered IV for more severe cases, but primaquine is only available in an oral formulation); and atovaquone suspension **(BI),**[91,110] which is less effective than TMP-SMX for mild-to-moderate PCP but has fewer side effects. Clinicians should be aware that the absorption of atovaquone is highly variable; plasma concentrations ≥15 µg/mL are associated with an improved response rate, but atovaquone therapeutic drug monitoring is not routinely available.[91,111] People with HIV should be tested for G6PD levels before primaquine or dapsone is administered. An alternative agent should be used if the patient is found to have G6PD deficiency.

Alternative therapeutic regimens for people with HIV who have moderate-to-severe PCP include primaquine plus clindamycin **(AI)** or IV pentamidine **(AI).**[109,112,113] Some clinicians prefer primaquine plus clindamycin because this combination is more effective and less toxic than pentamidine.[109,114-116]

Aerosolized pentamidine **should not be used** to treat PCP because it has limited efficacy and is associated with more frequent relapse **(AI).**[112,117,118]

The recommended duration of therapy for PCP (irrespective of regimen) is 21 days **(AII)**[19]; shorter durations may also be effective but have not been systematically studied.[119] The probability and rate of response to therapy depend on the agent used, number of previous PCP episodes, severity of pulmonary illness, degree of immunodeficiency, timing of initiation of therapy, and comorbidities.

Although the overall prognosis for people with HIV with PCP-associated respiratory failure is poor, over the past decades, survival for people with HIV who require intensive care unit (ICU) care has improved with advances in the management of respiratory failure and HIV comorbidities.[120-123] Special attention is necessary regarding the use of ART in such critically ill patients.[124]

Special Considerations Regarding ART Initiation (Including IRIS)

If not already started, ART should be initiated in patients, when possible, within 2 weeks of PCP diagnosis **(AI).** In a randomized controlled trial of 282 people with HIV with opportunistic infections (OIs) other than TB, 63% of whom had definite or presumptive PCP, the incidence of AIDS progression or death (a secondary study endpoint) was significantly lower among participants who initiated ART early than among those who delayed ART (median 12 days vs. 45 days after OI therapy initiation, respectively).[125] Of note, none of the participants with PCP enrolled in the study had respiratory failure requiring intubation.[125] Initiating ART in intubated patients can be managed with attention to formulations that can be crushed for gastrointestinal administration when an IV options is unavailable (such as primaquine). Providers should be aware of the unpredictable absorption of oral medications, and potential drug–drug or drug–nutrient interactions commonly encountered in the ICU.[126]

Paradoxical immune reconstitution inflammatory syndrome (IRIS) following an episode of PCP is rare but has been reported.[127,128] Most cases occurred within weeks of the PCP episode; symptoms

included fever and recurrence or exacerbation of pulmonary symptoms including cough and shortness of breath, as well as worsening of a previously improving chest radiograph. Although IRIS in the setting of PCP has rarely been life-threatening,[129] people with HIV should be closely followed for recurrence of symptoms after initiation of ART. Management of PCP-associated IRIS is not well defined; some experts recommend use of corticosteroids in people with HIV with respiratory deterioration if other causes are ruled out.

Monitoring of Response to Pneumocystis *Pneumonia Therapy and Adverse Events*

Careful monitoring during PCP therapy is important to evaluate treatment response and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially if therapy has been with an agent other than TMP-SMX or was shortened because of toxicity.

In people with HIV, rates of adverse reactions to TMP-SMX are high (20% to 85% of patients).[91,92,106,108,113,130-134] Common adverse effects are rash (30% to 55% of patients) (including Stevens-Johnson syndrome), fever (30% to 40% of patients), leukopenia (30% to 40% of patients), thrombocytopenia (15% of patients), azotemia (1% to 5% of patients), hepatitis (20% of patients), hyperkalemia, and rarely, aseptic meningitis. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued **(AIII).** Mild rashes (e.g., rash without vesicles, bullae, or ulcerations), nausea, and fever can often be "treated through" with antihistamines, antiemetics, and antipyretics, respectively.[59] High-dose trimethoprim inhibits tubular secretion of creatinine without affecting glomerular filtration rate, and this effect may be additive with other medications. As noted above, therapy should be permanently discontinued in the setting of **life-threatening adverse reactions *including*** possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis **(AIII).**

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone[92,106]; azotemia, pancreatitis, hypoglycemia or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine[110,112,113,133]; anemia, rash, fever, and diarrhea with primaquine and clindamycin[92,107,108]; and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.[91,132] Patients who exhibit persistent hypoxemia despite an apparent positive clinical response should undergo evaluation for methemoglobinemia if they are taking potentially causative medications.

Managing Treatment Failure

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases after 4 to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of people with HIV with mild-to-moderate PCP disease.[91,92] However, there are not any convincing clinical trial data on which to base recommendations for the management of PCP treatment failure due to lack of drug efficacy.

Clinicians should wait 4 to 8 days before switching therapy for lack of clinical improvement **(BIII).** In the absence of corticosteroid therapy, early and reversible deterioration within the first 3 to 5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infectious and non-infectious processes must be

excluded as a cause of clinical failure[28,29]; bronchoscopy with BAL should be strongly considered to evaluate for this possibility, even if bronchoscopy was used to make the initial diagnosis.

Treatment-limiting toxicities occur in up to one-third of patients.[92] Switching to another regimen is the appropriate management for treatment-related toxicity **(BII).** When TMP-SMX is not effective or cannot be used for moderate-to-severe disease because of toxicity, the common practice is to use parenteral pentamidine **(BII)** or oral primaquine combined with IV clindamycin **(BII).**[108,109,113] For mild disease, atovaquone is a reasonable alternative **(BII).** Although a meta-analysis, systematic review, and cohort study concluded that the combination of primaquine and clindamycin might be the most effective regimen for salvage therapy,[109,115,116] no prospective clinical trials have evaluated the optimal approach for people with HIV who experience a therapy failure with TMP-SMX.

Preventing Recurrence

Recommendations for Preventing Recurrence of *Pneumocystis* Pneumonia (Secondary Prophylaxis)

Indications for Initiating Secondary Prophylaxis

- Prior PCP

Preferred Therapy

- TMP-SMX, 1 DS tablet PO daily[a] (AI), *or*
- TMP-SMX, 1 SS tablet PO daily[a] (AI)
- Note: TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections. Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).

Alternative Therapy

- The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*:
  - TMP-SMX one DS tablet PO three times weekly (BI), or
  - Dapsone[a] 50 mg PO daily with pyrimethamine 50 mg plus leucovorin 25 mg PO weekly (BI), or
  - Dapsone[a] 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg PO weekly (BI), or
  - Atovaquone 1,500 mg PO daily with food (BI)
- The following regimens should only be used in people who are seronegative for *Toxoplasma gondii*:
  - Dapsone[a] 100 mg PO daily (BI), or
  - Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month (BI), or
  - Intravenous pentamidine 300 mg every 28 days (CIII)

Indications for Discontinuing Secondary Prophylaxis

- CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months as a result of ART (AII), *or*
- Can consider if CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limits of detection of assay used for 3 to 6 months (BII)
- For people with HIV in whom PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 to 6 months, although there are no data to support recommendations in this setting (CIII).

- Note: If an episode of PCP occurs at a CD4 count >200 cells/mm^3 while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, especially with plasma HIV RNA below level of detection, regardless of how high the CD4 cell count rises as a consequence of ART (BIII).

Indications for Restarting Secondary Prophylaxis

- CD4 count <100 cells/mm^3 regardless of HIV RNA (AIII), *or*
- CD4 count 100–200 cells/mm^3 and HIV RNA above detection limit of the assay used (AIII)

Prepregnancy and Pregnancy Considerations

- For patients receiving PCP prophylaxis, clinicians who are providing prepregnancy care can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued (BIII) due to potential concerns about possible adverse effects of trimethoprim on the fetus.
- Women of childbearing potential who choose not to defer pregnancy while on TMP-SMX should consider increasing the dose of folic acid to 4 mg/day (BIII).
- During pregnancy, chemoprophylaxis for PCP should be administered as it is for other adults and adolescents (AIII). TMP-SMX is the recommended prophylactic agent (AIII). For women who are on TMP-SMX, clinicians should consider giving supplemental folic acid 4 mg/day in their first trimester (BIII).
- Given theoretical concerns about possible teratogenicity associated with first-trimester TMP-SMX exposures, alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone can be used in during the first trimester (BII).
- Dapsone should be used in the first trimester only if the other alternatives are not available or tolerated due to concerns about hemolytic anemia in mothers or exposed fetuses (BIII).

Note regarding G6PD deficiency and use of primaquine or dapsone in pregnancy: As with other adults with HIV, G6PD levels should be checked before administration of primaquine or dapsone. While G6PD level in a fetus are generally unknown during pregnancy, G6PD deficiency is an X-linked inherited condition and primaquine or dapsone can be considered if both the pregnant woman and biologic father have normal G6PD activity.

Other Considerations/Comments

- For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution of therapy should be considered after the reaction has resolved (AII). The dose of TMP-SMX can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII).
- TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse events, ***including*** suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for secondary PCP prophylaxis.

[a] Whenever possible, people with HIV should be tested for G6PD deficiency before administration of dapsone. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

When to Start Secondary Prophylaxis

Secondary PCP prophylaxis with TMP-SMX should be initiated immediately upon successful completion of PCP therapy and maintained until immune reconstitution occurs as a result of ART (see below) **(AI).**[135] For people with HIV who are intolerant of TMP-SMX, the alternatives are dapsone **(BI),** dapsone plus pyrimethamine plus leucovorin **(BI),** atovaquone **(BI),** and aerosolized pentamidine **(BI)** or IV pentamidine **(CIII).**

When to Stop Secondary Prophylaxis

Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from <200 cells mm^3 to ≥200 cells mm^3 for ≥3 months as a result of ART **(AII).** Reports from observational studies[77,83,136,137] and from two randomized trials[84,138] and a combined analysis of European cohorts being followed prospectively[139,140] support this recommendation. In these studies, people with HIV responded to ART with an increase in CD4 counts to ≥200 cells/mm^3 for ≥3 months. At the time secondary PCP prophylaxis was discontinued, the median CD4 count was >300 cells/mm^3 and most people with HIV had a CD4 cell percentage >14%. Most people with HIV had sustained suppression of plasma HIV RNA levels below the limits of detection for the assay employed; the longest follow-up was 40 months. Based on results from the COHERE study, secondary prophylaxis in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 can potentially be discontinued if HIV plasma RNA levels remain below limits of detection for 3 to 6 months **(BII).**[141]

When to Restart Primary or Secondary Prophylaxis

Primary or secondary PCP prophylaxis should be reintroduced if the patient's CD4 count decreases to <100 cells/mm^3 **(AIII)** regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 with HIV plasma viral load above detection limits of the assay used **(AIII).** Based on results from the COHERE study, primary or secondary PCP prophylaxis may not need to be restarted in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 who have had HIV plasma RNA levels below limits of detection for 3 to 6 months **(BII).**[86,139]

If an episode of PCP occurs at a CD4 count >200 cells/mm^3 while a patient is on ART, it would be prudent for the patient to continue PCP prophylaxis for life, regardless of how high their CD4 cell count rises as a consequence of ART **(BIII).** For people with HIV in whom PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV plasma RNA levels are suppressed to below limits of detection for 3 to 6 months, although there are no data to support recommendations in this setting **(CIII).**

Special Considerations Regarding Pregnancy

Some data suggest an increased risk of PCP-associated mortality in pregnancy.[142] All-cause pneumonia during pregnancy increases rates of preterm labor and delivery.[143]

Women at >20 weeks gestation who have PCP should be closely monitored for signs or symptoms of preterm labor (e.g., abdominal cramping, uterine tightening, fluid leakage) **(BIII).**

Prepregnancy Care

For patients receiving PCP prophylaxis, clinicians who are providing prepregnancy care can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued **(BIII)** due to concerns about possible adverse effects of trimethoprim on the fetus (see the Primary and Secondary Prophylaxis section below). All women of childbearing potential should take supplemental folic acid at a dose of 0.4 mg/day **(AI);** those who choose not to defer pregnancy while on TMP-SMX should consider increasing the dose of folic acid to 4 mg/day **(BIII)** (see below).

Pregnancy Care

Note: Specific drugs recommended for prophylaxis are discussed in the section on Primary and Secondary Prophylaxis. This information is not repeated in the Treating Disease section and only medications recommended exclusively for treatment are discussed in this section.

Primary and Secondary Prophylaxis

During pregnancy, chemoprophylaxis for PCP should be administered as it is for other adults and adolescents **(AIII).** The preferred regimen for prophylaxis is TMP-SMX **(AIII).** Given concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone can be used during the first trimester **(BII).** Dapsone should be used in the first trimester only if the other alternatives are not available or tolerated due to concerns about hemolytic anemia in pregnant women or exposed fetuses **(BIII).** As with other adults with HIV, G6PD levels should be checked before dapsone administration.

No adequate and well-controlled large studies of pregnancy outcomes after exposure to sulfamethoxazole and trimethoprim have been published. Trimethoprim is classified as a folic acid antagonist, acting as a dihydrofolate reductase inhibitor; older case-control studies found that first-trimester exposure has been associated with an increased risk of neural tube defects and cardiovascular, oral clefts, urinary tract, and multiple anomalies.[144-146] A systematic review and meta-analysis in 2014, including 24 studies,[147] reported congenital anomalies in 232 infants among 4,196 women receiving TMP-SMX in pregnancy, with a pooled prevalence of 3.5% (95% confidence interval [CI], 1.8% to 5.1%) and three studies reported 31 infants with neural tube defects associated with first-trimester exposure, with a crude prevalence of 0.7% (95% CI, 0.5% to 1.0%). The quality of the evidence was considered very low and the authors supported continued recommendation for TMP-SMX when indicated for pregnant women with HIV. A recent systematic review of antimicrobials used for management of plague during pregnancy included 23,602 prenatal exposures to TMP-SMX found that first-trimester exposure was associated with an increased risk of neural tube defects (pooled odds ratio [OR] 2.5; 95% CI, 1.4–4.3).[148] This study also found increased odds of spontaneous abortion (OR 3.5; 95% CI, 2.3–5.6), preterm delivery (OR 1.5; 95% CI, 1.1–2.1) and the fetus being small for gestational age (OR 1.6; 95% CI, 1.2–2.2). In a nested case-control study (n = 77,429; 7,039 cases of spontaneous abortion) based on prescription fills, first-trimester exposure to TMP-SMX, after adjusting for potential confounders, was associated with increased odds of spontaneous abortion (adjusted odds ratio [aOR] 2.94, 95% CI, 1.89–4.57, including 25 exposed cases and 77 controls).[149] Exposure to TMP-SMX in the last two trimesters of pregnancy was associated with low birth weight, adjusted for gestational age and sex (OR 1.61; 95% CI, 1.16–2.23) in a case-control study within the Quebec Pregnancy Registry (8,192 cases, 55,146 controls).[150] Data from a large Canadian administrative database was used to retrospectively compare the occurrence of placenta-mediated adverse pregnancy outcomes between pregnant women exposed to folic acid antagonists and women without exposure to these agents.[151] TMP-SMX was the most frequently prescribed dihydrofolate reductase inhibitor (11,386 exposures during the preconception period and all three trimesters compared to 45,456 unexposed women) and exposure was associated with increased odds of preeclampsia (aOR 1.13; 95% CI, 1.01–1.26), placental abruption (aOR 1.26; 95% CI, 1.03–1.55), and fetal growth restriction defined as less than the third percentile (aOR 1.20; 95% CI, 1.07–1.33).

Folic acid supplementation at 0.4 mg/day is routinely recommended for all women of reproductive potential,[152] to reduce the risk of neural tube defects **(AI).** Since neural tube closure occurs early in pregnancy, often before pregnancy is diagnosed, all persons planning a pregnancy or with reproductive potential should take daily folic acid supplementation. There is also evidence that folic acid supplementation may decrease risk of congenital heart defects, cleft lip and palate,[153] preterm birth,[154] low birth weight, and the fetus being small for gestational age.[155,156] There are no trials evaluating whether supplementation at higher levels (e.g., 4 mg/day as recommended for pregnant women who previously had an infant with a neural tube defect) would reduce the risk of birth defects associated with first-trimester TMP-SMX use. A multicenter double-blind randomized clinical trial in women of childbearing age who planned pregnancy within 12 months failed to show an advantage of folic acid 4 mg versus 0.4 mg daily on the occurrence of congenital malformations; however, the higher dose was associated with lower occurrence of spontaneous abortion, the fetus being small for gestational age, and preterm delivery.[157] The authors noted that the study was underpowered for the outcome of congenital malformations.[157] Other studies have found that higher doses of folic acid (4–6 mg/day) are associated with less frequent neural tube defects, oral clefts, and recurrent preeclampsia.[158-160] In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use in pregnancy were not seen in women also receiving folic acid supplementation, most of whom received folic acid 6 mg/day (OR 1.24; 95% CI, 0.94–1.62).[144]

Although the risk of multiple congenital abnormalities associated with TMP-SMX use persisted despite supplemental folic acid, the OR decreased from 6.4 for TMP-SMX without folic acid to 1.9 for TMP-SMX plus folic acid. Based on these findings, with the suggestion of a dose-response effect of folic acid supplementation and the known effects of TMP-SMX as a folic acid antagonist, for women who are on TMP-SMX, clinicians should consider giving them supplemental folic acid 4 mg/day prior to pregnancy if they are capable of becoming pregnant or as soon as possible in the first trimester in those who are pregnant **(BIII).** Leucovorin (folinic acid) is an active form of folate and is commonly used to counteract the effect of folic acid antagonists, especially as an adjunct in the treatment of various cancers. However, it is chemically different from folic acid and is not interchangeable. A randomized, controlled trial demonstrated that adding leucovorin to TMP-SMX for the treatment of PCP was associated with an increased risk of therapeutic failure and death.[95] In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent leucovorin use.[161] If a higher dose of supplemental folic acid is given, its use should be limited to the first trimester **(AIII).** Whether or not a person receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for subsequent follow-up scans **(BIII).**

Although historically there has been concern about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, reviews have found no cases of kernicterus reported in neonates after maternal ingestion of sulfonamides or with the use of TMP-SMX in neonates.[162-164] For several decades, dapsone has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.[165,166] Long-term therapy is associated with a risk of mild maternal hemolysis, and exposed fetuses with G6PD deficiency are at potential risk (albeit extremely low) of acute hemolytic anemia.[167]

Data on atovaquone in human pregnancy are limited but preclinical studies have not demonstrated teratogenicity in rats or rabbits at plasma concentrations corresponding to estimated human exposure during malaria treatment.[168] A systematic review of the safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy found miscarriages in 21 of 260 women (8.08%;

95% CI, 5.07% to 12.08%) and congenital anomalies in 11 of 430 women (2.56%; 95% CI, 1.28% to 4.53%), both well within expected rates.[169] When considering only results from this one randomized clinical trial of atovaquone-proguanil, there was no significant difference in these outcomes when compared to quinine, although the number was extremely small (n = 81).[170]

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.[171] There is limited experience with systemic use in human pregnancy and no human studies of pregnancy outcomes after exposure to pentamidine have been published. It is unknown if pentamidine crosses the placental barrier at significant concentrations when administered via the aerosolized route. Given anecdotal experience to date during pregnancy without signs of adverse effects or teratogenicity, pentamidine should be considered an alternative when indicated either via aerosolized or IV route.

Treatment

The preferred initial therapy for PCP during pregnancy, regardless of disease severity, is TMP-SMX **(AIII).**[134]

Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, people with PCP in the first trimester should be treated with TMP-SMX because of its considerable benefit in reducing morbidity and mortality, which outweighs the potential risk **(AIII).** Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX and capable of pregnancy or as soon as possible in the first trimester **(BIII).** Doses of supplemental folic acid of 4 mg/day should be limited to the first trimester during the teratogenic window and can be reduced to 0.4 mg at 12 weeks continuing to 4 to 6 weeks postpartum or discontinuation of breastfeeding **(AIII).**

If an alternative therapeutic regimen is required for moderate-to-severe PCP, IV pentamidine is preferred **(BIII).** Primaquine plus clindamycin should be used only if other alternatives are not available or tolerated **(BIII).** If an alternative therapeutic regimen is required for mild-to-moderate PCP, atovaquone suspension is preferred **(BIII);** dapsone plus TMP can be used if atovaquone is not available or tolerated **(BIII).** As with other adults with HIV, G6PD levels should be checked before administration of dapsone**.** Because of concerns about hemolytic anemia in exposed fetuses who are G6PD-deficient (which cannot be diagnosed antenatally), primaquine or dapsone should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk **(AIII).**

During pregnancy, adjunctive corticosteroid therapy should be used to improve treatment outcomes as indicated in any other person with HIV **(AIII).**[172-175] Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air PO_2 <70 mmHg or A-a gradient PO_2 ≥35 mmHg, should receive adjunctive corticosteroids as early as possible. Corticosteroids have commonly been used in pregnancy for autoimmune conditions and are considered low risk for use in pregnancy.[176] Although an earlier systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4-fold increase in the odds of delivering a baby with an oral cleft,[177] more recent data from a prospective controlled study in Israel, a large population-based registry in Sweden,[178] and an updated analysis from the National Birth Defect Prevention Study,[179,180] have failed to demonstrate an association between first-trimester corticosteroids and major congenital anomalies, including orofacial clefts. A recent systematic review and meta-analysis also found no association between first-trimester corticosteroid exposure and risk of congenital heart defects.[181] Long-term corticosteroid use in pregnancy may be associated

with an increased risk of maternal hypertension, preeclampsia, hyperglycemia, premature rupture of membranes, intrauterine growth restriction,[182] and infection, although the magnitude is not known.[183]

Maternal glucose levels and blood pressure as well as fetal growth should be monitored closely when corticosteroids are used in pregnancy **(AIII).** Based on available observational data from pregnant and nonpregnant surgical patients, pregnant women who are on chronic steroid therapy during pregnancy for non-hypothalamic-pituitary-adrenal axis disorders do not need stress doses of steroids for vaginal or cesarean delivery, but they should be continued on their therapeutic dose of steroids without interruption **(BIII).** HPA axis suppression is rarely seen among neonates born to women who received chronic corticosteroids during pregnancy.

Clindamycin is considered safe for use throughout pregnancy **(BIII).** Clindamycin is recommended as an alternative antibiotic for prevention of group B streptococcal disease in newborns and for antimicrobial prophylaxis during cesarean delivery.[184,185] However, there are no well-controlled studies of clindamycin use in pregnant women during the first trimester. In animal studies, clindamycin was not teratogenic following oral doses up to six times the maximum recommended adult human dose.[186] During clinical trials, the systemic administration of clindamycin to pregnant women during the second and third trimesters did not increase the frequency of congenital abnormalities.[186]

There are no adequate or well-controlled studies of primaquine use in pregnant women, and animal data is scant. Although some data from animal studies suggest evidence of genotoxicity, as well as fetal abnormalities at doses multiple times the maximal dose in humans,[187] another animal study at doses 0.25 to 3.0 mg/kg early in gestation found no harmful effects on mother or offspring.[188] In an observational study from Brazil, 59 women were found to have been prescribed primaquine for malaria during pregnancy, approximately one-third in the first trimester; no adverse birth outcomes were found, although G6PD testing was not done on the infants.[189] The Centers for Disease Control and Prevention recommend that primaquine not be administered during pregnancy because of the risk of hemolytic anemia in a G6PD-deficient fetus.[190] The degree of intravascular hemolysis appears to be associated with both the dose of primaquine and severity of G6PD deficiency.[168] G6PD deficiency is an X-linked inherited condition and primaquine can be considered if both the pregnant woman and biologic father have normal G6PD activity.[191] Primaquine should be used in pregnancy only if other alternatives are not available or tolerated and the benefit is felt to outweigh the risk **(AIII).**

References

1. Nevez G, Totet A, Matos O, Calderon EJ, Miller RF, Le Gal S. It is still PCP that can stand for *Pneumocystis* pneumonia: appeal for generalized use of only one acronym. *Med Mycol*. 2021;59(8):842-844. Available at: https://pubmed.ncbi.nlm.nih.gov/34003930.

2. Pifer LL, Hughes WT, Stagno S, Woods D. *Pneumocystis carinii* infection: evidence for high prevalence in normal and immunosuppressed children. *Pediatrics*. 1978;61(1):35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/400818.

3. Keely SP, Stringer JR, Baughman RP, Linke MJ, Walzer PD, Smulian AG. Genetic variation among *Pneumocystis carinii hominis* isolates in recurrent pneumocystosis. *J Infect Dis*. 1995;172(2):595-598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7542688.

4. Helweg-Larsen J, Tsolaki AG, Miller RF, Lundgren B, Wakefield AE. Clusters of *Pneumocystis carinii* pneumonia: analysis of person-to-person transmission by genotyping. *QJM*. 1998;91(12):813-820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10024946.

5. Huang L, Beard CB, Creasman J, et al. Sulfa or sulfone prophylaxis and geographic region predict mutations in the *Pneumocystis carinii* dihydropteroate synthase gene. *J Infect Dis*. 2000;182(4):1192-1198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10979917.

6. Sassi M, Ripamonti C, Mueller NJ, et al. Outbreaks of *Pneumocystis* pneumonia in 2 renal transplant centers linked to a single strain of *Pneumocystis*: implications for transmission and virulence. *Clin Infect Dis*. 2012;54(10):1437-1444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22431811.

7. de Boer MG, Kroon FP, le Cessie S, de Fijter JW, van Dissel JT. Risk factors for *Pneumocystis jirovecii* pneumonia in kidney transplant recipients and appraisal of strategies for selective use of chemoprophylaxis. *Transpl Infect Dis*. 2011;13(6):559-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21689251.

8. Arichi N, Kishikawa H, Mitsui Y, et al. Cluster outbreak of *Pneumocystis* pneumonia among kidney transplant patients within a single center. *Transplant Proc*. 2009;41(1):170-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19249506.

9. Gianella S, Haeberli L, Joos B, et al. Molecular evidence of interhuman transmission in an outbreak of *Pneumocystis jirovecii* pneumonia among renal transplant recipients. *Transpl Infect Dis*. 2010;12(1):1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19744285.

10. Mori S, Cho I, Sugimoto M. A cluster of *Pneumocystis jirovecii* infection among outpatients with rheumatoid arthritis. *J Rheumatol*. 2010;37(7):1547-1548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20595296.

11. Schmoldt S, Schuhegger R, Wendler T, et al. Molecular evidence of nosocomial *Pneumocystis jirovecii* transmission among 16 patients after kidney transplantation. *J Clin Microbiol*. 2008;46(3):966-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18216217.

12. Yazaki H, Goto N, Uchida K, Kobayashi T, Gatanaga H, Oka S. Outbreak of *Pneumocystis jiroveci* pneumonia in renal transplant recipients: *P. jiroveci* is contagious to the susceptible host. *Transplantation*. 2009;88(3):380-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19667941.

13. Phair J, Munoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. 1990;322(3):161-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1967190.

14. Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-defining opportunistic infections in a multicohort analysis of HIV-infected persons in the United States and Canada, 2000-2010. *J Infect Dis*. 2016;214(6):862-872. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27559122.

15. Sezgin E, Van Natta ML, Thorne JE, Puhan MA, Jabs DA, Longitudinal Studies of the Ocular Complications of AIDS Research Group. Secular trends in opportunistic infections, cancers and mortality in patients with AIDS during the era of modern combination antiretroviral therapy. *HIV Med*. 2018;19(6):411-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29573311.

16. Bielick C, Strumpf A, Ghosal S, McMurry T, McManus KA. National hospitalization rates and in-hospital mortality rates of HIV-related opportunistic infections in the United States, 2011–2018. *Clin Infect Dis*. 2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38306316.

17. Lundberg BE, Davidson AJ, Burman WJ. Epidemiology of *Pneumocystis carinii* pneumonia in an era of effective prophylaxis: the relative contribution of non-adherence and drug failure. *AIDS*. 2000;14(16):2559-2566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11101068.

18. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest*. 2001;120(6):1888-1893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11742918.

19. Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med*. 1984;100(5):663-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6231873.

20. Selwyn PA, Pumerantz AS, Durante A, et al. Clinical predictors of *Pneumocystis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. *AIDS*. 1998;12(8):885-893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9631142.

21. Chiliza N, Du Toit M, Wasserman S. Outcomes of HIV-associated *Pneumocystis* pneumonia at a South African referral hospital. *PLoS One*. 2018;13(8):e0201733. Available at: https://pubmed.ncbi.nlm.nih.gov/30071089.

22. Ng VL, Yajko DM, Hadley WK. Extrapulmonary pneumocystosis. *Clin Microbiol Rev*. 1997;10(3):401-418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9227859.

23. Smith DE, McLuckie A, Wyatt J, Gazzard B. Severe exercise hypoxaemia with normal or near normal x-rays: a feature of *Pneumocystis carinii* infection. *Lancet*. 1988;2(8619):1049-1051. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2903279.

24. Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis*. 1988;137(4):796-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3258483.

25. Opravil M, Marincek B, Fuchs WA, et al. Shortcomings of chest radiography in detecting *Pneumocystis carinii* pneumonia. *J Acquir Immune Defic Syndr*. 1994;7(1):39-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8263751.

26. Metersky ML, Colt HG, Olson LK, Shanks TG. AIDS-related spontaneous pneumothorax. Risk factors and treatment. *Chest*. 1995;108(4):946-951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7555166.

27. Sepkowitz KA, Telzak EE, Gold JW, et al. Pneumothorax in AIDS. *Ann Intern Med*. 1991;114(6):455-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1994791.

28. Baughman RP, Dohn MN, Frame PT. The continuing utility of bronchoalveolar lavage to diagnose opportunistic infection in AIDS patients. *Am J Med*. 1994;97(6):515-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7985710.

29. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med*. 1984;101(1):1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6375497.

30. Gruden JF, Huang L, Turner J, et al. High-resolution CT in the evaluation of clinically suspected *Pneumocystis carinii* pneumonia in AIDS patients with normal, equivocal, or nonspecific radiographic findings. *AJR Am J Roentgenol*. 1997;169(4):967-975. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9308446.

31. Hidalgo A, Falco V, Mauleon S, al. e. Accuracy of high-resolution CT in distinguishing between *Pneumocystis carinii* pneumonia and non-*Pneumocystis carinii* pneumonia in AIDS patients. *Eur Radiol*. 2003;13:1179-1184. Available at: https://pubmed.ncbi.nlm.nih.gov/12695843.

32. Roger PM, Vandenbos F, Pugliese P, et al. Persistence of *Pneumocystis carinii* after effective treatment of *P. carinii* pneumonia is not related to relapse or survival among patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1998;26(2):509-510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9502487.

33. Cruciani M, Marcati P, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of diagnostic procedures for *Pneumocystis carinii* pneumonia in HIV-1-infected patients. *Eur Respir J*. 2002;20(4):982-989. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12412693.

34. Flori P, Bellete B, Durand F, et al. Comparison between real-time PCR, conventional PCR and different staining techniques for diagnosing *Pneumocystis jiroveci* pneumonia from

bronchoalveolar lavage specimens. *J Med Microbiol*. 2004;53(Pt 7):603-607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15184529.

35. Armbruster C, Pokieser L, Hassl A. Diagnosis of *Pneumocystis carinii* pneumonia by bronchoalveolar lavage in AIDS patients. Comparison of Diff-Quik, fungifluor stain, direct immunofluorescence test and polymerase chain reaction. *Acta Cytol*. 1995;39(6):1089-1093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7483981.

36. Aderaye G, Woldeamanuel Y, Asrat D, et al. Evaluation of Toluidine Blue O staining for the diagnosis of *Pneumocystis jiroveci* in expectorated sputum sample and bronchoalveolar lavage from HIV-infected patients in a tertiary care referral center in Ethiopia. *Infection*. 2008;36(3):237-243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18483698.

37. Raab SS, Cheville JC, Bottles K, Cohen MB. Utility of Gomori methenamine silver stains in bronchoalveolar lavage specimens. *Mod Pathol*. 1994;7(5):599-604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7524071.

38. Tiley SM, Marriott DJ, Harkness JL. An evaluation of four methods for the detection of *Pneumocystis carinii* in clinical specimens. *Pathology*. 1994;26(3):325-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7527514.

39. Procop GW, Haddad S, Quinn J, et al. Detection of *Pneumocystis jiroveci* in respiratory specimens by four staining methods. *J Clin Microbiol*. 2004;42(7):3333-3335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15243109.

40. Thomas CF, Jr., Limper AH. *Pneumocystis* pneumonia. *N Engl J Med*. 2004;350(24):2487-2498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15190141.

41. Guegan H, Roojee M, Le Gal S, et al. Evaluation of the PneumoGenius® PCR assay for the diagnosis of *Pneumocystis pneumonia* and the detection of *Pneumocystis* dihydropteroate synthase mutations in respiratory samples. *Med Mycol*. 2023;61(4). Available at: https://pubmed.ncbi.nlm.nih.gov/37028929.

42. Lussac-Sorton F, Fleur T, Voisin T, et al. Interest of a commercialized *Pneumocystis jirovecii* quantitative PCR to discriminate colonization from *Pneumocystis pneumonia* according to the Revised EORTC/MSGERC Criteria. *J Clin Med*. 2022;12(1). Available at: https://pubmed.ncbi.nlm.nih.gov/36615116.

43. Nijhuis RHT, Godschalk PCR, Smink JHI, van der Zee C, van Hannen EJ. Comparison of the PneumoGenius® and RealStar® *Pneumocystis jirovecii* PCR CE-IVD assays with a lab developed test for the detection of *Pneumocystis jirovecii*. *Med Mycol*. 2022;60(1). Available at: https://pubmed.ncbi.nlm.nih.gov/34894244.

44. Pisculli ML, Sax PE. Use of a serum beta-glucan assay for diagnosis of HIV-related *Pneumocystis jiroveci* pneumonia in patients with negative microscopic examination results. *Clin Infect Dis*. 2008;46(12):1928-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18540807.

45. Sax PE, Komarow L, Finkelman MA, et al. Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. *Clin Infect Dis*. 2011;53(2):197-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21690628.

46. Li WJ, Guo YL, Liu TJ, Wang K, Kong JL. Diagnosis of *Pneumocystis pneumonia* using serum (1-3)-beta-D-Glucan: a bivariate meta-analysis and systematic review. *J Thorac Dis*. 2015;7(12):2214-2225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26793343.

47. Del Corpo O, Butler-Laporte G, Sheppard DC, Cheng MP, McDonald EG, Lee TC. Diagnostic accuracy of serum (1-3)-β-D-glucan for *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2020;26(9):1137-1143. Available at: https://pubmed.ncbi.nlm.nih.gov/32479781.

48. Corsi-Vasquez G, Ostrosky-Zeichner L, Pilkington EF, 3rd, Sax PE. Point-counterpoint: should serum β-d-glucan testing be used for the diagnosis of *Pneumocystis jirovecii* pneumonia? *J Clin Microbiol*. 2019;58(1). Available at: https://pubmed.ncbi.nlm.nih.gov/31434728.

49. Choukri F, Menotti J, Sarfati C, et al. Quantification and spread of *Pneumocystis jirovecii* in the surrounding air of patients with *Pneumocystis* pneumonia. *Clin Infect Dis*. 2010;51(3):259-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20572759.

50. Pliquett RU, Asbe-Vollkopf A, Hauser PM, et al. A *Pneumocystis jirovecii* pneumonia outbreak in a single kidney-transplant center: role of cytomegalovirus co-infection. *Eur J Clin Microbiol Infect Dis*. 2012;31(9):2429-2437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22402816.

51. Centers for Disease Control and Prevention. Guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for persons infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep*. 1989;38(Suppl 5):1-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2524643.

52. Heald A, Flepp M, Chave JP, et al. Treatment for cerebral toxoplasmosis protects against *Pneumocystis carinii* pneumonia in patients with AIDS. The Swiss HIV Cohort Study. *Ann Intern Med*. 1991;115(10):760-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1929023.

53. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):693-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7854375.

54. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. The Dutch AIDS Treatment Group. *N Engl J Med*. 1992;327(26):1836-1841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1360145.

55. Schneider MM, Nielsen TL, Nelsing S, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii*

pneumonia in patients with human immunodeficiency virus. Dutch AIDS Treatment Group. *J Infect Dis*. 1995;171(6):1632-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7769306.

56. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected persons. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). *Clin Infect Dis*. 1999;29(4):775-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10589887.

57. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. 1992;117(2):106-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1351371.

58. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. *N Engl J Med*. 1992;327(26):1842-1848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1448121.

59. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1. July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

60. Para MF, Finkelstein D, Becker S, Dohn M, Walawander A, Black JR. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr*. 2000;24(4):337-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11015150.

61. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11574913.

62. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis* pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. 1995;122(10):755-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7717598.

63. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1995;20(3):531-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7756472.

64. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and

toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. 1993;328(21):1514-1520. Available at: https://pubmed.ncbi.nlm.nih.gov/8479488.

65. McCollam S, Lewis JS, 2nd, Bubalo J, Diaz A. *Pneumocystis jirovecii* pneumonia prophylaxis with intravenous pentamidine in adult allogeneic hematopoietic stem cell transplant patients. *Antimicrob Agents Chemother*. 2022;66(11):e0083322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36214573.

66. Awad WB, Asaad A, Al-Yasein N, Najjar R. Effectiveness and tolerability of intravenous pentamidine for *Pneumocystis carinii* pneumonia prophylaxis in adult hematopoietic stem cell transplant patients: a retrospective study. *BMC Infect Dis*. 2020;20(1):400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32503449.

67. Ena J, Amador C, Pasquau F, et al. Once-a-month administration of intravenous pentamidine to patients infected with human immunodeficiency virus as prophylaxis for *Pneumocystis carinii* pneumonia. *Clin Infect Dis*. 1994;18(6):901-904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8086550.

68. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis*. 1999;180(2):369-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10395851.

69. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9862944.

70. Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against *Pneumocystis carinii* pneumonia and toxoplasma encephalitis in HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;15(2):104-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9241108.

71. Antinori A, Murri R, Ammassari A, et al. Aerosolized pentamidine, cotrimoxazole and dapsone-pyrimethamine for primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis. *AIDS*. 1995;9(12):1343-1350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8605054.

72. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf*. 2010;33(9):713-726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20701405.

73. ISSA. Occupational risk prevention in aerosol therapy (pentamidine). 2015. Available at: https://ww1.issa.int/prevention-health/publications?page=2.

74. Pediatric Oncology Group of Ontario. Pentamidine administration. 2022. Available at: https://www.pogo.ca/satellite-manual/4-0-supportive-care-practice-tools/4-2-pentamidine-administration/4-2-1-inhaled-pentamidine.

75. Jacobson MA, Besch CL, Child C, et al. Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. Community Programs for Clinical Research on AIDS. *Lancet*. 1992;339(8789):333-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1346413.

76. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *N Engl J Med*. 1999;340(17):1301-1306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10219064.

77. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10915098.

78. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. 2000;181(5):1635-1642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10823763.

79. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. 1999;353(9148):201-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9923876.

80. Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group. *Lancet*. 1999;353(9161):1293-1298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10218526.

81. Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD. Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. HIV Outpatient Study (HOPS) Investigators. *Ann Intern Med*. 2000;132(3):201-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10651600.

82. Furrer H, Opravil M, Rossi M, et al. Discontinuation of primary prophylaxis in HIV-infected patients at high risk of *Pneumocystis carinii* pneumonia: prospective multicentre study. *AIDS*. 2001;15(4):501-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11242147.

83. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. 1999;13(13):1647-1651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10509565.

84. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. *N Engl J Med*. 2001;344(3):159-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11172138.

85. Green H, Hay P, Dunn DT, McCormack S, Investigators S. A prospective multicentre study of discontinuing prophylaxis for opportunistic infections after effective antiretroviral therapy. *HIV Med*. 2004;5(4):278-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15236617.

86. Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), Mocroft A, Reiss P, et al. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20645862.

87. Atkinson A, Zwahlen M, Barger D, et al. Withholding primary *Pneumocystis* pneumonia prophylaxis in virologically suppressed patients with human immunodeficiency virus: an emulation of a pragmatic trial in COHERE. *Clin Infect Dis*. 2021;73(2):195-202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32448894.

88. Chaiwarith R, Praparattanapan J, Nuntachit N, Kotarathititum W, Supparatpinyo K. Discontinuation of primary and secondary prophylaxis for opportunistic infections in HIV-infected patients who had CD4+ cell count <200 cells/mm(3) but undetectable plasma HIV-1 RNA: an open-label randomized controlled trial. *AIDS Patient Care STDS*. 2013;27(2):71-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23373662.

89. D'Egidio GE, Kravcik S, Cooper CL, Cameron DW, Fergusson DA, Angel JB. *Pneumocystis jiroveci* pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/microl when viral replication is suppressed. *AIDS*. 2007;21(13):1711-1715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17690568.

90. Miro J, Esteve A, Furrer H, Opportunistic Infection Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Safety of stopping primary *T. gondii* prophylaxis with suppressed viremia and CD4>100/mm3. Presented at: CROI; 2016. Boston, MassachusettsAvailable at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2016/765.pdf.

91. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. *N Engl J Med*. 1993;328(21):1521-1527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8479489.

92. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. 1996;124(9):792-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8610948.

93. Butler-Laporte G, Smyth E, Amar-Zifkin A, Cheng MP, McDonald EG, Lee TC. Low-dose TMP-SMX in the treatment of *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2020;7(5):ofaa112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32391402.

94. Sattler FR, Cowan R, Nielsen DM, Ruskin J. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired

immunodeficiency syndrome. A prospective, noncrossover study. *Ann Intern Med*. 1988;109(4):280-287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3260759.

95. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. *J Infect Dis*. 1994;170(4):912-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7930736.

96. Crothers K, Beard CB, Turner J, et al. Severity and outcome of HIV-associated *Pneumocystis pneumonia* containing Pneumocystis jirovecii dihydropteroate synthase gene mutations. *AIDS*. 2005;19(8):801-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867494.

97. Huang L, Crothers K, Atzori C, et al. Dihydropteroate synthase gene mutations in *Pneumocystis* and sulfa resistance. *Emerg Infect Dis*. 2004;10(10):1721-1728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15504256.

98. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jiroveccii* pneumonia. *Emerg Infect Dis*. 2004;10(10):1760-1765. Available at: https://pubmed.ncbi.nlm.nih.gov/15504261.

99. Alvarez-Martinez MJ, Miro JM, Valls ME, et al. Prevalence of dihydropteroate synthase genotypes before and after the introduction of combined antiretroviral therapy and their influence on the outcome of *Pneumocystis* pneumonia in HIV-1-infected patients. *Diagn Microbiol Infect Dis*. 2010;68(1):60-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20727472.

100. Nielsen TL, Eeftinck Schattenkerk JK, Jensen BN, et al. Adjunctive corticosteroid therapy for *Pneumocystis carinii* pneumonia in AIDS: a randomized European multicenter open label study. *J Acquir Immune Defic Syndr*. 1992;5(7):726-731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1613673.

101. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323(21):1451-1457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2233917.

102. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for *Pneumocystis* Pneumonia. Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med*. 1990;323(21):1500-1504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2136587.

103. Montaner JS, Lawson LM, Levitt N, Belzberg A, Schechter MT, Ruedy J. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med*. 1990;113(1):14-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2190515.

104. Gallant JE, Chaisson RE, Moore RD. The effect of adjunctive corticosteroids for the treatment of *Pneumocystis carinii* pneumonia on mortality and subsequent complications. *Chest*. 1998;114(5):1258-1263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9823998.

105. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV-infection. *Cochrane Database Syst Rev*. 2006;3:CD006150(3):CD006150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16856118.

106. Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med*. 1990;323(12):776-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2392131.

107. Black JR, Feinberg J, Murphy RL, et al. Clindamycin and primaquine therapy for mild-to-moderate episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: AIDS Clinical Trials Group 044. *Clin Infect Dis*. 1994;18(6):905-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8086551.

108. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). CTN-PCP Study Group. *Clin Infect Dis*. 1998;27(3):524-530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9770152.

109. Smego RA, Jr., Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. *Arch Intern Med*. 2001;161(12):1529-1533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11427101.

110. Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for *Pneumocystis carinii* pneumonia in patients with AIDS. Atovaquone Study Group. *Ann Intern Med*. 1994;121(3):174-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7880228.

111. Robin C, Le MP, Melica G, et al. Plasma concentrations of atovaquone given to immunocompromised patients to prevent *Pneumocystis jirovecii*. *J Antimicrob Chemother*. 2017;72(9):2602-2606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28651341.

112. Conte JE, Jr., Chernoff D, Feigal DW, Jr., Joseph P, McDonald C, Golden JA. Intravenous or inhaled pentamidine for treating *Pneumocystis carinii* pneumonia in AIDS. A randomized trial. *Ann Intern Med*. 1990;113(3):203-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2197911.

113. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective randomized trial. *Ann Intern Med*. 1986;105(1):37-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3521428.

114. Kim T, Kim SH, Park KH, et al. Clindamycin-primaquine versus pentamidine for the second-line treatment of *Pneumocystis pneumonia*. *J Infect Chemother*. 2009;15(5):343-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19856077.

115. Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. *J*

Antimicrob Chemother. 2009;64(6):1282-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858161.

116. Benfield T, Atzori C, Miller RF, Helweg-Larsen J. Second-line salvage treatment of AIDS-associated *Pneumocystis jirovecii* pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr*. 2008;48(1):63-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18360286.

117. Soo Hoo GW, Mohsenifar Z, Meyer RD. Inhaled or intravenous pentamidine therapy for *Pneumocystis carinii* pneumonia in AIDS. A randomized trial. *Ann Intern Med*. 1990;113(3):195-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2197910.

118. Montgomery AB, Feigal DW, Jr., Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for *Pneumocystis carinii* in acquired immune deficiency syndrome. *Am J Respir Crit Care Med*. 1995;151(4):1068-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7697233.

119. McDonald EG, Butler-Laporte G, Del Corpo O, et al. On the treatment of *Pneumocystis jirovecii* pneumonia: current practice based on outdated evidence. *Open Forum Infect Dis*. 2021;8(12):ofab545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34988242.

120. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. *J Infect Dis*. 2001;183(9):1409-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11294675.

121. Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS*. 2003;17(1):73-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12478071.

122. Miller RF, Allen E, Copas A, Singer M, Edwards SG. Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. *Thorax*. 2006;61(8):716-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16601092.

123. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients with HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest*. 2009;135(1):11-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18719058.

124. Andrade HB, Shinotsuka CR, da Silva IRF, et al. Highly active antiretroviral therapy for critically ill HIV patients: a systematic review and meta-analysis. *PLoS One*. 2017;12(10):e0186968. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29065165.

125. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19440326.

126. Akgun KM, Miller RF. Critical care in human immunodeficiency virus-infected patients. *Semin Respir Crit Care Med*. 2016;37(2):303-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26974306.

127. Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. *PLoS One*. 2010;5(7):e11416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20617176.

128. Roade Tato L, Burgos Cibrian J, Curran Fabregas A, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients with *Pneumocystis jirovecii* pneumonia. *Enferm Infecc Microbiol Clin*. 2018;36(10):621-626. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29187293.

129. Jagannathan P, Davis E, Jacobson M, Huang L. Life-threatening immune reconstitution inflammatory syndrome after *Pneumocystis* pneumonia: a cautionary case series. *AIDS*. 2009;23(13):1794-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19684486.

130. Eeftinck Schattenkerk JK, Lange JM, van Steenwijk RP, Danner SA. Can the course of high dose cotrimoxazole for *Pneumocystis carinii* pneumonia in AIDS be shorter? A possible solution to the problem of cotrimoxazole toxicity. *J Intern Med*. 1990;227(5):359-362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2341830.

131. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. 1984;100(4):495-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6230976.

132. Hughes WT, LaFon SW, Scott JD, Masur H. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related *Pneumocystis carinii* pneumonia. *J Infect Dis*. 1995;171(5):1295-1301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7751706.

133. Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: results of a large prospective randomized treatment trial. *AIDS*. 1992;6(3):301-305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1567574.

134. Sattler FR, Frame P, Davis R, et al. Trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate to severe episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: a prospective, controlled multicenter investigation of the AIDS Clinical Trials Group Protocol 029/031. *J Infect Dis*. 1994;170(1):165-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8014493.

135. Masur H, Kaplan JE, Holmes KK, U.S. Public Health Service, Infectious Diseases Society of America. Guidelines for preventing opportunistic infections among HIV-infected persons--2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Ann Intern Med*. 2002;137(5 Pt 2):435-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12617574.

136. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2000;14(4):383-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10770540.

137. Zellweger C, Opravil M, Bernasconi E, et al. Long-term safety of discontinuation of secondary prophylaxis against *Pneumocystis* pneumonia: prospective multicentre study. *AIDS*. 2004;18(15):2047-2053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577626.

138. Mussini C, Pezzotti P, Antinori A, et al. Discontinuation of secondary prophylaxis for *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients: a randomized trial by the CIOP Study Group. *Clin Infect Dis*. 2003;36(5):645-651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12594647.

139. Furrer H, for the OI working group of COHERE in EuroCoord. HIV replication is a major predictor of primary and recurrent *Pneumocystis* pneumonia - implications for prophylaxis recommendations. Presented at: 15th European AIDS Conference; 2015. Barcelona.

140. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med*. 2001;344(3):168-174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11188837.

141. Atkinson A, Miro JM, Mocroft A, et al. No need for secondary *Pneumocystis jirovecii* pneumonia prophylaxis in adult people living with HIV from Europe on ART with suppressed viraemia and a CD4 cell count greater than 100 cells/microL. *J Int AIDS Soc*. 2021;24(6):e25726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34118121.

142. Ahmad H, Mehta NJ, Manikal VM, et al. *Pneumocystis carinii* pneumonia in pregnancy. *Chest*. 2001;120(2):666-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11502676.

143. Chen YH, Keller J, Wang IT, Lin CC, Lin HC. Pneumonia and pregnancy outcomes: a nationwide population-based study. *Am J Obstet Gynecol*. 2012;207(4):288 e281-287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23021691.

144. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. 2001;15(6):637-646. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11738517.

145. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. 2000;343(22):1608-1614. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11096168.

146. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *Am J Epidemiol*. 2001;153(10):961-968. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11384952.

147. Ford N, Shubber Z, Jao J, Abrams EJ, Frigati L, Mofenson L. Safety of cotrimoxazole in pregnancy: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2014;66(5):512-521. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24853309.

148. Yu PA, Tran EL, Parker CM, et al. Safety of antimicrobials during pregnancy: a systematic review of antimicrobials considered for treatment and postexposure prophylaxis of plague. *Clin Infect Dis*. 2020;70(70 Suppl 1):S37-S50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32435799.

149. Muanda FT, Sheehy O, Berard A. Use of trimethoprim-sulfamethoxazole during pregnancy and risk of spontaneous abortion: a nested case control study. *Br J Clin Pharmacol*. 2018;84(6):1198-1205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29424001.

150. Santos F, Sheehy O, Perreault S, Ferreira E, Berard A. Exposure to anti-infective drugs during pregnancy and the risk of small-for-gestational-age newborns: a case-control study. *BJOG*. 2011;118(11):1374-1382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21749628.

151. Wen SW, Zhou J, Yang Q, Fraser W, Olatunbosun O, Walker M. Maternal exposure to folic acid antagonists and placenta-mediated adverse pregnancy outcomes. *CMAJ*. 2008;179(12):1263-1268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19047607.

152. Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep*. 1992;41(RR-14):1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1522835.

153. Darjazini Nahas L, Hmadieh M, Audeh M, Yousfan A, Almasri IA, Martini N. Cleft lip and palate risk factors among otorhinolaryngology: Head and neck surgery patients in two hospitals. *Medicine (Baltimore)*. 2023;102(42):e34419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37861535.

154. Alvestad S, Husebye ESN, Christensen J, et al. Folic acid and risk of preterm birth, preeclampsia, and fetal growth restriction among women with epilepsy: a prospective cohort study. *Neurology*. 2022;99(6):e605-e615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35577577.

155. Bulloch RE, Wall CR, Thompson JMD, et al. Folic acid supplementation is associated with size at birth in the Screening for Pregnancy Endpoints (SCOPE) international prospective cohort study. *Early Hum Dev*. 2020;147:105058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32531744.

156. Jonker H, Capelle N, Lanes A, Wen SW, Walker M, Corsi DJ. Maternal folic acid supplementation and infant birthweight in low- and middle-income countries: A systematic review. *Matern Child Nutr*. 2020;16(1):e12895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31680411.

157. Bortolus R, Filippini F, Cipriani S, et al. Efficacy of 4.0 mg versus 0.4 mg folic acid supplementation on the reproductive outcomes: a randomized controlled trial. *Nutrients*. 2021;13(12). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34959975.

158. Czeizel AE, Timar L, Sarkozi A. Dose-dependent effect of folic acid on the prevention of orofacial clefts. *Pediatrics*. 1999;104(6):e66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10586000.

159. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *The Lancet*. 1991;338(8760):131-137. Available at: https://www.sciencedirect.com/science/article/pii/014067369190133A?via%3Dihub.

160. Zheng L, Huang J, Kong H, Wang F, Su Y, Xin H. The effect of folic acid throughout pregnancy among pregnant women at high risk of pre-eclampsia: a randomized clinical trial. *Pregnancy Hypertens*. 2020;19:253-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31987769.

161. Razavi B, Lund B, Allen BL, Schlesinger L. Failure of trimethoprim/sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia with concurrent leucovorin use. *Infection*. 2002;30(1):41-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11876516.

162. Forna F, McConnell M, Kitabire FN, et al. Systematic review of the safety of trimethoprim-sulfamethoxazole for prophylaxis in HIV-infected pregnant women: implications for resource-limited settings. *AIDS Rev*. 2006;8(1):24-36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16736949.

163. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17536875.

164. Thyagarajan B, Deshpande SS. Cotrimoxazole and neonatal kernicterus: a review. *Drug Chem Toxicol*. 2014;37(2):121-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24099411.

165. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15230645.

166. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in *Plasmodium falciparum*-endemic sub-Saharan Africa. *Trop Med Int Health*. 2003;8(6):488-506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12791054.

167. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. 1989;82(5):668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2717998.

168. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1(1):1-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18690910.

169. Andrejko KL, Mayer RC, Kovacs S, et al. The safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy: a systematic review. *Travel Med Infect Dis*. 2019;27:20-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30654041.

170. McGready R, Ashley EA, Moo E, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. *J Infect Dis*. 2005;192(5):846-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16088834.

171. Harstad TW, Little BB, Bawdon RE, Knoll K, Roe D, Gilstrap LC, 3rd. Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats. *Am J Obstet Gynecol*. 1990;163(3):912-916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2403167.

172. Albino JA, Shapiro JM. Respiratory failure in pregnancy due to *Pneumocystis carinii*: report a successful outcome. *Obstet Gynecol*. 1994;83(5 Pt 2):823-824. Available at: https://pubmed.ncbi.nlm.nih.gov/8159362.

173. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? *Am J Obstet Gynecol*. 1989;161(3):657-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2782348.

174. Koonin LM, Ellerbrock TV, Atrash HK, et al. Pregnancy-associated deaths due to AIDS in the United States. *JAMA*. 1989;261(9):1306-1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2783746.

175. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. *Am J Obstet Gynecol*. 1982;144(4):413-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7124859.

176. Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. ACOG Committee opinion: immune modulating therapies in pregnancy and lactation. *Obstetrics & Gynecology*. 2019;133(4):e287-e295. Available at: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/04/immune-modulating-therapies-in-pregnancy-and-lactation.

177. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. 2000;62(6):385-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11091360.

178. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics*. 1956;18(4):614-625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13370229.

179. Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts. *Birth Defects Res A Clin Mol Teratol*. 2014;100(6):499-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24777675.

180. Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol*. 2004;18(1):93-101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15013068.

181. Wei J, Xia F, Miao J, Wang T, Chen L, Yan X. Correction to: The risk of congenital heart defects associated with corticosteroids use during the first trimester of pregnancy: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2023;79(1):13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36416939.

182. Peltoniemi OM, Kari MA, Hallman M. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2011;90(7):719-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21426310.

183. Ostensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8(3):209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16712713.

184. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 199: Use of prophylactic antibiotics in labor and delivery. *Obstet Gynecol*. 2018;132(3):e103-e119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30134425.

185. Prevention of group B streptococcal early-onset disease in newborns: ACOG Committee opinion summary, number 797. *Obstet Gynecol*. 2020;135(2):489-492. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31977793.

186. CLEOCIN HCl [package insert]. Pfizer Pharmacia & Upjohn Company. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050162s102lbl.pdf.

187. Primaquine phosphate tablets [package insert]. Sanofi-Aventis U.S. LLC. 2017. Available at: https://products.sanofi.us/primaquine/primaquine.pdf.

188. de Azevedo EN, Santos AS, Rocha Mendes ET, Simões MJ, Kulay L. Efeitos do uso crônico do difosfato de primaquina sobre a prenhez da rata. *Rev Bras Ginecol Obstet*. 1998;20(9):505-508. Available at: https://www.scielo.br/j/rbgo/a/kxBPq3JwNx6QgmwDKf694dC/?lang=pt.

189. Pincelli A, Neves PAR, Lourenco BH, et al. The hidden burden of *Plasmodium vivax* malaria in pregnancy in the Amazon: an observational study in northwestern Brazil. *Am J Trop Med Hyg*. 2018;99(1):73-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29741155.

190. Tan KR, Abanyie F. Malaria. In: CDC Yellow Book 2024. Centers for Disease Control and Prevention (CDC), ed. New York, NY: Oxford University Press; 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria.

191. DeBaun MR. Overview of hemolytic anemias in children. 2022. Available at: https://www.uptodate.com/contents/overview-of-hemolytic-anemias-in-children.

Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the human polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] JCV has a worldwide distribution, and 20% to 70% of people exhibit serologic evidence of exposure by their late teens or as adults.[3-7] Primary JCV infection usually occurs asymptomatically in childhood resulting in a chronic carrier state in most individuals. Viral DNA is detected in the urine of 20% to 30% of healthy adults.[4,8-12]

PML is a rare manifestation of JCV reactivation and characteristically manifests as a complication of HIV-1 infection and other immunocompromising diseases or therapies.[13-16] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab[17] and efalizumab.[18] Concern has been raised about a possible increased risk of PML in persons with HIV (PWH) treated with rituximab for non-Hodgkin lymphoma,[19,20] but PML has not been documented in that setting. PML can occur during chronic immunosuppression after organ transplantation and often has a poor prognosis.[21]

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[22-24] and was almost invariably fatal; spontaneous remissions were rare.[25] With the widespread use of ART, incidence of PML decreased substantially,[26,27] and mortality in PWH who develop the disease has declined.[28-30] Although most CNS opportunistic infections are effectively prevented when CD4 T lymphocyte (CD4) cell counts are maintained above 100 to 200 cells/mm^3, PML still occurs occasionally in patients treated with ART.[2,31,32] PML also can develop in the setting of immune reconstitution after ART initiation, which is discussed below.[2,30,33]

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Although some regions seem to be more favored, any region of the CNS can be involved, including the occipital lobes (hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[13] Spinal cord involvement is rare, and the optic nerves are not involved.[34] Although lesions can be multiple, one lesion is clinically predominant. Initial symptoms and signs usually begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis), as individual lesions expand concentrically or along white matter tracts. Less localized clinical syndromes—such as behavioral changes, dementia, or encephalopathy—result from multiple lesions in the setting of PML and are rarely the presenting clinical phenotype.[35]

The time course of evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral

infarcts begin even more abruptly. Nonetheless, PML is sometimes mistaken for an evolving stroke, which, like PML, is bright on diffusion-weighted magnetic resonance imaging (MRI). Focal brain lesion can mimic strokes; however, the progressive course should make this diagnosis less likely, and PML must be considered. Headache and fever are not characteristic of PML, and when present may indicate presence of another opportunistic infection. Seizures occur in nearly 20% of PML cases and are associated with lesions immediately adjacent to the cortex.[36,37]

Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings: steady progression of focal neurological deficits with MRI almost always demonstrating distinct white matter lesions in areas of the brain corresponding to the clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid-attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.[2] The T1 findings can be subtle and may help distinguish lesions due to PML from those of other pathologies, including the white matter lesions of HIV encephalitis. A linear, paramagnetic band or rim in the paralesional U-fibers has been described as a common finding in PML and has been proposed to have diagnostic value independent of underlying predisposing disease. Histopathological studies show this band corresponds to iron accumulation within phagocytic cells, although the pathophysiology leading to this remains unclear.[38,39]

Brain imaging with magnetic resonance (MR) or computed tomography is critical to identifying PML and differentiating it from other important treatable diseases that occur in advanced HIV. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident in PML imaging. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques—such as diffusion-weighted imaging (DWI) and MR spectroscopy—may provide additional diagnostic information.[40-42] New PML lesions and the advancing edge of large lesions have a high signal on DWI and a normal-to-low apparent diffusion coefficient, signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. MR spectroscopy can show areas of decreased N-acetylaspartate and increased choline related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.[43] Recently, a hyperintense cortical signal seen on MRI scan in non-enhanced T1-weighted cortex images has been associated with seizures complicating inflammatory PML.[37]

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Because the primary treatment method for PML is restoring the patient's immune function, confirming the diagnosis is especially important to ensure ART is initiated rapidly.

JCV DNA is virtually never detected in normal cerebrospinal fluid (CSF) samples. Thus, the usual first step in confirming the diagnosis is to test CSF by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context—namely, subacute onset of focal neurological abnormalities and suggestive imaging findings.[10,44] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[45] In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.[46,47] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded. Given that in AIDS patients, multiple opportunistic conditions are sometimes encountered, evaluation of CSF is often indicated to rule out *Cryptococcus*, neurosyphilis,

cytomegalovirus encephalitis, varicella-zoster encephalitis, herpes simplex encephalitis, and tuberculosis. Further, CSF PCR analyses for *Toxoplasma* and consideration of Epstein-Barr virus generally associated with primary CNS lymphoma is often indicated with progressive multifocal brain disease in the setting of AIDS. Because JCV DNA viral load in CSF may be very low even with active PML, highly sensitive PCR performance is desirable. Sensitive assays that detect as few as 50 copies/mL are now available, with some research laboratories exceeding this level of sensitivity; detection of JCV virus in CSF in any amount with the appropriate clinical and imaging findings strongly supports the diagnosis of PML.[48] Analysis of plasma samples for detection of JCV by PCR when positive are relatively specific for PML (~92% in patients with HIV), while the sensitivity is less than 40% in this setting.[49]

In some instances, brain biopsy is required in order to rule out other diagnoses. PML usually can be identified by the characteristic tissue cytopathology—including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages—with identification of JCV or cross-reacting polyoma virus by immunohistochemistry, *in situ* nucleic acid hybridization, or electron microscopy.[13,50,51]

Generally, serologic testing is not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment.[6] Significant increases in JCV-specific antibody titers[52] and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[53] but require further prospective study. The value of anti-JCV antibodies in stimulating Fc receptor-bearing effector cell activity contributing to outcome of PML requires further studies.[54]

Preventing Exposure

Currently, no known way exists to prevent exposure to the virus because most individuals are infected in childhood.

Preventing Disease

In many individuals, JCV infection is likely latent and intermittently productive, although clinically silent, in the kidney or other anatomic sites. Systemic infection may increase in the presence of immunosuppression. It remains a subject of debate whether JCV infection is also latent in the CNS or whether PML results from hematogenous dissemination of infection to the brain resulting in subsequent PML lesion development within months of entry to the CNS.[55,56] Therefore, the only known way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII).**

Treating Disease

Recommendations for Treating and Monitoring PML
Treatment
The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART. • In patients not on ART who are diagnosed with PML, ART should be (re)started immediately (AII). • In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression (AIII).

• No role for ART intensification in patients with HIV viral suppression (BII). • ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score (BII). • No effective direct-acting antiviral therapy exists for preventing or treating JCV infections or PML. • The following agents are not recommended for the treatment of PML: cytarabine (AII), cidofovir (AII), interferon-alpha (BIII), interleukin-2 (BIII), topotecan (BIII), pembrolizumab (BIII). • The following agents are not recommended due to limited data: 5HT2a receptor antagonist (e.g., olanzapine, ziprasidone, mirtazapine, cyproheptadine, risperidone) (BIII), mefloquine (BIII). Expert consultation is recommended prior to initiation of these agents. • PML-IRIS may require administration of corticosteroid therapy (BIII). The optimal corticosteroid regimen has not been established but should be tailored to individual patients. ART should NOT be discontinued during PML-IRIS (AIII).
Monitoring
• Timing of follow-up assessments (clinical, lumbar puncture, and MRI) should be guided by clinical progress (BIII). • In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation (BIII). • In patients who clinically worsen before or after this 6- to 8-week period, repeat MRI should be obtained as soon as worsening is recognized (BIII).

Key: ART = antiretroviral therapy; CPE = Central Nervous System (CNS) Penetration Effectiveness; IRIS = immune reconstitution inflammatory syndrome; JCV = JC virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus.[57] In patients with PML who are not on therapy, ART should be started immediately **(AII).** In this setting, more than half of PML patients with HIV experience a remission in which disease progression stops. Although neurological deficits often persist, some patients experience clinical improvement.[28,29,58-63] In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.[63] Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another retrospective case series reported that 42% of PML survivors on ART had moderate or severe disability.[64] Peripheral blood CD4 count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm^3 compared with patients who had higher CD4 counts. In other case series, worse prognosis also was associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and presence of lesions in the brain stem.[29,32,59,60,62,63,65] Contrast enhancement on imaging may predict better outcomes, as it is indicative of an immune response to the virus.[31] In multiple sclerosis patients with PML, younger age, more restricted unilobar disease, and lower CSF JCV DNA copy numbers are associated with better outcomes; whether these associations are true for PML in PWH is unknown.[66]

ART should be optimized for HIV virologic suppression in patients with PML who have received ART but remain viremic because of inadequate adherence or ARV resistance **(AIII).** More problematic are patients who develop PML despite successful HIV virologic suppression while

taking ART. A preliminary report of PML with patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher-than-anticipated survival,[67] but it has not yet been followed by structured trial. Therefore, no evidence supports ART intensification for PML **(BII).**

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their chemical characteristics as well as demonstrated entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV activity.[68] One report found at the beginning of the combination ART era that a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.[69] Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.[70,71] ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score **(BII).**

Several studies have evaluated targeted treatments for PML. However, many anecdotal reports of efficacy have not been confirmed by controlled studies and are therefore not recommended. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.[72] Therefore, treatment with cytarabine is **not recommended (AII).** Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-analysis that included patients from five large studies—demonstrated no benefit.[45,61-63,73] Thus, treatment with cidofovir is also **not recommended (AII).**

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,[74,75] drugs that block the 5HT2a receptor, including olanzapine, ziprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[76] although the rationale for this practice has been questioned.[77] Again, anecdotes about favorable outcomes[1,78-81] have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, treatment with serotonergic 5HT2a receptor blockers is **not recommended (BIII).**

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[82] an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.[83] At this time, topotecan is **not recommended (BIII).**

A Phase I/II clinical trial of the antimalarial drug mefloquine was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsor because demonstration of efficacy was futile.[84] Mefloquine use for PML treatment is **not recommended (BIII).** Immunomodulatory approaches to the treatment of PML in PWH also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,[85] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha is **not recommended (BIII).**[86] A single report described failure of interferon-beta treatment of HIV-associated PML[87] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[17] Case

reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected and were treated with IL-2: one with Hodgkin lymphoma treated with autologous bone marrow transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome.[88-90] Like the other reports, these too have not been followed up with more substantial trials; therefore, treatment of PML with IL-2 is **not recommended (BIII).** Recent interest in recombinant IL-7 for treatment of PML when CD4 lymphopenia is persistent, sometimes in combination with VP-1 vaccination strategy, are under consideration as an alternative adjuvant immune therapy to improve PML outcomes.[91-95] Checkpoint inhibitor therapy has been considered recently as a means of enhancing the immune response to JCV most commonly in settings outside of HIV where immune reconstitution may be futile. The outcome of reports is conflicting, and further research is required.[96,97] Use of checkpoint inhibitors for PML in the setting of HIV is **not recommended (BIII).**

Adoptive transfer of autologous or allogeneic virus-specific T cells, either against JCV or the closely related BK virus, have been used for the treatment of PML. Across the several small case series published to date, a single patient with HIV-associated PML was treated with benefit.[98-100] Use of disease-specific T cells is actively being explored, but at present cannot be recommended for HIV-associated PML. In summary, immunomodulatory agents are **not recommended (BIII).**

Special Considerations for ART

ART should be (re)started as soon as possible for all patients, ideally before PML develops. For patients with suspected PML, it is especially imperative to start ART quickly **(AII).** For patients already on treatment who have demonstrated plasma HIV viremia and are adherent to therapy, ART should be adjusted, if possible, based on plasma virus susceptibility **(AII).**

Monitoring of Response to Therapy and Adverse Events (Including Immune Reconstitution Inflammatory Syndrome)

Treatment response should be monitored with clinical examination and brain MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantification of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress **(BIII).** Often disease progression occurs before stabilization and improvement occurs.[67] In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response and can serve as a further baseline for subsequent scans should the patient begin to deteriorate **(BIII).** In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII).**

PML-Immune Reconstitution Inflammatory Syndrome

PML has been reported to occur within the first weeks to months after initiating ART[2,32,33,101-103] with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course.[38,104] As with other presentations of immune reconstitution inflammatory syndrome (IRIS), it is more likely after advanced HIV with low CD4 counts and greater decline in HIV viral load on initiation of ARV. This presentation has been referred to as inflammatory PML or PML-IRIS. Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.[105-108]

Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses.

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting with reported benefit.[2,102,109] Further study of corticosteroids for treatment of PML-IRIS is needed to confirm efficacy and refine dosage and duration. At present, however, use of corticosteroids to treat of PML-IRIS may be justified in some PML where edema or mass effect causes serious clinical deterioration **(BIII).** The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response could be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids appear to have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5-day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued **(AIII).**

Several case reports suggest that maraviroc might be beneficial for PML-IRIS,[110] presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, no comparative studies in HIV-associated PML have confirmed benefit of including of maraviroc in HIV therapy in this setting.[110,111] A retrospective cohort study of 27 patients with PML in whom maraviroc was used failed to show utility in preventing PML-IRIS.[112] Maraviroc is not recommended as a component of treatment of PML **(BIII).**

Managing Treatment Failure

PML remission can take several weeks, and no strict criteria exist to define treatment failure. However, a working definition of treatment failure may be continued clinical worsening after 3 months of ART initiation. Changes in plasma HIV RNA levels and blood CD4 count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for the use of ART (see Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines). When PML continues to worsen despite fully suppressive ART, one of the unproven therapies described above could be considered after consultation with an expert **(CIII),** although the possibility of toxicity must be balanced against the unproven benefits of these treatments. The search for other potentially treatable comorbid conditions, like hepatitis C virus and associated cirrhosis, also should be considered in this setting.[113]

Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence unless ART is interrupted.[61,114] The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 counts **(AII).**

Special Considerations During Pregnancy

During pregnancy, the diagnostic evaluation of PML should be the same as in any other person with HIV. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen.

References

1. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? *Ann Neurol*. 2006;60(2):162-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16862584.

2. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. 2009;9(10):625-636. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19778765.

3. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Pathog*. 2009;5(3):e1000363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19325891.

4. Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. *J Infect Dis*. 2009;199(6):837-846. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19434930.

5. Antonsson A, Green AC, Mallitt KA, et al. Prevalence and stability of antibodies to the BK and JC polyomaviruses: a long-term longitudinal study of Australians. *J Gen Virol*. 2010;91(Pt 7):1849-1853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20219899.

6. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*. 2010;68(3):295-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20737510.

7. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). *Adv Exp Med Biol*. 2006;577:19-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16626025.

8. Kitamura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. *J Infect Dis*. 1990;161(6):1128-1133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2161040.

9. Sundsfjord A, Flaegstad T, Flo R, et al. BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. *J Infect Dis*. 1994;169(3):485-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8158020.

10. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(2):253-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9932940.

11. Lednicky JA, Vilchez RA, Keitel WA, et al. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2003;17(6):801-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12660526.

12. Kato A, Kitamura T, Takasaka T, et al. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. *J Neurovirol*. 2004;10(4):244-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15371154.

13. Richardson EP, Jr., Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. *Prog Clin Biol Res*. 1983;105:191-203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6304757.

14. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J Hematol*. 2005;80(4):271-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16315252.

15. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology*. 2010;75(15):1326-1332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20938025.

16. Anand P, Hotan GC, Vogel A, Venna N, Mateen FJ. Progressive multifocal leukoencephalopathy: a 25-year retrospective cohort study. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/31554669.

17. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9(4):438-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20298967.

18. Molloy ES, Calabrese LH. Therapy: targeted but not trouble-free: efalizumab and PML. *Nat Rev Rheumatol*. 2009;5(8):418-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19648939.

19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol*. 2006;24(25):4123-4128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16896005.

20. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. *Br J Haematol*. 2007;136(5):685-698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17229246.

21. Mateen FJ, Muralidharan R, Carone M, et al. Progressive multifocal leukoencephalopathy in transplant recipients. *Ann Neurol*. 2011;70(2):305-322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21823157.

22. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *J Neuropathol Exp Neurol*. 1986;45(6):635-646. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3021914.

23. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS. UCLA experience and review. *Am J Pathol*. 1986;124(3):537-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2876640.

24. Lang W, Miklossy J, Deruaz JP, et al. Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. *Acta Neuropathol*. 1989;77(4):379-390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2540610.

25. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology*. 1988;38(7):1060-1065. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3386823.

26. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol*. 2004;55(3):320-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14991809.

27. Casado JL, Corral I, Garcia J, et al. Continued declining incidence and improved survival of progressive multifocal leukoencephalopathy in HIV/AIDS patients in the current era. *Eur J Clin Microbiol Infect Dis*. 2014;33(2):179-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23948752.

28. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(3):623-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10025799.

29. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol*. 2003;9 Suppl 1:47-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12709872.

30. Melliez H, Mary-Krause M, Bocket L, et al. Risk of progressive multifocal leukoencephalopathy in the combination antiretroviral therapy era in the French Hospital Database on Human Immunodeficiency Virus (ANRS-C4). *Clin Infect Dis*. 2018;67(2):275-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29635465.

31. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. 1998;44(3):341-349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9749600.

32. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. *J Neurovirol*. 2003;9 Suppl 1:73-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12709876.

33. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003;9 Suppl 1:25-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12709868.

34. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *J Neurovirol*. 2007;13(5):474-476. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17994433.

35. Zunt JR, Tu RK, Anderson DM, Copass MC, Marra CM. Progressive multifocal leukoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. *Neurology*. 1997;49(1):263-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9222204.

36. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology*. 2006;66(2):262-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16434670.

37. Khoury MN, Alsop DC, Agnihotri SP, et al. Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive

multifocal leukoencephalopathy. *Ann Neurol*. 2014;75(5):659-669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24752885.

38. Post MJ, Thurnher MM, Clifford DB, et al. CNS-immune reconstitution inflammatory syndrome in the setting of HIV infection, part 2: discussion of neuro-immune reconstitution inflammatory syndrome with and without other pathogens. *AJNR Am J Neuroradiol*. 2013;34(7):1308-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22790252.

39. Mahajan KR, Amin M, Poturalski M, et al. Juxtacortical susceptibility changes in progressive multifocal leukoencephalopathy at the gray-white matter junction correlates with iron-enriched macrophages. *Mult Scler*. 2021;27(14):2159-2169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33749379.

40. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology*. 1997;48(4):836-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9109865.

41. Mader I, Herrlinger U, Klose U, Schmidt F, Kuker W. Progressive multifocal leukoencephalopathy: analysis of lesion development with diffusion-weighted MRI. *Neuroradiology*. 2003;45(10):717-721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12942223.

42. da Pozzo S, Manara R, Tonello S, Carollo C. Conventional and diffusion-weighted MRI in progressive multifocal leukoencephalopathy: new elements for identification and follow-up. *Radiol Med*. 2006;111(7):971-977. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17021685.

43. Shah R, Bag AK, Chapman PR, Cure JK. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. 2010;65(6):431-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20451009.

44. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997;11(1):1-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9110070.

45. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS*. 2008;22(14):1759-1767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753934.

46. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Ann Neurol*. 1999;45(6):816-821. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10360779.

47. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2005;40(5):738-744. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15714422.

48. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80(15):1430-1438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23568998.

49. Ferretti F, Bestetti A, Yiannoutsos CT, et al. Diagnostic and prognostic value of JC virus DNA in plasma in progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2018;67(1):65-72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29346632.

50. Silver SA, Arthur RR, Erozan YS, Sherman ME, McArthur JC, Uematsu S. Diagnosis of progressive multifocal leukoencephalopathy by stereotactic brain biopsy utilizing immunohistochemistry and the polymerase chain reaction. *Acta Cytol*. 1995;39(1):35-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7847007.

51. Jochum W, Weber T, Frye S, Hunsmann G, Luke W, Aguzzi A. Detection of JC virus by anti-VP1 immunohistochemistry in brains with progressive multifocal leukoencephalopathy. *Acta Neuropathol*. 1997;94(3):226-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9292691.

52. Viscidi RP, Khanna N, Tan CS, et al. JC virus antibody and viremia as predictors of progressive multifocal leukoencephalopathy in human immunodeficiency virus-1-infected individuals. *Clin Infect Dis*. 2011;53(7):711-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21852452.

53. Knowles WA, Luxton RW, Hand JF, Gardner SD, Brown DW. The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leucoencephalopathy. *Clin Diagn Virol*. 1995;4(2):183-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15566839.

54. Tan CS, Ghofrani J, Geiger E, Koralnik IJ, Jost S. Brief report: decreased JC virus-specific antibody-dependent cellular cytotoxicity in HIV-seropositive PML survivors. *J Acquir Immune Defic Syndr*. 2019;82(2):220-224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31513076.

55. Perez-Liz G, Del Valle L, Gentilella A, Croul S, Khalili K. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol*. 2008;64(4):379-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18688812.

56. Tan CS, Ellis LC, Wuthrich C, et al. JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. *J Virol*. 2010;84(18):9200-9209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20610709.

57. Dunham SR, Schmidt R, Clifford DB. Treatment of progressive multifocal leukoencephalopathy using immune restoration. *Neurotherapeutics*. 2020;17(3):955-965. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32166631.

58. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. *J Infect Dis*. 1999;180(3):621-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10438348.

59. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on

potent combined antiretroviral therapy. *J Neurovirol*. 1999;5(4):421-429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10463864.

60. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *AIDS*. 1999;13(14):1881-1887. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10513646.

61. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. *J Neurovirol*. 2001;7(4):358-363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11517417.

62. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS*. 2002;16(13):1791-1797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12218391.

63. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis*. 2003;36(8):1047-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12684918.

64. Lima MA, Bernal-Cano F, Clifford DB, Gandhi RT, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. 2010;81(11):1288-1291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20710013.

65. Pazzi AL, Galli M, et al. The relationship between outcome of progressive multifocal leukoencephalopathy and type and response to ART in previously HAART-untreated patients. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; 2007. Los Angeles, CA.

66. Dong-Si T, Gheuens S, Gangadharan A, et al. Predictors of survival and functional outcomes in natalizumab-associated progressive multifocal leukoencephalopathy. *J Neurovirol*. 2015;21(6):637-644. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25771865.

67. Gasnault J, Costagliola D, Hendel-Chavez H, et al. Improved survival of HIV-1-infected patients with progressive multifocal leukoencephalopathy receiving early 5-drug combination antiretroviral therapy. *PLoS One*. 2011;6(6):e20967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21738597.

68. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65(1):65-70. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18195140.

69. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: association with antiretroviral CNS Penetration-Effectiveness score. *Neurology*. 2011;76(7):644-651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21248274.

70. Garvey L, Winston A, Walsh J, et al. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. *Neurology*. 2011;76(8):693-700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21339496.

71. Fanjul F, Riveiro-Barciela M, Gonzalez J, et al. Evaluation of progressive multifocal leukoencephalopathy treatments in a Spanish cohort of HIV-infected patients: do protease inhibitors improve survival regardless of central nervous system penetration-effectiveness (CPE) score? *HIV Med*. 2013;14(5):321-325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23217049.

72. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med*. 1998;338(19):1345-1351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9571254.

73. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol*. 2001;7(4):375-381. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11517420.

74. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*. 2004;306(5700):1380-1383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15550673.

75. O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res*. 2008;132(1-2):97-103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18093678.

76. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone [correction of zisprasidone], risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. *Med Hypotheses*. 2005;65(3):585-586. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16004936.

77. Santagata S, Kinney HC. Mechanism of JCV entry into oligodendrocytes. *Science*. 2005;309(5733):381-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16020715.

78. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: a clinical, neuroradiological and virological response after treatment with risperidone. *Antiviral Res*. 2007;74(2):156-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17140673.

79. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry*. 2006;77(9):1079-1082. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16914758.

80. Lanzafame M, Ferrari S, Lattuada E, et al. Mirtazapine in an HIV-1 infected patient with progressive multifocal leukoencephalopathy. *Infez Med*. 2009;17(1):35-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19359824.

81. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*. 2009;66(2):255-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19204164.

82. Kerr DA, Chang CF, Gordon J, Bjornsti MA, Khalili K. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology*. 1993;196(2):612-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8396804.

83. Royal W, 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol*. 2003;9(3):411-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12775425.

84. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J Neurovirol*. 2013;19(4):351-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23733308.

85. Huang SS, Skolasky RL, Dal Pan GJ, Royal W, 3rd, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol*. 1998;4(3):324-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9639075.

86. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. 2001;7(4):353-357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11517416.

87. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with beta-interferon. *Neurology*. 2006;66(1):149-150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16401874.

88. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transplant*. 1997;20(11):983-987. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9422479.

89. Buckanovich RJ, Liu G, Stricker C, et al. Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. *Ann Hematol*. 2002;81(7):410-413. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12185517.

90. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. *Neurology*. 2005;65(9):1510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16275856.

91. Sospedra M, Schippling S, Yousef S, et al. Treating progressive multifocal leukoencephalopathy with interleukin 7 and vaccination with JC virus capsid protein VP1. *Clin Infect Dis*. 2014;59(11):1588-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25214510.

92. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M, Progressive Multifocal Leukeoncephalopathy Consortium. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord*. 2015;8(6):255-273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26600871.

93. Soleimani-Meigooni DN, Schwetye KE, Angeles MR, et al. JC virus granule cell neuronopathy in the setting of chronic lymphopenia treated with recombinant interleukin-7. *J Neurovirol*. 2017;23(1):141-146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27421731.

94. Miskin DP, Chalkias SG, Dang X, Bord E, Batson S, Koralnik IJ. Interleukin-7 treatment of PML in a patient with idiopathic lymphocytopenia. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(2):e213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27144212.

95. Ray U, Cinque P, Gerevini S, et al. JC polyomavirus mutants escape antibody-mediated neutralization. *Sci Transl Med*. 2015;7(306):306ra151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26400912.

96. Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2019;380(17):1597-1605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30969503.

97. Clifford DB. Checkpoint therapy for progressive multifocal leukoencephalopathy: pointless? *Eur J Neurol*. 2020;27(11):2114-2116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32644212.

98. Berzero G, Basso S, Stoppini L, et al. Adoptive transfer of JC virus-specific T lymphocytes for the treatment of progressive multifocal leukoencephalopathy. *Ann Neurol*. 2021;89(4):769-779. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33459417.

99. Muftuoglu M, Olson A, Marin D, et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2018;379(15):1443-1451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30304652.

100. Cortese I, Beck ES, Al-Louzi O, et al. BK virus-specific T cells for immunotherapy of progressive multifocal leukoencephalopathy: an open-label, single-cohort pilot study. *Lancet Neurol*. 2021;20(8):639-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34302788.

101. Vendrely A, Bienvenu B, Gasnault J, Thiebault JB, Salmon D, Gray F. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol*. 2005;109(4):449-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15739098.

102. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology*. 2009;72(17):1458-1464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19129505.

103. Sainz-de-la-Maza S, Casado JL, Perez-Elias MJ, et al. Incidence and prognosis of immune reconstitution inflammatory syndrome in HIV-associated progressive multifocal leucoencephalopathy. *Eur J Neurol*. 2016;23(5):919-925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26914970.

104. Clifford DB. Neurological immune reconstitution inflammatory response: riding the tide of immune recovery. *Curr Opin Neurol*. 2015;28(3):295-301. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25887769.

105. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. *AIDS*. 2001;15(14):1900-1902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11579261.

106. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive

multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. 2002;35(10):1250-1257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12410486.

107. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry*. 2003;74(8):1142-1144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12876257.

108. Di Giambenedetto S, Vago G, Pompucci A, et al. Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: a new clinical entity? *Neurology*. 2004;63(12):2452-2453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15623736.

109. Fournier A, Martin-Blondel G, Lechapt-Zalcman E, et al. Immune reconstitution inflammatory syndrome unmasking or worsening AIDS-related progressive multifocal leukoencephalopathy: a literature review. *Front Immunol*. 2017;8:577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28588577.

110. Martin-Blondel G, Cuzin L, Delobel P, et al. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? *AIDS*. 2009;23(18):2545-2546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19907215.

111. Januel E, Martin-Blondel G, Lamirel C, et al. Do CCR5 antagonists improve the overall survival of patients with AIDS-related progressive multifocal leucoencephalopathy? *J Neurol Neurosurg Psychiatry*. 2018;89(10):1125-1126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29305436.

112. Bernard-Valnet R, Moisset X, Maubeuge N, et al. CCR5 blockade in inflammatory PML and PML-IRIS associated with chronic inflammatory diseases' treatments. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728496.

113. Hentzien M, Guihot A, de Maindreville D, et al. Progressive multifocal leukoencephalopathy despite immune recovery in a HIV/HCV co-infected patient. *J Neurovirol*. 2020;26(4):607-610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32458280.

114. Crossley KM, Agnihotri S, Chaganti J, et al. Recurrence of progressive multifocal leukoencephalopathy despite immune recovery in two HIV seropositive individuals. *J Neurovirol*. 2016;22(4):541-545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26727910.

Syphilis

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Epidemiology

Syphilis, caused by *Treponema pallidum*, is associated with an increased risk of sexual acquisition and transmission of HIV.[1-8] In the United States, the national rate of primary and secondary syphilis has increased since 2001.[9-12] Although HIV infection, particularly in the advanced stages, may modify the diagnosis, natural history, or management of *T. pallidum* infection, the principles of syphilis management remain the same for people with and without HIV.[13-18]

Clinical Manifestations

The effects of HIV on the protean manifestations of syphilis have been documented in multiple case reports and small case series, and in a limited number of large studies. In most people with HIV and syphilis, the clinical manifestations of syphilis are similar to those observed in people without HIV. Some studies suggest that infection with HIV may affect the clinical presentation of syphilis, as atypical or multiple genital lesions are more apparent, and accelerated progression of syphilis may be seen in people with advanced immunosuppression.[16,17,19-22] Primary or secondary syphilis also may cause a transient decrease in CD4 T lymphocyte (CD4) cell count and an increase in HIV viral load that improves with recommended syphilis treatment regimens.[13,23-27] Independent of HIV, previous syphilis can attenuate the clinical and laboratory manifestations of incident infection with *T. pallidum*.[28-30]

Primary syphilis commonly presents as a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, multiple or atypical painful chancres may occur, and primary lesions may be absent or missed in people with HIV.[16,21,31] Progression to secondary syphilis typically follows 2 to 8 weeks after primary syphilis, but an overlap in primary and secondary manifestations can occur, especially in people with HIV. The most common manifestations of secondary syphilis are mucocutaneous lesions that are macular, maculopapular, papulosquamous, or pustular. These lesions can involve the palms and soles and are often accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache.[13,17,18] Mpox (formerly known as monkeypox) lesions can have a similar appearance and can occur simultaneously with early syphilis.[32] Condylomata lata (moist, flat papular lesions in warm intertriginous regions) can occur and may resemble condylomata acuminata caused by human papillomavirus. Lues maligna is a rare manifestation of secondary syphilis, characterized by papulopustular skin lesions that can evolve into ulcerative lesions with sharp borders and a dark central crust.[33-35] Manifestations of secondary syphilis involving other locations can occur (e.g., ocular and otic syphilis, meningoencephalitis, hepatitis, nephrotic syndrome, gastritis, pneumonia). In people with secondary syphilis, non-focal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities, such as lymphocytic pleocytosis with a mildly elevated CSF protein, can occur.[19,22,31,36-40] Signs and symptoms of primary and secondary syphilis can overlap or persist from a few days to several weeks before resolving. In some instances, recrudescence of symptoms may occur after secondary infection with subsequent evolution to latent stages.

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Latent syphilis can be categorized as early latent syphilis if ≤1 year duration, late latent syphilis if

>1 year duration, or latent syphilis of unknown duration if there is insufficient information to determine the duration of infection. Tertiary syphilis refers to gumma, cardiovascular syphilis, psychiatric manifestations (e.g., memory loss, personality changes), or late neurosyphilis that can develop 10 to 30 years after untreated infection.

Neurosyphilis, similar to ocular and otic syphilis, can occur at any stage of syphilis with different clinical presentations, including cranial nerve dysfunction, meningitis, stroke, acute or chronic change in mental status, and loss of vibration sense. Manifestations of neurosyphilis in people with HIV are similar to those in individuals who do not have HIV. However, clinical manifestations of neurosyphilis, such as concomitant ocular syphilis (including uveitis) or meningitis, may be more common in people with HIV.[19,22,40-46]

Syphilitic uveitis or other ocular syphilis manifestations (e.g., neuroretinitis and optic neuritis) can occur during any stage of syphilis and can manifest as isolated abnormalities or can be associated with neurosyphilis. Syphilis can involve almost any ocular structure, but posterior uveitis and panuveitis are the most common presentations. Other common manifestations can include interstitial keratitis, recurrent anterior uveitis, retinal vasculitis, and optic neuropathy.[47]

All people with ocular symptoms and reactive syphilis serology need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among people with isolated ocular symptoms (no cranial nerve dysfunction or other neurologic abnormalities), reactive syphilis serology, and confirmed ocular abnormalities on examination, CSF examination is unnecessary before treatment. CSF analysis might be helpful in evaluating people with ocular symptoms and reactive syphilis serology who do not have ocular findings on examination. If ocular syphilis is suspected, immediate referral to and management in collaboration with an ophthalmologist is crucial. Ocular syphilis should be treated similarly to neurosyphilis, even if a CSF examination is normal.

Isolated hearing loss or other otologic symptoms can occur at any stage of syphilis or can be associated with neurosyphilis. Among people with isolated auditory abnormalities and reactive syphilis serology, CSF evaluation is likely to be normal and is not necessary before treatment.[48]

Diagnosis

Direct Detection

Darkfield microscopy and molecular tests to detect *T. pallidum* in lesion exudates or tissue (e.g., biopsy with silver stain) are definitive for diagnosing early syphilis.[49] Although *T. pallidum* direct antigen detection tests are no longer commercially available, some laboratories provide locally developed and validated polymerase chain reaction (PCR) tests for the direct detection of *T. pallidum*.

Serologic Testing

Serologic diagnosis of syphilis traditionally has involved screening for nontreponemal antibodies with confirmation of reactive tests by treponemal-based assays.[13,50,51] A serologic diagnosis of syphilis is based on nontreponemal tests (i.e., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]), followed by confirmation with treponemal tests (i.e., *T. pallidum* particle agglutination [TP-PA], enzyme immunoassays [EIAs], chemiluminescence

immunoassays [CIAs], fluorescent treponemal antibody absorbed [FTA-ABS], or immunoblots). Rapid treponemal assays are also available to screen for syphilis; however, these tests can not differentiate recent or past infection, so testing with a nontreponemal test is indicated to inform further patient management.[50-52] Use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-negative results among people tested during primary syphilis and false-positive results among people without syphilis or previously treated syphilis.

Traditional Algorithm

False-positive nontreponemal test results can be associated with medical conditions and other factors unrelated to syphilis, including HIV, autoimmune disease, vaccinations, injection drug use, pregnancy, and older age.[50] Individuals with a reactive nontreponemal test should always receive a treponemal test to confirm the syphilis diagnosis. Nontreponemal test antibody titers can correlate with disease activity and are used for monitoring treatment response. Sequential serologic tests should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. VDRL and RPR are equally valid assays; however, quantitative results from the two tests cannot be compared directly with each other because the methods are different, and RPR titers frequently are slightly higher than VDRL titers.

Nontreponemal test titers usually decrease after treatment and can become nonreactive with time. However, in some instances nontreponemal antibodies might decrease less than fourfold after treatment (i.e., inadequate serologic response) or might decline appropriately but fail to serorevert and persist for a long period. Atypical nontreponemal serologic test results (e.g., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV status. When serologic tests do not correspond with clinical findings indicative of primary, secondary, or latent syphilis, presumptive treatment is recommended for people with risk factors for syphilis, and use of other tests (e.g., biopsy for histology and immunostaining and PCR of lesion) should be considered. For most people with HIV, serologic tests are accurate and reliable for diagnosing syphilis and evaluating response to treatment.[28]

Reverse-Sequence Algorithm

Most people who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of adequate treatment or disease activity and do not predict treatment response.

Some laboratories have initiated a reverse-sequence screening algorithm using treponemal EIA or CIA as a screening test, followed by a reflex-quantitative nontreponemal test if the EIA or CIA is positive.

This reverse-sequence algorithm can identify people previously treated for syphilis, those with untreated or incompletely treated syphilis, and those with false-positive results that can occur with a low likelihood of infection.[13,53] People with a positive treponemal screening test should have a standard quantitative nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions.

In the reverse-sequence screening strategy, having a positive treponemal EIA or CIA and a negative reflex-quantitative nontreponemal test requires a second treponemal test (based on different antigens from the initial test) to confirm the results of the positive initial treponemal test. If a second

treponemal test is positive, people who have been treated appropriately for their stage of syphilis will require no further treatment unless sexual risk history suggests likelihood of re-exposure or there is a sustained fourfold increase in nontreponemal antibody titers. In this instance, a repeat nontreponemal test 2 to 4 weeks after the most recent possible exposure is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection (e.g., early-stage syphilis), previously untreated people should be treated for late latent syphilis. If the second treponemal test is negative and the risk of syphilis is low, no treatment is indicated.[13,54] However, if the risk of syphilis is high, treatment should be considered. Multiple studies demonstrate that high quantitative index values or high signal-to-cutoff ratio from treponemal EIA or CIA tests correlate with TP-PA positivity, which might eliminate the need for additional confirmatory testing; however, the range of index values varies among different treponemal immunoassays, and the values that correspond to high levels of reactivity with confirmatory testing might differ by immunoassay.[51,55,56]

In the absence of neurologic signs or symptoms, risk of neurosyphilis is low in people with a reactive treponemal test and a nonreactive nontreponemal test[55,57]; examination of CSF is not recommended.

Early-stage disease (i.e., primary, secondary, and early latent syphilis) is identified using the same diagnostic tests used in people without HIV: standard serologic tests and darkfield microscopy of mucocutaneous lesions, if available. VDRL and RPR titers may be higher, lower (in rare instances), or delayed in people with HIV with early-stage syphilis.[58-62] No data indicate that treponemal tests perform differently among people with HIV[51]; although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.[61,62] When serologic tests do not correspond with clinical findings indicative of primary or secondary syphilis, presumptive treatment is recommended for people with risk factors for syphilis, and dilution of the sample for prozone phenomenon should be considered. For most people with HIV, serologic tests are accurate and reliable for diagnosing syphilis and for determining response to treatment.

By definition, people with latent syphilis have serological evidence of syphilis (nontreponemal and treponemal testing) in the absence of clinical manifestations. Early latent syphilis may occur in the interval between the primary and secondary stage of infection or following resolution of secondary manifestations and is defined by evidence of infection during the preceding year by—

- A documented seroconversion or fourfold or greater increase in nontreponemal titer; *or*
- Symptoms of primary or secondary syphilis; *or*
- A sex partner with documented primary, secondary, or early latent syphilis.[13]

Late latent syphilis is defined as syphilis in a person who does not have evidence of acquiring infection in the preceding year.

All people with syphilis and signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, altered mental status) warrant evaluation for neurosyphilis.

CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early-stage syphilis[36] and in people with HIV, even those with no neurologic symptoms. The clinical and prognostic significance of CSF laboratory abnormalities with early-stage syphilis in people without neurologic symptoms is unknown. Several studies have demonstrated that in people with syphilis and HIV, CSF laboratory abnormalities are associated with CD4 counts ≤350 cells/mm^3 or in combination with RPR titers ≥1:32.[39,40,63,64] However, unless neurologic signs and symptoms are

present, a CSF examination has not been associated with improved clinical outcomes. Although laboratory testing is helpful in supporting the diagnosis of neurosyphilis, no single test can be used to diagnose neurosyphilis. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count, CSF protein, and CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. CSF examination may indicate mononuclear pleocytosis (6–200 cells/mm^3), mildly elevated protein concentration, or a reactive CSF-VDRL. Among people with HIV, the CSF leukocyte count can be elevated (>5 white blood cell count [WBC]/mm^3); using a higher cutoff (>20 WBC/mm^3) may improve the specificity of neurosyphilis diagnosis.[39] In people with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood) is considered diagnostic of neurosyphilis; however, it is thought to have a very low sensitivity and therefore may miss true disease. Therefore, in people with neurologic signs or symptoms, reactive serologic test results, lymphocytic pleocytosis, or elevated protein, neurosyphilis should be considered even when the CSF-VDRL is negative. In that instance, additional evaluation by using FTA-ABS or TP-PA testing on CSF might be warranted.[13] The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Fewer data are available regarding CSF TP-PA; however, the sensitivity and specificity appears similar to the CSF FTA-ABS.[65,66] Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among people with nonspecific neurologic signs and symptoms.

RPR tests of the CSF have been associated with a high false-negative rate and are not recommended.[67] PCR-based diagnostic methods are not currently recommended as diagnostic tests for neurosyphilis.

Preventing Disease

Recommendations for Preventing Syphilis

Management of Sexual Partners After Exposure to *Treponema pallidum* (Syphilis) to Prevent Disease
Indication for Treatment • Individuals exposed sexually within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner regardless of syphilis serologic status (AII) • Individuals exposed >90 days before syphilis diagnosis in a sex partner, if syphilis serologic test results are not available immediately and the opportunity for follow-up is uncertain (AIII) Treatment • See therapy for early-stage syphilis in the Recommendations for Treating Syphilis table.

Note: Additional logistical information is available from the Centers for Disease Control and Prevention at https://www.cdc.gov/std/treatment/drug-notices.htm.

The resurgence of syphilis and other sexually transmitted infections (STIs), as well as the emergence of mpox, in men who have sex with men (MSM) with HIV underscores the importance of primary prevention of syphilis in this population, which should begin with a behavioral risk assessment and routine discussion of sexual behaviors. Health care providers should discuss patient-centered risk reduction messages and advise specific actions that can reduce the risk of acquiring STIs and of transmitting HIV.[13,68-72] Routine serologic screening for syphilis is recommended at least annually for all people with HIV who are sexually active, with more frequent screening (every 3–6 months) for those who have multiple or anonymous partners.[13,73-75] The occurrence of syphilis or any other STI in a person with HIV is an indication of risk behaviors that should prompt intensified risk assessment

and counseling messages about the manifestations of syphilis, risk of HIV transmission, and prevention strategies with strong consideration for behavioral intervention.[76,77] People undergoing screening or treatment for syphilis also should be evaluated for other STIs, including mpox, chlamydia, and gonorrhea at anatomic sites of exposure in men and chlamydia, gonorrhea, and trichomonas infections in women.[13,78]

Frequent serologic screening can identify people with recent infection and, in some instances, before infectious lesions develop. Treatment can prevent disease progression in the individual and transmission to their partners. Studies in the pre-HIV era demonstrated that approximately one-third of the sexual partners of people who have primary syphilis will develop syphilis within 30 days of exposure; empiric treatment of sexual partners exposed to syphilis will prevent the development of disease and onward syphilis transmission.[79-82] Individuals with recent sexual contact with a person with syphilis in any stage should be evaluated clinically and serologically and treated presumptively. People who have had sexual contact with an individual diagnosed with primary, secondary, or early latent syphilis during the 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AII).**

People who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain **(AIII).** If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and the stage of syphilis. Long-term sexual partners of people who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings. Sexual partners of people with syphilis should be notified of their exposure and the importance of evaluation for testing and empiric therapy.[13] The following sex partners of people with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within (1) 3 months plus the duration of symptoms for people who receive a diagnosis of primary syphilis, (2) 6 months plus the duration of symptoms for those diagnosed with secondary syphilis, and (3) 1 year for people diagnosed with early latent syphilis.

Pre-Exposure Prophylaxis and Post-Exposure Prophylaxis for Prevention

Doxycycline pre-exposure prophylaxis (PrEP) has been examined for prevention of bacterial STIs. In a pilot study, 30 MSM with HIV with previous syphilis were randomly assigned to doxycycline 100 mg daily for 48 weeks versus a financial incentive–based behavioral intervention; doxycycline was associated with a lower incidence of syphilis, but this did not reach statistical significance due to small sample size.[83]

Post-exposure prophylaxis (doxycycline 200 mg after unprotected anal sex) has been studied among MSM and transgender women, with a reduction in incident syphilis by 73%.[84] Several recent randomized open-label clinical trials have found that doxycycline 200 mg after condomless sex among MSM or transgender women with HIV or on HIV PrEP significantly reduced chlamydia, gonorrhea, and syphilis acquisition; a randomized trial of cisgender women on HIV PrEP administered doxycycline 200 mg within 72 hours after sex did not reduce chlamydia, gonorrhea, or syphilis acquisition.[85] There is ongoing evaluation regarding the potential impact of STI postexposure prophylaxis on antimicrobial resistance and the microbiome. Other studies are underway or in development regarding doxycycline prophylaxis for bacterial STIs.[86,87]

Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.[88] Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in people with HIV and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum.*[89-93]

Treatment

Recommendations for Treating Syphilis

General Considerations for Treating Syphilis
• Selection of the appropriate penicillin preparation is important because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by certain forms of penicillin. • Combinations of oral benzathine penicillin and procaine penicillin or short-acting benzathine-procaine penicillin (Bicillin C-R) preparations are not appropriate for syphilis treatment. • The efficacy of non-penicillin alternatives has not been well evaluated in people with HIV and should be undertaken only with close clinical and serologic monitoring. • The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache, fever, and myalgias that can occur within the first 24 hours after therapy. It occurs more frequently in people with early syphilis and can induce early labor or cause fetal distress during pregnancy. Patients should be informed about this potential reaction to treatment and that it is not an allergic reaction to penicillin.
Treating *Treponema pallidum* Infections (Syphilis) Depending on Stage of Disease
Primary, Secondary, and Early Latent Syphilis [≤1 year] *Recommended Therapy* • Benzathine penicillin G 2.4 million units IM in a single dose (AII)[a] *Alternative Therapy (For Penicillin-Allergic Patients; See Note Below)* • Doxycycline 100 mg PO twice daily for 14 days (BII),[b] *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days (BII)[b] Note: People with penicillin allergy whose compliance or follow-up cannot be ensured and who have syphilis during pregnancy should undergo penicillin desensitization and treatment with benzathine penicillin. For management of early syphilis during pregnancy, limited evidence indicates a second dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention (BII). **Late Latent (>1 year) or Latent of Unknown Duration** *Recommended Therapy* • Benzathine penicillin G 2.4 million units IM weekly for three doses (AII)[a] *Alternative Therapy (For Penicillin-Allergic Patients)* • Doxycycline 100 mg PO twice daily for 28 days (BIII) Note: People with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (AII).

Tertiary—Cardiovascular or Gummatous Disease

- Perform CSF examination and obtain infectious diseases consultation to guide management.
- People with CSF abnormalities should be treated with a regimen for neurosyphilis (AII).

Recommended Therapy

- Benzathine penicillin G 2.4 million units IM weekly for three doses for people without neurosyphilis (AII)[a]

Neurosyphilis, Otic, or Ocular Syphilis

Recommended Therapy

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or by continuous IV infusion for 10–14 days (AII), *with or without*
- Benzathine penicillin G 2.4 million units IM x 1 after completion of aqueous crystalline penicillin G infusion (CIII)[a]

Alternative Therapy

- Procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII). Procaine penicillin has been discontinued by the manufacturer as of June 13, 2023 (see FDA Drug Shortages).

Note: People who are allergic to sulfa-containing medications should not be given probenecid; thus, the procaine penicillin regimen is not recommended (AIII).

For Penicillin-Allergic Patients with Neurosyphilis, Otic, or Ocular Syphilis

Recommended Therapy

- Desensitization to penicillin

Alternative Therapy (If Desensitization Is Not Feasible and Not Pregnant)

- Ceftriaxone 2 g IV daily for 10–14 days (BII)

Note: People who have a history of IgE-mediated penicillin hypersensitivity may lose their sensitivity after 10 years, and a subsequent negative skin test evaluation followed by oral challenge can be considered. Among people for whom the only option is penicillin (e.g., syphilis in pregnancy) and among those with a positive skin test, desensitization to penicillin is the preferred approach.

[a] Benzathine penicillin is currently on the FDA drug shortage webpage due to limited supply. Updates on the expected duration for the shortage are available on the FDA Drug Shortage webpage.

[b] Skin testing for penicillin allergy can be useful in circumstances in which the reagents and expertise are available.

Note: Additional logistical information is available from the Centers for Disease Control and Prevention at https://www.cdc.gov/std/treatment/drug-notices.htm.

Key: CNS = central nervous system; CSF = cerebrospinal fluid; FDA = U.S. Food and Drug Administration; IgE = immunoglobulin E; IM = intramuscular; IV = intravenously; PO = orally

Treatment regimens for syphilis demonstrate that most people with HIV respond appropriately to single dose benzathine penicillin G after exposure to syphilis and for primary, secondary, and early latent syphilis (within the previous 12 months).[13,59,94,95] However, in people with HIV, more frequent clinical and serologic evaluation is recommended—at least every 3 months rather than every 6 months—because serologic nonresponse and neurologic complications may be more frequent.[19,96,97] Use of antiretroviral therapy (ART) in people with syphilis has also been associated with a reduced risk of serologic failure of syphilis treatment[22] and a lower risk of developing neurosyphilis.[22]

Benzathine penicillin G remains the treatment of choice for syphilis. People with HIV with early-stage (primary, secondary, or early latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million units of benzathine penicillin G **(AII).**[13] High-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.[59] People with a penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G **(AIII).**

The efficacy of alternative non-penicillin regimens in people with HIV and early syphilis has not been well studied. The use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring. The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) supports the use of doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis **(BII).**[98,99] Based on limited clinical studies in people with and without HIV, ceftriaxone (1 g daily either IM or intravenously [IV] for 10–14 days) is also recommended for treating early-stage syphilis **(BII),** but the optimal dose and duration of therapy have not been defined.[100-102] There are limited data suggesting a single 2-g oral dose of oral azithromycin can be effective for treating early syphilis[103-105]; however, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been reported most commonly in MSM.[89-93,106] Azithromycin has not been well studied in people with HIV or during pregnancy. Therefore, azithromycin should not be used as treatment for syphilis **(AII).**

In people with HIV who have late latent syphilis, treatment with three weekly IM injections of 2.4 million units of benzathine penicillin G is recommended **(AII).** Alternative therapy is doxycycline, 100 mg orally twice daily for 28 days; however, it has not been sufficiently evaluated in people with HIV **(BIII).** Limited clinical studies and biologic and pharmacologic evidence suggest that ceftriaxone may be effective, but the optimal dose and duration of therapy have not been determined.[107,108] If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

People with HIV who have clinical evidence of tertiary syphilis (cardiovascular or gummatous disease) should have CSF examination to rule out CSF abnormalities before therapy is initiated. If the CSF evaluation is normal, the recommended treatment of late-stage syphilis is three weekly IM injections of 2.4 million units of benzathine penicillin G **(AII).**[13] However, due to the complexity of tertiary syphilis management, especially cardiovascular syphilis, health care providers are advised to consult an infectious disease specialist.

People with HIV diagnosed with neurosyphilis or ocular or otic syphilis should receive IV aqueous crystalline penicillin G, 18 to 24 million units daily, administered 3 to 4 million units IV every 4 hours or by continuous infusion for 10 to 14 days **(AII),** or procaine penicillin, 2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10 to 14 days **(BII).**[13] However, procaine penicillin has been recently discontinued by the manufacturer.[109]

People with HIV who are allergic to sulfa-containing medications should not be given probenecid because of potential allergic reaction; therefore, IV penicillin is recommended **(AIII).** Although systemic steroids are used frequently as adjunctive therapy for otic syphilis, such therapy has not been proven beneficial.

Because neurosyphilis treatment regimens are of shorter duration than those used in late latent syphilis, 2.4 million units of benzathine penicillin IM once after completion of IV penicillin G can be considered to provide a comparable duration of therapy **(CIII).**[13]

People who have a history of immunoglobulin E mediated penicillin hypersensitivity may lose their sensitivity after 10 years,[110,111] and a subsequent negative skin test evaluation followed by oral challenge can be considered. Among people for whom the only option is penicillin (e.g., syphilis in pregnancy) and among those with a positive skin test, desensitization to penicillin is the preferred approach. However, based on limited data, ceftriaxone (2 g daily IV for 10–14 days) is recommended as an acceptable alternative regimen **(BII).**[100,101,108] Other alternative regimens for neurosyphilis have not been evaluated adequately. Syphilis treatment recommendations are available in the 2021 Centers for Disease Control and Prevention STI Treatment Guidelines.[13]

Special Considerations with Regard to Starting Antiretroviral Therapy

There are no special considerations regarding the initiation of ART in patients with syphilis. Specifically, there is no evidence that treatment with ART needs to be delayed until treatment for syphilis has been completed. Immune reconstitution inflammatory syndrome in association with syphilis following treatment with ART in people with HIV is uncommon.[112,113]

Monitoring and Adverse Events

Clinical and serologic responses (fourfold decrease from the nontreponemal titer at the time of treatment) to treatment of early-stage (primary, secondary, and early latent) disease should be performed at 3, 6, 9, 12, and 24 months after therapy to ensure resolution of signs and symptoms within 3 to 6 months and seroreversion or a fourfold decline in nontreponemal titers within 24 months. Clinical and serologic responses to treatment are similar in people with HIV; subtle variations can occur, however, including a slower temporal pattern of serologic response in people with HIV.[13,59,79,94,95] Factors associated with the serologic response to treatment in people without HIV include younger age, earlier syphilis stage, and higher RPR titer.[114-116] If clinical signs and symptoms persist, treatment failure should be considered. If clinical signs or symptoms recur or there is a sustained fourfold increase in nontreponemal titers of greater than 2 weeks, treatment failure or reinfection should be considered and managed per recommendations (see Managing Possible Treatment Failure or Reinfection). The potential for reinfection should be based on the sexual history and risk assessment. Clinical trial data have demonstrated that 15% to 20% of people (including people with HIV) treated with recommended therapy for early-stage syphilis will not achieve the fourfold decline in nontreponemal titer used to define treatment response at 1 year.[13,59] Serum nontreponemal test titers may remain reactive, usually ≤1:8, although can be higher, for prolonged periods. In addition, people treated for early-stage syphilis who have a fourfold decline in titer may not serorevert to a negative nontreponemal test, which does not represent treatment failure but an inadequate serologic response.[117]

Response to therapy for late latent syphilis should be monitored using nontreponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a fourfold decline in titer, if initially high (≥1:32), within 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Many people with low titers and late latent syphilis do not have a fourfold decline in the initial titer. If clinical symptoms develop or a fourfold increase in nontreponemal titers is sustained over 2 weeks, then treatment failure or reinfection should be considered and managed per recommendations (see Managing Possible Treatment Failure or Reinfection). The potential for reinfection should be based on sexual history and risk assessment.[13]

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF-VDRL may respond more slowly. Limited data suggest that changes in CSF parameters

may occur more slowly in people with HIV, especially with advanced immunosuppression.[22,39] Among people with HIV who are on effective ART and people without HIV, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.[118,119] Therefore, repeated CSF examinations are unnecessary for people without HIV or among people with HIV who are on ART and who exhibit serologic and clinical responses to treatment.[13]

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, rigors, transient worsening of rash, myalgia, and sometimes even a sepsis-like syndrome, that can occur within the first 24 hours after initiation of treatment for syphilis. Antipyretics can be used to manage symptoms but have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction occurs most frequently in people with early syphilis, high nontreponemal antibody titers, and prior penicillin treatment.[120] People with syphilis should be warned about this reaction, instructed how to manage it, and informed that it is not an allergic reaction to penicillin.

Managing Possible Treatment Failure or Reinfection

Retreatment should be considered for people with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease, or a sustained fourfold increase in serum nontreponemal titers after an initial fourfold decrease following treatment. The assessment for potential reinfection should be informed by a sexual history and syphilis risk assessment including information about a recent sexual partner with signs or symptoms or recent treatment for syphilis. People who have had syphilis are at increased risk for reinfection. One study showed that 6% of MSM had a repeat early-stage syphilis infection within 2 years of initial infection; HIV infection and multiple sexual partners were associated with increased risk of reinfection.[11] Serologic response should be compared to the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, as definitive criteria for cure or failure have not been well established. People with HIV may be at increased risk of treatment failure, but the magnitude of these risks is not precisely defined and is likely low.[13,38,97]

People who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur, or a fourfold increase or greater in titer sustained for more than 2 weeks) and who are at low risk for reinfection should be managed for possible treatment failure. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with findings guiding management. People with nontreponemal titers that do not decrease fourfold within 12 to 24 months of therapy should also be managed as a possible treatment failure. Management should include neurologic examination and retreatment with benzathine penicillin G, 2.4 million units at 1-week intervals for 3 weeks **(BIII).** If titers do not respond appropriately after retreatment, the value of repeated CSF examination or additional therapy is unclear, but it is generally not recommended. The Panel supports benzathine penicillin treatment (2.4 million units IM) without a CSF examination (unless signs or symptoms of neurosyphilis are present) and close clinical follow-up in people with recurrent signs and symptoms of primary or secondary syphilis or a fourfold increase in nontreponemal titers within the past year who are at high risk of syphilis reinfection **(CIII).**

People treated for late latent syphilis should have a CSF examination and be re-treated if they develop clinical signs or symptoms of syphilis or have a sustained fourfold increase in serum nontreponemal test titer and are at low risk for reinfection; this can also be considered if they experience an inadequate serologic response (i.e., less than fourfold decline in an initially high [≥1:32] nontreponemal test titer) within 12 months for early syphilis and 24 months for late latent

syphilis. If CSF examination is consistent with CNS involvement, retreatment should follow the recommendations for treatment of neurosyphilis. People with a normal CSF examination or without ocular or otic symptoms should be treated with benzathine penicillin 2.4 million units IM weekly for three doses **(BIII).** The Panel supports benzathine penicillin treatment (2.4 million units IM) without a CSF examination (unless signs or symptoms of neurosyphilis are present) and close clinical follow-up in people with signs or symptoms of primary or secondary syphilis or a fourfold increase in nontreponemal titers within the past year who are at high risk of reinfection **(CIII)**.

Among people with HIV who are on effective ART and people without HIV, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.[118,119] Therefore, repeated CSF examinations are unnecessary for people with HIV who are on ART and who exhibit serologic and clinical responses after treatment.

Special Considerations During Pregnancy

In recent years, there has been a resurgence in neonatal syphilis in the United States. Syphilis in pregnancy is associated with increased risk of several adverse outcomes, including pregnancy loss, preterm birth, stillbirth, impaired fetal growth, neonatal mortality, and congenital infection, which can cause abnormalities in multiple organ systems. The clinical manifestations of syphilis in pregnancy are similar in people with and without HIV.

Serologic screening for syphilis should be conducted at the first prenatal visit and at 28 weeks. In communities and populations in which the prevalence of syphilis is high and in people at increased risk of infection (i.e., sex with multiple partners or new partner, sex in conjunction with drug use or transactional sex, late entry or no prenatal care, methamphetamine or heroin use, hepatitis C, alcohol misuse,[121] incarceration, STI in pregnancy or partner with STI, unstable housing or homelessness),[122] serologic testing should also be performed at delivery.[13] Providers should consider offering screening for syphilis to sexual partners of pregnant women.

Screening for syphilis during pregnancy should be offered at sites providing episodic care, including emergency departments, jails, and prisons.[123] Antepartum screening with nontreponemal testing is typical, but treponemal screening is being used in some settings. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA or CIA tests should be confirmed with a quantitative nontreponemal test (RPR or VDRL), as titers are essential to monitoring treatment response. If the nontreponemal test is negative and the prozone reaction is ruled out (false-negative nontreponemal test that results from high antibody titer) then the results are discordant; a second treponemal test should be performed, preferably on the same specimen (see Diagnosis section above).[124] If the second treponemal test is negative (i.e., EIA positive, RPR negative, and TP-PA negative), the positive EIA or CIA is more likely to represent a false-positive test result for people who are living in communities with low rates of syphilis, have a partner who is uninfected, and have no history of treated syphilis.[55,124] During pregnancy, if the patient is likely to follow up with clinical care and there is a low risk for syphilis, there are no signs or symptoms of primary syphilis, and the partner has no clinical or serologic evidence of syphilis, then repeat serologic testing within 4 weeks can be considered to determine whether the EIA or CIA remains positive or whether the RPR, VDRL, or TP-PA result becomes positive. If both the RPR and TP-PA remain negative, no further treatment is necessary. If follow-up is not likely, treatment appropriate for the stage of syphilis is recommended for people with an isolated reactive treponemal test without a history of syphilis treatment.

No postpartum individual or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at least once during pregnancy.[13] All individuals who have a fetal death after 20 weeks of gestation also should be tested for syphilis.

Rates of transmission to the fetus and adverse pregnancy outcomes for untreated syphilis are highest with primary, secondary, and early latent syphilis and decrease with increasing duration of infection. Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results for syphilis infection in adults. Concurrent syphilis infection has been associated with increased risk of perinatal transmission of HIV to the infant.[125-131]

Syphilis infection during pregnancy should be considered in those with reactive syphilis serology unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is related to the quantitative maternal nontreponemal titer, especially if ≥1:8. However, risk for fetal infection is still substantial with late latent syphilis and low maternal titers. All neonates born to women with syphilis should be evaluated for congenital syphilis regardless of maternal treatment or response.

Sustained low nontreponemal titers after documented treatment for the appropriate stage of infection might not require additional treatment; however, rising or persistently high antibody titers may indicate reinfection or treatment failure, and retreatment should be considered.[13]

Benzathine penicillin G is recommended for the treatment of syphilis during pregnancy. Penicillin is the only known effective antimicrobial for preventing transmission to the fetus and for treatment of fetal infection; however, evidence is insufficient to determine the optimal penicillin regimen.[132] For management of early syphilis during pregnancy, limited evidence indicates that a second dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention.[13,129,133-135] If a second dose of benzathine penicillin is administered, it should be provided no later than 9 days after the first dose.[13] Sexual partners of pregnant women with syphilis should be referred for evaluation and treatment.

Since no alternatives to penicillin have been proven effective and safe for prevention of fetal infection, desensitization and treatment with penicillin should be performed in pregnancy for those who have a history of penicillin allergy **(AIII).**[13] Erythromycin and azithromycin should not be used because these regimens do not reliably cure infection in the pregnant woman or the fetus **(AII)**[132]; tetracyclines should be avoided in the second and third trimesters of pregnancy **(AII).**[129,136] Data are insufficient to recommend ceftriaxone[137,138] for treatment of antenatal infection and prevention of congenital syphilis **(BIII).**

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if a Jarisch-Herxheimer reaction occurs.[139,140] Obstetric attention is advised if contractions develop or a decrease in fetal movement is noted after treatment. During the second half of pregnancy, syphilis management can be facilitated with sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (e.g., hepatomegaly, ascites, fetal hydrops, thickened placenta) indicate a greater risk of fetal treatment failure.[141] Such cases should be managed in consultation with high-risk obstetric specialists. After 20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

Coordinated prenatal care and treatment are vital because providers should document that treatment is adequate for the syphilis stage and ensure that the clinical and antibody responses are appropriate for the patient's disease stage. Maternal serologic response during pregnancy after adequate therapy varies by stage of disease and timing of treatment.[142] If syphilis is diagnosed and treated at or before 24 weeks' gestation, serologic titers should not be repeated before 8 weeks after treatment but should be repeated again at delivery. Titers should be repeated sooner if reinfection or treatment failure is suspected. For syphilis diagnosed and treated after 24 weeks' gestation, serologic titers should be repeated at delivery.[13] A majority of women will not achieve a fourfold decrease in titers before delivery, although this does not indicate treatment failure. Inadequate antenatal treatment is likely if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal nontreponemal titer at delivery is fourfold higher than the pre-treatment titer. There is no evidence that pregnant women with syphilis and HIV are at increased risk for delayed syphilis treatment response compared with women without HIV.[143]

References

1. Dennis AM, Cressman A, Pasquale D, et al. Intersection of syphilis and HIV networks to identify opportunities to enhance HIV prevention. *Clin Infect Dis*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/33978757.

2. Wu MY, Gong HZ, Hu KR, Zheng HY, Wan X, Li J. Effect of syphilis infection on HIV acquisition: a systematic review and meta-analysis. *Sex Transm Infect*. 2021;97(7):525-533. Available at: https://pubmed.ncbi.nlm.nih.gov/33219164.

3. Hart-Malloy R, Rosenthal M, Patterson W, Currenti S, O'Donnell T, Gunn JK. Syphilis among adult males with a history of male-to-male sexual contact living with diagnosed HIV in New York State (excluding New York City): the challenge of intersecting epidemics. *PLoS One*. 2019;14(12):e0226614. Available at: https://pubmed.ncbi.nlm.nih.gov/31851719.

4. Pathela P, Braunstein SL, Schillinger JA, Shepard C, Sweeney M, Blank S. Men who have sex with men have a 140-fold higher risk for newly diagnosed HIV and syphilis compared with heterosexual men in New York City. *J Acquir Immune Defic Syndr*. 2011;58(4):408-416. Available at: https://pubmed.ncbi.nlm.nih.gov/21857351.

5. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75(1):3-17. Available at: https://pubmed.ncbi.nlm.nih.gov/10448335.

6. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis*. 2001;28(10):579-597. Available at: https://pubmed.ncbi.nlm.nih.gov/11689757.

7. Peterman TA, Newman DR, Maddox L, Schmitt K, Shiver S. High risk for HIV following syphilis diagnosis among men in Florida, 2000–2011. *Public Health Rep*. 2014;129(2):164-169. Available at: https://pubmed.ncbi.nlm.nih.gov/24587551.

8. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. 2014;59(7):1020-1026. Available at: https://pubmed.ncbi.nlm.nih.gov/24928295.

9. Centers for Disease Control and Prevention. Outbreak of syphilis among men who have sex with men—Southern California, 2000. *MMWR Morb Mortal Wkly Rep*. 2001;50(7):117-120. Available at: https://pubmed.ncbi.nlm.nih.gov/11393490.

10. Spicknall IH, Kreisel KM, Weinstock HS. Estimates of the prevalence and incidence of syphilis in the United States, 2018. *Sex Transm Dis*. 2021;48(4):247-252. Available at: https://pubmed.ncbi.nlm.nih.gov/33492091.

11. Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002–2006: implications for syphilis elimination efforts. *Am J Public Health*. 2012;102(1):e1-8. Available at: https://pubmed.ncbi.nlm.nih.gov/22095364.

12. Centers for Disease Control and Prevention. Syphilis surveillance supplemental slides, 2016–2020. 2022. Available at: https://www.cdc.gov/std/statistics/syphilis-supplement/default.htm.

13. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. *MMWR Recomm Rep*. 2021;70(4):1-187. Available at: https://pubmed.ncbi.nlm.nih.gov/34292926.

14. Rasoldier V, Gueudry J, Chapuzet C, et al. Early symptomatic neurosyphilis and ocular syphilis: a comparative study between HIV-positive and HIV-negative patients. *Infect Dis Now*. 2021;51(4):351-356. Available at: https://pubmed.ncbi.nlm.nih.gov/33239175.

15. Calza L, Manfredi R, Marinacci G, Tadolini M, Fortunato L, Chiodo F. Efficacy of penicillin G benzathine as antimicrobial treatment of cutaneous secondary syphilis in patients with HIV infection. *J Chemother*. 2002;14(5):533-534. Available at: https://pubmed.ncbi.nlm.nih.gov/12462435.

16. Rompalo AM, Lawlor J, Seaman P, Quinn TC, Zenilman JM, Hook EW, 3rd. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. *Sex Transm Dis*. 2001;28(8):448-454. Available at: https://pubmed.ncbi.nlm.nih.gov/11473216.

17. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med*. 1990;113(11):872-881. Available at: https://pubmed.ncbi.nlm.nih.gov/2240901.

18. Radolf JD, Kaplan RP. Unusual manifestations of secondary syphilis and abnormal humoral immune response to Treponema pallidum antigens in a homosexual man with asymptomatic human immunodeficiency virus infection. *J Am Acad Dermatol*. 1988;18(2 Pt 2):423-428. Available at: https://pubmed.ncbi.nlm.nih.gov/2963840.

19. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002–June 2004. *MMWR Morb Mortal Wkly Rep*. 2007;56(25):625-628. Available at: https://pubmed.ncbi.nlm.nih.gov/17597693.

20. Nieuwenburg SA, Sprenger RJ, Schim van der Loeff MF, de Vries HJC. Clinical outcomes of syphilis in HIV-negative and HIV-positive MSM: occurrence of repeat syphilis episodes and non-treponemal serology responses. *Sex Transm Infect*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/33608479.

21. Towns JM, Leslie DE, Denham I, Azzato F, Fairley CK, Chen M. Painful and multiple anogenital lesions are common in men with Treponema pallidum PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study. *Sex Transm Infect*. 2016;92(2):110-115. Available at: https://pubmed.ncbi.nlm.nih.gov/26378262.

22. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. 2008;22(10):1145-1151. Available at: https://pubmed.ncbi.nlm.nih.gov/18525260.

23. Muccini C, Crowell TA, Pinyakorn S, et al. Brief report: syphilis incidence and effect on viral load, CD4, and CD4/CD8 ratio in a Thai cohort of predominantly men who have sex with men living with HIV. *J Acquir Immune Defic Syndr*. 2021;86(2):219-223. Available at: https://pubmed.ncbi.nlm.nih.gov/33433124.

24. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. 2004;18(15):2075-2079. Available at: https://pubmed.ncbi.nlm.nih.gov/15577629.

25. Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infect Dis*. 2010;10(7):455-463. Available at: https://pubmed.ncbi.nlm.nih.gov/20610327.

26. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2007;44(3):356-359. Available at: https://pubmed.ncbi.nlm.nih.gov/17159654.

27. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. *Sex Transm Dis*. 2006;33(3):143-148. Available at: https://pubmed.ncbi.nlm.nih.gov/16505739.

28. Tuddenham S, Ghanem KG. Management of adult syphilis: key questions to inform the 2021 Centers for Disease Control and Prevention sexually transmitted infections treatment guidelines. *Clin Infect Dis*. 2022;74(Suppl_2):S127-S133. Available at: https://pubmed.ncbi.nlm.nih.gov/35416969.

29. Marra CM, Maxwell CL, Sahi SK, Tantalo LC, Dunaway SB, Lukehart SA. Previous syphilis alters the course of subsequent episodes of syphilis. *Clin Infect Dis*. 2020;71(5):1243-1247. Available at: https://pubmed.ncbi.nlm.nih.gov/31560366.

30. N'Gom PT, Jaffar S, Ricard D, et al. Immune stimulation by syphilis and malaria in HIV-2-infected and uninfected villagers in West Africa. *Br J Biomed Sci*. 1997;54(4):251-255. Available at: https://pubmed.ncbi.nlm.nih.gov/9624734.

31. Rompalo AM, Joesoef MR, O'Donnell JA, et al. Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. *Sex Transm Dis*. 2001;28(3):158-165. Available at: https://pubmed.ncbi.nlm.nih.gov/11289198.

32. Hussain A, Kaler J, Lau G, Maxwell T. Clinical conundrums: differentiating monkeypox from similarly presenting infections. *Cureus*. 2022;14(10):e29929. Available at: https://pubmed.ncbi.nlm.nih.gov/36348880.

33. Tambe S, Zambare U, Nayak C. Nodulo-ulcerative and erythrodermic secondary syphilis in human immunodeficiency virus-infected individuals. *Int J STD AIDS*. 2019;30(5):505-508. Available at: https://pubmed.ncbi.nlm.nih.gov/30630397.

34. Wang H, Wang X, Li S. A case of lues maligna in an AIDS patient. *Int J STD AIDS*. 2012;23(8):599-600. Available at: https://pubmed.ncbi.nlm.nih.gov/22930302.

35. Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. *Sex Transm Dis*. 2009;36(8):512-514. Available at: https://pubmed.ncbi.nlm.nih.gov/19455078.

36. Lukehart SA, Hook EW, 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. *Ann Intern Med*. 1988;109(11):855-862. Available at: https://pubmed.ncbi.nlm.nih.gov/3056164.

37. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis. Its occurrence after clinical and serologic cure of secondary syphilis with penicillin G. *Arch Neurol*. 1986;43(2):137-138. Available at: https://pubmed.ncbi.nlm.nih.gov/3947251.

38. Berry CD, Hooton TM, Collier AC, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Engl J Med*. 1987;316(25):1587-1589. Available at: https://pubmed.ncbi.nlm.nih.gov/3587291.

39. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. 2004;189(3):369-376. Available at: https://pubmed.ncbi.nlm.nih.gov/14745693.

40. Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? *Clin Infect Dis*. 2004;38(7):1001-1006. Available at: https://pubmed.ncbi.nlm.nih.gov/15034833.

41. Biotti D, Bidot S, Mahy S, et al. Ocular syphilis and HIV infection. *Sex Transm Dis*. 2010;37(1):41-43. Available at: https://pubmed.ncbi.nlm.nih.gov/20118676.

42. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. *Sex Transm Infect*. 2011;87(1):4-8. Available at: https://pubmed.ncbi.nlm.nih.gov/20798396.

43. Wagner LF, Lanzl I, Rothe K, et al. Clinical and ophthalmological characteristics of ocular syphilis in a retrospective tertiary hospital cohort. *Sex Transm Dis*. 2021;48(6):436-442. Available at: https://pubmed.ncbi.nlm.nih.gov/33156290.

44. Oliver SE, Aubin M, Atwell L, et al. Ocular syphilis – eight jurisdictions, United States, 2014–2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(43):1185-1188. Available at: https://pubmed.ncbi.nlm.nih.gov/27811837.

45. Cope AB, Mobley VL, Oliver SE, et al. Ocular syphilis and human immunodeficiency virus coinfection among syphilis patients in North Carolina, 2014–2016. *Sex Transm Dis*. 2019;46(2):80-85. Available at: https://pubmed.ncbi.nlm.nih.gov/30169474.

46. Woolston S, Cohen SE, Fanfair RN, Lewis SC, Marra CM, Golden MR. A cluster of ocular syphilis cases – Seattle, Washington, and San Francisco, California, 2014–2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(40):1150-1151. Available at: https://pubmed.ncbi.nlm.nih.gov/26469141.

47. Furtado JM, Simoes M, Vasconcelos-Santos D, et al. Ocular syphilis. *Surv Ophthalmol*. 2022;67(2):440-462. Available at: https://pubmed.ncbi.nlm.nih.gov/34147542.

48. Ramchandani MS, Litvack JR, Marra CM. Otosyphilis: a review of the literature. *Sex Transm Dis*. 2020;47(5):296-300. Available at: https://pubmed.ncbi.nlm.nih.gov/32149965.

49. Theel ES, Katz SS, Pillay A. Molecular and direct detection tests for treponema pallidum subspecies pallidum: a review of the literature, 1964–2017. *Clin Infect Dis*. 2020;71(Suppl 1):S4-S12. Available at: https://pubmed.ncbi.nlm.nih.gov/32578865.

50. Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. *Clin Infect Dis*. 2020;71(Suppl 1):S21-S42. Available at: https://pubmed.ncbi.nlm.nih.gov/32578862.

51. Park IU, Tran A, Pereira L, Fakile Y. Sensitivity and specificity of treponemal-specific tests for the diagnosis of syphilis. *Clin Infect Dis*. 2020;71(Suppl 1):S13-S20. Available at: https://pubmed.ncbi.nlm.nih.gov/32578866.

52. Bristow CC, Klausner JD, Tran A. Clinical test performance of a rapid point-of-care syphilis treponemal antibody test: a systematic review and meta-analysis. *Clin Infect Dis*. 2020;71(Suppl 1):S52-S57. Available at: https://pubmed.ncbi.nlm.nih.gov/32578863.

53. Ortiz DA, Shukla MR, Loeffelholz MJ. The traditional or reverse algorithm for diagnosis of syphilis: pros and cons. *Clin Infect Dis*. 2020;71(Suppl 1):S43-S51. Available at: https://pubmed.ncbi.nlm.nih.gov/32578864.

54. Centers for Disease Control and Prevention. Syphilis testing algorithms using treponemal tests for initial screening—four laboratories, New York City, 2005–2006. *MMWR Morb Mortal Wkly Rep*. 2008;57(32):872-875. Available at: https://pubmed.ncbi.nlm.nih.gov/18701877.

55. Park IU, Chow JM, Bolan G, Stanley M, Shieh J, Schapiro JM. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. *J Infect Dis*. 2011;204(9):1297-1304. Available at: https://pubmed.ncbi.nlm.nih.gov/21930610.

56. Wong EH, Klausner JD, Caguin-Grygiel G, et al. Evaluation of an IgM/IgG sensitive enzyme immunoassay and the utility of index values for the screening of syphilis infection in a high-risk population. *Sex Transm Dis*. 2011;38(6):528-532. Available at: https://pubmed.ncbi.nlm.nih.gov/21233789.

57. Wohrl S, Geusau A. Neurosyphilis is unlikely in patients with late latent syphilis and a negative blood VDRL-test. *Acta Derm Venereol*. 2006;86(4):335-339. Available at: https://pubmed.ncbi.nlm.nih.gov/16874420.

58. Rompalo AM, Cannon RO, Quinn TC, Hook EW, 3rd. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. *J Infect Dis*. 1992;165(6):1124-1126. Available at: https://pubmed.ncbi.nlm.nih.gov/1583332.

59. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med*. 1997;337(5):307-314. Available at: https://pubmed.ncbi.nlm.nih.gov/9235493.

60. Augenbraun MH, DeHovitz JA, Feldman J, Clarke L, Landesman S, Minkoff HM. Biological false-positive syphilis test results for women infected with human immunodeficiency virus. *Clin Infect Dis*. 1994;19(6):1040-1044. Available at: https://pubmed.ncbi.nlm.nih.gov/7888531.

61. Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. A diagnostic dilemma. *Ann Intern Med*. 1987;107(4):492-495. Available at: https://pubmed.ncbi.nlm.nih.gov/3307583.

62. Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. *Arch Dermatol*. 2005;141(4):431-433. Available at: https://pubmed.ncbi.nlm.nih.gov/15837859.

63. Libois A, De Wit S, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. *Sex Transm Dis*. 2007;34(3):141-144. Available at: https://pubmed.ncbi.nlm.nih.gov/16865051.

64. Ghanem KG. Sensitivity and specificity of lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms reply. *Clin Infect Dis*. 2009;49:162-163. Available at: https://pubmed.ncbi.nlm.nih.gov/19187028.

65. Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B, Schroeter AL. Tests for treponemal antibody in CSF. *Arch Intern Med*. 1978;138(2):252-255. Available at: https://pubmed.ncbi.nlm.nih.gov/343742.

66. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. *Sex Transm Dis*. 2012;39(4):291-297. Available at: https://pubmed.ncbi.nlm.nih.gov/22421696.

67. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. *Sex Transm Dis*. 2012;39(6):453-457. Available at: https://pubmed.ncbi.nlm.nih.gov/22592831.

68. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA*. 1998;280(13):1161-1167. Available at: https://pubmed.ncbi.nlm.nih.gov/9777816.

69. U.S. Preventive Services Task Force, Krist AH, Davidson KW, et al. Behavioral counseling interventions to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement. *JAMA*. 2020;324(7):674-681. Available at: https://pubmed.ncbi.nlm.nih.gov/32809008.

70. Metsch LR, Feaster DJ, Gooden L, et al. Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: the AWARE randomized clinical

trial. *JAMA*. 2013;310(16):1701-1710. Available at: https://pubmed.ncbi.nlm.nih.gov/24150466.

71. Brookmeyer KA, Hogben M, Kinsey J. The role of behavioral counseling in sexually transmitted disease prevention program settings. *Sex Transm Dis*. 2016;43(2 Suppl 1):S102-112. Available at: https://pubmed.ncbi.nlm.nih.gov/26779681.

72. Patel P, Bush T, Mayer K, et al. Routine brief risk-reduction counseling with biannual STD testing reduces STD incidence among HIV-infected men who have sex with men in care. *Sex Transm Dis*. 2012;39(6):470-474. Available at: https://pubmed.ncbi.nlm.nih.gov/22592834.

73. Tuite AR, Shaw S, Reimer JN, Ross CP, Fisman DN, Mishra S. Can enhanced screening of men with a history of prior syphilis infection stem the epidemic in men who have sex with men? A mathematical modelling study. *Sex Transm Infect*. 2018;94(2):105-110. Available at: https://pubmed.ncbi.nlm.nih.gov/28705938.

74. de Voux A, Bernstein KT, Bradley H, et al. Syphilis testing among sexually active men who have sex with men and who are receiving medical care for human immunodeficiency virus in the United States: Medical Monitoring Project, 2013–2014. *Clin Infect Dis*. 2019;68(6):934-939. Available at: https://pubmed.ncbi.nlm.nih.gov/29985985.

75. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2021;73(11):e3572-e3605. Available at: https://pubmed.ncbi.nlm.nih.gov/33225349.

76. Kidd SE, Grey JA, Torrone EA, Weinstock HS. Increased methamphetamine, injection drug, and heroin use among women and heterosexual men with primary and secondary syphilis - United States, 2013–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):144-148. Available at: https://pubmed.ncbi.nlm.nih.gov/30763294.

77. Copen CE, Brookmeyer KA, Haderxhanaj LT, Hogben M, Torrone EA. Sexual risk behaviors among persons diagnosed with primary and secondary syphilis who reported high-risk substance use: data from the National Notifiable Diseases Surveillance System, 2018. *Sex Transm Dis*. 2022;49(2):99-104. Available at: https://pubmed.ncbi.nlm.nih.gov/34475356.

78. Centers for Disease Control and Prevention. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. *MMWR Recomm Rep*. 2008;57(RR-9):1-83; quiz CE81-84. Available at: https://pubmed.ncbi.nlm.nih.gov/18987617.

79. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med*. 2020;382(9):845-854. Available at: https://pubmed.ncbi.nlm.nih.gov/32101666.

80. Moore MB, Jr., Price EV, Knox JM, Elgin LW. Epidemiologic treatment of contacts to infectious syphilis. *Public Health Rep*. 1963;78:966-970. Available at: https://pubmed.ncbi.nlm.nih.gov/14084872.

81. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *JAMA*. 1971;218(5):711-713. Available at: https://pubmed.ncbi.nlm.nih.gov/5171497.

82. Schober PC, Gabriel G, White P, Felton WF, Thin RN. How infectious is syphilis? *Br J Vener Dis*. 1983;59(4):217-219. Available at: https://pubmed.ncbi.nlm.nih.gov/6871650.

83. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis*. 2015;42(2):98-103. Available at: https://pubmed.ncbi.nlm.nih.gov/25585069.

84. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis*. 2018;18(3):308-317. Available at: https://pubmed.ncbi.nlm.nih.gov/29229440.

85. Stewart J, Oware K, Donnell D, et al. Doxycycline postexposure prophylaxis for prevention of STIs among cisgender women. Presented at: Conference on Retroviruses and Opportunistic Infections. 2023. Seattle, WA. Available at: https://www.natap.org/2023/CROI/croi_04.htm.

86. Grant JS, Stafylis C, Celum C, et al. Doxycycline prophylaxis for bacterial sexually transmitted infections. *Clin Infect Dis*. 2020;70(6):1247-1253. Available at: https://pubmed.ncbi.nlm.nih.gov/31504345.

87. Luetkemeyer AF, Donnell D, Dombrowski J, et al. Doxy-PEP and antimicrobial resistance in S. aureus, N. gonorrhoeae, and commensal Neisseria. Presented at: Conference on Retroviruses and Opportunistic Infections. 2023. Seattle, WA. Available at: https://www.natap.org/2023/CROI/croi_11.htm.

88. Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. *Lancet*. 2003;361(9354):313-314. Available at: https://pubmed.ncbi.nlm.nih.gov/12559870.

89. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. *Clin Infect Dis*. 2006;42(3):337-345. Available at: https://pubmed.ncbi.nlm.nih.gov/16392078.

90. Wu H, Chang SY, Lee NY, et al. Evaluation of macrolide resistance and enhanced molecular typing of Treponema pallidum in patients with syphilis in Taiwan: a prospective multicenter study. *J Clin Microbiol*. 2012;50(7):2299-2304. Available at: https://pubmed.ncbi.nlm.nih.gov/22518868.

91. Chen CY, Chi KH, Pillay A, Nachamkin E, Su JR, Ballard RC. Detection of the A2058G and A2059G 23S rRNA gene point mutations associated with azithromycin resistance in *Treponema pallidum* by use of a TaqMan real-time multiplex PCR assay. *J Clin Microbiol*. 2013;51(3):908-913. Available at: https://pubmed.ncbi.nlm.nih.gov/23284026.

92. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. *N Engl J Med*. 2004;351(2):154-158. Available at: https://pubmed.ncbi.nlm.nih.gov/15247355.

93. Centers for Disease Control and Prevention. Azithromycin treatment failures in syphilis infections—San Francisco, California, 2002–2003. *MMWR Morb Mortal Wkly Rep*. 2004;53(9):197-198. Available at: https://pubmed.ncbi.nlm.nih.gov/15017376.

94. Ganesan A, Mesner O, Okulicz JF, et al. A single dose of benzathine penicillin G is as effective as multiple doses of benzathine penicillin G for the treatment of HIV-infected persons with early syphilis. *Clin Infect Dis*. 2015;60(4):653-660. Available at: https://pubmed.ncbi.nlm.nih.gov/25389249.

95. Yang CJ, Lee NY, Chen TC, et al. One dose versus three weekly doses of benzathine penicillin G for patients co-infected with HIV and early syphilis: a multicenter, prospective observational study. *PLoS One*. 2014;9(10):e109667. Available at: https://pubmed.ncbi.nlm.nih.gov/25286091.

96. Malone JL, Wallace MR, Hendrick BB, et al. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med*. 1995;99(1):55-63. Available at: https://pubmed.ncbi.nlm.nih.gov/7598143.

97. Walter T, Lebouche B, Miailhes P, et al. Symptomatic relapse of neurologic syphilis after benzathine penicillin G therapy for primary or secondary syphilis in HIV-infected patients. *Clin Infect Dis*. 2006;43(6):787-790. Available at: https://pubmed.ncbi.nlm.nih.gov/16912958.

98. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. 2006;42(6):e45-49. Available at: https://pubmed.ncbi.nlm.nih.gov/16477545.

99. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. *Am J Med*. 2008;121(10):903-908. Available at: https://pubmed.ncbi.nlm.nih.gov/18823862.

100. Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. *Lancet Infect Dis*. 2021;21(10):1441-1447. Available at: https://pubmed.ncbi.nlm.nih.gov/34051142.

101. Cao Y, Su X, Wang Q, et al. A multicenter study evaluating ceftriaxone and benzathine penicillin G as treatment agents for early syphilis in Jiangsu, China. *Clin Infect Dis*. 2017;65(10):1683-1688. Available at: https://pubmed.ncbi.nlm.nih.gov/29020150.

102. Hook EW, 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. *J Infect Dis*. 1988;158(4):881-884. Available at: https://pubmed.ncbi.nlm.nih.gov/3171231.

103. Kiddugavu MG, Kiwanuka N, Wawer MJ, et al. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis*. 2005;32(1):1-6. Available at: https://pubmed.ncbi.nlm.nih.gov/15614114.

104. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med*. 2005;353(12):1236-1244. Available at: https://pubmed.ncbi.nlm.nih.gov/16177249.

105. Hook EW, 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis*. 2010;201(11):1729-1735. Available at: https://pubmed.ncbi.nlm.nih.gov/20402591.

106. Martin IE, Tsang RS, Sutherland K, et al. Molecular characterization of syphilis in patients in Canada: azithromycin resistance and detection of Treponema pallidum DNA in whole-blood samples versus ulcerative swabs. *J Clin Microbiol*. 2009;47(6):1668-1673. Available at: https://pubmed.ncbi.nlm.nih.gov/19339468.

107. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. *Am J Med*. 1992;93(5):481-488. Available at: https://pubmed.ncbi.nlm.nih.gov/1442850.

108. Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS*. 2004;15(5):328-332. Available at: https://pubmed.ncbi.nlm.nih.gov/15117503.

109. U. S. Food and Drug Administration. Current and resolved drug shortages and discontinuations reported to FDA. 2023. Available at: https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Penicillin%20G%20Procaine%20Injectable%20Suspension&st=d.

110. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321(2):188-199. Available at: https://pubmed.ncbi.nlm.nih.gov/30644987.

111. Pham MN, Ho HE, Desai M. Penicillin desensitization: treatment of syphilis in pregnancy in penicillin-allergic patients. *Ann Allergy Asthma Immunol*. 2017;118(5):537-541. Available at: https://pubmed.ncbi.nlm.nih.gov/28477786.

112. Frunza-Stefan S, Acharya G, Kazlouskaya V, Vukasinov P, Chiou Y, Thet Z. Immune reconstitution inflammatory syndrome associated with secondary syphilis. *Int J STD AIDS*. 2017;28(3):302-305. Available at: https://pubmed.ncbi.nlm.nih.gov/27566775.

113. Bernal E, Munoz A, Ortiz Mdel M, Cano A. [Syphilitic panuveitis in an HIV-infected patient after immune restoration]. *Enferm Infecc Microbiol Clin*. 2009;27(8):487-489. Available at: https://pubmed.ncbi.nlm.nih.gov/19406524.

114. Sena AC, Wolff M, Behets F, et al. Response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. *Clin Infect Dis*. 2013;56(3):420-422. Available at: https://pubmed.ncbi.nlm.nih.gov/23118269.

115. Sena AC, Wolff M, Martin DH, et al. Predictors of serological cure and Serofast State after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis*. 2011;53(11):1092-1099. Available at: https://pubmed.ncbi.nlm.nih.gov/21998287.

116. Jinno S, Anker B, Kaur P, Bristow CC, Klausner JD. Predictors of serological failure after treatment in HIV-infected patients with early syphilis in the emerging era of universal antiretroviral therapy use. *BMC Infect Dis*. 2013;13:605. Available at: https://pubmed.ncbi.nlm.nih.gov/24369955.

117. Ghanem KG, Hook EW, 3rd. The terms "serofast" and "serological nonresponse" in the modern syphilis era. *Sex Transm Dis*. 2021;48(6):451-452. Available at: https://pubmed.ncbi.nlm.nih.gov/33534408.

118. Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. *Clin Infect Dis*. 2008;47(7):893-899. Available at: https://pubmed.ncbi.nlm.nih.gov/18715154.

119. Xiao Y, Tong ML, Lin LR, et al. Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients. *Sci Rep*. 2017;7(1):9911. Available at: https://pubmed.ncbi.nlm.nih.gov/28855625.

120. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors. *Clin Infect Dis*. 2010;51(8):976-979. Available at: https://pubmed.ncbi.nlm.nih.gov/20825309.

121. Aaron KJ, Brill I, Causey-Pruitt Z, et al. Factors associated with syphilis seroprevalence in women with and at-risk for HIV infection in the Women's Interagency HIV Study (1994–2015). *Sex Transm Infect*. 2022;98(1):4-10. Available at: https://pubmed.ncbi.nlm.nih.gov/33408096.

122. Trivedi S, Williams C, Torrone E, Kidd S. National trends and reported risk factors among pregnant women with syphilis in the United States, 2012–2016. *Obstet Gynecol*. 2019;133(1):27-32. Available at: https://pubmed.ncbi.nlm.nih.gov/30531570.

123. U.S. Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for syphilis infection in pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2018;320(9):911-917. Available at: https://pubmed.ncbi.nlm.nih.gov/30193283.

124. Mmeje O, Chow JM, Davidson L, Shieh J, Schapiro JM, Park IU. Discordant syphilis immunoassays in pregnancy: perinatal outcomes and implications for clinical management. *Clin Infect Dis*. 2015;61(7):1049-1053. Available at: https://pubmed.ncbi.nlm.nih.gov/26063719.

125. Adachi K, Xu J, Yeganeh N, et al. Combined evaluation of sexually transmitted infections in HIV-infected pregnant women and infant HIV transmission. *PLoS One*. 2018;13(1):e0189851. Available at: https://pubmed.ncbi.nlm.nih.gov/29304083.

126. Berman SM. Maternal syphilis: pathophysiology and treatment. *Bull World Health Organ*. 2004;82(6):433-438. Available at: https://pubmed.ncbi.nlm.nih.gov/15356936.

127. Tess BH, Rodrigues LC, Newell ML, Dunn DT, Lago TD. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *AIDS*. 1998;12(5):513-520. Available at: https://pubmed.ncbi.nlm.nih.gov/9543450.

128. Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. *Int J Gynaecol Obstet*. 1998;63(3):247-252. Available at: https://pubmed.ncbi.nlm.nih.gov/9989893.

129. Wendel GD, Jr., Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sanchez PJ. Treatment of syphilis in pregnancy and prevention of congenital syphilis. *Clin Infect Dis*. 2002;35(Suppl 2):S200-209. Available at: https://pubmed.ncbi.nlm.nih.gov/12353207.

130. Kreitchmann R, Fuchs SC, Suffert T, Preussler G. Perinatal HIV-1 transmission among low income women participants in the HIV/AIDS Control Program in Southern Brazil: a cohort study. *BJOG*. 2004;111(6):579-584. Available at: https://pubmed.ncbi.nlm.nih.gov/15198786.

131. Mwapasa V, Rogerson SJ, Kwiek JJ, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. *AIDS*. 2006;20(14):1869-1877. Available at: https://pubmed.ncbi.nlm.nih.gov/16954728.

132. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. *Cochrane Database Syst Rev*. 2001(3):CD001143. Available at: https://pubmed.ncbi.nlm.nih.gov/11686978.

133. Donders GG, Desmyter J, Hooft P, Dewet GH. Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-seronegative African women. *Sex Transm Dis*. 1997;24(2):94-101. Available at: https://pubmed.ncbi.nlm.nih.gov/9111755.

134. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol*. 2002;186(3):569-573. Available at: https://pubmed.ncbi.nlm.nih.gov/11904625.

135. Zhu L, Qin M, Du L, Xie RH, Wong T, Wen SW. Maternal and congenital syphilis in Shanghai, China, 2002 to 2006. *Int J Infect Dis*. 2010;14 Suppl 3:e45-48. Available at: https://pubmed.ncbi.nlm.nih.gov/20137991.

136. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. *Am J Obstet Gynecol*. 2003;188(3):714-718. Available at: https://pubmed.ncbi.nlm.nih.gov/12634646.

137. Zhou P, Gu Z, Xu J, Wang X, Liao K. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. *Sex Transm Dis*. 2005;32(8):495-498. Available at: https://pubmed.ncbi.nlm.nih.gov/16041252.

138. Katanami Y, Hashimoto T, Takaya S, et al. Amoxicillin and ceftriaxone as treatment alternatives to penicillin for maternal syphilis. *Emerg Infect Dis*. 2017;23(5):827-829. Available at: https://pubmed.ncbi.nlm.nih.gov/28418316.

139. Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol*. 1990;75(3 Pt 1):375-380. Available at: https://pubmed.ncbi.nlm.nih.gov/2304710.

140. Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg*. 2017;96(1):46-52. Available at: https://pubmed.ncbi.nlm.nih.gov/28077740.

141. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD, Jr. Fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol*. 2001;97(6):947-953. Available at: https://pubmed.ncbi.nlm.nih.gov/11384701.

142. Rac MW, Bryant SN, Cantey JB, McIntire DD, Wendel GD, Jr., Sheffield JS. Maternal titers after adequate syphilotherapy during pregnancy. *Clin Infect Dis*. 2015;60(5):686-690. Available at: https://pubmed.ncbi.nlm.nih.gov/25414264.

143. Webster CM, Kasaro MP, Price JT, et al. Seroreduction of syphilis non-treponemal titers during pregnancy for women with and without HIV co-infection. *Int J Gynaecol Obstet*. 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/35122676.

Talaromycosis (Formerly Penicilliosis)

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Epidemiology

Talaromycosis is an invasive fungal infection caused by the thermally dimorphic fungus *Talaromyces marneffei* (formerly *Penicillium marneffei*), which is endemic in Southeast Asia (in northern Thailand, Vietnam, and Myanmar), East Asia (in southern China, Hong Kong, and Taiwan), and South Asia (in northeastern India).[1-4] *Talaromyces marneffei* was formerly classified under the *Penicillium* subgenus *Biverticillium* based on morphological characteristics. In 2011, the subgenus *Biverticillium* was found to form a monophyletic group with *Talaromyces* that is distinct from *Penicillium*, and was taxonomically unified with the *Talaromyces* genus.[5] Hence, *Penicillium marneffei* was changed to *Talaromyces marneffei*, and the disease penicilliosis is now called talaromycosis.

The wild bamboo rat is the only known animal reservoir of *T. marneffei*[6,7]; however, case-control studies suggest that human infection results from inhalation of fungal spores released from a soil-related environmental reservoir (plants and farmed animals) rather than from direct bamboo rat-to-human transmission.[8,9] Talaromycosis incidence increases 30% to 50% during the rainy months (May–November)[3,10] because of expansion of the environmental reservoir and increased humidity.[11] Reactivation of latent infection has been demonstrated in non-autochthonous cases with a history of remote travel to endemic countries, occurring up to 52 years after exposure.[12-14] There has been one case of presumed laboratory-acquired talaromycosis. Donor-acquired transmission has been reported in a lung transplant recipient from Belgium.[15,16]

HIV is a major risk factor for talaromycosis, accounting for approximately 88% of disease in hyperendemic regions.[2] *T. marneffei* is a major cause of HIV-associated opportunistic infections in these regions, making up 4% to 16% of hospital admissions due to advanced HIV disease,[2,3,17-19] and is a leading cause of HIV-associated bloodstream infection and HIV-associated deaths in Vietnam and southern China.[17,20-22] Infection occurs predominantly in individuals[2,3,23] who have very advanced HIV disease with a CD4 T lymphocyte (CD4) cell count of <100 cells/mm^3. Talaromycosis is increasingly diagnosed in immunocompromised individuals, including those with HIV, who are returning travelers or immigrants from the endemic regions.[12,13,24] People who have a primary immunodeficiency condition (e.g., idiopathic CD4 lymphopenia, anti-interferon-gamma autoantibody-associated immunodeficiency, conditions due to mutations in CYBB or CD40L, or gain-of-function mutation in STAT1/STAT3 pathways) or a secondary immunosuppressive condition (e.g., other autoimmune diseases, solid organ and hematopoietic stem cell transplantations, T lymphocyte–depleting immunosuppressive drugs, and novel anticancer targeted therapies, such as anti-CD20 monoclonal antibodies and kinase inhibitors) are also at risk for talaromycosis.[25] It is estimated that worldwide each year approximately 17,300 people with HIV or other immunocompromising conditions are diagnosed with talaromycosis, and approximately 4,900 infection-related deaths occur .[26] Talaromycosis-related mortality approaches 30% in people both with and without HIV, despite antifungal therapy.[2,3,23,27,28]

Clinical Manifestations

Disseminated infection involving multiple organ systems is the most common manifestation of talaromycosis in people with advanced HIV disease. The infection frequently begins as a subacute illness characterized by fever, weight loss, hepatosplenomegaly, lymphadenopathy, and respiratory and gastrointestinal abnormalities.[3,29] These clinical features are nonspecific and are indistinguishable from those of disseminated tuberculosis, other systemic mycoses, or infections due to intracellular pathogens, such as *Salmonella* species.

Skin lesions are the most specific, albeit late, clinical manifestations of talaromycosis and are present in 40% to 80% of patients.[27] Skin lesions are typically central-umbilicated papules that appear first on the face and then spread to the trunk and extremities. Pulmonary symptoms such as cough or shortness of breath occur in approximately 40% of patients. Gastrointestinal symptoms including diarrhea or abdominal pain occur in 30% of patients. Hepatosplenomegaly is common, presenting in up to 60% of patients, and together with intra-abdominal lymphadenopathy causes abdominal distention and pain.[3,18] A rare complication occurring in about 4% of patients is meningoencephalitis, with a rapid disease course and a high mortality of up to 80%.[30] Coinfection with oropharyngeal candidiasis occurs in up to 50% of patients and with tuberculosis in 22% of patients.[3]

Common laboratory findings associated with talaromycosis include anemia and thrombocytopenia due to bone marrow infiltration. Anemia can be profound and may require multiple red cell transfusions. Elevation of aminotransferases is common, with a serum aspartate aminotransferase over alanine aminotransferase ratio of approximately 2.[3]

Chest radiographical abnormalities are broad and nonspecific, ranging from diffuse interstitial disease to reticulonodular infiltrates to alveolar infiltrates.[3,31]

Diagnosis

A diagnosis of talaromycosis should be considered in all people with HIV with a CD4 count of <100 cells/mm^3 who have traveled to or have lived in talaromycosis-endemic areas and present with a systemic infection involving the reticuloendothelial system (i.e., lymph nodes, liver, spleen, and bone marrow).

Skin lesions in talaromycosis develop on the face, trunk, and extremities and typically have a central-necrotic appearance. However, skin lesions are a late manifestation of talaromycosis and are absent in up to 60% of patients.[1,3,32] Diagnostic methods for talaromycosis are still primarily based on conventional microscopy, histology, and culture. Culture results usually return within 4 to 5 days but can take up to 28 days. Diagnostic delay, particularly in patients presenting without fever or skin lesions, is associated with increased mortality.[2,3,25,33] The development of antigen detection and polymerase chain reaction (PCR)–based assays has offered rapid, sensitive, and specific non-culture-based diagnostics that may substantially change the way talaromycosis is diagnosed and managed (discussed in more detail in the Nucleic Acid Diagnosis and Antigen Diagnosis sub-sections below).[34-36]

Microscopy, Histology, and Culture Are the Gold Standard Diagnostic Methods

Microscopy. A presumptive diagnosis of talaromycosis can be made based on the microscopic examination of Giemsa-, Wright's-, or Grocott-Gomori Methenamine Silver–stained samples of skin

lesion scrapings, lymph node aspirate, bone marrow aspirate, or tissue sections showing round-to-oval extracellular and intramacrophage yeast-like organisms measuring 3 to 6 µm in diameter. Presence of a clear midline septum in a dividing yeast cell distinguishes *T. marneffei* from *Histoplasma, Emergomyces,* or *Candida* species.[1] In some patients, the fungus can be identified by microscopic examination of a Wright's-stained peripheral blood smear.[37]

Histology. A definitive diagnosis of talaromycosis can be made by the histopathologic demonstration of the organism in biopsy specimens. There are three histopathological forms: (1) a granulomatous reaction formed by histiocytes, lymphocytes, epithelioid, and giant cells, which can be seen in reticuloendothelial organs in patients who are HIV-negative or immunocompetent; (2) a suppurative reaction that develops with the joining of multiple abscesses seen in the lung and subcutaneous tissues of immunocompetent patients; and (3) an anergic and necrotizing reaction characterized by focal necrosis surrounded by distended histiocytes containing proliferating fungi seen in the lung, liver, and spleen of immunocompromised patients.[38]

Culture. Most frequently, a definitive diagnosis of talaromycosis is based on isolation of the organism from cultures of blood and/or other clinical specimens.

Compared to other endemic dimorphic fungi, *T. marneffei* grows more readily in standard BACTEC blood culture media and Sabouraud dextrose agar incubating between 4 and 14 days but can take up to 28 days to grow from selective fungal culture media. At 25ºC to 32ºC, the fungus grows as a mold producing yellow-green colonies with sulcate folds that produce a red pigment that diffuses into the surrounding media. Microscopically, filamentous hyphae with characteristic spore-bearing structures called conidiophores and conidia can be seen. At 32ºC to 37ºC, the fungus makes the morphological transition from a mold to a yeast, producing tan-colored colonies without a red diffusible pigment. In laboratory media, only the transitional sausage-shaped cells can be seen microscopically. The round-to-oval yeast cells are only seen in natural tissue.[1]

Culture yield is the highest from bone marrow (100%), followed by skin lesions (90%) and blood (50% to 70%).[3,39] Less commonly, talaromycosis has been diagnosed from sputum, pleural fluid, peritoneal fluid, cerebrospinal fluid, pericardial fluid, stool, and urine.

Nucleic Acid Diagnosis

Molecular diagnostics for talaromycosis have been based on real-time PCR amplification and sequence identification of the 5.8S rRNA and the 18S rRNA genes within the fungal ribosome's internally transcribed spacer regions and the *MP1* gene specific to *T. marneffei.*[40-43] These assays have improving sensitivity (60% to 88%) and high specificity (100%), making them excellent rapid rule in tests for talaromycosis.[44] At present, these real-time PCR assays are available as in-house assays at selected centers only, and have not been prospectively validated, standardized, or commercially developed for clinical use.

Antigen Diagnosis

Several *T. marneffei*–specific antigen tests are in late-stage clinical validation but are not yet widely available for clinical use. The commercial assay for the detection of *Aspergillus* galactomannan cross-reacts with *T. marneffei* with a sensitivity between 64.5% and 95.8%.[45,46] However, due to cross-reactivity with other endemic fungi, such as *Histoplasma* and *Blastomyces*, it has not been adopted clinically. A *T. marneffei*–specific cell wall mannoprotein Mp1p enzyme immunoassay has

been shown to be more sensitive than blood culture (86.3% vs. 72.8%) and highly specific (98.1%),[47] and is available non-commercially in the United States from the laboratory of Dr. Thuy Le at Duke University (1-919-684-0952). Several *T. marneffei*-specific point-of-care antigen assays with promising clinical performance are undergoing late-stage clinical validation, which would offer a tool for early diagnosis near the patient and a screen-and-treat approach that potentially reduces mortality.[34-36]

Antigen Screening in Patients With Advanced HIV Disease

In hyperendemic regions, prevalence of *T. marneffei* antigenemia in people with advanced HIV disease is high and progressively increases with lower CD4 counts. A study in China[11] found that prevalence of antigenemia increased from 4.5% to 28.4% as the CD4 count decreased from 200 to 50 cells/mm^3 and a study in Vietnam[48] identified a prevalence of antigenemia of 4.2% in asymptomatic people with CD4 counts <100 cells/mm^3. Importantly, antigenemia in asymptomatic patients with a CD4 count <100 cells/mm^3 was found to be independently associated with 12-month mortality,[48] and antigen can be detected weeks to months earlier than culture allows.[49] Thus, antigen tests have potential utility to detect subclinical infection for pre-emptive antifungal therapy in regions where these tests are available.

Matrix-Assisted Laser Desorption/Ionization–Time of Flight Method

The matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) mass spectrometry (MS) method has been used for identification of *Talaromyces* to the species level from cultured specimens based on either an in-house database generated from an institution's *T. marneffei* clinical strain collection[50,51] or from the comprehensive National Institutes of Health Mold Database.[52,53] MALDI-TOF MS represents a rapid and reliable tool for downstream fungal identification, eliminating the need to demonstrate thermal dimorphism.

Preventing Exposure

Two case-control studies in Thailand and Vietnam demonstrated that people with stage 4 HIV disease, as defined by the World Health Organization, or a CD4 count <100 cells/mm^3 who had an occupational exposure to plants and farmed animals had twofold higher odds of infection.[8,9] The risk was higher in the rainy and humid months between May and November.[3,10]

Residency or a history of traveling to the highland regions (as short as 3 days) was a risk factor for talaromycosis in people with advanced HIV disease in southern Vietnam.[8] These data suggest that people with HIV who have a CD4 count <100 cells/mm^3 or individuals whose T cell function is suppressed due to a health condition (e.g., primary immune deficiency) or medication (e.g., immunosuppressants or prolonged corticosteroids) should avoid visiting the areas where talaromycosis is hyperendemic, particularly highland regions during the rainy and humid months **(BIII).**

Preventing Disease

Recommendations for Preventing First Episode of Talaromycosis (Primary Prophylaxis)

Indication for Primary Prophylaxis

People with a CD4 count <100 cells/mm^3 who are not taking ART or who have treatment failure without access to effective ART options, or people with a CD4 count ≥100 cells/mm^3 but have a condition that suppresses their T cell function, *and* who either—

- Reside in the hyperendemic regions in northern Thailand, throughout Vietnam, and southern China (particularly in highland regions during the rainy humid months) (BI) *or*
- Are from countries outside of the hyperendemic region and must travel to the region (BIII).

Primary Prophylaxis

For Individuals Residing in Hyperendemic Areas

- Preferred Therapy: Itraconazole 200 mg PO once daily (BI)
- Alternative Therapy: Fluconazole 400 mg PO once weekly (BII)

For Individuals Traveling to Hyperendemic Areas

- Primary prophylaxis for travelers should begin 3 days prior to travel to allow serum drug level to reach steady state and may continue for 1 week after travel (BIII).
- Preferred Therapy: Begin itraconazole 200 mg PO once daily 3 days before travel and continue for 1 week after leaving the hyperendemic area (BIII).
- Alternative Therapy: Begin fluconazole 400 mg PO 3 days before travel, then continue 400 mg PO once weekly while in the area and take final dose after leaving the endemic area (BIII).

Indication for Discontinuing Primary Prophylaxis for People Who Reside in Hyperendemic Areas

- CD4 count ≥100 cells/mm^3 for ≥6 months in response to ART (BII) *or*
- Virologic suppression for ≥6 months on ART (BIII)

Indication for Restarting Primary Prophylaxis

- CD4 count decreases to <100 cells/mm^3 (BII) and person still resides in or travels to hyperendemic areas.

Pregnancy Considerations

- Given the teratogenic risks of azole antifungals, individuals on primary prophylaxis with itraconazole or fluconazole should postpone pregnancy until their CD4 counts have been restored with ART, such that prophylaxis can be discontinued (BIII). If a woman becomes pregnant while receiving itraconazole or fluconazole prophylaxis, the decision as to whether to continue should be individualized based on current CD4 count, virologic suppression, with shared decision-making between the clinician and patient.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

Primary prophylaxis has been shown to reduce the incidence of talaromycosis and other invasive fungal infections. A double-blind, placebo-controlled trial in Chiang Mai, Thailand,[54] demonstrated that oral itraconazole 200 mg daily for primary prophylaxis significantly reduced the occurrence of invasive fungal infections (predominantly cryptococcosis and talaromycosis) in people with HIV with a CD4 count <200 cells/mm^3. In a retrospective study in Chiang Mai, fluconazole (400 mg weekly) was shown to be as effective as itraconazole (200 mg daily) for primary prophylaxis.[55]

Indication for Primary Prophylaxis

Primary prophylaxis is only recommended for patients with HIV with CD4 counts <100 cells/mm^3 who reside in the hyperendemic regions in northern Thailand, southern China, and northern and southern Vietnam who are unable to have antiretroviral therapy (ART) for whatever reasons or have treatment failure without access to effective antiretroviral options **(BI).** The drug choices for prophylaxis are oral itraconazole 200 mg once daily **(BI)** or oral fluconazole 400 mg once weekly **(BII).**

Primary prophylaxis is **not recommended** in people with HIV who are on effective ART with an undetectable viral load and is **not recommended** in geographic areas outside of the mentioned hyperendemic regions **(AIII).**

For people with HIV from the United States and from other countries outside of the endemic region who are not on effective ART and have a CD4 count <100 cells/mm^3 or people with a CD4 count ≥100 cells/mm^3 but who have a condition that suppresses their T cell function, and who must travel to the hyperendemic areas mentioned, primary prophylaxis with either itraconazole (preferred) or fluconazole should begin 3 days prior to travel to allow serum drug level to reach steady state and may continue for 1 week after travel **(BIII).**

Discontinuation of Primary Prophylaxis

Primary prophylaxis for talaromycosis can reasonably be discontinued in people with HIV who are on effective ART and have a sustained CD4 count ≥100 cells/mm^3 for at least 6 months **(BII).** In areas where viral load monitoring has replaced CD4 count monitoring, primary prophylaxis can reasonably be discontinued in people with HIV who achieve sustained virologic suppression for at least 6 months **(BIII).**[54-56] Once stopped, primary prophylaxis should be restarted in individuals whose CD4 count decreases to <100 cells/mm^3 **(BII)** if the person still resides in or travels to hyperendemic areas.

Antigen Screen-and-Treat Strategy for Disease Prevention

In hyperendemic areas, emerging data suggest that *T. marneffei* antigen can be detected weeks to months before culture detection in people with advanced HIV disease[49,57]; thus providing a window of opportunity for screening preclinical or asymptomatic disease and providing pre-emptive treatment to prevent disease development. Point-of-care antigen detection assays in development may allow for research to determine the benefit of a screen-and-treat approach as more cost-effective strategy for disease prevention.

Treating Disease

Recommendations for Treating Disseminated Talaromycosis Infection
Induction Therapy *Preferred Therapy* • Liposomal amphotericin B 3 to 5 mg/kg/day IV for 2 weeks (AIII), followed by consolidation therapy • If liposomal amphotericin B is not available: Amphotericin B deoxycholate 0.7 mg/kg/day IV for 2 weeks (AI), followed by consolidation therapy

Alternative Therapy (if amphotericin B is not available, contraindicated, or not tolerated)

- Voriconazole 6 mg/kg IV every 12 hours on Day 1 (loading dose) and then voriconazole 4 mg/kg IV every 12 hours for 2 weeks (BII), followed by consolidation therapy, *or*
- Voriconazole 600 mg PO every 12 hours on Day 1 (loading dose) and then voriconazole 400 mg PO every 12 hours for 2 weeks (BII); followed by consolidation therapy

Note: Itraconazole is **not recommended** as induction therapy for talaromycosis regardless of disease severity (AI).

Consolidation Therapy (after induction therapy)

- Itraconazole* 200 mg PO every 12 hours for 10 weeks (AI), followed by maintenance therapy or secondary prophylaxis, *or*
- Voriconazole 200 mg PO every 12 hours for 10 weeks (BII), followed by maintenance therapy or secondary prophylaxis

Maintenance Therapy (after consolidation therapy)

- Itraconazole* 200 mg PO daily (AI)

Criteria for Discontinuing Chronic Maintenance Therapy

- CD4 count ≥100 cells/mm^3 for ≥6 months in response to ART (BII), *or*
- Virologic suppression for ≥6 months on ART (BIII)

Criteria for Restarting Chronic Maintenance Therapy

- CD4 count decreases to <100 cells/mm^3 (BIII)

* Itraconazole capsules should be taken after a meal or taken with a cola drink as gastric acidification is required for optimal absorption. Itraconazole solution should be taken on an empty stomach.

Other Considerations

- ART should be initiated as early as one week after the initiation of induction therapy for talaromycosis to improve overall outcomes (AII).
- ART should not be withheld because of concerns for possible development of IRIS (AIII).

Therapeutic Drug Monitoring for Itraconazole and Voriconazole

- Given erratic absorption of itraconazole, extensive interindividual variability due to differences in CYP2C19 alleles associated with voriconazole metabolism, nonlinear PK of voriconazole, and potential for drug interactions with ARV drugs; when available, TDM to guide therapy is recommended. (see the Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines for further recommendations).
- Itraconazole and voriconazole concentrations should be monitored beginning 5 days after initiation of therapy, and doses adjusted as needed to obtain serum trough concentrations >0.5 µg/mL for itraconazole (for a combined level of itraconazole plus its antifungal active metabolite hydroxyitraconazole) and >1 µg/mL for voriconazole (BIII). Because it is more bioavailable, itraconazole solution is generally preferred over the capsule formulation.

Pregnancy Considerations

- Itraconazole and voriconazole should be avoided during the first trimester of pregnancy unless the benefit is felt to outweigh the risk (BIII).
- Amphotericin B should be used instead of high-dose azoles in the first trimester of pregnancy (BIII).
- After the first trimester, treatment with itraconazole should be considered for consolidation or maintenance therapy (AIII).

- Women on maintenance therapy with itraconazole or other azoles should postpone pregnancy until their CD4 counts have been restored with ART, such that prophylaxis can be discontinued (BIII).
- Voriconazole is not recommended for use during pregnancy, especially in the first trimester (AIII).

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CYP = cytochrome P450; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; PK = pharmacokinetic; PO = orally; TDM = therapeutic drug monitoring

Disseminated talaromycosis, its most common manifestation, is fatal if untreated.[58] With antifungal therapy, case fatality rates range from 10% to 30%.[2,3,17,27] Therefore, early initiation of antifungal therapy is necessary.

Antifungal therapy for talaromycosis consists of induction, consolidation, and maintenance phases. Treatment recommendations are based on several observational studies in Thailand and China[59-63] and a multicenter randomized controlled trial of Itraconazole Versus Amphotericin B for Penicilliosis (IVAP) in Vietnam.[64]

In an earlier noncomparative prospective study of 74 patients in Thailand, induction therapy with amphotericin B deoxycholate for 2 weeks, followed by consolidation therapy with itraconazole for 10 weeks was shown to be highly effective. Treatment success rate (defined by negative blood culture and resolution of fever and skin lesions at the end of a 12-week treatment course) was 97%.[59]

Voriconazole has been used for induction therapy in case series of patients who could not tolerate amphotericin B. It was shown to have favorable clinical and microbiological outcomes in 8 of 9 (88.9%) patients in Thailand,[61] and in 10 of 14 (71.4%) patients and in 47 of 57 (82.5%) patients in two studies conducted in China.[60,63]

The IVAP trial randomized 440 patients across five hospitals in Vietnam and demonstrated that induction therapy with amphotericin B was superior to itraconazole with respect to 6-month mortality (absolute risk of death was 11% and 21%, respectively; absolute risk difference, 9.7 percentage points; 95% confidence interval, 2.8 to 16.6; $P = 0.006$). Patients in the amphotericin B arm had significantly lower rates of disease complications, including disease relapse and immune reconstitution inflammatory syndrome (IRIS), and had a fourfold faster rate of blood fungal clearance. The difference in mortality between the arms was not dependent on disease severity (based on positive blood culture, blood fungal count, or requirement for oxygen support at presentation) or by a participant's immune status (CD4 count <50 cells/mm^3 or ≥50 cells/mm^3), ART status, or intravenous (IV) drug use.[64]

The recommended induction therapy for all patients with disseminated disease, regardless of clinical severity, is amphotericin B: preferably liposomal amphotericin B 3 to 5 mg/kg/day IV for 2 weeks where available **(AIII),** or amphotericin B deoxycholate 0.7 mg/kg/day IV for 2 weeks **(AI).**

Induction therapy should be followed by consolidation therapy with oral itraconazole, 200 mg every 12 hours for a subsequent duration of 10 weeks **(AI).**[64] After this period, maintenance therapy with oral itraconazole 200 mg/day is recommended to prevent recurrence until the CD4 count rises above 100 cells/mm^3 for ≥6 months **(AI).**[65]

For patients unable to tolerate any form of amphotericin B, induction therapy with IV voriconazole 6 mg/kg every 12 hours on Day 1 (loading dose), then 4 mg/kg every 12 hours **(BII),** or with oral voriconazole 600 mg every 12 hours on Day 1 (loading dose), then 400 mg every 12 hours for 2 weeks is recommended **(BII).**[60,61] Thereafter, either oral itraconazole **(AI)** or oral voriconazole

(BII) at a dose of 200 mg every 12 hours can be used for consolidation therapy for 10 weeks, followed by itraconazole 200 mg/day for maintenance therapy **(AI).** The optimal dose of voriconazole for maintenance therapy beyond 12 weeks has not been studied.

Itraconazole is **not recommended** as an induction therapy for talaromycosis, regardless of disease severity **(AI).**[64]

In Vitro *Antifungal Susceptibility Profile of Available Antifungal Drugs*

The minimum inhibitory concentrations (MIC) are low for itraconazole (MICs 0.008–0.25 µg/mL), intermediate for amphotericin B (MICs 0.5–1 µg/mL), and high for fluconazole (MICs 0.5–16 µg/mL) across studies. One study correlated MIC data of 30 clinical isolates with patient outcomes and showed poor clinical response in patients treated with fluconazole, consistent with the higher MICs for fluconazole. The MICs are low for flucytosine (MICs 0.06–0.5 µg/ml), voriconazole (MICs 0.016–0.063 µg/mL), and posaconazole (MICs 0.001–0.002 µg/ml), but are high for echinocandins (2–8 µg/mL).[66-68] These results suggest promising activity of voriconazole, posaconazole, and flucytosine for the treatment of talaromycosis, and suggest that the echinocandins are less effective against *T. marneffei*. Data are lacking on the frequencies of primary or acquired antifungal resistance on therapy, and clinical cut-off threshold to define resistance has not been defined.

Special Considerations Regarding Antiretroviral Therapy Initiation

In a multicenter randomized controlled trial in China, early initiation of ART (<2 weeks after initiation of talaromycosis treatment, median 11 days, interquartile range [IQR] 7–13) was associated with significantly lower mortality and AIDS-defining events over 48 weeks compared to delayed initiation (2–4 weeks after initiation of talaromycosis treatment, median 21 days, IQR 17–29).[69] The certainty of evidence was reduced as significantly more patients in the early ART arm were excluded from the final analysis.

In the IVAP trial, the median time to ART initiation in both arms was 3 weeks (range 1–5 weeks). Paradoxical IRIS events occurred in 6.4% in the itraconazole arm and 0% in the amphotericin B arm, suggesting that ART can be safely initiated as early as 1 week after starting effective induction therapy with amphotericin B.[64]

ART should therefore be initiated as early as 1 week after the initiation of induction therapy for talaromycosis to improve outcomes **(AII).**

Prevention and Management of IRIS

Both unmasking and paradoxical IRIS have been described in patients with talaromycosis after ART is initiated.[70-72] In the IVAP trial, 188 of 432 (44%) patients had started ART a median of 3 to 4 months before developing talaromycosis, indicating the role of ART in the unmasking of subclinical infection in a significant proportion of patients.[64] This finding highlights the need to screen for subclinical infection with a sensitive antigen test (where available) and the potential utility of pre-emptive antifungal therapy to prevent disease and unmasking IRIS. In patients starting ART after a diagnosis of talaromycosis, paradoxical IRIS events only occurred in patients treated with itraconazole induction therapy,[64] demonstrating the role of effective induction therapy with

amphotericin B in the prevention of paradoxical IRIS. ART should not be withheld because of concerns for possible development of IRIS **(AIII).**

Patients with paradoxical IRIS typically present with inflammatory manifestations that include erythematous or immunological skin lesions such as erythema nodosum, large and painful peripheral lymph nodes, and synovitis of small joints. Most symptoms can be managed by judicious use of nonsteroidal anti-inflammatory drugs. Corticosteroids are reserved for synovitis that interferes with daily function.[72] Although the IRIS events in the IVAP trial were managed effectively with continuation of ART and antifungal therapy, they were associated with higher morbidity, lower quality of life, increased diagnostic testing, duration of hospitalization, and cost.[64]

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

Adverse Event Monitoring

Patients treated with amphotericin B (or liposomal amphotericin B) should be monitored for infusion-related adverse reactions (fever, rigors, nausea, vomiting), electrolyte disturbances (particularly hypokalemia and hypomagnesemia), nephrotoxicity (rise in creatinine), and anemia. Hydration with 500 mL to 1,000 mL of normal saline and potassium supplementation before each amphotericin B infusion reduces the risk of nephrotoxicity during treatment. Infusion-related adverse reactions can be ameliorated by pre-treatment with acetaminophen and diphenhydramine.[73] Patients on azoles should be regularly monitored for liver function test abnormalities, as all have risk of hepatotoxicity. Additionally, individuals on voriconazole should be monitored for vision changes, neurotoxicity, skin rash, photosensitivity, adrenal insufficiency, and periostitis while those on itraconazole should be monitored for peripheral edema, hypertension, hypokalemia, and congestive heart failure.

Drug–Drug Interactions and Therapeutic Drug Monitoring

Itraconazole and voriconazole and antiretroviral (ARV) drugs such as protease inhibitors, some integrase strand transfer inhibitors, and non-nucleoside reverse transcriptase inhibitors can have bidirectional interactions with each other, leading to increased or decreased drug concentrations (see Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines). Close monitoring or use with non-interacting ART regimens (e.g., dolutegravir/tenofovir alafenamide/emtricitabine) is recommended when using these drugs together.

In settings where therapeutic drug monitoring (TDM) is available, serum itraconazole and voriconazole levels should be monitored in all patients starting 5 days after therapy initiation to ensure optimal drug exposure **(BIII).** For timing to obtain a trough level of each drug, see the Fungus Education Hub Antifungal Therapeutic Drug Monitoring web page. TDM is recommended because itraconazole and voriconazole can interact with some ARV drugs. Absorption of itraconazole is highly dependent on gastric acid pH. Extensive interindividual variability in voriconazole pharmacokinetics is expected due to differences in cytochrome P450 2C19 alleles associated with voriconazole metabolism and nonlinear pharmacokinetics of voriconazole. Optimal target serum concentrations of antifungals for talaromycosis are not well defined.[74] In line with recommendations for other endemic fungi, target serum trough concentrations for itraconazole should be >0.5 µg/mL (for a combined itraconazole and its antifungal active metabolite hydroxyitraconazole level) and >1 µg/mL for voriconazole **(BIII).** Because it is more bioavailable, itraconazole solution is generally

preferred over the capsule formulation. For maximal absorption, the itraconazole capsule should be taken with food or a cola drink, and itraconazole liquid should be taken on an empty stomach.

Managing Treatment Failure and Relapse

Talaromycosis treatment failure and disease relapse were associated with ineffective induction therapy with itraconazole,[64] highlighting the importance of using the more potent drug amphotericin B as induction therapy. Based on case series that included very few patients and on clinical experiences, voriconazole is an alternative therapy for patients who are unable to tolerate amphotericin B induction treatment and is an effective choice for consolidation therapy given its higher oral bioavailability **(BII).**

Disease relapse is associated with higher mortality[64] and occurs mainly in patients who are not adherent to ART or have virologic failure, as well as in those who are not adherent to itraconazole consolidation or maintenance therapy. Therapy adherence counseling and TDM for itraconazole and voriconazole, if available, are recommended **(BIII).**

Preventing Recurrence

When to Start Chronic Maintenance Therapy

A double-blind, placebo-controlled study conducted in Chiang Mai, Thailand, demonstrated that people not on ART who discontinued oral itraconazole 200 mg daily had a talaromycosis relapse rate of 57% compared to 0% in those who continued itraconazole therapy ($P < 0.001$).[65] All patients who successfully complete induction and consolidation treatment for talaromycosis should receive chronic maintenance therapy with oral itraconazole 200 mg/day until they reach criteria for stopping maintenance therapy **(AI).**

When to Stop Chronic Maintenance Therapy

No randomized controlled study has been conducted to evaluate the safety of discontinuation of secondary prophylaxis for talaromycosis. However, a retrospective cohort study[56] reported no relapse of talaromycosis after itraconazole was discontinued in patients receiving ART whose CD4 counts were ≥100 cells/mm^3. Therefore, chronic maintenance therapy for talaromycosis can be discontinued in patients who are ART adherent and have CD4 counts ≥100 cells/mm^3 for at least 6 months **(BII).** In settings where CD4 monitoring is not possible, secondary prophylaxis can be reasonably discontinued in patients with sustained virologic suppression for at least 6 months while on ART **(BIII).**

Chronic maintenance therapy should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(BIII).**

Special Considerations During Pregnancy

During pregnancy, the diagnosis and treatment of talaromycosis is similar to that in other adults with HIV, with the following considerations regarding antifungal use in pregnancy. There are limited data regarding the natural history of talaromycosis and its effect on maternal and fetal outcomes in pregnancy. Clinicians treating talaromycosis during pregnancy should take several factors into considerations. Amphotericin B has not been shown to be teratogenic in animals, and no increase in

fetal anomalies has been seen with its use in humans. There remain significant gaps in determining optimal dosing of amphotericin B in pregnancy; a review of dosing strategies in pregnancy recommended use of ideal body weight rather than total body weight to minimize risk of adverse effects to the fetus while maintaining efficacy.[75] Neonates born to women on chronic amphotericin B at delivery may be at increased risk for renal toxicity and electrolyte abnormalities and should be appropriately evaluated as newborns.[76]

Itraconazole at high doses has been shown to be teratogenic in animals, but because humans lack the metabolic mechanism accounting for these defects, animal teratogenicity data are not applicable to humans. Prospective cohort studies of over 300 women with first-trimester itraconazole exposure did not show an increased risk of congenital malformations, but these studies report on varying doses and durations and have low power to detect differences.[77,78]

Voriconazole (at doses lower than recommended human doses) is teratogenic (cleft palate and renal defects) in rats and embryotoxic in rabbits; no adequately controlled studies have assessed their teratogenicity and embryotoxicity in humans.

Azole antifungals **should be avoided** during the first trimester of pregnancy unless the benefit is felt to outweigh risk **(BIII).** Amphotericin B should be used instead of high-dose azoles in the first trimester for treatment of acute infection **(BIII).** After the first trimester, treatment with itraconazole should be considered for consolidation or maintenance therapy **(AIII).** Women on maintenance therapy with itraconazole or other azoles should postpone pregnancy until their CD4 counts have been restored with ART, such that prophylaxis can be discontinued **(BIII).** If a woman becomes pregnant while receiving itraconazole prophylaxis, the decision as to whether to continue should be individualized based on current CD4 count, virologic suppression, and patient preference. Voriconazole is **not recommended** for use during pregnancy, especially in the first trimester **(AIII).**

References

1. Vanittanakom N, Cooper CR, Jr., Fisher MC, Sirisanthana T. Penicillium marneffei infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. 2006;19(1):95-110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16418525.
2. Hu Y, Zhang J, Li X, et al. Penicillium marneffei infection: an emerging disease in mainland China. *Mycopathologia*. 2013;175(1-2):57-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22983901.
3. Le T, Wolbers M, Chi NH, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated Penicillium marneffei infection in Ho Chi Minh City, Viet Nam. *Clin Infect Dis*. 2011;52(7):945-952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21427403.
4. Ranjana KH, Priyokumar K, Singh TJ, et al. Disseminated Penicillium marneffei infection among HIV-infected patients in Manipur state, India. *J Infect*. 2002;45(4):268-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12423616.
5. Samson RA, Yilmaz N, Houbraken J, et al. Phylogeny and nomenclature of the genus Talaromyces and taxa accommodated in Penicillium subgenus Biverticillium. *Stud Mycol*. 2011;70(1):159-183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22308048.
6. Cao C, Liang L, Wang W, et al. Common reservoirs for Penicillium marneffei infection in humans and rodents, China. *Emerg Infect Dis*. 2011;17(2):209-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21291590.
7. Huang X, He G, Lu S, Liang Y, Xi L. Role of Rhizomys pruinosus as a natural animal host of Penicillium marneffei in Guangdong, China. *Microb Biotechnol*. 2015;8(4):659-664. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25824250.
8. Le T, Jonat B, Kim Cuc N, al E. The exposure and geospatial risk factors for AIDS-associated penicilliosis in Vietnam. Presented at: Conference on Retroviruses and Opportunistic Infections; 2015. Seattle, WA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2015/843.pdf.
9. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Praparattanapan J, Nelson KE. Case-control study of risk factors for Penicillium marneffei infection in human immunodeficiency virus-infected patients in northern Thailand. *Clin Infect Dis*. 1997;24(6):1080-1086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9195061.
10. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE. Seasonal variation of disseminated Penicillium marneffei infections in northern Thailand: a clue to the reservoir? *J Infect Dis*. 1996;173(6):1490-1493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8648227.
11. Wang YF, Xu HF, Han ZG, et al. Serological surveillance for Penicillium marneffei infection in HIV-infected patients during 2004-2011 in Guangzhou, China. *Clin Microbiol Infect*. 2015;21(5):484-489. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25677258.
12. Antinori S, Gianelli E, Bonaccorso C, et al. Disseminated Penicillium marneffei infection in an HIV-positive Italian patient and a review of cases reported outside endemic regions. *J Travel Med*. 2006;13(3):181-188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16706952.
13. Cristofaro P, Mileno MD. Penicillium marneffei infection in HIV-infected travelers. *AIDS Alert*. 2006;21(12):140-142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17191362.
14. Castro-Lainez MT, Sierra-Hoffman M, J LL-Z, et al. Talaromyces marneffei infection in a non-HIV non-endemic population. *IDCases*. 2018;12:21-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29942740.
15. Hermans F, Ombelet S, Degezelle K, et al. First-in-man observation of Talaromyces marneffei-transmission by organ transplantation. *Mycoses*. 2017;60(3):213-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27687582.

16. Hilmarsdottir I, Coutellier A, Elbaz J, et al. A French Case of Laboratory-Acquired Disseminated Penicillium marneffei Infection in a Patient with AIDS. *Clinical Infectious Diseases*. 1994;19(2):357-358. Available at: https://doi.org/10.1093/clinids/19.2.357.
17. Jiang J, Meng S, Huang S, et al. Effects of Talaromyces marneffei infection on mortality of HIV/AIDS patients in southern China: a retrospective cohort study. *Clin Microbiol Infect*. 2019;25(2):233-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29698815.
18. Larsson M, Nguyen LH, Wertheim HF, et al. Clinical characteristics and outcome of Penicillium marneffei infection among HIV-infected patients in northern Vietnam. *AIDS Res Ther*. 2012;9(1):24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22897817.
19. Wu TC, Chan JW, Ng CK, Tsang DN, Lee MP, Li PC. Clinical presentations and outcomes of Penicillium marneffei infections: a series from 1994 to 2004. *Hong Kong Med J*. 2008;14(2):103-109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18382016.
20. Feng RF, Ma Y, Liu ZF, et al. [Specific causes of death among 381 AIDS patients who died in hospitals]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2013;34(12):1237-1241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24518028.
21. Nga TV, Parry CM, Le T, et al. The decline of typhoid and the rise of non-typhoid salmonellae and fungal infections in a changing HIV landscape: bloodstream infection trends over 15 years in southern Vietnam. *Trans R Soc Trop Med Hyg*. 2012;106(1):26-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22137537.
22. Qi T, Zhang R, Shen Y, et al. Etiology and clinical features of 229 cases of bloodstream infection among Chinese HIV/AIDS patients: a retrospective cross-sectional study. *Eur J Clin Microbiol Infect Dis*. 2016;35(11):1767-1770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27502930.
23. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated Penicillium marneffei infection in southeast Asia. *Lancet*. 1994;344(8915):110-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7912350.
24. Narayanasamy S, Dat VQ, Thanh NT, et al. A global call for talaromycosis to be recognised as a neglected tropical disease. *Lancet Glob Health*. 2021;9(11):e1618-e1622. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34678201.
25. Chan JF, Lau SK, Yuen KY, Woo PC. Talaromyces (Penicillium) marneffei infection in non-HIV-infected patients. *Emerg Microbes Infect*. 2016;5:e19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26956447.
26. Ning C, Wei W, Xu B, et al. Global distribution, drivers, and burden of talaromycosis, 1964-2018. Presented at: Conference on Retroviruses and Opportunistic Infections; 2020. Boston, MA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2020/1430_8_Ning_00749.pdf.
27. Son VT, Khue PM, Strobel M. Penicilliosis and AIDS in Haiphong, Vietnam: evolution and predictive factors of death. *Med Mal Infect*. 2014;44(11-12):495-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25391487.
28. Kawila R, Chaiwarith R, Supparatpinyo K. Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infection in Northern Thailand: a retrospective study. *BMC Infect Dis*. 2013;13:464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24094273.
29. Sirisanthana T. Penicillium marneffei infection in patients with AIDS. *Emerg Infect Dis*. 2001;7(3 Suppl):561. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11485672.
30. Le T, Huu Chi N, Kim Cuc NT, et al. AIDS-associated Penicillium marneffei infection of the central nervous system. *Clin Infect Dis*. 2010;51(12):1458-1462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21054180.
31. Narayanasamy S, Dougherty J, van Doorn HR, Le T. Pulmonary talaromycosis: a window into the immunopathogenesis of an endemic mycosis. *Mycopathologia*. 2021;186(5):707-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34228343.

32. Chen J, Zhang R, Shen Y, et al. Clinical characteristics and prognosis of penicilliosis among human immunodeficiency virus-infected patients in eastern China. *Am J Trop Med Hyg*. 2017;96(6):1350-1354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28719279.
33. Zheng J, Gui X, Cao Q, et al. A clinical study of acquired immunodeficiency syndrome associated Penicillium marneffei infection from a non-endemic area in China. *PLoS One*. 2015;10(6):e0130376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26083736.
34. Venugopalan S, Nguyen T, Bloss K, et al. Clinical validation of a novel point of care Mp1p antigen lateral flow immunoassay to diagnose *talaromyces marneffei* infection. *Open Forum Infectious Diseases*. 2023;10. Available at: https://www.researchgate.net/publication/375955757_988_Clinical_Validation_of_a_Novel_Point_of_Care_Mp1p_Antigen_Lateral_Flow_Immunoassay_to_Diagnose_Talaromyces_marneffei_Infection.
35. Kinnamon DS, Heggestad JT, Liu J, et al. Environmentally resilient microfluidic point-of-care immunoassay enables rapid diagnosis of talaromycosis. *ACS Sens*. 2023;8(6):2228-2236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37279466.
36. Pruksaphon K, Intaramat A, Simsiriwong P, et al. An inexpensive point-of-care immunochromatographic test for Talaromyces marneffei infection based on the yeast phase specific monoclonal antibody 4D1 and Galanthus nivalis agglutinin. *PLoS Negl Trop Dis*. 2021;15(5):e0009058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33945531.
37. Supparatpinyo K, Sirisanthana T. Disseminated Penicillium marneffei infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clin Infect Dis*. 1994;18(2):246-247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8161635.
38. Deng Z, Ribas JL, Gibson DW, Connor DH. Infections caused by Penicillium marneffei in China and Southeast Asia: review of eighteen published cases and report of four more Chinese cases. *Rev Infect Dis*. 1988;10(3):640-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3293165.
39. Supparatpinyo K, Chiewchanvit S, Hirunsri P, Uthammachai C, Nelson KE, Sirisanthana T. Penicillium marneffei infection in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1992;14(4):871-874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1315586.
40. LoBuglio KF, Taylor JW. Phylogeny and PCR identification of the human pathogenic fungus Penicillium marneffei. *J Clin Microbiol*. 1995;33(1):85-89. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7699073.
41. Pornprasert S, Praparattanapan J, Khamwan C, et al. Development of TaqMan real-time polymerase chain reaction for the detection and identification of Penicillium marneffei. *Mycoses*. 2009;52(6):487-492. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19207847.
42. Hien HTA, Thanh TT, Thu NTM, et al. Development and evaluation of a real-time polymerase chain reaction assay for the rapid detection of Talaromyces marneffei MP1 gene in human plasma. *Mycoses*. 2016;59(12):773-780. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27453379.
43. Dankai W, Pongpom M, Vanittanakom N. Validation of reference genes for real-time quantitative RT-PCR studies in Talaromyces marneffei. *J Microbiol Methods*. 2015;118:42-50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26327538.
44. Khanh DH, Brown L, My PTH, et al. Optimization and clinical evaluation of a 5.8S rRNA quantitative PCR assay for the diagnosis of talaromycosis. *Med Mycol*. 2025;63(4). Available at: https://pubmed.ncbi.nlm.nih.gov/40240298/.
45. Huang YT, Hung CC, Liao CH, Sun HY, Chang SC, Chen YC. Detection of circulating galactomannan in serum samples for diagnosis of Penicillium marneffei infection and cryptococcosis among patients infected with human immunodeficiency virus. *J Clin Microbiol*. 2007;45(9):2858-2862. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17596363.

46. Chen X, Ou X, Wang H, et al. Talaromyces marneffei Mp1p antigen detection may play an important role in the early diagnosis of talaromycosis in patients with acquired immunodeficiency syndrome. *Mycopathologia*. 2022;187(2-3):205-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35237935.
47. Thu NTM, Chan JFW, Ly VT, et al. Superiority of a novel Mp1p antigen detection enzyme immunoassay compared to standard BACTEC blood culture in the diagnosis of talaromycosis. *Clin Infect Dis*. 2021;73(2):e330-e336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32564074.
48. Thu NTM, Dat VQ, Chan JFW, et al. Asymptomatic Talaromyces (Penicillium) marneffei Antigenemia and Mortality in Advanced HIV Disease. Presented at Conference of Retroviruses and Opportunistic Infections 2019. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2019/1430_Thu_0710.pdf.
49. Ly VT, Thanh NT, Thu NTM, et al. Occult Talaromyces marneffei Infection Unveiled by the Novel Mp1p Antigen Detection Assay. *Open Forum Infect Dis*. 2020;7(11):ofaa502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33269295.
50. Borman AM, Fraser M, Szekely A, Johnson EM. Rapid and robust identification of clinical isolates of Talaromyces marneffei based on MALDI-TOF mass spectrometry or dimorphism in Galleria mellonella. *Med Mycol*. 2019;57(8):969-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30649411.
51. Lau SK, Lam CS, Ngan AH, et al. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry for rapid identification of mold and yeast cultures of Penicillium marneffei. *BMC Microbiol*. 2016;16:36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26965891.
52. Li L, Chen K, Dhungana N, Jang Y, Chaturvedi V, Desmond E. Characterization of clinical isolates of Talaromyces marneffei and related species, California, USA. *Emerg Infect Dis*. 2019;25(9):1765-1768. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31441765.
53. Lau AF, Drake SK, Calhoun LB, Henderson CM, Zelazny AM. Development of a clinically comprehensive database and a simple procedure for identification of molds from solid media by matrix-assisted laser desorption ionization-time of flight mass spectrometry. *J Clin Microbiol*. 2013;51(3):828-834. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3592033/.
54. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clin Infect Dis*. 2002;34(2):277-284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11740718.
55. Chaiwarith R, Fakthongyoo A, Praparattanapan J, Boonmee D, Sirisanthana T, Supparatpinyo K. Itraconazole vs fluconazole as a primary prophylaxis for fungal infections in HIV-infected patients in Thailand. *Curr HIV Res*. 2011;9(5):334-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21916838.
56. Chaiwarith R, Charoenyos N, Sirisanthana T, Supparatpinyo K. Discontinuation of secondary prophylaxis against penicilliosis marneffei in AIDS patients after HAART. *AIDS*. 2007;21(3):365-367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17255744.
57. Ly V, Thu N, Thanh NT, et al. Superior accuracy of the Mp1p antigen assay over cultures in diagnosing talaromycosis - a prospective study. Presented at: Conference Retrovirus Opportunistic Infections; 2020. Boston, MA. Available at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2020/1430_9_Vo_00750.pdf.
58. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated Penicillium marneffei infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother*. 1993;37(11):2407-2411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8285625.

59. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated Penicillium marneffei infection in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1998;26(5):1107-1110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9597237.
60. Ouyang Y, Cai S, Liang H, Cao C. Administration of voriconazole in disseminated Talaromyces (Penicillium) marneffei infection: a retrospective study. *Mycopathologia*. 2017;182(5-6):569-575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28108867.
61. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic Penicillium marneffei infections in AIDS patients. *Am J Trop Med Hyg*. 2007;77(2):350-353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17690411.
62. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al. An efficacy study of itraconazole in the treatment of Penicillium marneffei infection. *J Med Assoc Thai*. 1992;75(12):688-691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1339213.
63. Huang W, Li T, Zhou C, Wei F, Cao C, Jiang J. Voriconazole versus amphotericin B as induction therapy for talaromycosis in HIV/AIDS patients: a retrospective study. *Mycopathologia*. 2021;186(2):269-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33616828.
64. Le T, Kinh NV, Cuc NTK, et al. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. *N Engl J Med*. 2017;376(24):2329-2340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28614691.
65. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients infected with the human immunodeficiency virus. *N Engl J Med*. 1998;339(24):1739-1743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9845708.
66. Lau SK, Lo GC, Lam CS, et al. In vitro activity of posaconazole against Talaromyces marneffei by broth microdilution and etest methods and comparison to itraconazole, voriconazole, and anidulafungin. *Antimicrob Agents Chemother*. 2017;61(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/28031205.
67. Lei HL, Li LH, Chen WS, et al. Susceptibility profile of echinocandins, azoles and amphotericin B against yeast phase of Talaromyces marneffei isolated from HIV-infected patients in Guangdong, China. *Eur J Clin Microbiol Infect Dis*. 2018;37(6):1099-1102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29536323.
68. Thu NTM, Borda H, Vitsupakorn S, et al. Development and validation of a colorimetric antifungal susceptibility testing method for the dimorphic fungus Talaromyces marneffei. *Med Mycol*. 2023;61(11). Available at: https://www.ncbi.nlm.nih.gov/pubmed/37994652.
69. Qin Y, Zhou Y, Liu S, et al. HIV-associated talaromycosis: does timing of antiretroviral therapy matter? *The Journal of Infection*. 2021;84(3):410-417. Available at: https://europepmc.org/article/med/34963636.
70. Hall C, Hajjawi R, Barlow G, Thaker H, Adams K, Moss P. Penicillium marneffei presenting as an immune reconstitution inflammatory syndrome (IRIS) in a patient with advanced HIV. *BMJ Case Rep*. 2013;2013. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23362074.
71. Liu X, Wu H, Huang X. Disseminated Penicillium marneffei infection with IRIS. *IDCases*. 2015;2(4):92-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26793468.
72. Thanh NT, Vinh LD, Liem NT, et al. Clinical features of three patients with paradoxical immune reconstitution inflammatory syndrome associated with Talaromyces marneffei infection. *Med Mycol Case Rep*. 2018;19:33-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29379703.
73. Bahr NC, Rolfes MA, Musubire A, et al. Standardized electrolyte supplementation and fluid management improves survival during amphotericin therapy for cryptococcal meningitis in resource-limited settings. *Open Forum Infect Dis*. 2014;1(2):ofu070. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25734140.

74. Stott KE, Le T, Nguyen T, et al. Population pharmacokinetics and pharmacodynamics of itraconazole for disseminated infection caused by Talaromyces marneffei. *Antimicrob Agents Chemother*. 2021;65(11):e0063621. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34370587.
75. O'Grady N, McManus D, Briggs N, Azar MM, Topal J, Davis MW. Dosing implications for liposomal amphotericin B in pregnancy. *Pharmacotherapy*. 2023;43(5):452-462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36862037.
76. Pharma A AmBisome® (amphotericin B) liposome for injection. Astellas Pharma; 2015.www.astellas.com/us/system/files/AMBISOME.pdf
77. De Santis M, Di Gianantonio E, Cesari E, Ambrosini G, Straface G, Clementi M. First-trimester itraconazole exposure and pregnancy outcome: a prospective cohort study of women contacting teratology information services in Italy. *Drug Saf*. 2009;32(3):239-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19338381.
78. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. 2000;183(3):617-620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10992182.

Toxoplasmosis

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Toxoplasma gondii is a protozoan that can commonly cause asymptomatic infection, a mononucleosis-like syndrome, retinochoroiditis, or congenital infection in immunocompetent individuals, but it presents most often as *Toxoplasma* encephalitis (TE) in people with HIV who are severely immunocompromised.[1-4] Toxoplasmosis in people with HIV appears to occur mainly due to reactivation of latent tissue cysts from a prior infection; primary infection is occasionally associated with acute cerebral or disseminated disease.

Epidemiology

Primary infection occurs most commonly after consumption of undercooked meat, unwashed fruits or vegetables, water, or unpasteurized milk containing viable organisms, or ingesting oocysts that have been shed in cat feces and sporulated in the environment, a process that takes at least 24 hours. In up to 50% of individuals, primary infection can occur in the absence of conventional risk factors.[5] Infection can also be transmitted congenitally, or rarely following organ transplant or blood transfusion.[6-9] The organism is not transmitted through direct person-to-person contact.

Seroprevalence of anti-*Toxoplasma* antibody, indicating prior infection, can vary substantially within the United States based on geography and demographics, with an overall prevalence of approximately 11%, versus 40% to 80% in certain European, Latin American, Asian, and African countries.[10-12] In the era before antiretroviral therapy (ART), the 12-month incidence of TE was approximately 33% in patients with advanced immunodeficiency who were seropositive for *T. gondii* and not receiving prophylaxis with drugs active against the disease. A very low incidence of toxoplasmosis is seen in people with HIV who are seronegative for *T. gondii*. In these individuals, their toxoplasmosis presumably represents primary infection, reactivation of latent disease in individuals who cannot produce detectable antibodies, or the use of insensitive assays.[13,14]

Clinical Manifestations

Clinical disease related to immunodeficiency is rare among people with HIV with CD4 T lymphocyte (CD4) cell counts >200 cells/mm^3. People with CD4 counts <50 cells/mm^3 are at greatest risk.[1,3,14,15] Among people with HIV, the most common clinical presentation of *T. gondii* infection is focal encephalitis, with subacute onset of headache, focal neurologic deficits (e.g., hemiparesis), and sometimes fever.[1,3,15] People with HIV also may present with non-focal encephalitis, with manifestations including isolated headache and generalized seizures.[16] Focal neurological abnormalities may be present on physical examination. In the absence of treatment, disease progression may result in seizures, stupor, coma, and death. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain following intravenous contrast administration will typically show multiple contrast-enhancing lesions, with a predilection for the basal ganglia, often with edema and associated mass effect.[1,15,17-19] Toxoplasmosis can more rarely manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies.[16] The latter presentation tends to be rapidly progressive and fatal. Retinochoroiditis, pneumonia, adenopathy, and evidence of other multifocal organ system involvement can occur but are uncommon in people with HIV.

Diagnosis

People with HIV and concomitant TE are usually seropositive for anti-*Toxoplasma* immunoglobulin G (IgG) antibodies.[1,3,15,20] The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-*Toxoplasma* immunoglobulin M (IgM) antibodies are usually absent and should not be requested unless primary infection is suspected. Quantitative antibody titers are not useful for diagnosis.

Definitive diagnosis of TE requires a compatible clinical syndrome, identification of one or more mass lesions by CT or MRI, and detection of the organism in a clinical sample. A presumptive diagnosis is based on a consistent clinical and radiographic presentation, presence of anti-*Toxoplasma* IgG antibodies, and response to anti-*Toxoplasma* therapy, but without detection of the organism. Most diagnoses are made either presumptively or based on a positive cerebrospinal fluid (CSF) *Toxoplasma* polymerase chain reaction (PCR).

On imaging studies, toxoplasmosis presents as contrast-enhancing lesions (typically ring-enhancing), with a predilection for the basal ganglia. MRI has sensitivity superior to that of CT and should be obtained in patients with equivocal or negative CT studies. Positron emission tomography[18] or single-photon emission CT scanning[19] may be helpful in distinguishing between TE and primary central nervous system (CNS) lymphoma, but no imaging technique is completely specific. For TE, detection of the organism requires either a brain biopsy, most commonly stereotactic, or a positive CSF PCR test. Hematoxylin and eosin stains can be used for detection of *T. gondii* in biopsies, but sensitivity is significantly increased if immunoperoxidase staining is used and if experienced laboratories process the specimens.[21]

If safe and feasible, a lumbar puncture should be performed for *T. gondii* PCR, as well as for cytology, culture, cryptococcal antigen, and PCR for *Mycobacterium tuberculosis*, Epstein-Barr virus (EBV), and JC virus (JCV) depending on imaging findings. PCR for cytomegalovirus and varicella-zoster virus, as well as testing for syphilis, may also be considered. Detection of *T. gondii* by PCR in CSF has high specificity (96% to 100%), but low sensitivity (50%), especially once specific anti-*Toxoplasma* therapy has been started.[22-25]

The differential diagnosis of CNS lesions with mass effect in patients with advanced HIV disease most often includes primary CNS lymphoma, tuberculosis, and endemic fungal infection (e.g., cryptococcosis). Lymphoma can be indistinguishable from TE radiographically, both frequently presenting with ring-enhancing lesions, although lymphoma presents more often with a single lesion.[26] In the absence of immune reconstitution inflammatory syndrome (IRIS), progressive multifocal leukoencephalopathy (PML) can be distinguished based on imaging studies. PML lesions typically involve white matter rather than gray matter, are usually non-contrast-enhancing, and produce no mass effect. There are a large number of less common causes of focal neurologic disease including Chagas disease, metastatic tumors, and pyogenic brain abscess, particularly in people who inject drugs.

Given the risks associated with a brain biopsy, and the difficulty in obtaining one at many centers, a presumptive diagnosis of TE is established based on an objective response to empiric therapy.[27] Brain biopsy is then reserved for patients who fail to respond to specific therapy, although earlier biopsy should be strongly considered if results from imaging, serology, or CSF PCR do not confirm toxoplasmosis or suggest an etiology other than toxoplasmosis. In patients with contrast-enhancing lesions, detection of EBV in the CSF by PCR should raise concern for CNS lymphoma, especially

when quantitative results show CSF levels above 10,000 EBV copies/mL; however, it is not diagnostic by itself.[28-30] In people with HIV receiving ART, PML-IRIS may also present with contrast-enhancing lesions, in which case JCV by PCR in CSF is highly suggestive of PML.[31]

Preventing Exposure

People with HIV should be counseled regarding sources of *Toxoplasma* infection. Those with CD4 counts <200 cells/mm^3 should be tested for IgG antibody to *Toxoplasma* soon after they are diagnosed with HIV to detect latent infection with *T. gondii* (**BIII).**

To minimize risk of acquiring toxoplasmosis, people with HIV, especially those with CD4 counts <200 cells/mm^3, should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison, and not to eat raw shellfish, including oysters, clams, and mussels **(BIII).** Lamb, beef, venison, and pork should be cooked to an internal temperature of 165 °F to 170 °F;[32] meat cooked until it is no longer pink inside usually has an internal temperature of 165 °F to 170 °F, and therefore, from a more practical perspective, satisfies this requirement. People with HIV should wash their hands after contact with raw meat and after gardening or other contact with soil; they should also wash fruits and vegetables well before eating them raw **(BIII).**

Cat owners with HIV whose CD4 counts are <200 cells/mm^3 and who are seronegative should be advised to have a nonpregnant person without HIV change the litter box daily. If a person with HIV must change the litter box themselves, they should wear gloves and wash their hands thoroughly afterward **(BIII).** They also should be encouraged to keep their cats inside and not to adopt or handle stray cats **(BIII).** Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII).** People with HIV do not need to be advised to part with their cats or to have their cats tested for toxoplasmosis **(BIII).**

Preventing Disease

Recommendations for Preventing First Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis)
Indications for Initiating Primary Prophylaxis
• *Toxoplasma* IgG positive patients with CD4 count <100 cells/mm^3 (AII)
Note: Listed regimens are also effective against PCP.
Preferred Regimen
• TMP-SMX one DS PO daily (AII)
Alternative Regimens
• TMP-SMX one SS PO daily (BIII), *or*
• Dapsone[a] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI), *or*
• (Dapsone[a] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (CI), *or*
• Atovaquone[b] 1,500 mg PO daily (CIII), *or*

• (Atovaquone[b] 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily (CIII) Indication for Discontinuing Primary Prophylaxis • CD4 count >200 cells/mm^3 for >3 months and sustained HIV RNA below limits of detection in response to ARV therapy (AI); *or* • Can consider if CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limits of detection for at least 3–6 months (BII) Indication for Restarting Primary Prophylaxis • CD4 count <100 cells/mm^3 (AIII) • CD4 count 100–200 cells/mm^3 and HIV RNA above detection limits (AIII)
Pregnancy Considerations
Indication, drugs, and doses are the same as for all people with HIV.

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

[b] Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

Indication for Primary Prophylaxis

Toxoplasma-seropositive people who have CD4 counts <100 cells/mm^3 should receive prophylaxis against TE **(AII).**[33,34]

The preferred primary prophylaxis regimen is one double-strength tablet daily of TMP-SMX **(AII).** This is also the preferred prophylaxis regimen for *Pneumocystis jirovecii* pneumonia (PCP), which all people at risk for toxoplasmosis are also at risk for developing. TMP-SMX, one double-strength tablet three times weekly, is an alternative **(BII).** TMP-SMX, one single-strength tablet daily, is also an option **(BIII).** If TMP-SMX cannot be tolerated, the recommended alternative is dapsone plus pyrimethamine plus leucovorin, which also is effective against PCP (see table for rating based on dapsone and pyrimethamine doses).[35-37] Atovaquone with or without pyrimethamine plus leucovorin is active against PCP and can also be considered for toxoplasmosis **(CIII).** For people in whom other alternatives are not possible, pyrimethamine (plus leucovorin) alone may have some efficacy as primary prophylaxis **(CIII).**[14] Aerosolized pentamidine does not protect against TE and **is not recommended** for anti-*Toxoplasma* prophylaxis **(AI).**[33,38]

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued in adults and adolescents with HIV receiving ARV therapy with sustained suppression of plasma HIV RNA levels below the detection limits of available assays whose CD4 counts increase to >200 cells/mm^3 for more than 3 months **(AI).**[39-43] In this setting primary TE prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, likelihood of development of drug-resistant pathogens, and cost.

A combined analysis of 10 European cohorts found a low incidence of TE in patients with CD4 counts between 100 and 200 cells/mm^3, who were receiving ARVs and had HIV RNA plasma viral loads <400 copies/mL, and who had stopped or never received TE prophylaxis; this observation suggests that primary TE prophylaxis can be safely discontinued in patients with CD4 counts 100 to 200 cells/mm^3 and HIV plasma RNA levels below limits of detection with commercial assays.[44] Similar observations have been made with regard to stopping primary or secondary prophylaxis for PCP.[44-46] Some clinicians would stop primary prophylaxis in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 if HIV plasma RNA levels remain below limits of detection for ≥3 months to 6 months; definitive data for a more precise recommendation are lacking **(BII).**[44]

Treating Disease

Recommendations for Treating Toxoplasmosis

Preferred Regimens for Acute Infection

- Pyrimethamine 200 mg PO once, followed by weight-based dosing (AI):
  - Body weight ≤60 kg: pyrimethamine 50 mg PO daily + sulfadiazine 1,000 mg PO every 6 hours + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or twice daily)
  - Body weight >60 kg: pyrimethamine 75 mg PO daily + sulfadiazine 1,500 mg PO every 6 hours + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or twice daily)

or

- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) twice daily (AII)

Note: If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (AII).

Alternative Regimens for Acute Infection

- (Pyrimethamine + leucovorin)[c] plus clindamycin 600 mg IV or PO every 6 hours (AI); preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine[b]-sulfadiazine; must add additional agent for PCP prophylaxis (AII), *or*
- Atovaquone[b] 1,500 mg PO twice daily + (pyrimethamine + leucovorin)[c] (BII), *or*
- Atovaquone[b] 1,500 mg PO twice daily + sulfadiazine[d] (BII), *or*
- Atovaquone[b] 1,500 mg PO twice daily (BII)
- For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies (BI).
- During the desensitization phase, atovaquone 1,500 mg PO should be administered twice daily until therapeutic doses of TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) twice daily are achieved (CIII).

Total Duration for Treating Acute Infection

- At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks
- After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below.

Chronic Maintenance Therapy for *Toxoplasma gondii* Encephalitis

Preferred Regimens

- Pyrimethamine 25–50 mg PO daily + sulfadiazine 2,000–4,000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily (AI), *or*
- TMP-SMX DS one tablet twice daily (AII)

Alternative Regimens

- (Pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily plus clindamycin 1,800 mg PO daily dose (in 3 or 4 divided doses) (BI); must add additional agent to prevent PCP (AII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily (BII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily + sulfadiazine 2,000–4,000 mg PO daily (in 2 to 4 divided doses) (BII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily (BII)

Criteria for Discontinuing Chronic Maintenance Therapy (BI)

- Successfully completed initial therapy, *and*
- Asymptomatic of signs and symptoms of TE, *and*
- CD4 count >200 cells/mm^3 for >6 months in response to ARVs

Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance

- CD4 count <200 cells/mm^3 regardless of HIV RNA level (AIII)

Other Considerations

- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat a mass effect associated with focal lesions or associated edema (BIII) or for control of clinically significant IRIS symptoms in conjunction with ART and anti-*Toxoplasma* therapy (CIII); discontinue as soon as clinically feasible. For patients in whom the diagnosis of TE is presumptive based in part on clinical response, one needs to be careful as CNS lymphoma may also respond to steroids clinically and radiologically.
- Antiseizure medications should be administered to patients with TE and associated seizures (AII) and continued through at least the period of acute treatment (BII); antiseizure medications should not be used as prophylaxis in patients without seizures (BII).

Pregnancy Considerations

Suspected or Confirmed Acute Toxoplasmosis During Pregnancy

Initial Therapy (Primary Infection During Pregnancy or Symptomatic Reactivation of T. gondii *Without Encephalitis)*

- Initiation of therapy before 14 weeks of pregnancy: spiramycin administered orally at a dosage of 1.0 g (or 3 million U) every 8 hours (total dosage of 3 g or 9 million U per day) (AII)
- Initiation of therapy on or after 14 weeks of pregnancy: pyrimethamine (50 mg PO twice daily x 2 days, then 50 mg PO daily) + sulfadiazine (75 mg/kg PO x 1 day, then 50 mg/kg PO twice daily) + leucovorin (10–20 mg/day during and 1 week after pyrimethamine use) (AII)

Fetal Assessment

- Amniocentesis for toxoplasmosis PCR to be done at 18 weeks gestation or later (BIII)
- Fetal ultrasonography every 4 weeks until delivery (AIII)
- If no evidence of fetal infection (negative amniotic fluid PCR, no fetal ultrasonographic abnormalities), continue initial therapy.

Treatment of *Toxoplasma* Encephalitis During Pregnancy

- Treatment regimen is the same as for all people with HIV (BIII).
- In general, pyrimethamine should be avoided in the first trimester of pregnancy because of teratogenicity concerns, but in the case of TE, the benefit of using pyrimethamine to the woman outweighs the risk to the fetus.

Fetal Infection

Criteria for Initiating Treatment for Fetal Infection

- Positive amniotic fluid PCR, *and/or*
- Fetal ultrasonographic findings suggestive of congenital toxoplasmosis

Treatment for Fetal Infection

- Pyrimethamine + sulfadiazine + leucovorin until delivery (AII)

Note: If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX DS one tablet twice daily plus spiramycin 1 g PO three times a day plus leucovorin 4 mg daily should be utilized in place of pyrimethamine-sulfadiazine (BII).

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

[b] Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

[c] Pyrimethamine and leucovorin doses: Same doses and frequency as listed in Preferred Regimen for Acute Infection

[d] Sulfadiazine dose: Same as weight-based dose and frequency listed in Preferred Regimen for Acute Infection

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CNS = central nervous system; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PO = orally; SMX = sulfamethoxazole; TE = *Toxoplasma* encephalitis; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

For many years, the initial therapy of choice for TE has been the combination of pyrimethamine plus sulfadiazine plus leucovorin **(AI).**[2,47-49] Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.[50] Leucovorin reduces the likelihood of hematologic toxicities associated with pyrimethamine therapy.[51] Pyrimethamine, however, has become extremely expensive and can be difficult to obtain in the United States.

TMP-SMX has been used with increasing frequency as a preferred regimen **(AII),** although large, randomized trials comparing TMP-SMX to pyrimethamine plus sulfadiazine have not been performed. In a small (77 patients) randomized trial, TMP-SMX was reported to be as effective and better tolerated than pyrimethamine-sulfadiazine.[52] Others have reported similar efficacy of TMP-SMX to pyrimethamine plus sulfadiazine in open-label observational studies.[53,54] A recent meta-analysis found that TMP-SMX was as effective as pyrimethamine plus sulfadiazine, but was associated with less toxicity.[55] If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be utilized **(AII).**

Pyrimethamine plus leucovorin plus clindamycin[47,48] is the preferred alternative regimen for patients with TE who cannot tolerate sulfa drugs or do not respond to first-line therapy **(AI).** This combination, however, does not prevent PCP, therefore additional PCP prophylaxis must be administered when it is used **(AII)** (see discussion under Preventing Recurrence).[56]

For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies **(BI).**[57-62] During the desensitization period, atovaquone with or without pyrimethamine should be administered until therapeutic doses of TMP-SMX are achieved **(CIII).**

No well-studied options exist for patients who cannot take an oral regimen. No parenteral formulation of pyrimethamine exists and the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Some specialists will use intravenous TMP-SMX **(BII)** or oral pyrimethamine plus parenteral clindamycin **(CIII)** as initial treatment in severely ill patients who require parenteral therapy**.**

Atovaquone (with meals or oral nutritional supplements) plus pyrimethamine plus leucovorin, atovaquone plus sulfadiazine, or (for patients intolerant of both pyrimethamine and sulfadiazine) atovaquone as a single agent also have been shown to be effective in treating TE **(BII).**[63,64,65] However, the relative efficacy of atovaquone-containing regimens compared with other regimens is unknown. Clinicians should be aware that the absorption of the drug varies substantially from patient to patient; plasma levels >18.5 µg/mL are associated with an improved response rate but atovaquone therapeutic drug monitoring is not routinely available.[64-66]

The following regimens have been reported to have activity in treatment of TE in small cohorts of patients or in case reports of one or several patients: azithromycin plus pyrimethamine plus leucovorin **(CII)**[67,68]; clarithromycin plus pyrimethamine plus leucovorin **(CIII)**[69]; 5-fluorouracil plus clindamycin **(CIII)**[70]; dapsone plus pyrimethamine plus leucovorin **(CIII)**[71]; and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin **(CIII).**[72,73] There is rarely a reason to use one of these regimens.

Clinical response to acute therapy occurs in ~90% of patients with TE within 14 days of initiating appropriate anti-*Toxoplasma* treatment.[2] The reasons why some patients fail therapy are not well understood; whether such failures are due to poor adherence, other host factors, or antimicrobial resistance has not been well delineated. Acute therapy for TE should be continued for 6 weeks, if there is clinical and radiologic improvement **(BII).**[1-4] Longer courses may be necessary if clinical or radiographic disease is extensive or response is incomplete at 6 weeks. After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below (see Preventing Recurrence section below). The radiologic goals for treatment include resolution of the lesion(s) in terms of size, contrast enhancement, and associated edema, although residual contrast-enhancing lesions may persist for prolonged periods, especially in people with HIV receiving ARVs.[74]

Adjunctive Therapies

Adjunctive corticosteroids such as dexamethasone should only be used for treatment of patients with TE when they are clinically indicated to treat a mass effect associated with focal lesions or associated edema **(BIII).** In those treated with corticosteroids, caution may be needed in diagnosing CNS toxoplasmosis on the basis of treatment response, since primary CNS lymphoma may respond clinically and radiographically to corticosteroids alone; these patients should be monitored carefully as corticosteroids are tapered. In addition, corticosteroids should be discontinued as soon as clinically feasible because of their potential to cause immunosuppression. Patients receiving corticosteroids should be monitored closely for development of other opportunistic infections (OIs), including cytomegalovirus retinitis and tuberculosis.

Antiseizure medications should be administered to patients with TE associated with seizures **(AII)** but **should not be administered** prophylactically to patients **without seizures (BII).** Anticonvulsants, if indicated, should be continued at least through the period of acute therapy **(BII).**

Special Considerations Regarding ART Initiation (Including IRIS)

There are no data on which to base a recommendation regarding when to start ARV therapy in people with HIV and TE. However, many physicians would initiate ARV therapy within 2 to 3 weeks after the diagnosis of toxoplasmosis, based on the significantly lower incidence of AIDS progression or death (a secondary study endpoint) seen in the early ARV therapy arm of a controlled trial of 282 patients with OIs other than tuberculosis (only 5% of whom had toxoplasmosis) who were randomized to early (median 12 days after initiation of OI therapy) versus deferred (median 45 days) initiation of ARV therapy.[75]

IRIS associated with TE has been reported but appears to be rare (~5% in one report).[76-78] Most cases develop as paradoxical worsening with increase in the size and number of lesions, peri-lesional edema, and an increase in contrast enhancement on MRI.[77,79,80] As for IRIS with other infections, corticosteroid therapy, dosed to control symptoms, can be administered in patients with clinically significant symptoms in conjunction with ARVs and anti-*Toxoplasma* therapy **(CIII).**

Monitoring of Response to Therapy and Adverse Events

Changes in antibody titers are not useful for monitoring responses to therapy. People with HIV with TE should be monitored routinely for adverse events and clinical and radiologic improvement **(AIII).**

Neurological improvement will occur by 14 days in over 90% of patients[2]; if no improvement is seen by that time, other diagnoses should be considered. Repeat imaging can be considered at 3 and 6 weeks, or sooner for clinical deterioration.[2] After 6 weeks, maintenance therapy at ~50% of treatment doses should be initiated assuming a clinical response has been seen.

Common pyrimethamine toxicities such as rash, nausea, and bone marrow suppression (neutropenia, anemia, and thrombocytopenia) often can be reversed by increasing the leucovorin dose to 10, 25, or 50 mg four times daily **(CIII).** Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, renal insufficiency, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Common atovaquone toxicities include nausea, vomiting, diarrhea, rash, headache, hepatotoxicity, and fever. Drug interactions between certain anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine), dexamethasone and antiretroviral (ARV) agents should be evaluated carefully; if necessary, doses should be adjusted, or alternative anticonvulsants or ARV agents should be used.

Managing Treatment Failure

A brain biopsy should be strongly considered in patients who did not have an initial biopsy prior to therapy and who fail to respond to initial therapy for TE **(BII)** as defined by clinical or radiologic deterioration during the first week despite adequate therapy, or who do not show clinical improvement within 10 to 14 days. A switch to an alternative regimen, as previously described, should be considered for those who undergo brain biopsy and have confirmed histopathologic

evidence of TE, or who have a CSF PCR positive for *T. gondii* **(BIII).** In patients who adhere to their regimens, disease recurrence is unusual in the setting of chronic maintenance therapy after an initial clinical and radiographic response.

Preventing Recurrence

When to Start Chronic Maintenance Therapy

Patients who have completed initial therapy for TE should be given chronic maintenance therapy to suppress infection **(AI)**[47,48] until immune reconstitution occurs as a consequence of ARV therapy. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE **(AI)** and provides protection against PCP **(AII).** Although sulfadiazine is routinely dosed as a four-times-a-day regimen, a pharmacokinetic study suggests bioequivalence for the same total daily dose when given either twice or four times a day,[81] and limited clinical experience suggests that twice-daily dosing is effective.[82]

For patients being treated with TMP-SMX, this drug should be continued as chronic maintenance at a reduced dose of one double-strength tablet twice daily **(AII).**[52] A small, uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin to reduce pill burden.[83]

Pyrimethamine plus leucovorin plus clindamycin is commonly used as suppressive therapy for patients with TE who cannot tolerate sulfa drugs **(BI).** Because of the high failure rate observed with lower doses,[47] a dose of 1,800 mg clindamycin daily in 3 or 4 divided doses is recommended. Because this regimen does not provide protection against PCP **(AII),**[56] an additional agent, such as dapsone or aerosol pentamidine, must be used. Atovaquone also is active against both TE[65,66] and PCP[84] and can be used alone, with sulfadiazine, or with pyrimethamine and leucovorin in patients with TE **(BII).**

When to Stop Chronic Maintenance Therapy

Chronic maintenance therapy for TE can be discontinued in adults and adolescents with HIV, if they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increased CD4 count to >200 cells/mm^3 for >6 months in response to ARV therapy **(BI),** although occasional recurrences have been reported.[40,43,85,86] As part of the evaluation to determine whether discontinuation of therapy is appropriate, some specialists recommend obtaining an MRI of the brain to assess for resolution of brain lesions, although residual contrast-enhancing lesions can be seen for prolonged periods in some ARV-treated patients.

When to Restart Primary Prophylaxis or Maintenance Therapy

Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(AIII)** regardless of the HIV plasma viral load. Based on results from the COHERE study, an observational study of multiple cohorts, primary prophylaxis may not need to be restarted in patients with CD4 counts of 100 to 200 cells/mm^3 who have had HIV plasma RNA levels below limits of detection for at least 3 to 6 months **(BII).**[44,45] For patients with CD4 counts of 100 to 200 cells/mm^3 with HIV plasma viral load above detection limits of the utilized assay, PCP prophylaxis should be reintroduced, and most, but not all, regimens will provide prophylaxis for toxoplasmosis as well **(AIII).**

Because there are no published data examining the risk of recurrence in patients stopping chronic maintenance therapy for TE when the CD4 count is between 100 and 200 cells/mm^3, and recurrent TE can be debilitating and potentially life-threatening, maintenance therapy should be reintroduced if the CD4 count decreases to <200 cells/mm^3 **(AIII)** regardless of the HIV plasma viral load.[87]

Special Considerations During Pregnancy

Diagnosis During Pregnancy

During pregnancy, documentation of baseline *T. gondii* serologic status (IgG only) should be obtained because of concerns regarding congenital toxoplasmosis. Although perinatal transmission of *T. gondii* normally occurs only with acute infection in the immunocompetent host, case reports have documented transmission with reactivation of chronic infection in pregnant women with HIV with severe immunosuppression.[88-92] Knowing toxoplasmosis serostatus at the beginning of pregnancy may be helpful in delineating future risks and interpreting serologic testing performed later in pregnancy should there be heightened concerns for maternal infection and/or fetal transmission.

Toxoplasma infection during pregnancy is usually asymptomatic. Non-specific symptoms may include fever, fatigue, headache, and myalgia after a 5- to 23-day incubation period. In the setting of parasitemia during pregnancy, the placenta may become infected and result in fetal infection. The risk of congenital toxoplasmosis (infection of the fetus) is highest in the setting of a primary infection during pregnancy as compared to reactivation. While the risk of transmission to the fetus increases with gestational age, with the highest risk in the third trimester, the sequelae to the fetus are more severe when toxoplasmosis is acquired early in gestation.[93,94]

Toxoplasmosis diagnostic considerations are not affected by pregnancy. Primary *T. gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, immunoglobulin A, and immunoglobulin E antibodies; IgG avidity; and the differential agglutination tests.[95,96] Because serologic testing is often difficult to interpret and prompt treatment and counseling is particularly important during pregnancy, people with HIV with suspected primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine specialist where available. The care team may elect to access specialized laboratory testing[96,97] (e.g., the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory [PAMF-TSL], Palo Alto, CA, at 650-853-4828 and toxolab@pamf.org; and the National Collaborative Chicago-based Congenital Toxoplasmosis Study [NCCCTS], Toxoplasmosis Center, Chicago, IL, 773-834-4130, eFax 773-834 3577 and rmcleod@midway.uchicago.edu).

Screening

The value of routine toxoplasmosis screening programs is debated in the United States but generally accepted in other countries. In countries such as France where screening and treatment for *T. gondii* during pregnancy is universal, offspring who acquire toxoplasmosis are reported to have primarily mild disease and rarely severe disease. In contrast, in countries without a universal screening program (e.g., United States), offspring who acquire toxoplasmosis mostly present with severe disease.[98] Toxoplasmosis is not a nationally notifiable illness, is only reportable in eight states, and case definitions vary.[12]

Preventing Congenital Infection: Initial Therapy and Surveillance

During pregnancy, evidence of primary toxoplasmic infection without TE should be evaluated and managed in consultation with appropriate specialists **(BIII).** Recent studies support treatment of toxoplasmosis during pregnancy in an effort to decrease congenital transmission and reduce the severity of clinical signs in the offspring.[99-105]

In the setting of primary infection during pregnancy or symptomatic reactivation of *T. gondii*, initial therapy depends on the gestational age at time of acquisition/reactivation.

- For patients presumed to have acquired/reactivated infection at less than 14 weeks gestation, spiramycin is recommended to prevent congenital transmission **(AII).** Spiramycin is not commercially available in the United States. To obtain spiramycin, the provider must call the U.S. Food and Drug Administration directly (301-796-1400) after consultation with PAMF-TSL or NCCCTS (see Diagnosis During Pregnancy for contact information). A clinical pharmacist will assist with the proper paperwork.
- For patients presumed to have acquired/reactivated infection at 14 weeks gestation or beyond, pyrimethamine plus sulfadiazine plus leucovorin is recommended, as the risk of fetal transmission is higher **(AII).** If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, a combination of TMP-SMX, spiramycin, and leucovorin should be utilized in place of pyrimethamine-sulfadiazine **(BII).**[106,107]

In cases of suspect primary or symptomatic reactivation of *T. gondii* during pregnancy, detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done monthly regardless of gestational age at the time of diagnosis **(AIII).**[96] In addition, patients should undergo an amniocentesis with PCR testing for *T. gondii* DNA in the amniotic fluid.[108] Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in people receiving ARV therapy.[109] Therefore, PCR of amniotic fluid can be considered during gestation in pregnant women on ARV therapy with serologic evidence of recently acquired *Toxoplasma* infection; women suspected to have reactivated their *Toxoplasma* latent infection during pregnancy; and those with ultrasound findings suggestive of fetal *T. gondii* infection **(BIII).**[96] In an effort to minimize false-negative results, amniotic fluid testing for *T. gondii* PCR should be avoided at less than 18-week gestation.[110]

Congenital Infection

For patients whose evaluations do not suggest congenital infection (i.e., no ultrasound findings and negative amniotic fluid PCR), initial therapy should be continued until delivery. For patients started on spiramycin as initial therapy who are found to have a positive PCR in the amniotic fluid and/or ultrasound findings concerning for congenital transmission, therapy should be escalated to pyrimethamine/sulfadiazine/leucovorin **(AII),** or if pyrimethamine is unavailable, TMP-SMX, spiramycin, and leucovorin **(AII).**

Pediatric-care providers should be informed about mothers with HIV who have suspected or confirmed *T. gondii* infection to allow evaluation of their neonates for evidence of congenital infection **(AIII).**

Toxoplasma *Encephalitis During Pregnancy*

During pregnancy, treatment of TE should be the same as in other adults with HIV **(BIII),** including pyrimethamine plus sulfadiazine plus leucovorin **(AIII),** and in consultation with appropriate specialists **(BIII).**[2,47-49] In general pyrimethamine should be avoided in the first trimester of pregnancy because of teratogenicity concerns, but in the case of TE, the benefit of using pyrimethamine to the mother outweighs the risk to the fetus. Of note, this regimen is often used in the treatment of fetuses with toxoplasmosis.[96] The preferred alternative regimen for pregnant women with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin **(AIII).**[47,48] If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin **(BIII).**

Prophylaxis During Pregnancy

During pregnancy, the indications for primary prophylaxis for TE, and the medications and dosages used, are the same as for other persons with HIV. TMP-SMX is the preferred therapy. The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk of TE. Secondary prophylaxis should be provided, using the same indications as for other people with HIV. Over the past several decades, dapsone (also used for primary prophylaxis) has been used safely in pregnancy to treat leprosy, malaria, and various dermatologic conditions.[111,112] Dapsone appears to cross the placenta.[111,113]

When providing preconception care for women of pregnancy potential with HIV who are receiving TE prophylaxis, providers should discuss the option of deferring pregnancy until TE prophylaxis can be safely discontinued **(BIII).**

Pregnancy-Specific Medication Concerns

Spiramycin is recommended to prevent transmission at <14 weeks gestation in the setting of acute primary infection during pregnancy or symptomatic reactivation of *T. gondii* **(AII).**[104,106,114] Spiramycin is not commercially available in the United States. Please see Preventing Congenital Infection: Initial Therapy and Surveillance on how to obtain spiramycin.

Pyrimethamine to prevent transmission should be avoided in the first trimester because of teratogenicity concerns with birth defects in animals, however it is recommended as first-line treatment for maternal TE **(BIII),** where the benefit of using pyrimethamine in a pregnant woman outweighs the risk to the fetus. Additionally, pyrimethamine is often used in the setting of a positive fetal diagnosis.[115,116] Pyrimethamine can be administered after the first trimester since human data have not suggested an increased risk of birth defects.[117-121]

Sulfadiazine appears safe in pregnancy, without clear evidence of adverse fetal or neonatal outcome.[122,123] Although there are no studies published to date directly linking late third-trimester maternal sulfadiazine to neonatal death or kernicterus, the infant's care provider should be notified of maternal sulfa use in late pregnancy.

Clindamycin, suggested as part of an alternative regimen for patients with TE, is considered safe throughout pregnancy. Atovaquone, used both for prophylaxis and treatment of TE, may be used if indicated. While there are limited data on atovaquone safety in human pregnancy, preclinical studies

have not demonstrated maternal or fetal toxicity.[118] As noted above, dapsone has been used safely in pregnant women for TE prophylaxis though with long-term therapy, there is a risk of mild hemolysis and a potential—although extremely low—risk of hemolytic anemia in exposed fetuses with glucose-6-phosphate dehydrogenase (or G6PD) deficiency.[111,124]

A detailed discussion of TMP-SMX and pregnancy, including the use of folic acid, is reviewed in the PCP chapter.

References

1. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet*. 1983;1(8328):781-784. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6132129.
2. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med*. 1993;329(14):995-1000. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8366923.
3. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med*. 1984;100(1):36-42. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6691657.
4. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of *Toxoplasma* infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. *J Acquir Immune Defic Syndr*. 1993;6(4):414-418. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8455146.
5. Boyer KM, Holfels E, Roizen N, et al. Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. *Am J Obstet Gynecol*. 2005;192(2):564-571. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15696004.
6. Siegel SE, Lunde MN, Gelderman AH, et al. Transmission of toxoplasmosis by leukocyte transfusion. *Blood*. 1971;37(4):388-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4927414.
7. Gay J, Gendron N, Verney C, et al. Disseminated toxoplasmosis associated with hemophagocytic syndrome after kidney transplantation: a case report and review. *Transpl Infect Dis*. 2019;21(5):e13154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31373746.
8. Ramanan P, Scherger S, Benamu E, et al. Toxoplasmosis in non-cardiac solid organ transplant recipients: a case series and review of literature. *Transpl Infect Dis*. 2020;22(1):e13218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31769583.
9. Vanjak A, Canoui E, Honsel V, et al. Early primary toxoplasmosis transmitted by liver graft: a case report. *Infect Dis Now*. 2021;51(3):315-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33934813.
10. Safarpour H, Cevik M, Zarean M, et al. Global status of *Toxoplasma gondii* infection and associated risk factors in people living with HIV. *AIDS*. 2020;34(3):469-474. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31714356.
11. Jones JL, Kruszon-Moran D, Elder S, et al. Toxoplasma gondii infection in the United States, 2011-2014. *Am J Trop Med Hyg*. 2018;98(2):551-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29260660.
12. McCall J, Rothfeldt L, Giesbrecht K, et al. Public health surveillance and reporting for human toxoplasmosis - six states, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(28):889-893. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35834417.
13. Abgrall S, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French Hospital Database on HIV. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active

antiretroviral therapy era. *Clin Infect Dis*. 2001;33(10):1747-1755. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11595976.
14. Leport C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. *J Infect Dis*. 1996;173(1):91-97. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8537688.
15. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA*. 1984;252(7):913-917. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6748191.
16. Gray F, Gherardi R, Wingate E, et al. Diffuse "encephalitic" cerebral toxoplasmosis in AIDS.Report of four cases. *J Neurol*. 1989;236(5):273-277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2760644.
17. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes R. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. *Magn Reson Imaging*. 1990;8(1):51-57. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2325518.
18. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. *Ann Intern Med*. 1995;123(8):594-598. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7677300.
19. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from *Toxoplasma* encephalitis in AIDS patients. *AJNR Am J Neuroradiol*. 1994;15(10):1885-1894. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7863938.
20. Derouin F, Leport C, Pueyo S, et al. Predictive value of Toxoplasma gondii antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. ANRS 005/ACTG 154 Trial Group. *AIDS*. 1996;10(13):1521-1527. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8931787.
21. Conley FK, Jenkins KA, Remington JS. *Toxoplasma gondii* infection of the central nervous system. Use of the peroxidase-antiperoxidase method to demonstrate *Toxoplasma* in formalin fixed, paraffin embedded tissue sections. *Hum Pathol*. 1981;12(8):690-698. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7026410.
22. Robert-Gangneux F, Darde ML. Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin Microbiol Rev*. 2012;25(2):264-296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22491772.
23. Novati R, Castagna A, Morsica G, et al. Polymerase chain reaction for *Toxoplasma gondii* DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS*. 1994;8(12):1691-1694. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7888118.
24. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997;11(1):1-17. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9110070.
25. Mesquita RT, Ziegler AP, Hiramoto RM, Vidal JE, Pereira-Chioccola VL. Real-time quantitative PCR in cerebral toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *J Med Microbiol*. 2010;59(Pt 6):641-647. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20150319.

26. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg*. 1990;73(5):720-724. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2213162.
27. Raffi F, Aboulker JP, Michelet C, et al. A prospective study of criteria for the diagnosis of toxoplasmic encephalitis in 186 AIDS patients. The BIOTOXO Study Group. *AIDS*. 1997;11(2):177-184. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9030364.
28. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. 1997;48(3):687-694. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9065549.
29. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. *J Clin Oncol*. 1999;17(2):554-560. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10080599.
30. Corcoran C, Rebe K, van der Plas H, Myer L, Hardie DR. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. *J Clin Virol*. 2008;42(4):433-436. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18455472.
31. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(2):253-260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9932940.
32. U.S. Department of Health and Human Services. FoodSafety.gov: your gateway to federal food safety information. Available at: https://www.foodsafety.gov Accessed: March 26
33. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. 1992;117(2):106-111. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1351371.
34. Miro JM, Murray HW, Katlama C. Toxoplasmosis. R. Dolin, H. Masur and M. S. Saag, eds.In. AIDS Therapy Third.ed New York, New York. Churchill Livingstone 2008:659-681. Accessed: September 22, 2022.
35. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. 1995;122(10):755-761. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7717598.
36. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1995;20(3):531-541. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7756472.
37. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. 1993;328(21):1514-1520. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8479488.

38. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):693-699. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7854375.
39. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10915098.
40. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. 1999;13(13):1647-1651. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10509565.
41. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. *Lancet*. 2000;355(9222):2217-2218. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10881897.
42. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. 2000;181(5):1635-1642. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10823763.
43. Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of primary and secondary *Toxoplasma gondii* prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. *Clin Infect Dis*. 2006;43(1):79-89. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16758422.
44. Miro J, Esteve A, Furrer H, Opportunistic Infection Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Safety of stopping primary *T. gondii* prophylaxis with suppressed viremia and CD4>100. Presented at: Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: https://www.croiconference.org/sessions/safety-stopping-primary-t-gondii-prophylaxis-suppressed-viremia-and-cd4100.
45. Opportunistic Infections Project Team of the Collaboration of Observational HIVERiE, Mocroft A, Reiss P, et al. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611-619. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20645862.
46. Atkinson A, Miro JM, Mocroft A, et al. No need for secondary *Pneumocystis jirovecii* pneumonia prophylaxis in adult people living with HIV from Europe on ART with suppressed viraemia and a CD4 cell count greater than 100 cells/microL. *J Int AIDS Soc*. 2021;24(6):e25726. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34118121.
47. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. 1996;22(2):268-275. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8838183.

48. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med*. 1992;116(1):33-43. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1727093.
49. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Efficacy of long-term continuous therapy. *Am J Med*. 1988;84(1):94-100. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3337134.
50. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS*. 1992;6(9):1040-1041. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1388895.
51. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for *Toxoplasma* encephalitis are associated with better outcome. *J Infect Dis*. 1996;173(5):1294-1295. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8627092.
52. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother*. 1998;42(6):1346-1349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9624473.
53. Pellegrino D, Gryschek R, de Oliveira ACP, Marcusso R, Correia A, Vidal JE. Efficacy and safety of trimethoprim-sulfamethoxazole in HIV-infected patients with cerebral toxoplasmosis in Brazil: a single-arm open-label clinical trial. *Int J STD AIDS*. 2019;30(12):1156-1162. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31558125.
54. Beraud G, Pierre-Francois S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994–2006. *Am J Trop Med Hyg*. 2009;80(4):583-587. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19346380.
55. Prosty C, Hanula R, Levin Y, Bogoch, II, McDonald EG, Lee TC. Revisiting the evidence base for modern-day practice of the treatment of toxoplasmic encephalitis: a systematic review and meta-analysis. *Clin Infect Dis*. 2023;76(3):e1302-e1319. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35944134.
56. Girard PM, Lepretre A, Detruchis P, Matheron S, Coulaud JP. Failure of pyrimethamine-clindamycin combination for prophylaxis of *Pneumocystis carinii* pneumonia. *Lancet*. 1989;1(8652):1459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2567474.
57. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. 2004;24(3):425-443, vi. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15242719.
58. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis*. 1995;20(4):849-853. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7795084.
59. Nguyen MT, Weiss PJ, Wallace MR. Two-day oral desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients. *AIDS*. 1995;9(6):573-575. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7662195.
60. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse

reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11574913.
61. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol*. 1998;102(6 Pt 1):1033-1036. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9847446.
62. Bonfanti P, Pusterla L, Parazzini F, et al. The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicentric study. C.I.S.A.I. Group. *Biomed Pharmacother*. 2000;54(1):45-49. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10721462.
63. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. *Clin Infect Dis*. 2002;34(9):1243-1250. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11941551.
64. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. *Lancet*. 1992;340(8820):637-638. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1355212.
65. Torres RA, Weinberg W, Stansell J, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. *Clin Infect Dis*. 1997;24(3):422-429. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9114194.
66. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. *AIDS*. 1996;10(10):1107-1112. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8874627.
67. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):853-856. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8112357.
68. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. 2001;15(5):583-589. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11316995.
69. Fernandez-Martin J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute *Toxoplasma* encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. 1991;35(10):2049-2052. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1836943.
70. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS*. 1993;7(1):143-144. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8442914.
71. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-*Toxoplasma* effects of dapsone alone and combined with pyrimethamine. *Antimicrob Agents Chemother*. 1991;35(2):252-255. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2024957.
72. Lacassin F, Schaffo D, Perronne C, Longuet P, Leport C, Vilde JL. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with

human immunodeficiency virus. *Antimicrob Agents Chemother*. 1995;39(1):276-277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7695324.
73. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis*. 1993;25(1):157-160. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8460343.
74. Coleman B, Smith BR, Kapoor R, et al. Persistence of human immunodeficiency virus-associated cerebral toxoplasmosis lesions in successfully treated patients receiving combination antiretroviral therapy. *Open Forum Infect Dis*. 2023;10(5):ofad208. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37213420.
75. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19440326.
76. Pfeffer G, Prout A, Hooge J, Maguire J. Biopsy-proven immune reconstitution syndrome in a patient with AIDS and cerebral toxoplasmosis. *Neurology*. 2009;73(4):321-322. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19636053.
77. Tremont-Lukats IW, Garciarena P, Juarbe R, El-Abassi RN. The immune inflammatory reconstitution syndrome and central nervous system toxoplasmosis. *Ann Intern Med*. 2009;150(9):656-657. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19414855.
78. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. 2011;82(6):691-693. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20660912.
79. Cabral RF, Valle Bahia PR, Gasparetto EL, Chimelli L. Immune reconstitution inflammatory syndrome and cerebral toxoplasmosis. *AJNR Am J Neuroradiol*. 2010;31(7):E65-66. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20507930.
80. van Bilsen WPH, van den Berg C, Rijnders BJA, et al. Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients. *AIDS*. 2017;31(10):1415-1424. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28375874.
81. Jordan MK, Burstein AH, Rock-Kress D, et al. Plasma pharmacokinetics of sulfadiazine administered twice daily versus four times daily are similar in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2004;48(2):635-637. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14742225.
82. Podzamczer D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Spanish Toxoplasmosis Study Group. *Eur J Clin Microbiol Infect Dis*. 2000;19(2):89-95. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10746493.
83. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS*. 2004;18(9):1342-1344. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15362670.
84. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9862944.

85. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2000;14(4):383-386. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10770540.
86. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. 2006;12(7):666-671. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16774564.
87. Miro JM. Stopping secondary TE prophylaxis in suppressed patients with CD4 100-200 is not safe. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA. Available at: https://www.croiconference.org/sessions/stopping-secondary-te-prophylaxis-suppressed-patients-cd4-100-200-not-safe.
88. Marty P, Bongain A, Rahal A, et al. Prenatal diagnosis of severe fetal toxoplasmosis as a result of toxoplasmic reactivation in an HIV-1 seropositive woman. *Prenat Diagn*. 1994;14(5):414-415. Available at: https://pubmed.ncbi.nlm.nih.gov/8084862.
89. Minkoff H, Remington JS, Holman S, Ramirez R, Goodwin S, Landesman S. Vertical transmission of toxoplasma by human immunodeficiency virus-infected women. *Am J Obstet Gynecol*. 1997;176(3):555-559. Available at: https://pubmed.ncbi.nlm.nih.gov/9077606.
90. Biedermann K, Flepp M, Fierz W, Joller-Jemelka H, Kleihues P. Pregnancy, immunosuppression and reactivation of latent toxoplasmosis. *J Perinat Med*. 1995;23(3):191-203. Available at: https://pubmed.ncbi.nlm.nih.gov/8568611.
91. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. European Collaborative Study and Research Network on Congenital Toxoplasmosis. *Eur J Obstet Gynecol Reprod Biol*. 1996;68(1-2):93-96. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8886688.
92. Campos FA, Andrade GM, Lanna Ade P, Lage BF, Assumpção MV, Pinto JA. Incidence of congenital toxoplasmosis among infants born to HIV-coinfected mothers: case series and literature review. *Braz J Infect Dis*. 2014;18(6):609-617. Available at: https://pubmed.ncbi.nlm.nih.gov/25017666.
93. Li XL, Wei HX, Zhang H, Peng HJ, Lindsay DS. A meta analysis on risks of adverse pregnancy outcomes in *Toxoplasma gondii* infection. *PLoS One*. 2014;9(5):e97775. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24830795.
94. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet*. 1999;353(9167):1829-1833. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10359407.
95. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. 2002;185 Suppl 1:S73-82. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11865443.
96. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2008;47(4):554-566. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18624630.
97. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency

virus 1. *Pediatr Infect Dis J*. 1990;9(7):512-518. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2371084.
98. Peyron F, Mc Leod R, Ajzenberg D, et al. Congenital toxoplasmosis in France and the United States: one parasite, two diverging approaches. *PLoS Negl Trop Dis*. 2017;11(2):e0005222. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28207736.
99. Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med*. 2010;7(10). Available at: https://www.pubmed.ncbi.nlm.nih.gov/20967235.
100. Hotop A, Hlobil H, Gross U. Efficacy of rapid treatment initiation following primary *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2012;54(11):1545-1552. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22460980.
101. Kieffer F, Wallon M, Garcia P, Thulliez P, Peyron F, Franck J. Risk factors for retinochoroiditis during the first 2 years of life in infants with treated congenital toxoplasmosis. *Pediatr Infect Dis J*. 2008;27(1):27-32. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18162934.
102. Prusa AR, Kasper DC, Pollak A, Gleiss A, Waldhoer T, Hayde M. The Austrian Toxoplasmosis Register, 1992–2008. *Clin Infect Dis*. 2015;60(2):e4-e10. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25216688.
103. Syrocot Study Group, Thiebaut R, Leproust S, Chene G, Gilbert R. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet*. 2007;369(9556):115-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17223474.
104. Mandelbrot L, Kieffer F, Sitta R, et al. Prenatal therapy with pyrimethamine + sulfadiazine vs spiramycin to reduce placental transmission of toxoplasmosis: a multicenter, randomized trial. *Am J Obstet Gynecol*. 2018;219(4):386 e381-386 e389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29870736.
105. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. *Clin Microbiol Rev*. 2018;31(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30209035.
106. Valentini P, Buonsenso D, Barone G, et al. Spiramycin/cotrimoxazole versus pyrimethamine/sulfonamide and spiramycin alone for the treatment of toxoplasmosis in pregnancy. *J Perinatol*. 2015;35(2):90-94. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25211284.
107. Buonsenso D, Pata D, Turriziani Colonna A, et al. Spyramicine and trimethoprim-sulfamethoxazole combination to prevent mother-to-fetus transmission of *Toxoplasma gondii* infection in pregnant women: a 28-years single-center experience. *Pediatr Infect Dis J*. 2022;41(5):e223-e227. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35175992.
108. de Oliveira Azevedo CT, do Brasil PE, Guida L, Lopes Moreira ME. Performance of polymerase chain reaction analysis of the amniotic fluid of pregnant women for diagnosis of congenital toxoplasmosis: a systematic review and meta-analysis. *PLoS One*. 2016;11(4):e0149938. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27055272.
109. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol*.

2009;200(2):160 e161-169. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18986640.
110. Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. *Obstet Gynecol*. 2001;97(2):296-300. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11165598.
111. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15230645.
112. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. *Trop Med Int Health*. 2003;8(6):488-506. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12791054.
113. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. 1986;11(4):299-315. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3530584.
114. Schneider MO, Faschingbauer F, Kagan KO, et al. Toxoplasma gondii infection in pregnancy - recommendations of the Working Group on Obstetrics and Prenatal Medicine (AGG - Section on Maternal Disorders). *Geburtshilfe Frauenheilkd*. 2023;83(12):1431-1445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38046526.
115. Remington JS MR, Thulliez P, Desmonts G. Toxoplasmosis. Remington JS, O'Klein J, Wilson C and Baker C, eds.In. Infectious diseases of the fetus and newborn infant 6th.ed Amsterdam. Elsevier. 2007:947. Accessed: May 10 ,2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675473.
116. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. *Obstet Gynecol*. 2015;125(6):1510-1525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26000539.
117. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17536875.
118. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1(1):1-15. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18690910.
119. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis*. 1994;18(6):853-861; quiz 862. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8086543.
120. Dunn CS, Beyer C, Kieny MP, et al. High viral load and CD4 lymphopenia in rhesus and cynomolgus macaques infected by a chimeric primate lentivirus constructed using the env, rev, tat, and vpu genes from HIV-1 Lai. *Virology*. 1996;223(2):351-361. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8806570.
121. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. 2001;95(4):424-428. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11579889.

122. Baskin CG, Law S, Wenger NK. Sulfadiazine rheumatic fever prophylaxis during pregnancy: does it increase the risk of kernicterus in the newborn? *Cardiology*. 1980;65(4):222-225. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7388849.
123. Yu PA, Tran EL, Parker CM, et al. Safety of antimicrobials during pregnancy: a systematic review of antimicrobials considered for treatment and postexposure prophylaxis of plague. *Clin Infect Dis*. 2020;70(70 Suppl 1):S37-S50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32435799.
124. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. 1989;82(5):668. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2717998.

Varicella-Zoster Virus Diseases

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Epidemiology

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella-zoster virus (VZV), mostly due to primary VZV infection, known as varicella (or chickenpox).[1] A varicella vaccine became available in the United States in 1995; most children born in the United States after 2005 are immune to varicella as a result of vaccination.[2] Reactivation of latent VZV results in herpes zoster (shingles). In the general population, the incidence of herpes zoster is about 3.6 cases per 1,000 person-years, with much higher incidence seen among elderly and immunocompromised individuals. Before the availability of antiretroviral therapy (ART), the incidence of herpes zoster was more than 15-fold higher among adults with HIV than among age-matched controls without HIV.[3,4] Herpes zoster can occur in adults with HIV at any CD4 T lymphocyte (CD4) cell count, but with CD4 counts <200 cells/mm^3, the risk of disease is higher.[5-8] In addition, HIV viremia is associated with an increased risk for incident herpes zoster.[9] ART has been shown to reduce the incidence of herpes zoster in adults with HIV, presumably because of immune restoration, although the risk of herpes zoster remains threefold higher in adults with HIV than in the general population.[7,10-13] Several studies have demonstrated that the risk of herpes zoster in adults with HIV is increased in the 6-month period immediately after initiation of ART, possibly because of an immune reconstitution inflammatory syndrome (IRIS)-related mechanism.[7,10,13,14]

Clinical Manifestations

Varicella rash tends to have a central distribution, with lesions first appearing on the head, then the trunk, and finally the extremities, evolving through stages of macules, papules, vesicles, pustules, and crusts. The rash is characterized by rapid evolution of lesions during the initial 8 to 12 hours after onset, by successive crops of new lesions, and by the presence of lesions in different stages of development. New vesicle formation continues for 2 to 4 days, accompanied by pruritus, fever, headache, malaise, and anorexia.[15] Primary varicella can cause substantial morbidity in adolescents and adults with HIV. Visceral dissemination, especially VZV pneumonitis, is well documented.[15] Because most adults with HIV in the United States are VZV seropositive, primary varicella is an uncommon occurrence in this population.

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40% to 50% of cases), followed by cranial nerve (20% to 25%), cervical (15% to 20%), lumbar (15%), and sacral (5%) dermatomes.[16] Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles and accompanied by pain, which may be severe. New vesicle formation typically continues for 3 to 5 days, followed by lesion pustulation and scabbing. Crusts typically persist for 2 to 3 weeks. About 20% to 30% of people with HIV have one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes. The probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10%.[5,17] Approximately 10% to 15% of people with HIV report post-herpetic neuralgia as a complication following herpes zoster.[5,18]

When herpes zoster involves the nasociliary branch of the trigeminal nerve, the eye can be affected (herpes zoster ophthalmicus [HZO]), resulting in keratitis (inflammation of the cornea) or anterior uveitis (inflammation of the iris and anterior ciliary body) or both. Vesicles on the tip of the nose (Hutchinson sign) are a clue that the nasociliary branch is involved. With corneal involvement, there may be an initial brief period during which the corneal epithelium is infected with VZV, but the major problem is inflammation of the corneal stroma, which can result in scarring, neovascularization, or necrosis with loss of vision. Stromal keratitis can be chronic. Once it occurs, VZV-associated anterior uveitis also tends to be chronic and can result in increased intraocular pressure or glaucoma, scarring of intraocular tissues, and cataract.

Stromal keratitis and anterior uveitis may not develop immediately after the appearance of skin vesicles on the forehead and scalp; therefore, patients with normal eye examinations initially should receive follow-up eye examinations, even after the skin lesions heal. Antiviral treatment of herpes zoster at the onset of cutaneous lesions reduces the incidence and severity of ophthalmic involvement.

Some patients with HZO may develop late dendriform lesions of the corneal epithelium that contain virus and will respond rapidly to systemic or topical anti-herpetic medications. These lesions are usually painful. In one study, the median time from onset of HZO to development of late dendriform lesions was 5 months, and the risk of recurrences decreased over time.[19] The frequency with which these late infectious lesions occur has not been determined.

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN occurs almost exclusively[20] in patients with AIDS with CD4 counts <100 cells/mm^3. In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of occlusive retinal vasculitis, and multiple discrete peripheral lesions that manifest initially as yellow foci of retinal opacification in the outer retinal layers.[21] PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.[22] Both ARN and PORN are associated with high rates of loss of vision.

People with HIV who have CD4 counts <200 cells/mm^3 are at highest risk of herpes zoster–related complications, including disseminated herpes zoster.[23] The central nervous system (CNS) is a target organ for herpes zoster dissemination in patients coinfected with HIV. Various VZV-related neurologic syndromes occur in people with HIV, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.[24]

Diagnosis

Varicella and herpes zoster are typically distinctive in appearance and usually can be diagnosed clinically. Varicella also can be diagnosed retrospectively by documenting seroconversion (i.e., immunoglobulin G [IgG] antibody negative to positive). In immunocompromised persons, varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); a history of VZV exposure, a rash that began with a dermatomal pattern, and VZV serologic testing to assess prior VZV infection may be helpful to distinguish disseminated herpes zoster from varicella. When lesions are atypical or difficult to distinguish from those due to other potential etiologies (including herpes simplex virus [HSV]), swabs of vesicular fluid from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase

chain reaction (PCR). Additionally, scabs may be adequate specimens for PCR testing. PCR of lesions is the most sensitive and specific method for diagnosis of VZV infections. Histopathology and PCR (of blood or fluids, such as cerebrospinal fluid or vitreous humor) can aid with diagnosis of VZV infections of visceral organs (e.g., pneumonitis, encephalitis, retinitis).[25]

Preventing Exposure

People with HIV who are susceptible to VZV (i.e., people who have no history of chickenpox or shingles, who are seronegative for VZV, and who have no history of vaccination against VZV) should avoid exposure to individuals with varicella or herpes zoster **(CIII).**

Household contacts of people with HIV without evidence of immunity to VZV should be vaccinated to prevent acquisition of varicella and potential transmission of wild-type VZV to susceptible contacts with HIV **(BIII).**

Preventing Disease

Vaccination to Prevent Primary Infection (Varicella)

The live attenuated varicella vaccine (Varivax®) has been documented to be safe and immunogenic in children with HIV who have relatively preserved immune systems (CD4 percentage ≥15%)[26-29] and is recommended for this population of children with HIV.[30] Varicella vaccination of children with HIV also reduces the risk of subsequent herpes zoster.[29,31]

VZV-seronegative adults are potential candidates for varicella vaccination. Some experts would serologically screen adults with HIV without a history of prior varicella or varicella vaccination for VZV IgG. However, the value of this approach may be limited by the lack of sensitivity of commercially available VZV antibody assays (particularly for vaccine-induced antibody).[32,33] No studies have evaluated the vaccine in adolescents or adults with HIV, but many experts recommend varicella vaccination (2 doses, administered 3 months apart) for VZV-susceptible people with HIV aged ≥18 years with CD4 counts ≥200 cells/mm^3 **(BIII).**[34] If varicella vaccination results in disease caused by vaccine virus (a rare event), therapy with acyclovir is recommended **(AIII).** Administration of varicella vaccine to more severely immunocompromised people with HIV (CD4 counts <200 cells/mm^3) is **contraindicated (AIII).** Given the high prevalence of VZV seropositivity in adults, administration of varicella vaccine for adults will be infrequent.

If post-exposure varicella-zoster immune globulin (VariZIG™) has been administered, an interval of at least 5 months is recommended before varicella vaccination **(CIII).**[35] If post-exposure acyclovir has been administered, an interval of at least 3 days is recommended before varicella vaccination **(CIII).**

Pre-Exposure Prophylaxis to Prevent Primary Infection (Varicella)

Long-term prophylaxis with anti-VZV drugs, such as acyclovir or valacyclovir, to prevent varicella **is not recommended (AIII).**

Post-Exposure Prophylaxis to Prevent Primary Infection (Varicella)

For people with HIV who are susceptible to VZV, post-exposure prophylaxis following known or suspected VZV exposure is recommended **(AII).** After close contact with a person who has active varicella or herpes zoster, adolescents and adults with HIV who are susceptible to VZV (particularly those with CD4 counts <200 cells/mm^3) should receive VariZIG as soon as possible (preferably within 96 hours), but up to 10 days after exposure **(AIII).**[36] Given the cost of obtaining VariZIG, it is reasonable to check VZV serology before administering VariZIG to people who do not have a clinical history of chickenpox or shingles and no documentation of varicella vaccination **(AIII).** The risk of VZV transmission is greater with exposure to varicella than localized herpes zoster. In the United States, VariZIG is commercially available from a broad network of specialty distributers (listed at: www.varizig.com). The duration of protection from VariZIG is at least 3 weeks. Patients receiving monthly infusions of high-dose intravenous immune globulin (IVIG >400 mg/kg) are likely to be protected and probably do not require VariZIG if they received a dose of IVIG <3 weeks before VZV exposure. A 5- to 7-day course of post-exposure acyclovir or valacyclovir beginning 7 to 10 days after exposure is recommended by some experts to prevent varicella among VZV-susceptible adolescents or adults with HIV, but this intervention has not been studied in these populations **(BIII).**[37] Among VZV-susceptible immunocompetent children, post-exposure varicella vaccination has been shown to reduce the risk for varicella and is more effective than pre-emptive therapy with antiviral drugs; however, the efficacy of post-exposure varicella vaccination for people with HIV has not been studied and **is not recommended.**

Antiviral Prophylaxis to Prevent Re-Activation Disease (Herpes Zoster)

Long-term administration of anti-VZV drugs to individuals with HIV to prevent episodes of herpes zoster is not routinely recommended **(AII).** However, in a randomized, placebo-controlled study in Africa that evaluated daily acyclovir prophylaxis (acyclovir 400 mg orally [PO] twice a day) administered to people with HIV/HSV-2 coinfection who were not taking ART, acyclovir prophylaxis reduced the rate of herpes zoster by 62%.[38] Acyclovir did not prevent recurrent zoster episodes in patients with prior history of herpes zoster.[38] People with HIV who are taking suppressive anti-herpes medications (i.e., acyclovir, valacyclovir, or famciclovir) for other indications—such as prevention of genital herpes—may receive some additional benefit in reduction of risk of herpes zoster, but the relative risk reduction in people who are receiving ART is unknown.

Vaccination to Prevent Reactivation Disease (Herpes Zoster)

One U.S. Food and Drug Administration (FDA)-approved vaccine is currently available for the prevention of herpes zoster in immunocompetent adults. In 2017, a subunit vaccine containing recombinant VZV glycoprotein E (gE) and adjuvant AS01B (i.e., recombinant zoster vaccine [RZV] Shingrix) was FDA approved and recommended by the Advisory Committee on Immunization Practices (ACIP) to prevent herpes zoster in immunocompetent adults aged ≥50 years, given on a 2-dose schedule.[39] The approval and recommendation for the vaccine were based on pivotal Phase 3 randomized, placebo-controlled clinical trials involving >30,000 participants aged ≥50 years in which the vaccine efficacy against herpes zoster in vaccinated participants was 97.2% overall and 91.3% in those aged ≥70 years.[40,41] The most common solicited adverse reactions in vaccine recipients were pain (78% of recipients), myalgia (45%), and fatigue (45%), with Grade 3 injection site reactions (pain, redness, and swelling) reported in 9.4% of vaccine recipients and Grade 3 solicited systemic events (myalgia, fatigue, headache, fever, and gastrointestinal symptoms) reported

by 10.8% of vaccine recipients.[39,42] Systemic Grade 3 reactions were reported more frequently after Dose 2 than after Dose 1.[42]

Data on use of RZV in people with HIV are limited. A Phase 1/2 randomized, placebo-controlled study enrolled 94 adults with HIV receiving ART[43] with CD4 count ≥200 cells/mm^3, 14 adults receiving ART with CD4 count <200 cells/mm^3, and 15 ART-naive adults with CD4 count ≥500 cells/mm^3. The participants' median age was 46 years. Participants received the vaccine in three doses administered at 0, 2, and 6 months. The vaccine increased humoral and cell-mediated immunity to VZV gE after two doses, including among people with CD4 counts <200 cells/mm^3. The most common side effects included pain at the injection sites (98.6% of participants, 16.4% Grade 3), fatigue (75.3%, 16.4% Grade 3), myalgia (74.0%, 13.7% Grade 3), and headache (64.4%, 8.2% Grade 3). No vaccine-related severe adverse events occurred during follow-up. Based on these very limited data in people with HIV, the vaccine appears safe and immunogenic. No efficacy data are available for the RZV among people with HIV.

Given that the risk of herpes zoster is high among people with HIV, and the vaccine appears safe, administration of RZV to people with HIV 18 years of age and older is recommended following the FDA-approved schedule for persons without HIV (intramuscular [IM] dose at 0 and 2–6 months) **(AIII).**

No data identify the optimal timing of vaccination for persons who have a CD4 count <200 cells/mm^3 or who are not suppressed virologically on ART. Following initiation of ART, some experts would administer the RZV vaccination series after CD4 count recovery **(CIII),** and others would administer the series after virologic suppression was achieved **(CIII).**

RZV is not a treatment of herpes zoster and should not be given during acute episodes **(AIII).** It also should not be given to individuals with VZV-related inflammatory eye disease (keratitis or anterior uveitis) during episodes of active inflammation **(AIII).**

A 1-dose attenuated live-zoster virus vaccine (i.e., zoster vaccine live [ZVL], Zostavax®) for prevention of herpes zoster was FDA approved for use in immunocompetent adults aged ≥50 years. However, as of November 18, 2020, it is no longer available for use in the United States, and recommendations for its use have been removed from these guidelines. Those who previously received ZVL should be revaccinated with RZV.

Treating Disease

Varicella

No controlled prospective studies of antiviral therapy for varicella in adults with HIV have been reported. For uncomplicated varicella, the preferred treatment options are valacyclovir (1 g PO three times daily) or famciclovir (500 mg PO three times daily), initiated as early as possible after lesion onset and continued for 5 to 7 days **(AII).** Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) is an alternative **(BII).** Intravenous (IV) acyclovir 10 mg/kg every 8 hours for 7 to 10 days is the recommended initial treatment for people with HIV with severe or complicated varicella **(AIII).**[15,44,45] If no evidence of visceral involvement with VZV is apparent, many experts recommend switching from IV to oral antiviral therapy after the patient has defervesced **(BIII).**[46]

Herpes Zoster

Antiviral therapy should be instituted as soon as possible for all people with HIV with herpes zoster diagnosed within 1 week of rash onset (or any time prior to full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in people with HIV are oral valacyclovir **(AII),** famciclovir **(AII),** or acyclovir **(BII)** (doses as above) for 7 to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident **(AII).**[47] A switch from IV acyclovir to oral antiviral therapy (to complete a 10- to 14-day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving **(BIII).** Adjunctive corticosteroid therapy for herpes zoster in people with HIV **is not recommended** because no data support its benefit in this population **(AIII).**

In patients with HZO, both stromal keratitis and anterior uveitis require treatment with topical corticosteroids; in many cases, chronic, low-dose topical corticosteroid therapy is necessary to maintain suppression of inflammation. Recurrences or exacerbations of inflammation are common. A role for antiviral agents in the management of chronic keratitis and uveitis has not been established.

ARN should be treated promptly with antiviral therapy. One treatment recommended by some experts is high-dose IV acyclovir (10 mg/kg every 8 hours for 10 to 14 days), followed by prolonged high-dose oral valacyclovir (1 g three times daily) **(AIII).** High-dose oral antiviral treatment for at least 14 weeks has been shown to decrease the risk of second eye involvement among those who present with unilateral ARN syndrome;[48,49] **(AIII)** however, many ophthalmologists and infectious disease specialists will continue oral antiviral therapy for much longer. Many experts would also include an intravitreous injection of ganciclovir as part of the initial induction therapy. Additional intravitreous injections can be given if there is concern for lack of treatment response, but injections should not be more frequent than twice weekly **(BIII).** Use of oral valaciclovir instead of IV acyclovir for initial treatment has been reported. This approach should be used with caution because serum drug levels with oral treatment will not be as high as those achieved with IV administration **(CIII).** Involvement of an experienced ophthalmologist in the management of patients with VZV ocular disease is strongly recommended **(AIII).**

Optimal antiviral therapy for PORN remains undefined and should be managed in consultation with an experienced ophthalmologist **(AIII).**[50-52] Outcomes with IV acyclovir or ganciclovir monotherapy were poor. Better results were obtained with IV ganciclovir (or the combination of ganciclovir plus foscarnet), along with intravitreal antiviral drug injections.[22,51,53] Specific treatment should include systemic therapy with at least one IV drug (either acyclovir or ganciclovir) **(AIII)** coupled with injections of at least one intravitreal drug (ganciclovir or foscarnet) **(BIII).**[53,54] Intravitreal cidofovir should not be used because such injections may be associated with loss of intraocular pressure and other adverse effects. Ganciclovir ocular implants previously recommended by some experts are no longer manufactured. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

When to Start Antiretroviral Therapy

All people with HIV should receive ART as soon as possible after diagnosis of HIV infection. The presence of disease caused by VZV is not an indication to defer or discontinue ART **(AIII).**

Monitoring of Response to Therapy and Adverse Events (Including IRIS)

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding guideline sections on Herpes Simplex Virus and Cytomegalovirus.

Initiation of ART appears to be associated with an increased frequency of VZV reactivation, peaking at about 3 months after ART initiation.[7,13,14,55,56] Observational studies have shown the risk of herpes zoster to increase twofold to fourfold between 4 and 16 weeks after initiating ART. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution is similar to that observed in other people with HIV, and episodes of herpes zoster in either setting should be managed in the same manner.

Managing Treatment Failure

Treatment failure caused by resistance of VZV to acyclovir and related drugs (e.g., famciclovir, ganciclovir) is rare, but should be suspected when clinical findings do not improve within 7 days of initiation of therapy or when skin lesions have an atypical (e.g., verrucous) appearance. A viral culture should be obtained, and if VZV is isolated, susceptibility testing performed to establish antiviral drug susceptibility and to document the need for alternative therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with IV foscarnet is recommended **(AII).**[57] IV cidofovir is a potential alternative **(CIII).** Both foscarnet and cidofovir are nephrotoxic agents and should be given in consultation with an expert in infectious diseases.

Special Considerations During Pregnancy

Pregnant women with HIV who are susceptible to VZV and are in close contact with a person with active varicella or herpes zoster should receive VariZIG as soon as possible (within 10 days)[36] after exposure to VZV **(AIII).** If oral acyclovir is used for post-exposure prophylaxis, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV **(CIII).** Pregnant women should not receive varicella vaccine **(AIII).**

For pregnant women without HIV with varicella, the risk of transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when varicella infection occurs at or before 12 weeks gestation, 2.2% with infection at 13 to 20 weeks, and negligible with infection after 20 weeks.[58] Women with varicella during the first half of pregnancy should be counseled about the risks to the fetus and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome.[58] Administration of VariZIG is recommended primarily to prevent complications in the mother; whether it has any benefit in prevention of congenital varicella syndrome is unknown. VariZIG should be administered to infants born to women who have varicella from 5 days before delivery to 2 days after delivery to reduce the severity and mortality of neonatal varicella acquired by exposure to maternal viremia **(AIII).**

Oral acyclovir or valacyclovir are the preferred treatments for pregnant women with HIV who have uncomplicated varicella during pregnancy **(BIII).** Pregnant women with HIV who have severe varicella or who exhibit signs or symptoms of VZV pneumonitis should be hospitalized and treated with IV acyclovir (10 mg/kg every 8 hours) **(AII).**

No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. Recommended therapy for uncomplicated herpes zoster in pregnant women with HIV is oral

acyclovir or valacyclovir **(BIII).** Pregnant women should not receive the herpes zoster vaccine **(AIII).**

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

Pre-Exposure Prevention of VZV Primary Infection

Indications

- Adults and adolescents with HIV who have CD4 counts ≥200 cells/mm^3 and who do not have documentation of varicella vaccination, a history or diagnosis of varicella or herpes zoster confirmed by a health care provider, or laboratory confirmation of VZV disease; and anyone with HIV who is VZV seronegative should avoid exposure to persons with varicella or herpes zoster (CIII).

Vaccination

- Household contacts who are VZV-susceptible should be vaccinated to prevent potential transmission of VZV to at-risk people with HIV (BIII).
- In VZV-seronegative persons aged ≥18 years with CD4 counts ≥200 cells/mm^3, administer primary varicella vaccination (Varivax™) in two doses (0.5 mL SQ) 3 months apart (BIII).
- If vaccination results in disease due to live-attenuated vaccine virus, treatment with acyclovir is recommended (AIII).
- If post-exposure VariZIG™ has been administered, wait ≥5 months before varicella vaccination (CIII).
- If post-exposure acyclovir has been administered, wait ≥3 days before varicella vaccination (CIII).
- Administration of varicella vaccine to severely immunocompromised people with HIV (CD4 counts <200 cells/mm3) is contraindicated (AIII).

Post-Exposure Prophylaxis of VZV Primary Infection

Indications

- Close contact with a person who has active varicella or herpes zoster, *and*
- Susceptible to VZV (i.e., no history of varicella vaccination, no history of varicella or herpes zoster, or known to be VZV seronegative)

Preferred Prophylaxis

- VariZIG 125 IU/10 kg (maximum of 625 IU) IM, administered as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster (AIII)
- If post-exposure VariZIG has been administered, wait ≥5 months before varicella vaccination (CIII).

Note: Patients receiving monthly high-dose IVIG (i.e., >400 mg/kg) are likely protected against VZV and probably do not require VariZIG if the last dose of IVIG they received was administered <3 weeks before VZV exposure.

Alternative Prophylaxis (Begin 7-10 Days After Exposure)

- Acyclovir 800 mg PO 5 times daily for 5 to 7 days (BIII), *or*
- Valacyclovir 1 gm PO 3 times daily for 5 to 7 days (BIII)

Note: Neither these pre-emptive interventions nor post-exposure varicella vaccination have been studied in adults and adolescents with HIV. If acyclovir or valacyclovir is used, varicella vaccines should not be given <72 hours after the last dose of the antiviral drug.

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

Preventing Herpes Zoster (Shingles)

Vaccination

Recombinant zoster vaccine (RZV, Shingrix) is the only available vaccine for prevention of shingles in the United States. As of November 18, 2020, attenuated zoster vaccine live (ZVL, Zostavax) is no longer available for use in the United States.

RZV

Recommended in adults with HIV aged ≥18 years, regardless of CD4 count:

- RZV 0.5 mL IM injection—2-dose series at 0 and then at 2 to 6 months (AIII).
- RZV should not be given during an acute episode of herpes zoster (AIII).
- Following initiation of ART, some experts would delay RZV vaccination until patients are suppressed virologically on ART (CIII) or until CD4 count recovery (CIII) to maximize immunologic response to the vaccine.

Treating Varicella Infections

Primary Varicella Infection (Chickenpox)

Uncomplicated Cases

Preferred Therapy

- Valacyclovir 1 g PO 3 times a day (AII), *or*
- Famciclovir 500 mg PO 3 times a day (AII)

Alternative Therapy

- Acyclovir 800 mg PO 5 times daily (BII)

Duration

- 5 to 7 days

Severe or Complicated Cases

- Acyclovir 10 mg/kg IV every 8 hours for 7 to 10 days (AIII)
- May switch to oral famciclovir, valacyclovir, or acyclovir after defervescence if there is no evidence of visceral involvement (BIII)

Herpes Zoster (Shingles)

Acute, Localized, Dermatomal

Preferred Therapy

- Valacyclovir 1,000 mg PO 3 times a day (AII), *or*
- Famciclovir 500 mg PO 3 times a day (AII)

Alternative Therapy

- Acyclovir 800 mg PO 5 times daily (BII)

Duration

- 7 to 10 days; longer duration should be considered if lesions resolve slowly

Herpes Zoster Ophthalmitis (HZO)

Late dendriform lesions of the corneal epithelium should be treated with systemic or topical anti-herpetic medications (AIII).

Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident (AII).
- Switch to oral therapy (valacyclovir 1 g 3 times a day, famciclovir 500 mg 3 times a day, or acyclovir 800 mg PO 5 times daily to complete a 10- to 14-day course) when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving (BIII).

Acute Retinal Necrosis (ARN)

- Acyclovir 10 mg/kg IV every 8 hours for 10 to 14 days, followed by valacyclovir 1 g PO 3 times a day for ≥14 weeks (AIII). In addition, an intravitreous injection of ganciclovir (2 mg/0.05 mL) can be given as a part of initial treatment, and injections can be repeated at a frequency of twice weekly until there is evidence of a treatment response (BIII). Involvement of an experienced ophthalmologist is recommended (AIII).
- Use of oral valaciclovir instead of IV acyclovir for initial treatment has been reported, but this approach should be used with caution, because serum drug levels with oral treatment will not be as high as those achieved with IV administration (CIII).

Progressive Outer Retinal Necrosis (PORN)

- Involvement of an experienced ophthalmologist is strongly recommended (AIII).
- Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg every 12 hours plus ganciclovir 2 mg/0.05 mL and/or foscarnet 1.2 mg/0.05 mL intravitreal twice weekly (AIII)
- Optimize ARV regimen (AIII).
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with an ophthalmologist.

Note: Ganciclovir ocular implants are no longer commercially available.

Key: ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; HZO = herpes zoster ophthalmicus; IM = intramuscular; IU = international unit; IV = intravenous; IVIG = intravenous immunoglobulin; PO = orally; PORN = progressive outer retinal necrosis; RZV = recombinant zoster vaccine; SQ = subcutaneous; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus; ZVL = zoster vaccine live

References

1. Reynolds MA, Kruszon-Moran D, Jumaan A, Schmid DS, McQuillan GM. Varicella seroprevalence in the U.S.: data from the National Health and Nutrition Examination Survey, 1999-2004. *Public Health Rep*. 2010;125(6):860-869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21121231.

2. Guris D, Jumaan AO, Mascola L, et al. Changing varicella epidemiology in active surveillance sites—United States, 1995-2005. *J Infect Dis*. 2008;197 Suppl 2:S71-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18419413.

3. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis*. 1992;166(5):1153-1156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1308664.

4. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med*. 1995;155(15):1605-1609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7618983.

5. Gebo KA, Kalyani R, Moore RD, Polydefkis MJ. The incidence of, risk factors for, and sequelae of herpes zoster among HIV patients in the highly active antiretroviral therapy era. *J Acquir Immune Defic Syndr*. 2005;40(2):169-174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16186734.

6. Vanhems P, Voisin L, Gayet-Ageron A, et al. The incidence of herpes zoster is less likely than other opportunistic infections to be reduced by highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2005;38(1):111-113. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15608535.

7. Grabar S, Tattevin P, Selinger-Leneman H, et al. Incidence of herpes zoster in HIV-infected adults in the combined antiretroviral therapy era: results from the FHDH-ANRS CO4 cohort. *Clin Infect Dis*. 2015;60(8):1269-1277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25601456.

8. Shearer K, Maskew M, Ajayi T, et al. Incidence and predictors of herpes zoster among antiretroviral therapy-naive patients initiating HIV treatment in Johannesburg, South Africa. *Int J Infect Dis*. 2014;23:56-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24680820.

9. Erdmann NB, Prentice HA, Bansal A, et al. Herpes zoster in persons living with HIV-1 infection: viremia and immunological defects are strong risk factors in the era of combination antiretroviral Therapy. *Front Public Health*. 2018;6:70. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29594092.

10. Jansen K, Haastert B, Michalik C, et al. Incidence and risk factors of herpes zoster among HIV-positive patients in the German Competence Network for HIV/AIDS (KompNet): a cohort study analysis. *BMC Infect Dis*. 2013;13:372. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23937603.

11. Blank LJ, Polydefkis MJ, Moore RD, Gebo KA. Herpes zoster among persons living with HIV in the current antiretroviral therapy era. *J Acquir Immune Defic Syndr*. 2012;61(2):203-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22766968.

12. Moanna A, Rimland D. Decreasing incidence of herpes zoster in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2013;57(1):122-125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23487391.

13. Nacher M, Basurko C, Adenis A, et al. Predictive factors of herpes zoster HIV-infected patients: another adverse effect of crack cocaine. *PLoS One*. 2013;8(11):e80187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24244647.

14. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med*. 2001;110(8):605-609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11382367.

15. Wallace MR, Hooper DG, Pyne JM, Graves SJ, Malone JL. Varicella immunity and clinical disease in HIV-infected adults. *South Med J*. 1994;87(1):74-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8284723.

16. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *J Pain*. 2008;9(1 Suppl 1):S3-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18166460.

17. Gnann JW, Jr., Crumpacker CS, Lalezari JP, et al. Sorivudine versus acyclovir for treatment of dermatomal herpes zoster in human immunodeficiency virus-infected patients: results from a randomized, controlled clinical trial. Collaborative Antiviral Study Group/AIDS Clinical Trials Group, Herpes Zoster Study Group. *Antimicrob Agents Chemother*. 1998;42(5):1139-1145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9593141.

18. Harrison RA, Soong S, Weiss HL, Gnann JW, Jr., Whitley RJ. A mixed model for factors predictive of pain in AIDS patients with herpes zoster. *J Pain Symptom Manage*. 1999;17(6):410-417. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10388246.

19. Hu AY, Strauss EC, Holland GN, Chan MF, Yu F, Margolis TP. Late varicella-zoster virus dendriform keratitis in patients with histories of herpes zoster ophthalmicus. *Am J Ophthalmol*. 2010;149(2):214-220 e213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19909942.

20. Engstrom RE, Jr., Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome. A variant of necrotizing herpetic retinopathy in patients with AIDS. *Ophthalmology*. 1994;101(9):1488-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8090452.

21. Ormerod LD, Larkin JA, Margo CA, et al. Rapidly progressive herpetic retinal necrosis: a blinding disease characteristic of advanced AIDS. *Clin Infect Dis*. 1998;26(1):34-45; discussion 46-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9455507.

22. Yin PD, Kurup SK, Fischer SH, et al. Progressive outer retinal necrosis in the era of highly active antiretroviral therapy: successful management with intravitreal injections and

monitoring with quantitative PCR. *J Clin Virol*. 2007;38(3):254-259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17280866.

23. Veenstra J, van Praag RM, Krol A, et al. Complications of varicella zoster virus reactivation in HIV-infected homosexual men. *AIDS*. 1996;10(4):393-399. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8728043.

24. Gray F, Belec L, Lescs MC, et al. Varicella-zoster virus infection of the central nervous system in the acquired immune deficiency syndrome. *Brain*. 1994;117 (Pt 5):987-999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7953606.

25. Leung J, Harpaz R, Baughman AL, et al. Evaluation of laboratory methods for diagnosis of varicella. *Clin Infect Dis*. 2010;51(1):23-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20504232.

26. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis*. 2006;194(2):247-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16779732.

27. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and immunogenicity of live varicella virus vaccine in children with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 2006;25(4):368-370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16567993.

28. Bekker V, Westerlaken GH, Scherpbier H, et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. *AIDS*. 2006;20(18):2321-2329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17117018.

29. Son M, Shapiro ED, LaRussa P, et al. Effectiveness of varicella vaccine in children infected with HIV. *J Infect Dis*. 2010;201(12):1806-1810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20441519.

30. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17585291.

31. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. Primary varicella and herpes zoster among HIV-infected children from 1989 to 2006. *Pediatrics*. 2008;121(1):e150-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18086820.

32. Breuer J, Schmid DS, Gershon AA. Use and limitations of varicella-zoster virus-specific serological testing to evaluate breakthrough disease in vaccinees and to screen for susceptibility to varicella. *J Infect Dis*. 2008;197 Suppl 2:S147-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18419389.

33. Ludwig B, Kraus FB, Allwinn R, Keim S, Doerr HW, Buxbaum S. Loss of varicella zoster virus antibodies despite detectable cell mediated immunity after vaccination. *Infection*. 2006;34(4):222-226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16896582.

34. Centers for Disease Control and Prevention. Recommended adult immunization schedule: United States, 2010. *Ann Intern Med*. 2010;152(1):36-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20048270.

35. Centers for Disease Control and Prevention. A new product (VariZIG) for postexposure prophylaxis of varicella available under an investigational new drug application expanded access protocol. *MMWR Morb Mortal Wkly Rep*. 2006;55(8):209-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16511443.

36. Centers for Disease C, Prevention. FDA approval of an extended period for administering VariZIG for postexposure prophylaxis of varicella. *MMWR Morb Mortal Wkly Rep*. 2012;61(12):212. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22456121.

37. American Academy of Pediatrics. Varicella-zoster virus infections. *In: Red Book: 2018–2021 Report of the Committee on Infectious Diseases*. 31st ed. 2018:869-883. Available at: https://redbook.solutions.aap.org/chapter.aspx?sectionid=189640215&bookid=2205.

38. Barnabas RV, Baeten JM, Lingappa JR, et al. Acyclovir prophylaxis reduces the incidence of herpes zoster among HIV-infected individuals: results of a randomized clinical trial. *J Infect Dis*. 2016;213(4):551-555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26142452.

39. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29370152.

40. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372(22):2087-2096. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25916341.

41. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375(11):1019-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27626517.

42. U.S. Food and Drug Administration. Shingrix [package insert]. 2017. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581605.pdf.

43. Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. *J Infect Dis*. 2015;211(8):1279-1287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25371534.

44. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chickenpox in immunosuppressed children—a collaborative study. *J Pediatr*. 1982;101(4):622-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6750068.

45. Arvin AM. Antiviral therapy for varicella and herpes zoster. *Semin Pediatr Infect Dis*. 2002;13(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12118839.

46. Carcao MD, Lau RC, Gupta A, Huerter H, Koren G, King SM. Sequential use of intravenous and oral acyclovir in the therapy of varicella in immunocompromised children. *Pediatr Infect Dis J*. 1998;17(7):626-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9686730.

47. Balfour HH, Jr., Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med*. 1983;308(24):1448-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6343861.

48. Palay DA, Sternberg P, Jr., Davis J, et al. Decrease in the risk of bilateral acute retinal necrosis by acyclovir therapy. *Am J Ophthalmol*. 1991;112(3):250-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1882936.

49. Jeon S, Kakizaki H, Lee WK, Jee D. Effect of prolonged oral acyclovir treatment in acute retinal necrosis. *Ocul Immunol Inflamm*. 2012;20(4):288-292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22621210.

50. Scott IU, Luu KM, Davis JL. Intravitreal antivirals in the management of patients with acquired immunodeficiency syndrome with progressive outer retinal necrosis. *Arch Ophthalmol*. 2002;120(9):1219-1222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12215102.

51. Moorthy RS, Weinberg DV, Teich SA, et al. Management of varicella zoster virus retinitis in AIDS. *Br J Ophthalmol*. 1997;81(3):189-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9135381.

52. Austin RB. Progressive outer retinal necrosis syndrome: a comprehensive review of its clinical presentation, relationship to immune system status, and management. *Clin Eye Vis Care*. 2000;12(3-4):119-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11137426.

53. Kim SJ, Equi R, Belair ML, Fine HF, Dunn JP. Long-term preservation of vision in progressive outer retinal necrosis treated with combination antiviral drugs and highly active antiretroviral therapy. *Ocul Immunol Inflamm*. 2007;15(6):425-427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18085485.

54. Gore DM, Gore SK, Visser L. Progressive outer retinal necrosis: outcomes in the intravitreal era. *Arch Ophthalmol*. 2012;130(6):700-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22801826.

55. Dunic I, Djurkovic-Djakovic O, Vesic S, Zerjav S, Jevtovic D. Herpes zoster as an immune restoration disease in AIDS patients during therapy including protease inhibitors. *Int J STD AIDS*. 2005;16(7):475-478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16004625.

56. Espinosa E, Pena-Jimenez A, Ormsby CE, Vega-Barrientos R, Reyes-Teran G. Later onset of herpes zoster-associated immune reconstitution inflammatory syndrome. *HIV Med*. 2009;10(7):454-457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19490175.

57. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis*. 1998;27(6):1525-1527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9868672.

58. Pastuszak AL, Levy M, Schick B, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med*. 1994;330(13):901-905. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8114861.

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Updated: July 14, 2025
Reviewed: July 14, 2025

This table provides recommendations for the use of chemoprophylaxis to prevent the first episode of opportunistic disease. For the use of immunizations to prevent certain infections in people with HIV, please refer to the Immunizations for Preventable Diseases in Adults and Adolescents With HIV section.

Opportunistic Infections	Indication	Preferred	Alternative
Coccidioidomycosis	A new positive *Coccidioides* IgM or IgG test in patients who previously tested negative; do not have signs, symptoms, or laboratory abnormalities compatible with active disease; and have CD4 count <250 cells/mm^3 (AIII)	Fluconazole 400 mg PO daily (AIII)	None
Cystoisosporiasis	CD4 count <200 cells/mm^3 and living in or traveling to regions endemic for *Cystoisospora belli* (CII)	TMP-SMX (160 mg/800 mg) PO three times weekly (AI), *or* TMP-SMX (160 mg/800 mg) PO daily (AI)	None
Histoplasma capsulatum Infection	CD4 count <150 cells/mm^3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases per 100 person-years) (BI)	Itraconazole 200 mg PO daily (BI)	None
Malaria	Travel to disease-endemic area	Recommendations are the same as for people without HIV. Recommendations are based on the region of travel, malaria risks, and drug susceptibility in the region. Refer to the Centers for Disease Control and Prevention webpage for the most recent recommendations based on region and drug susceptibility: Malaria.	
Mycobacterium avium Complex (MAC) Disease	CD4 count <50 cells/mm^3 AND not receiving ART or remains viremic on ART or has no options for a fully suppressive ART regimen (AI)	Azithromycin 1,200 mg PO once weekly (AI), *or* Clarithromycin 500 mg PO twice daily (AI), *or* Azithromycin 600 mg PO twice weekly (BIII)	Rifabutin (dose adjustment may be necessary with some ARV drugs, and rifabutin is not recommended if used with certain ARV drugs)[a] (BI); rule out active TB before starting rifabutin to avoid monotherapy in the setting of TB.

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
	Not recommended for those who immediately initiate ART after HIV diagnosis (AII) Disseminated MAC disease should be ruled out before starting primary prophylaxis. See the MAC section for more information.		
Mycobacterium tuberculosis Infection (TB) (i.e., treatment of latent TB infection [LTBI])	Positive screening test for LTBI,[b] no evidence of active TB, and no prior treatment for active TB or LTBI (AI), *or* Close contact with a person with infectious TB (with no evidence of active TB), regardless of screening test results and CD4 count (AII) For recommendations on management of drug interactions with ARVs, see the Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB Infection table in the *Mycobacterium tuberculosis* Infection and Disease section and the Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines.	3HP Rifapentine (see weight-based dosing below) plus INH 15 mg/kg (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks (AI) *Weight-Based Rifapentine Dose* • Weighing 25.1–32 kg: 600 mg PO once weekly • Weighing 32.1–49.9 kg: 750 mg PO once weekly • Weighing >50 kg: 900 mg PO once weekly Note: 3HP is recommended only for virally suppressed persons receiving EFV, RAL, or once daily DTG-based ARV regimen (AII). *or* 3HR INH 300 mg plus rifampin 600 mg plus pyridoxine 25–50 mg PO daily for 3 months (AI)	INH 300 mg plus pyridoxine 25–50 mg PO daily for 6–9 months (AII), *or* 4R: Rifampin 600 mg PO daily for 4 months (BI), *or* 1HP: Rifapentine (see weight-based dosing below) plus INH 300 mg plus pyridoxine 25–50 mg) PO once daily for 4 weeks (BI) Weight-Based Rifapentine Dose • *Weighing* <35 kg: 300 mg PO once daily • *Weighing* 35–45 kg: 450 mg PO once daily • *Weighing* >45 kg: 600 mg PO once daily Note: 1HP is recommended only for patients receiving an efavirenz-based ARV regimen (AI). For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts and public health authorities (AIII).
Pneumocystis Pneumonia (PCP)	CD4 count 100–200 cells/mm^3, if plasma HIV RNA level is above detection limits (AI), *or* CD4 count <100 cells/mm^3, regardless of plasma HIV RNA level (AIII) Note: Patients who are receiving pyrimethamine/ sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII).	TMP-SMX 1 DS tablet PO daily (AI), *or* TMP-SMX 1 SS tablet PO daily (AI) Note: TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections.	The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*: • TMP-SMX 1 DS PO three times weekly (BI), *or* • Dapsone[c] 50 mg PO daily with pyrimethamine[d] 50 mg plus leucovorin 25 mg PO weekly (BI), *or* • Dapsone[c] 200 mg plus pyrimethamine[d] 75 mg plus leucovorin 25 mg PO weekly (BI), *or*

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
			• Atovaquone 1,500 mg PO daily with food (BI) The following regimens should only be used if the person is seronegative for *Toxoplasma gondii*: • Dapsone[c] 100 mg PO daily or 50 mg PO twice daily (BI), *or* • Aerosolized pentamidine 300 mg via Respigard II nebulizer every month (BI), *or* • Intravenous pentamidine 300 mg every 28 days (CIII)
Syphilis	Individuals exposed sexually within ≤90 days of the diagnosis of primary, secondary, or early latent syphilis in a sex partner, regardless of serologic status (AII), *or* Individuals exposed >90 days before syphilis diagnosis in a sex partner, if serologic test results are not available immediately and the opportunity for follow-up is uncertain (AIII)	Benzathine penicillin G 2.4 million units IM for one dose (AII)	For penicillin-allergic patients: • Doxycycline 100 mg PO twice daily for 14 days (BII), *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days (BII)
Talaromycosis (Penicilliosis)	People with (1) CD4 cell counts <100 cells/mm^3 and who are not taking ART or have treatment failure without access to effective ART options or (2) CD4 counts ≥100 cells/mm^3 but have a condition that suppresses T-cell function, AND who either— • Reside in the hyperendemic regions in northern Thailand, throughout Vietnam, or in southern China (particularly in highland regions during the rainy humid months) (BI) *or* • Are from countries outside of the hyperendemic region and must travel to the region (BIII)	For people who reside in hyperendemic areas: • Itraconazole 200 mg PO once daily (BI) For those traveling to the hyperendemic regions: • Begin itraconazole 200 mg PO once daily 3 days before travel and continue for 1 week after leaving the hyperendemic area (BIII).	For people who reside in hyperendemic areas: • Fluconazole 400 mg PO once weekly (BII) For those traveling to the hyperendemic regions: • Take the first dose of fluconazole 400 mg 3 days before travel, continue 400 mg once weekly, and take the final dose after leaving the hyperendemic area (BIII).

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
Toxoplasma gondii Encephalitis	*Toxoplasma* IgG-positive patients with CD4 count <100 cells/mm^3 (AII) Note: All regimens recommended for primary prophylaxis against toxoplasmosis also are effective as PCP prophylaxis.	TMP-SMX 1 DS PO daily (AII)	TMP-SMX 1 DS PO three times weekly (BII), *or* TMP-SMX 1 SS PO daily (BIII), *or* Dapsone[c] 50 mg PO daily plus (pyrimethamine[d] 50 mg plus leucovorin 25 mg) PO weekly (BI), *or* (Dapsone 200 mg plus pyrimethamine[d] 75 mg plus leucovorin 25 mg) PO weekly (CI), *or* Atovaquone 1,500 mg PO daily (CIII), *or* (Atovaquone 1,500 mg plus pyrimethamine[d] 25 mg plus leucovorin 10 mg) PO daily (CIII)

[a] Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for dosing recommendations.

[b] Screening tests for latent tuberculosis infection include tuberculin skin tests and interferon-gamma release assays.

[c] Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) before administration of dapsone. An alternative agent should be used in patients found to have G6PD deficiency.

[d] Refer to Daraprim Direct for information regarding how to access pyrimethamine.

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Opportunistic Infection Guidelines.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; DS = double strength; DTG = dolutegravir; EFV = efavirenz; IgG = immunoglobulin G; IgM = immunoglobulin M; IM = intramuscular; INH = isoniazid; IV = intravenously; LTBI = latent tuberculosis infection; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; PO = orally; RAL= raltegravir; SS = single strength; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Updated: July 14, 2025
Reviewed: July 14, 2025

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections	Empiric Therapy Pending Definitive Diagnosis	For People With HIV and CD4 Count >500 Cells/mm^3, 1–2 Days of Loose Stool Without Fever or Blood in Stool • Oral hydration, no further workup, and no antibiotics For People With HIV and CD4 Count 200–500 Cells/mm^3 With Diarrhea Severe Enough to Compromise Quality of Life or the Ability to Work • Azithromycin 500 mg PO daily for 5 days (BIII), *or* • Ciprofloxacin 500–750 mg PO every 12 hours for 5 days (BIII) For People With HIV and Severe Disease (e.g., CD4 Count <200 Cells/mm^3 or Concomitant AIDS-Defining Illness and With Clinically Severe Diarrhea [≥6 Liquid Stools Per Day or Bloody Stool and/or Accompanying Fever or Chills]) • Hospitalization for diagnostic evaluation and IV antibiotics • Ceftriaxone IV 1–2 g every 24 hours (BIII) Note: If *Campylobacter* or *Shigella* bacteremia is suspected, a carbapenem is preferred (BIII). Therapy and duration should be adjusted based on microbiology and antibiotic sensitivity results. If no pathogen is identified and the patient recovers quickly, 5 days of therapy is recommended.		Diagnostic fecal specimens should be obtained before initiation of empiric antimicrobial therapy. If a pathogen is identified, antibiotic susceptibilities should be performed to confirm and inform antibiotic choices, given increased reports of antibiotic resistance. Oral or IV rehydration (if indicated) should be given to patients with diarrhea (AIII). Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI (BIII). Risk of bacteremia increases with decreasing CD4 count. If no clinical response is observed after 3–4 days, consider a follow-up stool culture with antibiotic susceptibility testing or alternative diagnostic tests (e.g., toxin assays, molecular testing) to evaluate alternative diagnoses, antibiotic resistance, or drug–drug interaction (BIII). MSM may be at increased risk for antibiotic resistant enteric infections.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
		For patients with persistent diarrhea (>14 days) without severe clinical signs, antibiotics therapy can be withheld until a diagnosis is made.		
	Campylobacteriosis	For Mild Disease If CD4 Count >200 Cells/mm^3 • No therapy unless symptoms persist for more than several days (CIII) For Mild to Moderate Disease (If Susceptible) • Azithromycin 500 mg PO daily for 5 days (BIII) (not recommended for patients with bacteremia [AIII]), *or* • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days (BIII) For *Campylobacter* Bacteremia • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for ≥14 days if the isolate is sensitive (BIII) plus an aminoglycoside (BIII) to limit the emergence of antibiotic resistance For Recurrent Infections • Duration of therapy may be extended to 2–6 weeks (BIII).	For Mild to Moderate Disease (If Susceptible) • Levofloxacin 750 mg (PO or IV) every 24 hours (BIII) • Add an aminoglycoside to fluoroquinolone in bacteremic patients (BIII) to limit the emergence of antibiotic resistance.	Oral or IV rehydration if indicated (AIII) Antimotility agents should be avoided (BIII). Third-generation cephalosporins are not reliably active, and use of alternative cell wall–active agents, such as carbapenems, may be necessary in severely ill people who require empiric IV therapy until antimicrobial susceptibilities return. In the United States in 2018, 29% of *C. jejuni* isolates were resistant to ciprofloxacin and 2% were resistant to azithromycin; among *C. coli* isolates, 40.5% were resistant to fluoroquinolone and 13.3% were resistant to azithromycin. Effective ART may reduce the frequency, severity, and recurrence of *Campylobacter* infections.
	Clostridium difficile Infection (CDI)	For Severe or Nonsevere CDI • Fidaxomicin 200 mg PO twice daily for 10 days (AI) For Recurrent CDI • 2021 IDSA CDI Guidelines suggest use of fidaxomicin over oral vancomycin because it has a greater likelihood for a sustained clinical response at 30 days (AI).	For Severe or Nonsevere CDI • Vancomycin 125 mg PO four times daily for 10 days (AI) For Nonsevere CDI *If Neither Fidaxomicin nor Vancomycin Is Available* • Metronidazole 500 mg (PO) three times daily for 10 days (CI)	Severe CDI: white blood cell count ≥15,000 cells/mL or serum creatinine concentrations >1.5 mg/dL; nonsevere CDI: white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

<table>
<tr><th colspan="2">Opportunistic Infection</th><th>Preferred Therapy</th><th>Alternative Therapy</th><th>Other Comments</th></tr>
<tr><td></td><td></td><td></td><td>Recurrent CDI
Vancomycin is an acceptable option (see IDSA Guideline for tapered and pulsed regimens) (AI).
FMT may be considered after three CDI episodes (i.e., an initial and two recurrent episodes) (CIII).</td><td></td></tr>
<tr><td></td><td>Salmonellosis</td><td colspan="2">All people with HIV and salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20-fold to 100-fold) and mortality (by up to sevenfold) compared with individuals without HIV (AIII).</td><td rowspan="2">Oral or IV rehydration if indicated (AIII)

Antimotility agents should be avoided (BIII).

The role of long-term secondary prophylaxis in patients with recurrent Salmonella bacteremia is not well established. Must weigh the benefits against the risks of long-term antibiotic exposure (BIII).

Effective ART may reduce the frequency, severity, and recurrence of salmonella infections.</td></tr>
<tr><td></td><td></td><td>For Invasive Disease (Suspected or Confirmed)
Ceftriaxone IV 1–2 g every 24 hours pending susceptibilities (BIII)
For Nontyphoidal Salmonella Gastroenteritis (With or Without Bacteremia) (If Susceptible)
Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (AIII)
Duration of Therapy
For Gastroenteritis Without Bacteremia
If CD4 count ≥200 cells/mm^3: 7–14 days (BIII)
If CD4 count <200 cells/mm^3: minimum of 2 weeks (may extend to up to 6 weeks if with severe disease) (BIII)
For Gastroenteritis With Bacteremia
If CD4 count ≥200/mm^3: 14 days or longer duration if bacteremia persists or if the infection is complicated (e.g., if metastatic foci of infection are present) (BIII)
If CD4 count <200 cells/mm^3: 2–6 weeks (BIII)</td><td>For Nontyphoidal Salmonella Gastroenteritis (With or Without Bacteremia) (If Susceptible)
Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), or
Moxifloxacin 400 mg (PO or IV) every 24 hours (BIII), or
TMP-SMX (160 mg/800 mg) PO (or IV) every 12 hours (BIII), or
Ceftriaxone 1–2 g IV every 24 hours (BIII)</td></tr>
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Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
		Secondary Prophylaxis Should Be Considered for Patients With— • Recurrent *Salmonella* bacteremia (BIII), *or* • Recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 with severe diarrhea (BIII)		
	Shigellosis	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (if MIC <0.12 μg/mL) (AIII) Duration of Therapy • Gastroenteritis: 5–7 days (AIII) (except ciprofloxacin [5–10 days] and azithromycin [5 days]) • Bacteremia: ≥14 days (BIII) • Recurrent infections: Up to 6 weeks (BIII) *In Severely Ill Patients Requiring Empiric Parenteral Therapy While Awaiting Susceptibility* • Consider initiating a carbapenem until antimicrobial susceptibilities are available (BIII). Note: Increased resistance of *Shigella* to fluoroquinolones in the United States. Alternative antibiotics should be considered if ciprofloxacin MIC is ≥0.12 μg/mL (BIII).	• Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), *or* • Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV every 12 hours for 5–7 days (BIII), *or* • Azithromycin 500 mg PO daily for 5 days (BIII), *or* • Ceftriaxone 1–2 g IV every 24 hours (BIII) Note: Azithromycin and TMP-SMX are not recommended for treatment of bacteremia. Note: Azithromycin-resistant *Shigella* spp. have been reported in MSM with HIV.	Therapy may slightly shorten the duration of illness and/or prevent the spread of infection (AIII). Oral or IV rehydration if indicated (AIII) Antimotility agents should be avoided (BIII). Many *Shigella* strains that are resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Antibiotic sensitivity testing of *Shigella* isolates from individuals with HIV should be performed routinely. Given increasing antimicrobial resistance and limited data showing that antibiotic therapy limits transmission, antibiotic treatment may be withheld in patients with CD4 count >500 cells/mm^3 whose diarrhea resolves prior to culture confirmation of *Shigella* infection (CIII). Effective ART may decrease the risk of recurrence of *Shigella* infections.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Bartonellosis	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis • Doxycycline 100 mg PO or IV every 12 hours (AII), *or* • Erythromycin 500 mg PO or IV every 6 hours (AII) CNS Infections • (Doxycycline 100 mg +/- RIF 300 mg) PO or IV every 12 hours (AIII) Confirmed *Bartonella* Endocarditis • (Doxycycline 100 mg IV plus RIF 300 mg PO or IV) every 12 hours for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours (BII) Other Severe Infections • (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) every 12 hours (BIII), *or* • (Erythromycin 500 mg PO or IV every 6 hours) +/- RIF 300 mg PO or IV every 12 hours (BIII) Duration of Therapy • At least 3 months (AII)	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, Osteomyelitis, and Other Severe Infection • Azithromycin 500 mg PO daily (BIII) • Clarithromycin 500 mg PO twice a day (BIII) Confirmed *Bartonella* Endocarditis • (Doxycycline 100 mg IV every 12 hours plus gentamicin 1 mg/kg IV every 8 hours) for 2 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours (BII)	When RIF is used, take into consideration the potential for significant interaction with ARV drugs and other medications (see Table 4 for dosing recommendations). If relapse occurs after initial (>3 month) course of therapy, long-term suppression with doxycycline or a macrolide is recommended as long as the CD4 count is <200 cells/mm^3 (AIII).
Candidiasis (Mucocutaneous)	For Oropharyngeal Candidiasis—Initial Episodes (For 7–14 Days) • Fluconazole 200 mg PO loading dose, followed by 100–200 mg PO daily (AI) For Esophageal Candidiasis (For 14–21 Days) • Fluconazole 200-mg loading dose, followed by 100–200 mg (up to 400 mg) PO or IV daily (AI). (Consider oral suspension for people with difficulty swallowing.)	For Oropharyngeal Candidiasis—Initial Episodes (For 7–14 Days) *Oral Therapy* • Itraconazole oral solution 200 mg PO daily (BI), *or* • Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily (BI), *or* • Posaconazole tablet 300 mg PO twice a day for 1 day, then 300 mg daily (BI)	Chronic or prolonged use of azoles may promote the development of resistance. Systemic azoles may have significant drug–drug interactions with ARV drugs. A higher relapse rate for esophageal candidiasis is seen with echinocandins use than with fluconazole.

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	For Uncomplicated Vulvovaginal Candidiasis • Fluconazole 150 mg PO for one dose (AII), *or* • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (AII), *or* • Ibrexafungerp 300 mg PO twice daily for 1 day (BI) For Severe or Recurrent Vulvovaginal Candidiasis • Fluconazole 100–200 mg PO daily for ≥7 days (AII), *or* • Topical antifungal ≥7 days (AII) For Recurrent Vulvovaginal Candidiasis Only *(The following regimens include treatment for the acute episode plus treatment to reduce recurrence.)* • Oteseconazole 600 mg PO at Day 1, 450 mg at Day 2, followed by once-weekly 150-mg dosing starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or* • Fluconazole 150 mg PO at Days 1, 4, and 7, followed by oteseconazole 150 mg PO daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); *or* • Fluconazole 150 mg PO every 72 hours for three doses, followed by ibrexafungerp 300 mg PO twice daily 1 day per month for 6 months (BI). (Use an effective form of contraception during treatment and for 4 days after the last dose.)	*Topical Therapy* • Miconazole mucoadhesive buccal 50-mg tablet once daily; apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet.) (BI), *or* • Clotrimazole troches 10 mg PO five times daily (BI), *or* • Nystatin suspension 4–6 mL four times a day (BII) For Esophageal Candidiasis (For 14–21 Days) • Itraconazole oral solution 200 mg PO daily (AI), *or* • Isavuconazole 400 mg PO loading dose, followed by 100 mg PO daily (BI), *or* • Isavuconazole 400 mg PO once weekly (BI), *or* • Voriconazole 200 mg PO or IV twice a day (BI), *or* • Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily (BI), *or* • Posaconazole tablet 300 mg PO twice a day for 1 day, then 300 mg daily (BI), *or* • Lipid formulation of amphotericin B 3–4 mg/kg IV daily (BI), *or* • Caspofungin 70 mg IV loading dose, followed by 50 mg IV daily (BI), *or* • Micafungin 150 mg IV daily (BI), *or* • Anidulafungin 100 mg IV once, then 50 mg IV daily (BI)	Suppressive therapy is usually not recommended (CIII) unless patients have frequent or severe recurrences. If the Decision Is to Use Suppressive Therapy *Oropharyngeal Candidiasis* • Fluconazole 100 mg PO once daily or three times weekly (BI) *Esophageal Candidiasis* • Fluconazole 100–200 mg PO daily (BI), *or* • Posaconazole oral suspension 400 mg PO twice a day (BII), *or* • Posaconazole tablet 300 mg PO daily (BII) *Vulvovaginal Candidiasis* • Fluconazole 150 mg PO once weekly (BII), *or* • Oteseconazole 600 mg at Day 1 and 450 mg at Day 2 for treatment of the acute episode, followed by once-weekly 150-mg doses starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or*

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		For Azole-Refractory *Candida glabrata* Vaginitis • Boric acid vaginal suppository 600 mg once daily for 14 days (BII)	• Fluconazole 150 mg at Days 1, 4, and 7 for treatment of the acute episode, followed by oteseconazole 150 mg daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); *or* • Ibrexafungerp 300 mg twice daily 1 day per month for 6 months (BI). (Use an effective form of contraception during treatment and for 4 days after the last dose.)
Chagas Disease (American Trypanosomiasis)	For Acute or Reactivated Disease • Benznidazole 5–8 mg/kg/day PO in two divided doses for 60 days (BIII) (commercially available at https://www.benznidazoletablets.com/en; most experts recommend a daily maximum of 300 mg), *or* • Nifurtimox (Lampit) 8–10 mg/kg/day PO in three divided doses for 60 days (BIII) (commercially available through retail sources)	None	Treatment is effective in reducing parasitemia and preventing clinical symptoms or slowing disease progression; however, these drugs have limited efficacy in achieving parasitological cure. Treatment is not recommended for patients with advanced chagasic cardiomyopathy. Duration of therapy has not been studied in patients with HIV. Initiation or optimization of ART is recommended for all people with HIV with concomitant *Trypanosoma cruzi* (AIII).

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Coccidioidomycosis	Mild to Moderate Pulmonary Infection • Fluconazole 400 mg PO daily (AII), *or* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) • Duration of therapy: clinical response to 3–6 months of therapy, CD4 count ≥250 cells/mm^3, and viral suppression on ART (AII) Severe Pulmonary or Extrapulmonary Infection (Except Meningitis) • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII), *or* • Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII) • Continue until clinical improvement, then switch to an azole (fluconazole 400 mg PO daily or itraconazole 200 mg PO twice daily) (BIII). Therapy should be continued for at least 12 months and usually much longer, and should be continued in patients with HIV viremia or with CD4 count <250 cells/mm^3 (BIII). Meningeal Infections • Fluconazole 800–1,200 mg PO daily (AII) • Duration of therapy: lifelong (AII)	Mild to Moderate Pulmonary Infection *For Patients Who Failed to Respond to Fluconazole or Itraconazole* • Voriconazole 400 mg PO twice daily on Day 1, then 200 mg PO twice a day (BIII) • Posaconazole delayed release tablet 300 mg PO twice a day on Day 1, then 300 mg PO once daily (BIII), *or* • Isavuconazole sulfate 372 mg PO every 8 hours for six doses, then 372 mg once daily (BIII) Severe Pulmonary or Extrapulmonary Infection (Except Meningitis) • Some specialists will combine amphotericin B with a triazole (fluconazole or itraconazole, with itraconazole preferred for bone disease) as initial therapy and continue triazole once amphotericin B is stopped (CIII). Meningeal Infections • Itraconazole 200 mg PO two or three times daily (BII), *or* • Voriconazole 200–400 mg PO twice daily (BIII), *or* • Posaconazole delayed release tablet 300 mg PO twice on Day 1, then 300 mg PO once daily (CIII), *or* • Isavuconazole sulfate 372 mg PO every 8 hours for six doses, then 372 mg once daily (CIII) • Intrathecal amphotericin B deoxycholate when triazole antifungals are ineffective (AIII)	Some patients with meningitis may develop hydrocephalus and require CSF shunting. Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of patients with HIV after discontinuation of triazole therapy (AII). See Table 4 for drug–drug interactions or triazole antifungal drugs and other drugs for treatment or prevention of OIs. Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and reduce concentration-related toxicities. Intrathecal amphotericin B should only be given in consultation with a specialist and administered by an individual with experience with the technique.

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Community-Acquired Pneumonia (CAP)	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available (BIII). Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy. Empiric Outpatient Therapy • A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) (AII) *Preferred Beta-Lactams* • High-dose amoxicillin or amoxicillin/clavulanate *Alternative Beta-Lactams* • Cefpodoxime or cefuroxime, *or* • Levofloxacin 750 mg PO once daily (AII), *or* moxifloxacin 400 mg PO once daily (AII), especially for patients with penicillin allergies Empiric Therapy for Hospitalized Patients With Nonsevere CAP • An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) (AI) *Preferred Beta-Lactams* • Ceftriaxone, cefotaxime, or ampicillin-sulbactam • Levofloxacin 750 mg IV once daily (AI), *or* moxifloxacin, 400 mg IV once daily (AI), especially for patients with penicillin allergies.	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available (BIII). Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy. Empiric Outpatient Therapy • A PO beta-lactam plus PO doxycycline (CIII) *Preferred Beta-Lactams* • High-dose amoxicillin or amoxicillin/clavulanate *Alternative Beta-Lactams* • Cefpodoxime or cefuroxime Empiric Therapy for Hospitalized Patients With Nonsevere CAP • An IV beta-lactam plus doxycycline (CIII) Empiric Therapy for Hospitalized Patients With Severe CAP *For Penicillin-Allergic Patients* • Aztreonam IV plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) (BIII)	Duration • For most patients, 5–7 days • Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics. • Longer duration is often required if severe CAP or bacteremia is present, and particularly if due to *S. pneumoniae* or complicated *S. aureus* pneumonia. Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated. Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance (up to 30%) (BIII). Patients receiving a macrolide for MAC prophylaxis may have bacterial resistance to macrolide due to chronic exposure. For patients begun on IV antibiotic therapy, switching to PO should be considered when they are clinically improved and able to tolerate oral medications. Antibiotic chemoprophylaxis is generally not recommended because of the potential for developing drug resistance and drug toxicities (AI).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Empiric Therapy for Hospitalized Patients With Severe CAP • An IV beta-lactam plus IV azithromycin (AI), *or* • An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) (AI) *Preferred Beta-Lactams* • Ceftriaxone, cefotaxime, or ampicillin-sulbactam Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia • An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every 8–12 hours or levofloxacin 750 mg IV once daily) (AI) *Preferred Beta-Lactams* • Piperacillin-tazobactam, cefepime, imipenem, or meropenem Empiric Therapy for Patients at Risk for Methicillin-Resistant *Staphylococcus aureus* Pneumonia • Add vancomycin IV or linezolid (IV or PO) to the baseline regimen (AII). • Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production (CII).	Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia • An IV antipneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus azithromycin (BII), *or* • An IV antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) (BIII) *For Penicillin-Allergic Patients* • Replace the beta-lactam with aztreonam (BIII).	

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptococcosis	For CNS and/or Disseminated Disease *Induction Therapy (For ≥2 Weeks, Followed by Consolidation Therapy)* • In the United States and other settings where daily electrolytes and kidney function monitoring and electrolyte and IV fluid administration is possible— o Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (AII) (Note: Flucytosine dose should be adjusted in patients with renal dysfunction.) • In resource-limited settings, as recommended by WHO— o Liposomal amphotericin B 10 mg/kg IV as a single dose on Day 1, followed by flucytosine 25 mg/kg four times a day plus fluconazole 1,200 mg daily for 2 weeks (AI) • If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative (BIII). *Consolidation Therapy (For ≥8 Weeks, Followed by Maintenance Therapy)* • Fluconazole 800 mg PO daily (AI) • For clinically stable patients with negative CSF cultures and ART has been started, dose can be reduced to 400 mg PO daily (AII) • If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, use one of the following two options for an additional 2 weeks before reducing the dose of fluconazole to 800 mg PO daily:	For CNS and/or Disseminated Disease *Induction Therapy (For ≥2 Weeks, Followed by Consolidation Therapy)* • Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (BII), *or* • Amphotericin B deoxycholate 1 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 1 week, followed by fluconazole 1,200 mg PO daily for an additional week (BI) *Additional Studied Induction Regimens (For 2 Weeks)* • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day (BI) • Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800–1,200 mg PO daily (BIII) • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus fluconazole 800–1,200 mg PO or IV daily (BI) • Fluconazole 1,200 mg PO or IV daily plus flucytosine 25 mg/kg PO four times a day (BII) *Consolidation Therapy (For ≥8 Weeks, Followed by Maintenance Therapy)* • If fluconazole is not available or not well tolerated: Itraconazole 200 mg PO twice a day for 8 weeks (CI)	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 25–100 μg/mL) or at least twice weekly monitoring of complete blood counts for cytopenia. Dosage should be adjusted in patients with renal insufficiency (BII). Irrespective of which regimen is used, patients must be followed carefully in hospital for at least 7 days and ideally 14 days (AII). For patients with CNS disease, LP should be performed at Day 7 and Day 14 to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily LP should be performed until the pressure is decreased into the normal range and symptoms have abated (AII). Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to effectively managing increased intracranial pressure.

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	o Fluconazole 1,200 mg PO daily with flucytosine 25 mg/kg PO four times a day for 2 weeks (BIII) o Fluconazole 1,200 mg PO daily for 2 weeks (BIII), *or* Note: Duration of consolidation therapy should be at least 8 weeks from the time of negative CSF culture (AII). *Maintenance Therapy* • Fluconazole 200 mg PO daily for ≥1 year from initiation of antifungal therapy (AI) For Non-CNS Extrapulmonary (BIII) or Diffuse Pulmonary Disease (BIII) or People With Non-CNS Symptoms With Normal CSF and Serum CrAg **≥1:640 by LFA (or ≥1:160 by EIA** or Latex Agglutination) (BII) • Treatment is the same as for CNS cryptococcosis. For Non-CNS Focal Pulmonary Infiltrates (With Mild Symptoms) • Fluconazole 400 mg daily for 6 to 12 months (duration guided by symptom resolution) (BIII) For Asymptomatic Antigenemia Without Meningitis and Serum **CrAg <1:640 by LFA (or <1:160** by EIA or Latex Agglutination) • Fluconazole: 800–1,200 mg PO daily for 2 weeks, followed by 400–800 mg PO daily for a total of 10 weeks, then fluconazole 200 mg PO daily for a total of 6 months plus effective ART (BIII)	*Maintenance Therapy* • If fluconazole is not available or not well tolerated: Itraconazole 200 mg PO twice a day (CI) • If susceptibility studies have been performed and the fluconazole MIC is ≥16 μg/mL, the fluconazole dose may be increased to 400 mg daily (BIII). For Non-CNS Extrapulmonary (BIII) or Diffuse Pulmonary Disease (BIII) or People With Non-CNS Symptoms With Normal **CSF and Serum CrAg ≥1:640 by LFA (or ≥1:160 by EIA or** Latex Agglutination) (BII) • Alternative treatment options are the same as for CNS cryptococcosis.	Corticosteroids and mannitol are ineffective in reducing ICP and are not recommended (AIII). Some specialists recommend a brief course of tapering dose of corticosteroid for management of severe IRIS symptoms (BIII). All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease. People with asymptomatic cryptococcal antigenemia, lower risk, and serum CrAg titer <1:80 by LFA (or <1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture (AI). All others with asymptomatic cryptococcal antigenemia should undergo CSF sampling to rule out CNS disease.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptosporidiosis	• Aggressive oral and/or IV rehydration and replacement of electrolyte loss (AIII), *and* • Symptomatic treatment of diarrhea with antimotility agents (AIII), *and* • ART initiation to achieve immune restoration to CD4 count >100 cells/mm^3 (AII).	No therapy has been shown to be effective without ART. Consider a trial of these agents in conjunction with ART, rehydration, and symptomatic treatment: • Nitazoxanide 500–1,000 mg PO twice a day with food for at least 14 days (CIII), *or* • Paromomycin 500 mg PO four times daily for 14–21 days (CIII)	Tincture of opium may be more effective than loperamide in management of diarrhea (CIII). Because diarrhea can cause lactase deficiency, patients should avoid milk products (CIII).
Cystoisosporiasis	For Acute Infection • TMP-SMX (160 mg/800 mg) PO (or IV) four times daily for 10 days (AII), *or* • TMP-SMX (160 mg/800 mg) PO (or IV) twice daily for 7 days (BI) • In patients with persistent or worsening symptoms while on twice-daily dosing, consider increasing the daily dose and/or the duration to 3–4 weeks (BIII). • IV TMP-SMX may be used for patients with potential or documented malabsorption. Chronic Maintenance Therapy (Secondary Prophylaxis) *In People With CD4 Count <200 Cells/mm^3* • TMP-SMX (160 mg/800 mg) PO three times weekly (AI), *or* • TMP-SMX (160 mg/800 mg) PO daily (AIII)	For Acute Infection • Pyrimethamine[b] 50–75 mg PO daily plus leucovorin 10–25 mg PO daily for 4 weeks (BIII), *or* • Ciprofloxacin 500 mg PO or 400 mg IV twice daily for 7 days (CI) Chronic Maintenance Therapy (Secondary Prophylaxis) *In People With CD4 Count <200 Cells/mm^3* • TMP-SMX (320 mg/1,600 mg) three times weekly (BIII), *or* • Pyrimethamine[b] 25 mg PO daily plus leucovorin 5–10 mg PO daily (BIII), *or* • Ciprofloxacin 500 mg three times weekly (CI) as a second-line alternative	Fluid and electrolyte management in patients with dehydration (AIII) Nutritional supplementation for patients who are malnourished (AIII) Immune reconstitution with ART may result in fewer relapses; therefore, ART initiation should not be deferred (AIII).
Cytomegalovirus (CMV) Disease	CMV Retinitis Induction Therapy (Followed by Maintenance Therapy) • Valganciclovir 900 mg PO every 12 hours for minimum 14–21 days, then maintenance therapy with valganciclovir 900 mg PO once daily (AI), *or* • Ganciclovir 5 mg/kg IV every 12 hours for minimum 14–21 days, then maintenance	CMV Retinitis Induction Therapy (Followed by Maintenance Therapy) • Foscarnet 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 14–21 days, then maintenance therapy with foscarnet 90 mg/kg or 120 mg/kg IV every 24 hours (BI), *or*	CMV retinitis treatment should be individualized based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and location of lesions as well as with the active participation of an ophthalmologist who is familiar with diagnosis and

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	therapy with valganciclovir 900 mg PO once daily (AI), *or* • Ganciclovir 5 mg/kg IV every 12 hours for minimum 14–21 days, then maintenance therapy with ganciclovir 5 mg/kg IV daily (AI) Note: Many clinicians prefer the IV formulation when retinitis is more central and sight-threatening or when adequate GI absorption is a concern; transition to oral valganciclovir can be considered when there is evidence of clinical response. CMV Retinitis—Immediate Sight-Threatening Lesions (Within 1,500 Microns of the Fovea or Optic Disc) • In addition to systemic therapy (as listed above): intravitreal injections of ganciclovir (2 mg/injection) *or* foscarnet (2.4 mg/injection), repeated weekly during the induction period until lesion inactivity is achieved (BIII), followed by systemic treatment alone for maintenance therapy. CMV Retinitis—Peripheral Lesions • Valganciclovir 900 mg PO every 12 hours for minimum 14–21 days, then maintenance therapy with valganciclovir 900 mg PO once daily (AI) Duration of Maintenance Therapy • Continue maintenance therapy for at least 3 months, and lesions are inactive, and CD4 count ≥100 cells/mm^3 for at least	• Cidofovir 5 mg/kg IV every week for 2 weeks, then maintenance therapy with cidofovir 5 mg/kg IV every other week. Administer 1 L of normal saline before and, if additional fluid load can be tolerated, administer another 1 L of normal saline after each cidofovir infusion. Administer probenecid 2 g PO 3 hours before each cidofovir dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) (CI). CMV Retinitis—Immediate Sight-Threatening Lesions (Within 1,500 Microns of the Fovea or Optic Disc) • In addition to systemic therapy (as listed above): intravitreal therapy as listed in the Preferred section CMV Esophagitis or Colitis • Foscarnet 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours (BIII)—for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance; *or* • Cidofovir (dosing as listed above) (CI) • Duration: 21–42 days or until signs and symptoms have resolved (AIII) CMV Pneumonia • Foscarnet 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours (BIII) • Duration: ≥ 21 days or until signs and symptoms have resolved (CII)	management of this retinal disease. Systemic therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred. After resolution of the acute non-ocular CMV disease and initiation of effective ART, chronic maintenance therapy is not routinely recommended for CMV GI disease, pneumonia, and central nervous system disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially Ophthalmologic monitoring is recommended during treatment and after discontinuation of maintenance therapy and is continued after immune reconstitution. See text for ophthalmic monitoring recommendations and frequency of follow-up. Initiate ART within 1–2 weeks after starting anti-CMV therapy for retinitis, esophagitis, colitis, or other end-organ diseases caused by CMV (BIII). With neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis, the Panel recommends initiating ART within 2 weeks, although clinical judgment

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	3 months in response to ART (AII) CMV Esophagitis or Colitis • Ganciclovir 5 mg/kg IV every 12 hours (AI); may switch to valganciclovir 900 mg PO every 12 hours when the patient can absorb and tolerate oral therapy (AIII). • Valganciclovir 900 mg PO every 12 hours can be used in patients with mild disease (AIII). • Duration: 21–42 days or until signs and symptoms have resolved (AIII) CMV Pneumonia • Ganciclovir 5 mg/kg IV every 12 hours (BIII) • Duration: ≥21 days or until signs and symptoms have resolved (CII) CMV Neurological Disease • Ganciclovir 5 mg/kg IV every 12 hours plus foscarnet (60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours) (BIII). • Duration: ≥21 days based on clinical response (AIII)		based on individual cases is needed (BIII). Immune recovery uveitis (IRU) may develop in the setting of immune reconstitution. See text for information on the treatment of IRU. Cidofovir should be avoided in patients with sulfonamide allergy because of cross-hypersensitivity with probenecid. • For people with renal insufficiency, see Table 6 for information on dosing adjustments for valganciclovir, ganciclovir, foscarnet, and cidofovir.
Hepatitis B Virus (HBV) Disease	ART is recommended for all patients with HIV/HBV coinfection regardless of CD4 cell count and HBV DNA level (AII). The ART regimen must include drugs that are active against both HBV and HIV (AII). **If CrCl ≥60 mL/min—** • (TAF [10 or 25 mg][a] plus FTC 200 mg) or (TAF 25 mg plus 3TC 300 mg) PO once daily (AII), *or* • (TDF 300 mg plus [FTC 200 mg or 3TC 300 mg]) once daily (AII)	For People on NRTI-Sparing ART • Entecavir 0.5 mg once daily may be used in place of (TAF or TDF) plus (3TC or FTC) (AIII).	Directly acting HBV drugs—such as emtricitabine, entecavir, lamivudine, and tenofovir—must not be given in the absence of a fully suppressive ART regimen to avoid selection of drug-resistant HIV (AI). Chronic administration of 3TC or FTC as the only HBV-active drug should be avoided because of the high rate of selection of HBV drug-resistance mutations (AI).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	If CrCl 30–59 mL/min— • TAF (10 or 25 mg)[a] plus FTC 200 mg PO once daily (AII) If CrCl <30 mL/min, Not on HD— • Renally dosed entecavir (in place of TDF/[FTC or 3TC] or TAF/FTC) with a fully suppressive ART regimen (AIII), *or* • ART with renally dose-adjusted TDF and (FTC or 3TC) can be used (AIII) if recovery of renal function is unlikely. • If CrCl ≥15 to 29 mL/min, then ART with TAF (10 or 25 mg)[a] once daily plus renally dose-adjusted FTC or 3TC is an option (AIII). o Some clinicians may continue full-dose FTC or 3TC to allow for people to remain on fixed-dose TAF/FTC products. If on HD— • Renally dose-adjusted TDF plus [FTC 200 mg or 3TC 300 mg once daily] (see Table 6) (AII) • TAF [10 or 25 mg][a] plus FTC 200 mg PO once daily (given after HD on dialysis days) (AII) Duration • Continue treatment indefinitely (AIII).		People with 3TC-resistant HBV will have cross-resistance to FTC and partial resistance to entecavir, these agents should not be used (AI). If 3TC resistance is suspected or documented, TDF or TAF should be added to the ART regimen (AIII). When changing ART regimens, continue agents with anti-HBV activity (AIII). If anti-HBV therapy is discontinued and a flare occurs, therapy should be reinstituted because it can be potentially lifesaving (AIII). Because HBV reactivation can occur during treatment for HCV with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation (AIII). If immunosuppressive therapy is given, HBV reactivation can occur. For people who are HBsAg-positive, treatment for HBV infection should be administered (AII). For detailed recommendations, see Hepatitis B Virus Infection.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Hepatitis C Virus (HCV) Disease	For Treatment-Naive Patients Without Cirrhosis (Any Genotype or No Pre-treatment Genotype) • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AI), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AI) Characteristics that exclude patients from receiving simplified approach to therapy are outlined in Box 1 of the Hepatitis C Virus section. For Treatment-Naive Patients With Compensated Cirrhosis (Recommendations Based on Genotypes) *Genotypes 1, 2, 4–6* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AIII), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AI) *Genotype 3* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AIII) For Treatment of Acute HCV Infection • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AII), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AII)	For Treatment-Naive Patients With Compensated Cirrhosis (Recommendations Based on Genotypes) *Genotypes 1, 2, 4–6* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 12 weeks (CI) *Genotype 3* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 12 weeks (CI), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily with or without ribavirin for 12 weeks, pending results of NS5A RAS testing (CI)	A simplified approach to HCV treatment can be used in treatment-naive patients with any genotype and without cirrhosis. This approach includes standardized treatment with no on-treatment testing or in-person follow-up and limited follow-up to confirm SVR. See the Hepatitis C Virus section to review a summary of drug–drug interactions between HCV therapy and ARV drugs. HCV treatment should not be withheld solely due to perceived lack of adherence to ART or untreated HIV (BIII). Effort should be made to document SVR (HCV RNA less than lower limits of quantification) at least 12 weeks after completion of therapy (AI). Patients without cirrhosis who achieve SVR do not require continued liver disease monitoring. Recommendations for treatment after DAA failure are not provided. The reader is referred to the corresponding section in the AASLD/IDSA HCV treatment guidance.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Herpes Simplex Virus (HSV) Disease	Orolabial Lesions (For 5–10 Days) • Valacyclovir 1 g PO twice a day (AIII), *or* • Famciclovir 500 mg PO twice daily (AIII), *or* • Acyclovir 400 mg PO three times daily (AIII) Initial Genital Lesions (For 7–10 Days) or Recurrent Genital Lesions (For 5–10 Days) • Valacyclovir 1 g PO twice daily (AI), *or* • Famciclovir 500 mg PO twice daily (AI), *or* • Acyclovir 400 mg PO three times daily (AI) Severe Mucocutaneous and Visceral or Disseminated HSV • Initial therapy: Acyclovir 10 mg/kg IV every 8 hours for 10–14 days (AIII) • For mucocutaneous lesions, change to PO therapy (dose as above) once lesions begin to regress (AIII); continue PO therapy until lesions have completely healed (AIII). • Some clinicians will extend the course of treatment for visceral or disseminated disease based on clinical response and degree of immunosuppression. Epithelial Keratitis • Valacyclovir 1 g PO twice daily for 5–10 days (BIII), *or* • Acyclovir 400 mg PO five times daily for 5–10 days (BIII), *or* • Trifluridine eye drops (BIII) (see mpox for dosing), *or*	For Acyclovir-Resistant HSV (Based on Clinical Response, Typically for 21–28 Days or Longer) *Preferred Therapy* • Foscarnet 40 mg/kg IV every 8–12 hours until clinical response (AI) *Alternative Therapy* • Topical imiquimod 5% three times weekly (BIII), *or* • Topical cidofovir 1% once daily (BIII), *or* • Topical trifluridine 1% three times daily (BIII), *or* • Topical foscarnet 1% five times daily (BIII), *or* • IV cidofovir once weekly for 2 weeks, then every other week (CIII). See CMV Retinitis for information on concomitant probenecid and hydration. Chronic Suppressive Therapy • Acyclovir 400 mg PO twice daily (AI), *or* • Famciclovir 500 mg PO twice daily (AI), *or* • Valacyclovir 500 or 1,000 mg PO once daily (CIII). See the Herpes Simplex Virus Disease section for additional information. • May continue indefinitely, regardless of CD4 count; re-evaluate at least annually, particularly if immune reconstitution has occurred (BIII).	HSV infection can be treated with episodic therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. For ophthalmic HSV disease, consultation with an ophthalmologist experienced with HSV ocular disease is strongly recommended (AIII). Topical formulations of trifluridine, cidofovir, and foscarnet are not commercially available but can be extemporaneously compounded. An expanded access program of oral pritelivir is available for immunocompromised patients with acyclovir-resistant HSV infection. See the AiCuris Pritelivir website. Chronic suppressive therapy is indicated for people with severe or frequent recurrences of genital herpes (AI), for people who want to minimize frequency of recurrences (AI), and to reduce the risk of genital ulcer disease in people with CD4 counts <250 cells/mm^3 who are starting ART (BI).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• Ganciclovir 0.15% gel: 1 drop into the affected eye five times a day (every 3 hours while awake) until re-epithelialization has occurred; then 1 drop three times a day for an additional 7 days (BIII) **Stromal Keratitis (For ≥1 Year)** • Acyclovir 400 mg PO twice daily (AII) *or* valacyclovir 500 mg once daily (AIII), *plus* • Prednisolone 1%: 1 drop into the affected eye six to eight times per day for at least 10 weeks followed by taper; exact course should be managed by ophthalmologist and based on individual patient course (AIII). HSV Meningitis (For 10–14 Days) (AIII) • Initial therapy: Acyclovir 10 mg/kg IV every 8 hours • After clinical improvement, change to valacyclovir 1 g PO three times a day HSV Encephalitis (For 14–21 Days) (CIII) • Acyclovir 10 mg/kg IV every 8 hours • Some clinicians will elect to extend the course based on clinical response and degree of immunosuppression. Chronic Suppressive Therapy • Valacyclovir 500 mg PO twice daily (AI) • May continue indefinitely, regardless of CD4 count; re-evaluate annually, particularly if immune reconstitution has occurred (BIII).		Recurrences following episodes of acyclovir-resistant HSV can be caused by either acyclovir-resistant or acyclovir-sensitive strains; after resolution of the acyclovir-resistant episode, suppressive therapy with acyclovir can be considered to prevent additional recurrences (CIII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Histoplasmosis	Severe Disseminated Disease *Induction Therapy (For ≥2 Weeks or Until Clinically Improved)* • Liposomal amphotericin B 3 mg/kg IV daily (AI) *Maintenance Therapy (For ≥12 Months)* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) Mild to Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in Persons With CD4 <300 Cells/mm^3 *Both Induction and Maintenance Therapy (For ≥12 Months)* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) Meningitis *Induction Therapy (4–6 Weeks Depending on Symptom Resolution and Improvement of CSF Findings)* • Liposomal amphotericin B 5 mg/kg IV daily (AIII) *Maintenance Therapy (For ≥12 Months and Until Resolution of Abnormal CSF Findings)* • Itraconazole 200 mg PO two to three times a day (AIII), with dose adjustment based on serum itraconazole concentration Long-Term Suppression Therapy *For Patients With Severe Disseminated or CNS Infection After Completion of ≥12 Months of Therapy (AIII) or Who Relapse Despite Appropriate Therapy (after reinduction therapy) (BIII)*	Severe Disseminated Disease *Induction Therapy* • Amphotericin B lipid complex 5 mg/kg IV daily (AIII) *Maintenance Therapy (For ≥12 Months)* • Posaconazole extended-release tablet 300 mg PO twice a day for 1 day, then 300 mg PO once daily (BIII) • Voriconazole 400 mg PO twice a day for 1 day, then 200 mg PO twice a day (BIII), *or* • Fluconazole 800 mg PO daily (CII) Mild to Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in People With CD4 Count <300 Cells/mm^3 *Both Induction and Maintenance Therapy (For ≥12 Months)* • Posaconazole extended-release tabet 300 mg PO twice a day for 1 day, then 300 mg PO once daily (BIII) • Voriconazole 400 mg PO twice a day for 1 day, then 200 mg PO twice a day (BIII), *or* • Fluconazole 800 mg PO daily (CII) Meningitis *Induction Therapy (4–6 Weeks Depending on Symptom Resolution and Improvement of CSF Findings)* • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (BIII)	Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities. Random serum concentration of itraconazole between 1–2 μg/mL is recommended. Frequency and severity of toxicities increase when concentration is ≥5 μg/mL. The recommendations for posaconazole, voriconazole, and fluconazole are based on very limited clinical data and for people who are only moderately ill.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• Itraconazole 200 mg PO daily (AIII)	*Maintenance Therapy (For ≥12 Months and Until Resolution of Abnormal CSF Findings)* • Voriconazole 400 mg PO twice a day for 1 day, then 200 mg twice a day (BIII), *or* • For people who cannot tolerate itraconazole and voriconazole: Fluconazole 800 mg PO daily (CII) Long-Term Suppression Therapy • Fluconazole 400 mg PO once daily (CII) • Voriconazole 200 mg PO twice daily (BIII) • Posaconazole 300 mg extended-release tablet PO once daily (BIII)	

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Human Herpesvirus-8 (HHV-8) Associated Diseases *(Kaposi Sarcoma [KS], Primary Effusion Lymphoma [PEL], Multicentric Castleman's Disease [MCD])*	KS *ACTG Stage T0 (Localized Involvement of Skin and/or Lymph Nodes and/or Minimal Oral Disease Only)* • ART (AII) alone, *or* • ART plus liposomal doxorubicin (AIII), if disease does not respond to ART alone *ACTG Stage T1 (Extensive and/or Symptomatic KS Skin Lesions, Extensive Oral Disease, Tumor-Associated Edema and/or Ulceration, or Any Visceral Involvement)* • ART plus liposomal doxorubicin (AI) MCD • MCD without KS: ART plus rituximab (BII) • MCD with KS: ART plus rituximab with liposomal doxorubicin (AII) PEL or HHV-8 DLBCL (With or Without KS) • PEL or HHV-8-associated DLBCL: ART plus combination chemotherapy, such as EPOCH (AIII) • PEL or HHV-8-associated DLBCL with MCD: ART plus dose-adjusted EPOCH plus rituximab (CII) KSHV-Associated Inflammatory Cytokine Syndrome • After excluding MCD and PEL, ART plus rituximab with combination chemotherapy for concurrent KS (CII)	KS *ACTG Stage T1 (Extensive and/or Symptomatic KS Skin Lesions, Extensive Oral Disease, Tumor-Associated Edema and/or Ulceration, or Any Visceral Involvement)* • ART plus paclitaxel, if liposomal doxorubicin is not available (AI), or to treat recurrence after treatment with liposomal doxorubicin (AII), *or* • ART with oral pomalidomide plus thromboprophylaxis (e.g., low-dose aspirin 81 mg daily) (BII) MCD • ART plus IV ganciclovir (or oral valganciclovir) with or without high-dose zidovudine—not for use in cases of multi-organ failure, such as renal and/or hepatic failure (CII)	Treatment should be undertaken in consultation with both oncology and infectious disease specialists, with additional input from centers specifically caring for people with HIV and cancer (AIII). All HHV-8–specific treatments should be given with ART (AI). ART given concurrently with chemotherapy should be chosen to minimize drug–drug interactions and additive toxicities (AIII). Systemic corticosteroids or other immunosuppressants in patients with KS should either be avoided or used under close observation, given the potential for exacerbation of KS (AIII). Although corticosteroids appear to be effective as an adjunctive therapy for MCD, they should be used with caution or avoided, especially in patients with concurrent KS, given potential for exacerbation of life-threatening KS (AIII). One-third of patients receiving rituximab may have subsequent exacerbations or emergence of KS.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Human Papillomavirus (HPV) Disease		Treatment of Genital Warts		Patients with HIV may have larger or more numerous warts and may not respond as well to therapy for genital warts when compared to individuals without HIV. Intralesional interferon is usually not recommended because of high cost, difficult administration, and potential for systemic side effects (CIII). In patients with HIV, the rate of recurrence of genital warts despite treatment is high. There is no consensus on the treatment of oral warts. Many treatments for anogenital warts cannot be used in the oral mucosa. Surgery is the most common treatment for oral warts that interfere with function or for aesthetic reasons.
		Patient-Applied Treatment Options for Uncomplicated External Warts That Can Be Easily Identified by Patients • Topical imiquimod 5% cream: Apply to genital warts at bedtime on three nonconsecutive nights per week for up to 16 weeks, until lesions are no longer visible. Each treatment should be washed with soap and water 6–10 hours after application (BII); *or* • Topical podophyllotoxin (e.g., podofilox 0.5% solution or 0.5% gel): Apply to genital warts twice a day for 3 days, followed by 4 days of no therapy. Can be repeated weekly for up to four cycles (BIII); *or* • Topical sinecatechins 15% ointment: Apply to affected areas three times a day for up to 16 weeks, until warts are completely cleared and not visible (BIII); *or* • Topical cidofovir 1%: Daily for 5 days per week for 8 weeks (CIII). Topical formulation is not commercially available but may be compounded.	Provider-Applied Therapy for Complex or Multicentric Lesions, or Lesions Inaccessible to Patient, or Due to Patient or Provider Preference • Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen. Repeat every 1–2 weeks for up to 4 weeks, until lesions are no longer visible (BIII). Some specialists allow the lesion to thaw, then freeze a second time in each session (BIII); *or* • Trichloroacetic acid or bichloroacetic acid cauterization (80–90% aqueous solution): Apply to warts only and allow to dry until a white frost develops. Repeat weekly for up to 6 weeks, until lesions are no longer visible (BIII); *or* • Intralesional cidofovir (15 mg/mL solution) injected directly into the wart (maximum 1 mL per session). May be repeated every 4 weeks for total of 3–4 treatments (CIII). • Surgical excision (BIII) or laser surgery (CIII) for external or anal warts	
Leishmaniasis	Visceral	For *Leishmania infantum/chagasi* • Liposomal amphotericin B 3–5 mg/kg IV daily (AII), *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, 38) (AII) • To achieve total dose of 20–60 mg/kg (AII)	For *Leishmania infantum/chagasi or donovani* • Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 g (BII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BII)	ART should be initiated or optimized as soon as possible (AIII). Pentavalent antimony is for investigational use only. For miltefosine, visit www.profounda.com.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
		For *Leishmania donovani* • Liposomal amphotericin B 5 mg/kg on Days 1, 3, 5, 7, 9, and 11 plus miltefosine 50 mg PO twice daily (for 28 days if from East Africa or 14 days if from Southeast Asia) (BI) Chronic Maintenance Therapy *For Patients With CD4 Count <200 Cells/mm³ (AII)* • Liposomal amphotericin B 4 mg/kg IV every 2–4 weeks (AII)	For *Leishmania donovani* • Liposomal amphotericin B 3–5 mg/kg IV daily to achieve total dose of 20–60 mg/kg (AII), *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg (AII), *or* • For Indian *L. donovani*: Miltefosine ~2.5–3.0 mg/kg PO daily in two or three divided doses (maximum 150 mg daily) for 28 days (BII) Chronic Maintenance Therapy (Secondary Prophylaxis) • Amphotericin B lipid complex 3 mg/kg IV every 21 days (BII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM every 4 weeks (BII), *or* • Pentamidine 4 mg/kg (maximum 300 mg) IV every 2–4 weeks (BII)	
	Cutaneous	For Initial Infection • Liposomal amphotericin B 4 mg/kg IV daily for 10 days (BIII) to achieve total dose of 20–60 mg/kg, *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg (BIII), *or* • Miltefosine 2.5 mg/kg/day PO in two or three divided doses for 28 days (maximum 150 mg per day) (BIII), *or* • Pentavalent antimony (meglumine antimoniate)	Possible Options • Cryotherapy, *or* • Topical paromomycin, *or* • Intralesional pentavalent antimony (meglumine antimoniate) or pentamidine, *or* • PO or IV fluconazole (*L. major and L. mexicana)* • IV pentamidine • Local heat therapy	ART should be initiated or optimized as soon as possible (AIII). Pentavalent antimony is for investigational use only. For miltefosine, visit www.profounda.com.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	20 mg/kg IV or IM daily for 28 days (BIII) Chronic Maintenance Therapy • May be indicated in immunocompromised patients with multiple relapses (CIII) • Drugs and doses same as for visceral leishmaniasis	No data exist for any of these agents in patients with HIV; choice and efficacy are dependent on species of *Leishmania.*	
Malaria	Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all patients with HIV with confirmed or suspected *P. falciparum* infection should be hospitalized for evaluation, initiation of treatment, and observation (AIII). Treatment recommendations for patients with HIV are the same as for patients without HIV (AIII). Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, region of infection, and the likely drug susceptibility of the infected species, and can be found at https://www.cdc.gov/malaria.	When suspicion for malaria is low, antimalarial treatment should not be initiated until the diagnosis is confirmed.	For treatment recommendations for specific regions, clinicians should refer to https://www.cdc.gov/malaria or call the CDC Malaria Hotline: 770-488-7788, Monday–Friday, 8 a.m.–4:30 p.m. ET, or 770-488-7100 after hours.
Microsporidiosis	For GI Infections Caused by *Enterocytozoon bienuesi* • Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 (AII), *plus* • Manage dehydration and diarrhea with fluid support (AII) and malnutrition and wasting with nutritional supplements (AIII). For Intestinal and Disseminated (Not Ocular) Infections Caused by Microsporidia Other Than *E. bienuesi* and *Vittaforma corneae* • Albendazole 400 mg PO twice daily (AII), continue until CD4 count >200 cells/mm^3 for	For GI Infections Caused by *E. bienuesi* • Fumagillin 60 mg/day (BII) and TNP-470 (a synthetic analog of fumagillin) (BIII) may be effective, but neither is available in the United States. • Nitazoxanide (1,000 mg twice daily) may have some effect, but response may be minimal in patients with low CD4 counts (CIII).	Antimotility agents can be used for diarrhea control if required (BIII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	>6 months after initiation of ART (BIII) For Disseminated Disease Caused by *Trachipleistophora* or *Anncaliia* • Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily (CIII) For Ocular Infection • Topical fumagillin bicylohexylammonium (Fumidil B) eyedrops 3 mg/mL in saline (fumagillin 70 µg/mL): two eyedrops every 2 hours for 4 days, then two eyedrops four times daily (investigational use only in United States) (BII) plus albendazole 400 mg PO twice daily, for management of systemic infection (BIII) *If CD4 Count >200 Cells/mm^3* • Continue until symptoms resolve (CIII). *If CD4 Count ≤200 Cells/mm^3* • Continue until resolution of ocular symptoms and CD4 count increases to >200 cells/mm^3 for >6 months in response to ART (BIII).		

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Mpox	For People With Mild to Moderate Disease Who Are Not at Risk for Severe Disease • Supportive care, including adequate pain control (BIII), and referral to clinical trials, if available (CIII). CDC can provide additional guidance to clinicians with patient management questions (see Other Comments for contact information). For Severe Disease or People at Risk for Severe Disease (See Other Comments for Definition) • Tecovirimat 600 mg PO every 12 hours (40 to <120 kg) or every 8 hours (≥120 kg) for 14 days (BIII) within 30 minutes of a fatty meal, *or* • Tecovirimat 200 mg IV every 12 hours for 14 days (35 to <120 kg) or 300 mg IV every 12 hours (≥120 kg) infused over 6 hours (BIII) if concern exists regarding altered GI absorption capacity, inability to take PO, or severity of illness *Adjunctive Therapy* • Cidofovir 5 mg/kg/week IV for two doses with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose and 1 g PO 8 hours after the dose (total of 4 g) (BIII), *or* • Brincidofovir 200 mg PO once weekly for two doses (BIII), *or* • VIGIV 6,000–9,000 units/kg IV single dose (BIII)	None	People with severe mpox or are at high risk for severe mpox should receive directed mpox antiviral treatment (BIII) with early consultation with CDC or an expert in mpox treatment and prompt use of combination therapy, ideally at the time of the first medical encounter and after considering the risks and benefits (CIII). Contact: poxvirus@cdc.gov or 770-488-7100 Tecovirimat, brincidofovir, and VIGIV are available via expanded access or emergency IND. People with severe immunocompromise might benefit from extended treatment (i.e., >14 days) if new confirmed mpox lesions occur or existing lesions or symptoms worsen despite treatment (CIII). Effective ART should be initiated as soon as possible (AIII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	For Ocular Mpox • Tecovirimat 600 mg PO every 12 hours (40 to <120 kg) or every 8 hours (≥120 kg) for 14 days (BIII) within 30 minutes of a fatty meal, *plus* • Trifluridine (Viroptic) 1 drop into affected eye(s) every 2 hours when awake (max: 9 drops/day) until reepithelialization, then every 4 hours (min: 5 drops/day) for 7 days, or until all periocular lesions have healed (BIII) in consultation with an ophthalmologist (BIII) o Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided (AII).		Definition for Severe Disease: Hemorrhagic disease; lesions affecting ≥25% of body surface that may be confluent, necrotic, and/or hemorrhagic in appearance or cause sepsis; disease resulting in airway compromise or affecting the nervous system; cardiac and/or neurologic disease; ocular or periorbital infections; other conditions requiring hospitalization. Consult the CDC's Tecovirimat webpage for more details. Definition for at Risk for Severe Disease: Not virologically suppressed, CD4 counts <200 cells/mm^3, have another immunocompromising condition, have atopic dermatitis/other conditions affecting skin integrity, or are children, pregnant, or breastfeeding. Consult the CDC's Tecovirimat webpage for more details.
Mycobacterium avium Complex (MAC) Disease	At Least Two Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance (AII) • Clarithromycin 500 mg PO twice daily (AI) plus ethambutol 15 mg/kg PO daily (AI), *or* • Azithromycin 500–600 mg plus ethambutol 15 mg/kg PO daily (AII) if drug interaction or intolerance precludes the use of clarithromycin. Duration • At least 12 months (AII) • Shorter duration may be considered. CD4 count should be >100 cells/mm^3 for ≥6 months in response to ART	Some experts would add a third drug if more severe disease is present. • Rifabutin 300 mg PO daily (dose adjustment may be necessary based on drug interactions) (CI) • Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table of the *Mycobacterium tuberculosis* section for dosing recommendations.	Testing of susceptibility to clarithromycin and azithromycin is recommended. NSAIDs can be used for moderate to severe symptoms attributed to IRIS (BIII). If IRIS symptoms persist, a short course (i.e., 4–8 weeks) of a systemic corticosteroid (equivalent to 20–40 mg of prednisone daily) can be used (BII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	before discontinuation of MAC therapy (CIII).	Some experts would add a fourth drug if the risk of mortality is high, emergence of drug resistance is likely, CD4 count <50 cells/mm^3, high mycobacterial loads (>2 log_{10} CFU/mL of blood) are present, or effective ART is absent (CIII). • A fluoroquinolone (CIII) (e.g., moxifloxacin 400 mg PO daily or levofloxacin 500 mg PO daily), *or* • An injectable aminoglycoside (CIII) (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily).	Bedaquiline, tedizolid, linezolid, and omadacycline have demonstrated *in vitro* activity against clinical isolates of MAC; these might also be considered in people with refractory MAC disease.
Mycobacterium tuberculosis (TB) Disease: Drug-Susceptible TB	Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for dosing recommendations. Intensive Phase (8 Weeks) • INH (plus pyridoxine) plus (RIF or RFB) plus PZA plus EMB PO daily (AI) • If drug-susceptibility report shows sensitivity to INH and RIF, then EMB may be discontinued before the end of 2 months (AI). Continuation Phase (Duration Depends on Site and Severity of Infection as Noted Below) • INH (plus pyridoxine) plus (RIF or RFB) PO daily (AII) Total Duration of Therapy for Drug-Susceptible TB • *Pulmonary, uncomplicated TB:* 6 months (BII)	Only for Patients Receiving an Efavirenz-Based ARV Regimen; Not Recommended for Extrapulmonary TB *Intensive Phase (8 Weeks)* INH plus RPT 1,200 mg plus moxifloxacin 400 mg plus PZA plus pyridoxine 25–50mg PO daily (AI)[c] *Continuation Phase (9 Weeks)* • INH plus RPT 1200 mg plus moxifloxacin 400 mg plus pyridoxine 25–50mg PO daily (AI)	DOT is recommended for all patients (AII). All rifamycins may have significant pharmacokinetic interactions with ARV drugs; please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations. Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• *Pulmonary TB with positive culture at 8 weeks of TB treatment, or severe cavitary or disseminated extrapulmonary TB:* 9 months (BII) • *TB meningitis:* 9–12 months (BII) • *Extrapulmonary TB in Other sites:* 6 months (BII)		Adjunctive corticosteroids for TB meningitis (AII): Dexamethasone 0.3–0.4mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day, and taper by 1 mg/week for total of 12 weeks. At doses above 16 mg, dexamethasone is a CYP3A4 inducer and can decrease certain ARVs that are substrates of CYP3A4 (e.g., DOR, RPV, and protease inhibitors). Consultation with a pharmacist is recommended. Adjunctive corticosteroid is not recommended for patients with TB pericarditis (AI). See text for recommendations on preventing and managing paradoxical TB-IRIS, including prednisone dosing recommendations.
Mycobacterium tuberculosis (TB) Disease: Drug-Resistant TB	Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for dosing recommendations. Empiric Therapy for Suspected Resistance to Rifamycin[d] +/- Resistance to Other Drugs • INH (plus pyridoxine) plus PZA plus EMB plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin[e]) (BII) Confirmed Resistance to INH • (Moxifloxacin or levofloxacin) plus (RIF or RFB) plus EMB plus PZA for 6 months (BII) Confirmed Resistance to Rifamycin +/- Other Drugs (AI) *For 14 Days* • Pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily plus bedaquiline 400 PO daily, *followed by* *For 24 Weeks* • Pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily, *and* • Bedaquiline 200 mg PO three times per week Omit moxifloxacin if resistant to fluoroquinolones (AI).	*Confirmed Resistance to Rifamycin +/- Other Drugs* • Therapy should be individualized based on drug-susceptibility results and clinical and microbiologic responses, to include ≥5 active drugs, and with close consultation with experienced specialists (BIII).	

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Duration • 6–24 months (see Managing Drug-Resistant TB in the *Mycobacterium tuberculosis* section for discussion)		
Pneumocystis Pneumonia (PCP)	People with HIV who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX (BIII). Duration of PCP treatment: 21 days (AII) For Moderate to Severe PCP • TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) IV given in divided doses every 6 or 8 hours (AI); may switch to PO formulations after clinical improvement (AI). For Mild to Moderate PCP • TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) PO given in three divided doses (AI), *or* • TMP-SMX: (160 mg/800 mg or DS) two tablets PO three times daily (AI) Secondary Prophylaxis, After Completion of PCP Treatment • TMP-SMX DS: one tablet PO daily (AI), *or* • TMP-SMX (80 mg/400 mg or SS): one tablet PO daily (AI)	For Moderate to Severe PCP • Primaquine 30 mg (base) PO daily plus (clindamycin 600 mg IV every 6 hours or 900 mg IV every 8 hours) or (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) (AI) (some clinicians prefer this option because it is more effective and less toxic than pentamidine), *or* • Pentamidine 4 mg/kg IV daily infused over ≥60 minutes (AI); can reduce dose to 3 mg/kg IV daily in the event of toxicities (BI) For Mild to Moderate PCP • Dapsone 100 mg PO daily plus TMP 15 mg/kg/day PO given in three divided doses (BI), *or* • Primaquine 30 mg (base) PO daily plus (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) (BI), *or* • Atovaquone 750 mg PO twice daily with food (BI) Secondary Prophylaxis, After Completion of PCP Treatment The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*: • TMP-SMX DS: one tablet PO three times weekly (BI), *or*	Indications for Adjunctive Corticosteroids for Moderate to Severe PCP (AI) • PaO_2 <70 mmHg at room air, *or* • A-a gradient ≥35 mmHg Prednisone Doses (Beginning as Early as Possible and Within 72 Hours of PCP Therapy) (AI) • Days 1–5: 40 mg PO twice daily • Days 6–10: 40 mg PO daily • Days 11–21: 20 mg PO daily IV methylprednisolone can be administered as 80% of prednisone dose. Benefit of using a corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate to severe PCP (BIII). Whenever possible, patients should be tested for G6PD before use of dapsone or primaquine. Alternative therapy should be used in patients found to have G6PD deficiency.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		• Dapsone 50 mg PO daily with pyrimethamine[b] 50 mg plus leucovorin 25 mg PO weekly (BI), *or* • Dapsone 200 mg plus pyrimethamine[b] 75 mg plus leucovorin 25 mg PO weekly (BI), *or* • Atovaquone 1,500 mg PO daily with food (BI) The following regimens should only be used if the person is seronegative for *Toxoplasma gondii*: • Dapsone 100 mg PO daily (BI), *or* • Aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer (BI), *or* • Intravenous pentamidine 300 mg every 28 days (CIII)	Patients who are receiving pyrimethamine[b]/sulfadiazine for the treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII). If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution should be considered after the reaction resolves (AII). The dose can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII). TMP-SMX should be permanently discontinued in patients with possible or definite Stevens-Johnson syndrome or toxic epidermal necrosis (AIII). See alternative options.
Progressive Multifocal Leukoencephalopathy (PML)/JC Virus Infections	There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse the immunosuppression caused by HIV. Initiate ART immediately in ART-naive patients (AII). Optimize ART to achieve viral suppression in patients who develop PML and receive ART but remain viremic (AIII).	None	Corticosteroids may be used for PML-IRIS (BIII). The optimal corticosteroid regimen has not been established but should be tailored to individual patients. ART should not be discontinued during PML-IRIS (AIII).
Syphilis (*Treponema pallidum* Infection)	Early-Stage (Primary, Secondary, and Early-Latent Syphilis) • Benzathine penicillin G 2.4 million units IM for one dose (AII)	Early-Stage (Primary, Secondary, and Early-Latent Syphilis) *For Penicillin-Allergic Patients* • Doxycycline 100 mg PO twice daily for 14 days (BII), *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days (BII)	The efficacy of non-penicillin alternatives has not been evaluated in patients with HIV, and they should be used only with close clinical and serologic monitoring.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Late-**Latent Disease (>1 Year) or** of Unknown Duration • Benzathine penicillin G 2.4 million units IM weekly for three doses (AII) Late-Stage (Tertiary–Cardiovascular or Gummatous Disease) • Benzathine penicillin G 2.4 million units IM weekly for three doses (AII) Note: Rule out neurosyphilis before initiation of benzathine penicillin. People with CSF abnormalities should be treated with a regimen for neurosyphilis [AII]. Neurosyphilis, Otic, or Ocular Syphilis • Aqueous crystalline penicillin G 18–24 million units per day (administered as 3–4 million units IV every 4 hours or by continuous IV infusion) for 10–14 days (AII) +/- benzathine penicillin G 2.4 million units IM x 1 dose after completion of IV therapy (CIII)	Late-Latent Disease (>1 **Year)** or of Unknown Duration *For Penicillin-Allergic Patients* • Doxycycline 100 mg PO twice a day for 28 days (BIII) Neurosyphilis • Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII), *or* • For penicillin-allergic patients, desensitization to penicillin is the preferred approach (BIII); if not feasible and the patient is not pregnant, ceftriaxone 2 g IV daily for 10–14 days (BII).	People with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (AII). For management of early syphilis during pregnancy, limited evidence indicates a second dose of benzathine penicillin G 2.4 million units IM one week after the single dose treatment may be of benefit for congenital syphilis prevention (BII). The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgia that can occur within the first 24 hours after therapy for syphilis. This reaction occurs most frequently in patients with early syphilis, high non-treponemal titers, and prior penicillin treatment. Procaine penicillin has been discontinued by the manufacturer as of June 13, 2023 (see FDA Drug Shortages).
Talaromycosis (Penicilliosis)	Induction Therapy • Liposomal amphotericin B 3–5 mg/kg/day IV (AIII) *Duration* • 2 weeks (AIII), followed by consolidation therapy Consolidation Therapy • Itraconazole 200 mg PO every 12 hours for 10 weeks (AI), followed by chronic maintenance therapy	Induction Therapy • Amphotericin B deoxycholate 0.7 mg/kg/day IV (if liposomal amphotericin B is not available) (AI) *Duration* • 2 weeks (AI), followed by consolidation therapy	Itraconazole is not recommended as induction therapy for talaromycosis (AI). ART should be initiated as early as 1 week after initiation of treatment for talaromycosis (AII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Chronic Maintenance Therapy • Itraconazole 200 mg PO once daily (AI)	*If Amphotericin B Is Not Available, Contraindicated, or Not Tolerated* • Voriconazole 6 mg/kg IV every 12 hours on Day 1 (loading dose), then 4 mg/kg IV every 12 hours (BII), *or* • Voriconazole 600 mg PO every 12 hours on Day 1 (loading dose), then 400 mg PO every 12 hours (BII) • *Duration:* 2 weeks (BII), followed by consolidation therapy with itraconazole (preferred) or voriconazole Consolidation Therapy • Voriconazole 200 mg PO every 12 hours for 10 weeks (BII), followed by chronic maintenance therapy Chronic Maintenance Therapy • Itraconazole should be used (AI). Optimal dose of voriconazole for maintenance therapy has not been studied.	Itraconazole and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations. Itraconazole and voriconazole concentrations should be monitored beginning at 5 days and dose adjusted as needed to obtain serum trough concentrations for itraconazole should be >0.5 µg/mL (for a combined itraconazole plus hydroxyitraconazole level) and >1 µg/mL for voriconazole (BIII). Itraconazole solution is generally preferred over the capsule formulation because of improved bioavailability.
Toxoplasma gondii Encephalitis	Treatment of Acute Infection • Pyrimethamine[b] 200 mg PO one time, followed by weight-based therapy (AI): o If ≤60 kg: Pyrimethamine[b] 50 mg PO once daily plus sulfadiazine 1,000 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily o If >60 kg: Pyrimethamine[b] 75 mg PO once daily plus sulfadiazine 1,500 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily o Note: Leucovorin dose can be increased to 50 mg daily or twice a day.	Treatment of Acute Infection • Pyrimethamine[b] (leucovorin)* plus clindamycin 600 mg IV or PO every 6 hours (AI), *or* • Atovaquone 1,500 mg PO twice a day with food plus pyrimethamine[b] (leucovorin)* (BII), *or* • Atovaquone 1,500 mg PO twice a day with food plus sulfadiazine 1,000–1,500 mg PO every 6 hours (weight-based dosing, as in preferred therapy) (BII), *or* • Atovaquone 1,500 mg PO twice a day with food (BII)	If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (AII). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI). Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO twice a day (AII) Duration for Acute Therapy • At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks • After completion of acute therapy, all patients should be initiated on chronic maintenance therapy. Chronic Maintenance Therapy • Pyrimethamine[b] 25–50 mg PO daily plus sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) plus leucovorin 10–25 mg PO daily (AI), *or* • TMP-SMX DS one tablet twice a day (AII)	Chronic Maintenance Therapy • (Pyrimethamine[b] 25–50 mg plus leucovorin 10–25 mg) PO daily plus clindamycin 600 mg PO every 8 hours plus (BI), *or* • Atovaquone 750–1,500 mg PO twice a day plus (pyrimethamine[b] 25 mg plus leucovorin 10 mg) PO daily (BII), *or* • Atovaquone 750–1,500 mg PO twice a day plus sulfadiazine 2,000–4,000 mg PO daily (in two to four divided doses) (BII), *or* • Atovaquone 750–1,500 mg PO twice a day with food (BII) * Pyrimethamine[b] and leucovorin doses are the same as for preferred therapy.	Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated edema (BIII); discontinue as soon as clinically feasible. Antiseizure medications should be administered to patients with a history of seizures (AII) and continued through acute treatment (BII) but should not be used as seizure prophylaxis (BII). If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP (AII).
Varicella Zoster Virus (VZV) Disease	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases* • Initiate as soon as possible after symptom onset and continue for 5–7 days: o Valacyclovir 1 g PO three times a day (AII), *or* o Famciclovir 500 mg PO three times a day (AII) *Severe or Complicated Cases* • Acyclovir 10 mg/kg IV every 8 hours for 7–10 days (AIII) • May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement (BIII).	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases (For 5–7 Days)* • Acyclovir 800 mg PO five times a day (BII) Herpes Zoster (Shingles) *Acute Localized Dermatomal* • For 7–10 days; consider longer duration if lesions are slow to resolve • Acyclovir 800 mg PO five times a day (BII)	In managing VZV of the eyes, consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended (AIII). Duration of therapy for VZV retinitis is not well defined and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses. Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) (AIII).

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Herpes Zoster (Shingles) *Acute Localized Dermatomal* • For 7–10 days; consider longer duration if lesions are slow to resolve. • Valacyclovir 1 g PO three times a day (AII), *or* • Famciclovir 500 mg three times a day (AII) Extensive Cutaneous Lesion or Visceral Involvement • Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident (AII) • May switch to PO therapy (valacyclovir, famciclovir, or acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV) to complete a 10- to 14-day course (BIII). ARN • Acyclovir 10 mg/kg IV every 8 hours for 10–14 days, followed by valacyclovir 1 g PO three times a day for >14 weeks (AIII), *plus* • Intravitreal ganciclovir 2 mg/0.05 mL twice weekly for 1–2 doses (BIII) PORN • Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg IV every 12 hours (AIII), *plus* • ≥1 intravitreal antiviral injection: ganciclovir 2 mg/0.05 mL or foscarnet 1.2 mg/0.05 mL twice weekly (AIII) • Initiate or optimize ART (AIII).		In patients with herpes zoster ophthalmicus who have stromal keratitis and anterior uveitis, topical corticosteroids to reduce inflammation may be necessary. The role of ART has not been established in these cases.

[a] TAF 10-mg dose is in the FDC tablets of EVG/c/TAF/FTC and DRV/c/TAF/FTC; when TAF is used with other antiretrovirals, the dose is 25 mg.

[b] Refer to Daraprim Direct for information on accessing pyrimethamine.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

[c] This regimen was not studied and is not recommended during pregnancy or breastfeeding or for people who are <40 kg or who have most types of extrapulmonary TB (other than pleural TB or lymphadenitis).

[d] Many patients with RIF resistance also have resistance to isoniazid. Susceptibility should be confirmed in any patient with RIF resistance to determine if isoniazid can be included in the treatment regimen.

[e] Given the risk of ototoxicity and nephrotoxicity with aminoglycosides, use of amikacin should generally be restricted to bridging regimens, while awaiting availability of less toxic medications and/or results of drug-susceptibility testing.

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Opportunistic Infection Guidelines.

Key: +/- = with or without; 3TC = lamivudine; A-a = alveolar-arterial; AASLD = American Association for the Study of Liver Diseases; ACTG = AIDS Clinical Trials Group; ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CDI = *Clostridium difficile* infection; CFU = colony-forming unit; CNS = central nervous system; CrCl = creatinine clearance; CSF = cerebrospinal fluid; DAA = direct-acting antiviral; DOT = directly observed therapy; DLBCL = diffuse large B-cell lymphoma; DRV = darunavir; DS = double strength; EMB = ethambutol; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin combination therapy; EVG = elvitegravir; FDA = U.S. Food and Drug Administration; FDC = fixed-dose combination; FMT = fecal microbiota therapy; FTC = emtricitabine; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HD = hemodialysis; HHV-8 = human herpesvirus 8; HSV = herpes simplex virus; IDSA = Infectious Diseases Society of America; IM = intramuscular; IND = investigational new drug; INH = isoniazid; IRIS = immune reconstitution inflammatory syndrome; IRU = immune recovery uveitis; IV = intravenous; KS = Kaposi sarcoma; KSHV = Kaposi sarcoma–associated herpesvirus; LFA = lateral flow assay; LP = lumbar puncture; MCD = multicentric Castleman's disease; MIC = minimum inhibitory concentration; MSM = men who have sex with men; NSAID = nonsteroidal anti-inflammatory drugs; OI = opportunistic infection; PaO_2 = partial pressure of oxygen; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PEL = primary effusion lymphoma; PO = oral; PORN = progressive outer retinal necrosis; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; SMX = sulfamethoxazole; SS = single strength; SVR = sustained virologic response; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TMP = trimethoprim; VIGIV = vaccinia immune globulin intravenous; WHO = World Health Organization

Table 3. Indications for Discontinuing and Restarting Primary and Secondary Prophylaxis (or Chronic Maintenance Therapy) for Selected Opportunistic Infections in Adults and Adolescents With HIV

Updated: July 14, 2025
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Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance Therapy
Bacterial Enteric Infections: Salmonellosis	Not applicable	Not applicable	Resolution of *Salmonella* infection and after response to ART with sustained viral suppression and CD4 counts >200 cells/mm^3 (CII)	No recommendation
Bartonellosis	Not applicable	Not applicable	• Received at least 3–4 months of treatment, *and* • CD4 count >200 cells/mm^3 for ≥6 months (CIII) Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by fourfold (CIII).	No recommendation
Candidiasis (Mucocutaneous)	Not applicable	Not applicable	If used, reasonable to discontinue when CD4 count >200 cells/mm^3 (AIII)	No recommendation
Coccidioidomycosis	CD4 count ≥250 cells/mm^3 with virologic suppression on ART (BIII)	No recommendation	Focal Coccidioidal Pneumonia (AII) • Clinically responded to 3–6 months of antifungal therapy, with CD4 count ≥250 cells/mm^3, and achieved viral suppression on ART. • Continue monitoring for recurrence after treatment discontinuation by using serial chest radiographs and coccidioidal serology. Diffuse Pulmonary or Disseminated Non-Meningeal Disease (BIII) • Clinical and serological response to ≥12 months of therapy, *and* • Consultation with experts	No recommendation

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance Therapy
			• For diffuse pulmonary disease, continue monitoring for recurrence after treatment discontinuation by using serial chest radiographs and coccidioidal serology. Coccidioidal Meningitis (AII) • Suppressive therapy should be continued indefinitely, even with an increase in CD4 count on ART.	
Cryptococcal Meningitis	Not applicable	Not applicable	If the following criteria are fulfilled (BII): • Completed initial (induction and consolidation) therapy, *and* • Received at least 1 year of antifungal therapy, *and* • Remain asymptomatic of cryptococcal infection, *and* • CD4 count ≥100 cells/mm^3 and with suppressed plasma HIV RNA in response to ART	CD4 count <100 cells/mm^3 (AIII)
Cystoisospora belli Infection	Sustained increase in CD4 count to ≥200 cells/mm^3 for >6 months in response to ART (BIII)	No recommendation	• Sustained increase in CD4 count to ≥200 cells/mm^3 for >6 months in response to ART and without evidence of active *C. belli* infection (BIII)	No recommendation
Cytomegalovirus Retinitis	Not applicable	Not applicable	If the following criteria are fulfilled (AII): • CMV treatment for at least 3 months, *and* • Lesions are inactive, *and* • CD4 count ≥100 cells/mm^3 for at least 3 months in response to ART Therapy should be discontinued only after consultation with an ophthalmologist. After discontinuation of anti-CMV maintenance therapy, ophthalmologic monitoring for early detection of CMV	CD4 count <100 cells/mm^3 (AIII)

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance Therapy
			relapse and IRU should be performed at least every 3 months and then yearly after immune reconstitution (AIII).	
Histoplasma capsulatum Infection	On ART with CD4 count ≥150 cells/mm^3 for 6 months and with viral suppression on ART (BIII)	For patients at high risk of acquiring histoplasmosis (as noted in Table 1), restart if CD4 count decreases to <150 cells/mm^3 (BIII).	If the following criteria (AI) are fulfilled: • Received azole therapy for >1 year, *and* • Negative fungal blood cultures, *and* • Serum or urine *Histoplasma* antigen below the level of quantification, *and* • Viral suppression on ART, *and* • CD4 count ≥150 cells/mm^3 for ≥6 months in response to ART	CD4 count <150 cells/mm^3 (BIII)
Leishmaniasis: Visceral (and possibly cutaneous leishmaniasis in immunocompromised patients with multiple relapses)	Not applicable	Not applicable	If CD4 count increases to >350 cells/mm^3 and HIV viral load is suppressed for 6 months in response to ART and there is no evidence of clinical relapse of visceral leishmaniasis (CIII)	No recommendation
Microsporidiosis	Not applicable	Not applicable	If there are no signs or symptoms of non-ocular (BIII) or ocular (CIII) microsporidiosis and CD4 count is >200 cells/mm^3 for >6 months in response to ART	No recommendation
Mycobacterium avium Complex Disease	Continuing a fully suppressive ART regimen (AI)	CD4 count <50 cells/mm^3 and not on fully suppressive ART (AIII)	If the following criteria are fulfilled (AI): • Completed ≥12 months of therapy, *and* • No signs and symptoms of MAC disease, *and* • Have sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART	If a fully suppressive ART regimen is not possible and CD4 count is consistently <100 cells/mm^3 (BIII)
Pneumocystis Pneumonia	CD4 count increased from <200 to ≥200 cells/mm^3 for ≥3 months in response to ART (AI)	CD4 count <100 cells/mm^3 regardless of HIV RNA level (AIII) CD4 count 100–200 cells/mm^3	CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months in response to ART (AII) Can consider when CD4 count is 100–200 cells/mm^3 if HIV RNA	CD4 count <100 cells/mm^3 regardless of HIV RNA level (AIII) CD4 count 100–200 cells/mm^3

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance Therapy
	Can consider when CD4 count is 100–200 cells/mm^3 if HIV RNA remains below limits of detection for ≥3 to 6 months (BII)	and HIV RNA above detection limit of the assay (AIII)	remains below limits of detection for 3–6 months (BII) If PCP occurs at a CD4 count >200 cells/mm^3 while on ART, continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART (BIII). If PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered when HIV RNA levels are suppressed to below limits of detection for ≥3 to 6 months (CIII).	and with HIV RNA above detection limit of the assay (AIII)
Talaromycosis (Penicilliosis)	CD4 count ≥100 cells/mm^3 for ≥6 months in response to ART (BII) *or* HIV viral suppression for ≥6 months on ART (BIII)	CD4 count <100 cells/mm^3 (BIII)and still resides in or travels to the hyperendemic area	CD4 count ≥100 cells/mm^3 for ≥6 months in response to ART (BII) *or* HIV viral suppression for ≥6 months (BIII)	CD4 count <100 cells/mm^3 (BIII)
Toxoplasma gondii Encephalitis	CD4 count increased to >200 cells/mm^3 for >3 months and sustained HIV RNA below limits of detection in response to ART (AI) Can consider when CD4 count is 100–200 cells/mm^3 if HIV RNA remains below limits of detection for at least 3–6 months (BII)	CD4 count <100 cells/mm^3 (AIII) CD4 count 100–200 cells/mm^3 and with HIV RNA above detection limit of the assay (AIII)	If the following criteria are fulfilled (BI): • Successfully completed initial therapy • Receiving maintenance therapy and remaining free of signs and symptoms of TE, *and* • CD4 count >200 cells/mm^3 for >6 months in response to ART	CD4 count <200 cells/mm^3 (AIII)

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Antiretroviral Guidelines.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CMV = cytomegalovirus; IRU = immune reconstitution uveitis; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; TE = *Toxoplasma* encephalitis

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Updated: July 14, 2025
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This table lists the known, predicted, or suspected pharmacokinetic (PK) interactions between drugs used for the treatment or prevention of HIV-associated opportunistic infections (OIs). Many of the drugs listed in this table may also interact with antiretroviral (ARV) drugs. Clinicians should refer to the Drug–Drug Interactions tables in the most current Adult and Adolescent Antiretroviral Guidelines to assess interaction potentials between OI drugs and ARV drugs.

Throughout the table, three recommendations are commonly used when concomitant administration of two drugs may lead to untoward consequences. The rationales for these recommendations are summarized below:

Do not coadminister.

There is either strong evidence or strong likelihood that the PK interaction cannot be managed with a dose modification of one or both drugs and will or may result in either—

- Increase in concentrations of one or both drugs, which may lead to excessive risk of toxicity; *or*
- Decrease in concentrations of one or both drugs, which may render one or both drugs ineffective.

Coadministration should be avoided, if possible.

There is a potential for significant PK interactions. If other more favorable options exist, clinicians are advised to consider changing components of the regimen to accommodate a safer or more effective regimen. However, coadministration of the drugs may be necessary when there are no other acceptable therapeutic options that provide a more favorable benefit-to-risk ratio. Therapeutic drug monitoring (TDM), if available, may facilitate any necessary dose adjustments.

Use with caution.

Drug combinations are recommended to be used with caution when—

- PK studies have shown a moderate degree of interaction of unknown clinical significance; *or*
- Based on the known metabolic pathway of the two drugs, there is a potential for PK interaction of unknown clinical significance.

Rifamycin-Related Induction Interactions

Rifamycin antibiotics are potent inducers of Phase 1 and Phase 2 drug-metabolizing reactions. They also affect various transporters. When a rifamycin antibiotic must be combined with an interacting drug, close monitoring for clinical efficacy of the coadministered agent is advised. TDM, if available, may facilitate any necessary dose adjustments.

- *Rifampin (also known as rifampicin):* Interactions may not be apparent in the first several days of rifampin therapy. However, with daily doses of rifampin, enzyme induction increases over a week or more. Based on

limited data, larger daily doses of rifampin (e.g., 1,200 mg or more) appear to produce about the same maximum induction as lower doses, but the induction effect occurs more rapidly.[1,2]

- *Rifabutin:* In general, rifabutin as a cytochrome P450 (CYP) 3A4 inducer is about 40% of the potency of rifampin, but this can vary by substrate and enzymatic reaction.[3] Rifabutin is also a substrate of CYP3A4 (unlike rifampin and rifapentine) and may be subject to changes in drug exposure when given concomitantly with 3A4 inhibitors or inducers. When used with interacting drug(s), rifabutin dosage modification, TDM, and/or more frequent monitoring for rifabutin-related toxicities may be needed.
- *Rifapentine:* In general, daily rifapentine is at least as potent an inducer as rifampin. However, the potential for drug interactions with once-weekly rifapentine is not well studied. Reduced exposure of concurrent drugs that are CYP3A4 substrates is likely to occur with once-weekly rifapentine, with the extent varying by drug.

Following discontinuation of rifamycins, the enzyme induction effects gradually diminish over time and vary depending on the drug's half-life, the time required to achieve maximal induction, and the degradation course of upregulated enzymes. Generally, after five half-lives, a drug is substantially eliminated from the body. Though rifampin has a short plasma half-life (3–5 hours), de-induction largely depends on the decay time of enzymes produced.[4,5] A 2-week interval after the final dose of rifampin was found sufficient for enzyme levels to return to baseline.[4] Rifapentine and rifabutin, characterized by longer half-lives (approximately 13 and 45 hours, respectively), may exhibit a more prolonged de-induction period than rifampin. Notably, rifabutin induces enzymes to a lesser extent than rifampin and rifapentine, necessitating a shorter de-induction phase.

Azole- and Macrolide-Related Inhibition Interactions

Azole antifungals—including fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole—are substrates and potent inhibitors of metabolic pathways, including CYP enzymes and/or drug transporters (e.g., p-glycoprotein). Interactions involving azole antifungals are common. When an azole antifungal must be combined with an interacting drug, close monitoring for clinical toxicity and efficacy of the azole and/or the coadministered agent may be needed. TDM, if available, may facilitate any necessary dose adjustments.

The newer azole antifungal oteseconazole is less prone to cause clinically significant drug–drug interactions. Oteseconazole does not undergo significant metabolism, and its drug interaction profile is limited to its ability to inhibit the Breast Cancer Resistance Protein (BCRP). Concomitant use of oteseconazole and BCRP substrates may increase the exposure of BCRP substrates.

Macrolides have been shown to form complexes with drug-oxidizing enzymes, including CYP enzymes, which render an inhibitory effect. In general, erythromycin and clarithromycin are moderate to strong inhibitors, whereas azithromycin's propensity for causing clinically relevant drug interactions is the lowest, as it does not form complexes with CYP enzymes that lead to enzyme inactivation.

Pharmacodynamic Interactions

Pharmacodynamic interactions are not addressed in this table. For example, many of the drug classes listed below independently possess a risk for QTc prolongation, including azoles, macrolides, and certain anti-tuberculosis and antimalarial medications. Coadministration of drugs in these classes may require monitoring for QTc prolongation, particularly in patients with predisposing risk factors.

Therapeutic Drug Monitoring

Drug interactions can alter oral absorption or systemic clearance of drugs. More than one interaction can occur at the same time, with potentially opposing effects. TDM, if available, may facilitate any necessary dose adjustments when

interacting drugs are coadministered. TDM allows the clinician to make informed, individualized decisions about dose adjustments that are more precise than standardized dose adjustments based upon anticipated, average effects. When available, "therapeutic ranges" are based on dose-ranging studies that have evaluated clinical outcomes. These ranges are proven to be predictive of efficacy or toxicity. When such data are not available, "normal ranges" are used to represent the drug exposure generally achieved with a standard dose of a drug. Excursions from "normal concentrations" might be associated with decreased efficacy (low concentrations) or increased toxicity (high concentrations), but specific data proving these risks are lacking. In such situations, clinicians should weigh the potential risks and benefits based upon TDM data. Consultations with experts for those drugs may be helpful.

TDM may be particularly useful in the following situations:

- Inadequate therapeutic response
- Overt toxicity
- Risk of serious drug–drug interactions
- Impaired drug absorption

In these cases, TDM can confirm the adequacy of the doses or suggest alternative doses that might lead to superior outcomes.

When TDM is desired, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution. Drugs in this table that are known to have assays (for clinical and/or research purposes) available within the United States and typically in Europe include the following:

- Atovaquone
- Bedaquiline
- Chloroquine
- Clarithromycin
- Dapsone
- Doxycycline
- Fluconazole
- Isavuconazole
- Itraconazole
- Linezolid
- Mefloquine
- Posaconazole
- Quinine
- Rifabutin
- Rifampin
- Rifapentine
- Sofosbuvir
- Tenofovir
- Voriconazole

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Note: To avoid redundancy, drug–drug interactions are listed only once by primary drug (listed alphabetically). Subsequently, when an interacting agent becomes the primary drug, guideline users are referred to the entry for the initial primary drug. See the Clarithromycin row for the first example of this format.

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether/ Lumefantrine	Clarithromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ lumefantrine possible	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Isavuconazole	↑ lumefantrine possible	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Itraconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Mefloquine	↓ lumefantrine possible	If mefloquine is administered immediately before artemether/lumefantrine, monitor for decreased efficacy of artemether/lumefantrine and encourage food intake.
	Posaconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Rifabutin[a]	↓ artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.
	Rifampin[a]	Artemether AUC ↓ 89% DHA AUC ↓ 85% Lumefantrine AUC ↓ 68%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ artemether, DHA, and lumefantrine expected	Do not coadminister.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
Atovaquone	Doxycycline	Atovaquone concentration ↓ approximately equal to 40% with tetracycline No interaction study with doxycycline	Dose adjustment not established; if coadministered, instruct patient to take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifabutin[a]	Atovaquone C_{ss} ↓ 34% Rifabutin C_{ss} ↓ 19%	Dose adjustment not established; if coadministered, instruct patient to take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifampin[a]	Atovaquone C_{ss} ↓ 52% Rifampin C_{ss} ↑ 37%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ atovaquone expected	Do not coadminister.
Bedaquiline	Clarithromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ bedaquiline possible	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Isavuconazole	↑ bedaquiline possible	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Itraconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities. If coadministration is required for >14 days, weigh the benefits of therapy against the risks of bedaquiline toxicities.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Posaconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Rifabutin[a]	↔ bedaquiline ↓ rifabutin possible	If coadministered, separate time of administration; perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	Bedaquiline AUC ↓ 53%	Do not coadminister.
	Rifapentine[a]	Daily Rifapentine Bedaquiline AUC ↓ 55% Weekly Rifapentine ↓ bedaquiline expected	Do not coadminister.
	Voriconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
Brincidofovir	Clarithromycin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone clarithromycin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone erythromycin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities. Consider azithromycin in place of erythromycin.
	Rifampin[a]	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone rifampin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities.
Caspofungin	Rifabutin[a]	↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifampin[a]	Caspofungin C_{min} ↓ 30%	If coadministered, caspofungin dose should be increased to 70 mg/day. Consider alternative echinocandin (e.g., micafungin or anidulafungin).
	Rifapentine[a]	Daily Rifapentine ↓ caspofungin expected Weekly Rifapentine ↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).
Chloroquine	Clarithromycin	↑ chloroquine expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ chloroquine expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Isavuconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Itraconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Posaconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Rifabutin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifampin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ chloroquine expected	Monitor for chloroquine efficacy.
	Voriconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
Clarithromycin	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Fluconazole	Clarithromycin AUC ↑ 18% and C_{min}↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	↑ isavuconazole and clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of both isavuconazole and clarithromycin. Role of isavuconazole TDM has not been established.
	Itraconazole	↑ itraconazole and clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of both itraconazole and clarithromycin; perform itraconazole and clarithromycin TDM and adjust dose accordingly.
	Mefloquine	↑ mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for mefloquine toxicity.
	Posaconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of clarithromycin; perform clarithromycin TDM and adjust dose accordingly.
	Quinine	↑ quinine expected ↑ clarithromycin possible	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Rifabutin[a]	Clarithromycin AUC ↓ 44% 14-OH clarithromycin AUC ↑ 57% Rifabutin AUC ↑ 76% to 99% des-rifabutin AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, consider reducing rifabutin dose, perform clarithromycin and rifabutin TDM and adjust dose accordingly. Monitor for rifabutin toxicities.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifampin[a]	Clarithromycin concentration ↓ 87% Rifampin AUC ↑ 60%	Do not coadminister. Use azithromycin in place of clarithromycin.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ clarithromycin expected ↑ 14-OH clarithromycin and rifapentine expected	Daily Rifapentine Do not coadminister. Use azithromycin in place of clarithromycin. Weekly Rifapentine Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for rifapentine toxicities and clarithromycin efficacy; perform clarithromycin and rifapentine TDM and adjust doses accordingly.
	Voriconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of clarithromycin; perform clarithromycin TDM and adjust dose accordingly.
Dapsone	Rifabutin[a]	Dapsone AUC ↓ 27% to 40%	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
	Rifampin[a]	Dapsone concentration ↓ sevenfold to tenfold and $t_{1/2}$ ↓ from 24 hours to 11 hours	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ dapsone expected	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
Doxycycline	Atovaquone	See Atovaquone.	See Atovaquone.
	Rifabutin[a]	↓ doxycycline possible	Monitor closely for doxycycline efficacy or consider alternative therapy.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifampin[a]	Doxycycline AUC ↓ 59%	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
	Rifapentine[a]	Daily Rifapentine ↓ doxycycline expected Weekly Rifapentine ↓ doxycycline possible	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
Erythromycin	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Fluconazole	↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	↑ erythromycin and isavuconazole possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Itraconazole	Itraconazole AUC ↑ 36% ↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ mefloquine possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Posaconazole	↑ erythromycin expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Quinine	↑ quinine expected ↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Rifabutin[a]	↓ erythromycin possible ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy and rifabutin toxicities; perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	↓ erythromycin expected	Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ erythromycin expected	Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy.
	Voriconazole	↑ erythromycin expected	Do not coadminister. Consider azithromycin in place of erythromycin.
Fluconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ fluconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and fluconazole toxicity.
	Rifabutin[a]	Rifabutin AUC ↑ 80% ↔ fluconazole expected	Use with caution. Monitor for rifabutin toxicities. Perform rifabutin TDM; may need to decrease rifabutin dose to 150 mg/day.
	Rifampin[a]	Fluconazole AUC ↓ 23% to 56%	Monitor for antifungal efficacy; may need to increase fluconazole dose.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ fluconazole expected	Monitor for antifungal efficacy; may need to increase fluconazole dose.
Glecaprevir/ Pibrentasvir	Rifabutin[a]	↓ glecaprevir and pibrentasvir possible	Coadministration should be avoided, if possible. Consider alternative agents.
	Rifampin[a]	Glecaprevir AUC ↓ 88% Pibrentasvir AUC ↓ 87%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ glecaprevir and pibrentasvir expected	Do not coadminister. Consider alternative agents.
	TDF	TFV AUC ↑ 29% when coadministered as EFV/TDF/FTC	Use usual dose. Monitor renal function or consider TAF.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	TAF	↔ TFV concentration when coadministered as EVG/c/TAF/FTC	No dose adjustment necessary.
Ibrexafungerp	Clarithromycin	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Erythromycin	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Itraconazole	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Posaconazole	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
	Rifabutin[a]	↓ Ibrexafungerp expected	Do not coadminister.
	Rifampin[a]	↓ Ibrexafungerp expected	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ Ibrexafungerp expected	Do not coadminister.
	Voriconazole	↑ Ibrexafungerp expected	Decrease ibrexafungerp dose to 150 mg twice daily for 1 day.
Isavuconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ isavuconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and isavuconazole toxicities.
	Rifabutin[a]	↓ isavuconazole expected ↑ rifabutin expected	Consider alternative agent(s). If alternative agents are not available, use with close monitoring for isavuconazole antifungal activity and rifabutin toxicity. Perform rifabutin and isavuconazole TDM and adjust dose accordingly.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifampin[a]	Isavuconazole AUC ↓ 97%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ isavuconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Itraconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Mefloquine	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ itraconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and itraconazole toxicities; perform itraconazole TDM and adjust dose accordingly.
	Rifabutin[a]	Itraconazole AUC ↓ 70% ↑ rifabutin expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifampin[a]	Itraconazole AUC ↓ 64% to 88%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ itraconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Linezolid	Rifabutin[a]	↓ linezolid possible	Monitor for linezolid efficacy.
	Rifampin[a]	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly.
	Rifapentine[a]	Daily Rifapentine ↓ linezolid expected	Daily Rifapentine Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
		Weekly Rifapentine ↓ linezolid possible	Weekly Rifapentine Monitor for linezolid efficacy.
Mefloquine	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Posaconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Rifabutin[a]	↓ mefloquine possible	Monitor for mefloquine efficacy.
	Rifampin[a]	Mefloquine AUC ↓ 68%	Do not coadminister. Use alternative antimalarial drug or rifabutin.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ mefloquine expected	Do not coadminister. Use alternative antimalarial drug or rifabutin.
	Voriconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
Posaconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	↑ quinine expected ↑ posaconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifabutin[a]	Posaconazole AUC ↓ 49% Rifabutin AUC ↑ 72%	Coadministration should be avoided, if possible. If coadministered, perform posaconazole and rifabutin TDM and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities.
	Rifampin[a]	↓ posaconazole expected	Do not coadminister when treating invasive fungal infections. If coadministered for treatment of noninvasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ posaconazole expected	Daily Rifapentine Do not coadminister when treating invasive fungal infections. If coadministered for treatment of noninvasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response. Weekly Rifapentine Coadministration should be avoided, if possible. If coadministered, perform posaconazole TDM and adjust dose accordingly; monitor clinical response.
Quinine	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Rifabutin[a]	↓ quinine possible ↑ rifabutin possible	Monitor for quinine efficacy. Monitor for rifabutin toxicity.
	Rifampin[a]	Quinine AUC ↓ 75% to 85%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ quinine expected	Do not coadminister.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	↑ quinine expected	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.
Rifabutin[a]	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Sofosbuvir/Velpatasvir	↓ velpatasvir, sofosbuvir expected	Do not coadminister.
	Tedizolid	↓ tedizolid possible	Monitor for tedizolid efficacy.
	TAF	↓ TAF, TFV, TFV-DP expected ↑ TFV-DP expected versus TDF alone	If coadministered, monitor for HIV and HBV treatment efficacy. Note: Interpretation extrapolated from TAF and rifampin (see Rifampin). FDA labeling recommends not to coadminister.
	TDF	↔ TDF, TFV, TFV-DP expected	No dosage adjustment necessary.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	Voriconazole AUC ↓ 79% Rifabutin AUC ↑ 4-fold	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s). Coadministration may be considered if both voriconazole and rifabutin TDM are available to guide therapy.
Rifampin[a]	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Sofosbuvir/Velpatasvir	Sofosbuvir AUC ↓ 72% Velpatasvir AUC ↓ 82%	Do not coadminister.
	Tedizolid	Tedizolid AUC ↓ 20%	Monitor for tedizolid efficacy.
	TAF	TAF Plus Rifampin • TAF AUC ↓ 55% • TFV AUC ↓ 54%	If coadministered, monitor for HIV and HBV treatment efficacy.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
		• TFV-DP AUC ↓ 36% Intracellular TFV-DP concentration is 4.2-fold greater than with TDF alone.	Note: FDA labeling recommends not to coadminister.
	TDF	TDF Plus Rifampin 600 mg Daily ↔ TFV	No dosage adjustment necessary
	Voriconazole	Voriconazole AUC ↓ 96%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Rifapentine[a]	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Tedizolid	Daily Rifapentine ↓ tedizolid expected Weekly Rifapentine ↓ tedizolid possible	Daily or Weekly Rifapentine Monitor for tedizolid efficacy.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	TAF	Daily and Weekly Rifapentine ↓ TAF, TFV, TFV-DP possible	If coadministered, monitor for HIV and HBV treatment efficacy. Note: FDA labeling recommends not to coadminister.
	TDF	↔ TDF, TFV, TFV-DP expected	No dosage adjustment necessary
	Sofosbuvir/Velpatasvir	↓ sofosbuvir, velpatasvir expected	Do not coadminister.
	Voriconazole	↓ voriconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Sofosbuvir/ Velpatasvir	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	TAF	TFV AUC ↑ 79% (when RPV/TAF/FTC given with SOF/VEL/VOX) TFV AUC ↑ 67% (when BIC/TAF/FTC given with SOF/VEL/VOX)	No dosage adjustment necessary.
	TDF	TFV AUC ↑ 35% to 40% (when given with EVG/c/FTC or RPV/FTC) TFV AUC ↑ 81% (when given with EFV/FTC and SOF/VEL) TFV AUC ↑ 39% (when given with DRV/r/FTC and SOF/VEL/VOX)	Monitor for TDF toxicities. Consider TAF in place of TDF.
Tedizolid	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
Tenofovir Alafenamide	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Tenofovir Disoproxil Fumarate	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
Voriconazole	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Ibrexafungerp	See Ibrexafungerp.	See Ibrexafungerp.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	See Quinine.	See Quinine.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.

[a] Refer to the subsection Rifamycin-Related Induction Interactions in the Table 4 introduction above.

Key to Symbols

↑ = increase
↓ = decrease
↔ = less than 20% change in AUC

Key: 14-OH = active metabolite of clarithromycin; AUC = area under the curve; BIC = bictegravir; C_{min} = minimum concentration; C_{ss} = concentration at steady state; DHA = dihydroartemisinin; DRV/r = darunavir/ritonavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; RPV = rilpivirine; SOF = sofosbuvir; $t_{1/2}$ = half-life; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TFV= tenofovir; TFV-DP = tenofovir diphosphate; VEL = velpatasvir; VOX = voxilaprevir

Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections

References

1. Ohnhaus EE, Breckenridge AM, Park BK. Urinary excretion of 6 beta-hydroxycortisol and the time course measurement of enzyme induction in man. *Eur J Clin Pharmacol*. 1989;36(1):39-46. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2917586.

2. Stemkens R, Jager V, Dawson R, et al. Drug interaction potential of high-dose rifampicin in patients with pulmonary tuberculosis. *Antimicrob Agents Chemother*. 2023;67(10):e0068323. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37768317.

3. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet*. 2001;40(5):327-341. Available at: https://pubmed.ncbi.nlm.nih.gov/11432536.

4. Baneyx G, Parrott N, Meille C, Iliadis A, Lavé T. Physiologically based pharmacokinetic modeling of CYP3A4 induction by rifampicin in human: influence of time between substrate and inducer administration. *Eur J Pharm Sci*. 2014;56:1-15. Available at: https://pubmed.ncbi.nlm.nih.gov/24530864.

5. Sanofi-Aventis U.S. LLC. RIFADIN (rifampin capsules USP) and RIFADIN® IV (rifampin for injection USP) 2023. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/050420s089,050627s034lbl.pdf.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Updated: December 31, 2024
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This table should not be considered a comprehensive list of all possible adverse reactions to each medication. For additional information, clinicians should consult other appropriate resources, such as the U.S. Food and Drug Administration prescribing information. The most serious or common adverse reactions for each drug in the table are generally listed first. For information regarding the effects of these medications on a pregnant woman and the fetus, please refer to the Special Considerations During Pregnancy section of the individual chapter in the guidelines (e.g., see Special Considerations During Pregnancy in the Herpes Simplex Virus chapter for information on the use of acyclovir during pregnancy).

Drug(s)	Adverse Reactions
Acyclovir	• Crystalluria and nephrotoxicity secondary to obstructive urolithiasis, particularly after rapid high-dose IV infusion. Risk is increased with dehydration or pre-existing renal impairment. o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Neurotoxicity with high doses (agitation, confusion, hallucination, seizure, coma), especially in people with renal impairment and/or older adults • Thrombophlebitis at peripheral IV infusion site • Nausea, vomiting, and headache
Adefovir	• Nephrotoxicity, especially in people with underlying renal insufficiency, predisposing comorbidities, or taking concomitant nephrotoxic drugs • Nausea and asthenia
Albendazole	• Rash, pruritus, and fever • Elevated transaminases • Alopecia • Nausea, vomiting, abdominal pain, headache, and dizziness • Bone marrow suppression (i.e., pancytopenia, aplastic anemia, agranulocytosis, and leukopenia) (rare) o Individuals with liver disease, including hepatic echinococcosis, appear to be at higher risk.
Amikacin	• Nephrotoxicity o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Ototoxicity, both hearing loss and vestibular toxicity, is possible. • Neuromuscular blockade, especially with myasthenia or Parkinson's disease and rapid infusion of large doses (rare)

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Amphotericin B Deoxycholate and Lipid Formulations	• Nephrotoxicity (lower incidence with liposomal formulations); irreversible nephrotoxicity is related to cumulative dose. o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Hypokalemia, hypomagnesemia, and hypocalcemia • Infusion-related reactions, including fever, chills, rigors, flank or back pain, and hypotension (lower incidence with liposomal formulations and slower infusion rates) • Thrombophlebitis • Elevated transaminases and bilirubin • Headache, nausea, vomiting, and diarrhea • Heart failure (rarely reported) • Anemia (rare)
Anidulafungin	• Refer to Echinocandins below.
Artemether/Lumefantrine	• QTc prolongation • Anemia, including delayed hemolytic anemia (rare) • Fever, chills, fatigue, arthralgia, and myalgia • Headache, dizziness, asthenia, and insomnia • Nausea, vomiting, diarrhea, abdominal pain, and anorexia • Rash and pruritus
Artesunate	• Acute renal failure requiring dialysis • Hemoglobinuria and jaundice, anemia, thrombocytopenia, neutropenia • Delayed hemolysis and immune hemolytic anemia • QTc prolongation and bradycardia • Hypersensitivity reactions (anaphylaxis) • Dizziness, nausea, and vomiting
Atovaquone	• Elevated transaminases • Rash, nausea, vomiting, abdominal pain, and diarrhea • Fever, headache, and insomnia
Atovaquone/Proguanil	• Abdominal pain, nausea, vomiting, anorexia, diarrhea, headache, asthenia, dizziness, and rash • Elevated transaminases
Azithromycin	• Ototoxicity with prolonged use or high concentrations • Elevated transaminases • Hypersensitivity reactions

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Nausea, vomiting, metallic taste, diarrhea, and abdominal pain • QTc prolongation
Benznidazole	• Photosensitivity and hypersensitivity reactions (including maculopapular rash, allergic dermatitis, TEN, and DRESS) • Paresthesia and peripheral neuropathy, headache, and insomnia • Bone marrow suppression • Nausea, vomiting, abdominal pain, anorexia, and weight loss
Bedaquiline	• QTc prolongation • Elevated transaminases • Nausea, vomiting, anorexia, diarrhea, elevated amylase, arthralgia, headache, and skin rash Note: Due to long medication half-life, adverse effects may persist even after discontinuation.
Bezlotoxumab	• Exacerbation of congestive heart failure • Nausea, fever, and headache • Infusion-related reactions
Brincidofovir	• Elevated transaminases and bilirubin • Nausea, vomiting, and diarrhea • Male infertility
Caspofungin	• Refer to Echinocandins below.
Chloroquine and Hydroxychloroquine	• Auditory and visual disturbances, including blurry vision. Retinal toxicity may occur with long-term use. • QTc prolongation and cardiac arrhythmias • Cardiomyopathy • Bone marrow suppression and hemolysis • Neuropsychiatric changes, including extrapyramidal reactions, suicidal behavior, and convulsive seizures • Hypersensitivity reactions (including TEN, SJS, and EM) • Severe hypoglycemia which may require adjustment of antidiabetic medications • Photosensitivity, pruritus, skin pigmentation, and exacerbation of psoriasis • Dizziness, headache, nausea, vomiting, diarrhea, anorexia, abdominal pain, and hepatitis • Neuromyopathy (may occur with long-term use) (rare)
Cidofovir	• Nephrotoxicity, proteinuria, azotemia, proximal tubular dysfunction (normoglycemic glycosuria, hypophosphatemia), and metabolic acidosis (including Fanconi's syndrome) o Administer IV fluid hydration and oral probenecid to reduce the risk for nephrotoxicity.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Neutropenia and anemia • Ocular hypotony and anterior uveitis/iritis • Nausea, vomiting, abdominal pain, anorexia, and diarrhea • Asthenia, fever, headache, and alopecia • Side effects most likely related to coadministration with probenecid: rash, nausea, vomiting, anorexia, and gout exacerbation.
Ciprofloxacin	• Refer to Fluoroquinolones below.
Clarithromycin	• Elevated transaminases and hepatotoxicity (rare) • Ototoxicity, including hearing loss and tinnitus, with high doses or prolonged use • QTc prolongation • Increased risk of cardiac complications or death in people with heart disease • Diarrhea • Headache, nausea, vomiting, diarrhea, abdominal cramps, and dysgeusia
Clindamycin	• Diarrhea, including *C. difficile*–associated diarrhea and pseudomembranous colitis • Metallic taste (with IV infusion), thrombophlebitis, and arrhythmia with rapid IV infusion • Hypersensitivity reactions (including SJS and TEN) • Nausea, vomiting, and abdominal pain • Elevated transaminases
Clotrimazole (Troche)	• Nausea, vomiting, anorexia, and metallic taste
Cycloserine	• Neuropsychiatric toxicities, including convulsions, psychosis, somnolence, confusion, inability to concentrate, hyperreflexia, headache, tremor, vertigo, paresis, dysarthria, depression (with suicidal ideation), peripheral neuropathy, and seizures (particularly with higher doses and in people with history of chronic alcoholism) o Administer with pyridoxine. • Hypersensitivity reactions (including SJS), allergic dermatitis, and rash
Dapsone	• Methemoglobinemia, hemolytic anemia, neutropenia, and agranulocytosis o Do not use in people with G6PD deficiency. o Risk may be increased with concomitant use of folic acid antagonists (e.g., pyrimethamine). • Rash, fever • Sulfone syndrome (fever, exfoliative dermatitis, lymphadenopathy, hepatic necrosis, and hemolysis) • Phototoxicity and severe cutaneous reactions (including SJS and TEN) • Drug-induced lupus erythematosus

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Hepatotoxicity and nephrotic syndrome • Peripheral neuropathy • Nausea and anorexia
Doxycycline	• Pill-induced esophagitis/esophageal ulceration • Intracranial hypertension • Photosensitivity and skin hyperpigmentation • Thrombophlebitis (with IV infusion) • Nausea and vomiting
Echinocandins (anidulafungin, caspofungin, micafungin)	• Histamine-related infusion reactions (flushing, rash, pruritus, hypotension, and dyspnea) and thrombophlebitis • Elevated transaminases and hepatotoxicity • Diarrhea, nausea, vomiting, fever, and headache • Hemolysis (micafungin) (rare)
Emtricitabine	• Headache, nausea, and diarrhea • Skin hyperpigmentation and rash (palms and soles)
Entecavir	• Headache, fatigue, dizziness, and nausea • Lactic acidosis
Ethambutol	• Optic neuritis (dose- and duration-dependent) and peripheral neuropathy • Headache, nausea, vomiting, anorexia, abdominal pain, and hyperuricemia/gout flare • Hypersensitivity reactions
Ethionamide	• Dose-dependent GI side effects, including nausea, vomiting, anorexia, diarrhea, abdominal pain, and metallic taste (dose titration may alleviate some symptoms) • Hepatotoxicity • Dizziness, drowsiness, confusion, clumsiness, visual disturbances, depression, peripheral neuropathy, and postural hypotension o Administer with pyridoxine. • Photosensitivity and severe cutaneous reactions (including SJS, TEN, and DRESS) • Endocrine side effects, including hypothyroidism (with or without goiter), gynecomastia, acne, alopecia, menstrual irregularities, impotence, and hypoglycemia
Famciclovir	• Nephrotoxicity (in people with underlying renal disease) • Headache, nausea, vomiting, and diarrhea
Fidaxomicin	• Nausea, vomiting, and abdominal pain

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Flucytosine	• Concentration-dependent (>100 mcg/mL) bone marrow suppression (anemia, neutropenia, agranulocytosis, and thrombocytopenia) • Elevated transaminases • Diarrhea, nausea, vomiting, and headache • Rash, pruritus, and photosensitivity
Fluconazole	• Hepatotoxicity • QTc prolongation • Alopecia (with doses ≥400 mg/day for ≥2 months) and dry skin • Nausea, vomiting, diarrhea, and abdominal pain
Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)	• Restlessness, insomnia, nightmares, confusion, anxiety, paranoia, tremors, seizures, hallucinations, depression, suicidal thoughts, and attempted and completed suicide • Tendonitis and tendon rupture (associated with age over 60, concurrent corticosteroids, diabetes, and kidney, heart, and lung transplant) • Diarrhea, including *C. difficile*–associated diarrhea and colitis • QTc prolongation • Photosensitivity/phototoxicity • Anemia, thrombocytopenia, and leukopenia • Arthralgia and myalgia • Peripheral neuropathy and retinal detachment • Hyper- and hypoglycemia, including hypoglycemic coma • Nausea, diarrhea, bloating, headache, dizziness, and malaise • Vasculitis • Aortic dissection (rare) • Elevated transaminases • Interstitial nephritis (rare) • Severe cutaneous reactions (including SJS and TEN) (rare)
Foscarnet	• Nephrotoxicity and electrolyte imbalances (e.g., hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, hypokalemia) o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Paresthesia and seizure (associated with electrolyte imbalances) • Anemia • Nausea, vomiting, anorexia, and headache • Genital ulceration • Thrombophlebitis

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Fumagillin (Investigational)	• Nausea, vomiting, diarrhea, anorexia, and abdominal cramps • Thrombocytopenia, anemia, and neutropenia • Vertigo
Ganciclovir	• Neutropenia, thrombocytopenia, anemia, and pancytopenia • Nephrotoxicity • Thrombophlebitis • Nausea, vomiting, fever, asthenia, and hyperhidrosis
Glecaprevir/Pibrentasvir	• Risk of hepatitis B virus reactivation • Hepatic decompensation/failure in people with advanced liver disease • Mild headache, fatigue, nausea, and diarrhea • Altered glucose tolerance in diabetic patients
Ibrexafungerp	• Diarrhea, nausea, abdominal pain, vomiting, and headache
Isavuconazonium Sulfate (Isavuconazole)	• Hepatotoxicity and cholelithiasis • Infusion-related reactions (hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia) • Hypersensitivity reactions (including SJS) • Shortening of QT interval • Nausea, vomiting, diarrhea, headache, dyspnea, and cough • Hypokalemia
Isoniazid	• Hepatotoxicity or asymptomatic elevation in aminotransferase enzymes • Peripheral neuropathy, paresthesia, seizures, psychosis (rare), and optic neuritis o Administering with pyridoxine may prevent or reduce these adverse effects. • Nausea, diarrhea, and flushing • Arthralgia and lupus-like syndrome • Hypersensitivity reactions (including TEN and DRESS) (rare)
Itraconazole	• New-onset or worsening heart failure, edema, adrenal insufficiency, and hypokalemia • QTc prolongation • Elevated transaminases and hepatotoxicity
Lamivudine	• Nausea and vomiting
Levofloxacin	• Refer to Fluoroquinolones above.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Linezolid	• Anemia, neutropenia, and thrombocytopenia (especially with treatment lasting longer than 2–4 weeks, renal insufficiency, or elevated trough concentrations) • Peripheral neuropathy and optic neuritis with long-term therapy • Nausea, vomiting, diarrhea, and headache • Serotonin syndrome (rare) • Seizure (in people with a history of seizure or with risk factors for seizure) (rare) • Lactic acidosis, hypoglycemia, and hyponatremia (rare) • Rhabdomyolysis
Mefloquine	• Depression, psychosis, anxiety, agitation, dizziness, headache, insomnia, and abnormal dreams • QTc prolongation and arrhythmias (extrasystole and sinus bradycardia) • Agranulocytosis and aplastic anemia • Nausea, vomiting, diarrhea, and epigastric pain Note: Due to long medication half-life, side effects may persist even after discontinuation.
Micafungin	• Refer to Echinocandins above.
Miconazole Buccal Tablets	• Dysgeusia, diarrhea, nausea, vomiting, upper abdominal pain, and headache • Local reactions (e.g., oral discomfort, burning, pain, tongue/mouth ulceration, gingival pruritus, swelling, and dry mouth) • Hypersensitivity reactions (may occur in people with known hypersensitivity reaction to milk product concentrate)
Miltefosine	• Nephrotoxicity and elevated transaminases and bilirubin • Retinal degeneration • Leukocytosis and thrombocytopenia • Impaired fertility, scrotal pain, and impaired ejaculation • Nausea, vomiting, diarrhea, anorexia, headache, and motion sickness • Severe cutaneous reactions (including SJS)
Moxifloxacin	• Refer to Fluoroquinolones above.
Nifurtimox	• People with a history of brain injury, seizures, psychiatric disease, and serious behavioral alterations may experience worsening of their conditions. • Vomiting, nausea, decreased appetite, weight loss, abdominal pain, headache, fever, polyneuropathy, insomnia, restlessness, tremors, dizziness, and vertigo • Carcinogenic and teratogenic potential and impaired fertility • Hypersensitivity reactions with hypotension, angioedema, dyspnea, pruritus, rash, or other severe skin reactions

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Nitazoxanide	• Nausea, vomiting, diarrhea, abdominal pain, headache, and chromaturia
Nystatin (Oral Preparations)	• Unpleasant taste, nausea, vomiting, anorexia, and diarrhea
Omadacycline	• Nausea, vomiting, and diarrhea • Elevated transaminases • Infusion site reactions
Oteseconazole	• Nausea, diarrhea, and headache
Paromomycin	• Nausea, vomiting, abdominal cramps, anorexia, rash, and headache • Nephrotoxicity (rare) o Inflammatory bowel disease and renal insufficiency may increase risk.
Penicillin G	All Penicillin G Preparations • Hypersensitivity (immediate or delayed reactions, including anaphylaxis), bone marrow suppression, nausea, vomiting, diarrhea, and drug fever • Jarisch-Herxheimer reaction when used for syphilis (occurs most frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment) Benzathine Penicillin G • IM injection-site reactions (pain and erythema), procaine neuropsychiatric reactions (with high dose), and neurovascular damage (due to inadvertent intravascular instead of IM injection) Aqueous Crystalline Penicillin G (IV) • Thrombophlebitis • Neurotoxicity at high doses—especially in people with renal dysfunction—and hyperkalemia or hypernatremia at high doses (depending on formulation)
Pentamidine	IV Administration • Nephrotoxicity, azotemia • Infusion-related hypotension and thrombophlebitis • QTc prolongation, arrhythmias (including Torsades de pointes), and electrolyte abnormalities • Hypoglycemia, hyperglycemia, and diabetes mellitus • Hepatotoxicity and GI intolerance • Leukopenia and thrombocytopenia • Rash • Pancreatitis (rare) Aerosolized Therapy • Bronchospasm, cough, dyspnea, tachypnea, and metallic taste

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Posaconazole	IV or PO Administration • Hepatotoxicity • QTc prolongation and hypokalemia • Pseudohyperaldosteronism (hypokalemia and hypertension) • Nausea, vomiting, diarrhea, abdominal pain, and headache IV Infusion • Thrombophlebitis, SBECD accumulation, and worsening renal function with IV formulation (especially in people with eGFR <50 mL/min per package labeling, but observational studies with IV voriconazole suggest that this may not be a concern)
Pretomanid	Adverse Events Reported When Used in Combination With Other Antituberculosis Medications • Nausea, vomiting, headache, and diarrhea • Elevated transaminases • Peripheral and optic neuropathy, myelosuppression, and lactic acidosis (with linezolid) • QTc prolongation (with bedaquiline) Other • Dose-related increase in serum creatinine without change in GFR
Primaquine	• Methemoglobinemia, hemolytic anemia (use with caution in people with mild-moderate G6PD deficiency; do not use if severe G6PD deficiency), leukopenia, and neutropenia • QTc prolongation • Abdominal cramps, nausea, vomiting, and dizziness
Pyrazinamide	• Hepatotoxicity • Polyarthralgia and myalgia • Hyperuricemia/gout flare • Thrombocytopenia and sideroblastic anemia • Nausea, vomiting, flushing, rash, and photosensitivity
Pyrimethamine	• Neutropenia, anemia, thrombocytopenia, and megaloblastic anemia o Administer with leucovorin to reduce the risk of bone marrow suppression. • Anorexia, nausea, vomiting, and rash
Quinine	• QTc prolongation and cardiac arrhythmias • Cinchonism (tinnitus, vertigo, and blurred vision) • Hemolytic anemia (especially in patients with G6PD deficiency), thrombocytopenia, and agranulocytosis • Vision abnormalities (e.g., photophobia, altered color perception, and blindness)

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Hypersensitivity reactions (including SJS and TEN) • Hypoglycemia • Headache, nausea, vomiting, and diarrhea
Rifabutin	• Concentration-dependent uveitis, neutropenia, and thrombocytopenia • Arthralgia • Hepatotoxicity • Rash • Nausea, vomiting, abdominal pain, diarrhea, and anorexia • Red-orange discoloration of body fluids (e.g., urine, sweat, saliva)
Rifampin	• Hepatotoxicity (cholestatic hepatitis) • Thrombocytopenia and hemolytic anemia • Renal failure • Hypersensitivity reactions with flu-like syndrome • Interstitial pulmonary disease • Nausea, vomiting, anorexia, abdominal pain, flatulence, diarrhea, headache, confusion, flushing, and rash • Red-orange discoloration of body fluids
Rifapentine	• Hepatotoxicity • Anemia, neutropenia, and lymphopenia • Hypersensitivity reactions, including flu-like symptoms • Arthralgia • Rash and pruritis • Nausea, vomiting, diarrhea, and anorexia • Red-orange discoloration of body fluids
Sofosbuvir/Velpatasvir	• Risk of hepatitis B virus reactivation • Headache, fatigue, and anemia (associated with ribavirin coadministration) • Altered glucose tolerance in diabetic persons
Streptomycin	• Neurotoxicity, including irreversible ototoxicity (both hearing loss and vestibular toxicity) • Nephrotoxicity • Neuromuscular blockade and respiratory paralysis (associated with rapid infusion of large aminoglycoside doses)
Sulfadiazine	• Severe cutaneous reactions (including SJS, EM, and TEN) and photosensitivity • Anemia, neutropenia, agranulocytosis, and thrombocytopenia

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Crystalluria (nephrolithiasis, urolithiasis) and nephrotoxicity o Administer oral or IV fluid hydration to reduce the risk of nephrotoxicity. • Hepatotoxicity • Drug fever • Peripheral neuritis, tinnitus, hallucinations, seizures (rare), vertigo, and insomnia • Nausea, vomiting, diarrhea, and headache
Tafenoquine	• Decreased hemoglobin as a result of methemoglobinemia and hemolytic anemia o Do not use in people with G6PD deficiency; may cause harm to fetuses and breastfeeding infants who are G6PD-deficient. • Psychiatric adverse reactions (in people with history of psychiatric illness) • Hypersensitivity reactions (angioedema and urticaria) • Visual disturbances • Dizziness, nausea, vomiting, and headache
Tecovirimat	IV or PO Administration • Headache, nausea, abdominal pain, and vomiting IV Infusion • Infusion site pain, swelling, erythema, and extravasation • Contains hydroxypropyl-β-cyclodextrin, which may accumulate in people with renal impairment and has the potential to cause renal toxicity
Tedizolid	• Nausea, vomiting, and diarrhea • Headache and dizziness • Infusion- or injection-related reactions • Thrombocytopenia
Tenofovir Disoproxil Fumarate	• Renal insufficiency and Fanconi syndrome (proximal renal tubulopathy with hypophosphatemia, hypouricemia, proteinuria, and normoglycemic glycosuria) • Decreased bone mineral density • Nausea and vomiting
Tenofovir Alafenamide	• Lower incidence of renal or bone toxicities than with tenofovir disoproxil fumarate
Trimethoprim-Sulfamethoxazole	• Cutaneous reactions (in some cases SJS, EM, and TEN) and photosensitivity • Anemia, neutropenia, agranulocytosis, and thrombocytopenia • Hepatotoxicity • Dose-dependent increase in serum creatinine (without change in eGFR), interstitial nephritis, crystalluria (in people with inadequate hydration), and hyperkalemia (with high-dose TMP) o Encourage oral hydration when using oral TMP-SMX.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Hypoglycemia and hyponatremia • Drug fever • Nausea and vomiting • Aseptic meningitis and pancreatitis (rare)
Valacyclovir	• Neurotoxicity (e.g., agitation, confusion, hallucination, seizure, coma) with high doses, especially in people with renal impairment • Nephrotoxicity o Encourage oral fluid hydration to reduce the risk of nephrotoxicity. • Nausea, vomiting, abdominal pain, and headache
Valganciclovir	• Bone marrow suppression • Confusion, fever, and tremor • Nephrotoxicity o Encourage oral fluid hydration to reduce the risk of nephrotoxicity. • Carcinogenic and teratogenic potential and impaired fertility • Nausea, vomiting, and diarrhea
Voriconazole	• Visual disturbances (e.g., abnormal vision, color vision change, and/or photophobia) • Optic neuritis (associated with >28 days treatment) • Headache, delirium, hallucination, peripheral neuropathy (rare), and encephalopathy (associated with trough >5.5 mcg/mL) • Hepatotoxicity • QTc prolongation • Photosensitivity • Voriconazole-associated cutaneous squamous cell carcinoma (with long-term use) • Fluorosis and periostitis with high dose and/or prolonged use • Fever, nausea, vomiting, chills, tachycardia, and peripheral edema • Nail changes and alopecia (with long-term use) • SBECD accumulation with IV formulation and worsening renal function (especially in people with eGFR <50 mL/min per package labeling, but observational studies suggest that this may not be a concern)

Key: DRESS = drug reaction with eosinophilia and systemic symptoms; eGFR = estimated glomerular filtration rate; EM = erythema multiforme; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; GI = gastrointestinal; IM = intramuscular; IV = intravenous; PO = oral; QTc = QT corrected for heart rate; SBECD = sulfobutylether cyclodextrin; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections that Require Dosage Adjustment in Adults With Renal Insufficiency

Updated: April 23, 2025
Reviewed: April 23, 2025

Individuals with reduced renal function are at risk of drug accumulation and concentration-dependent toxicities when taking medications that are primarily excreted by the kidneys. The dosage adjustment recommendations in Table 6 are based on estimates of renal function using either creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR). Although both methods are commonly used to determine dosage adjustments, it is important to note that CrCl and eGFR are not interchangeable and may yield differing results.

Renal clearance, though critical, is only one of several pharmacokinetic parameters that influence disposition of drugs that are primarily excreted by the kidneys. Other factors, such as alterations in volume of distribution or reduction in oral absorption, can also impact drug concentrations. For instance, although reduced renal clearance may necessitate a dose reduction to prevent drug accumulation, increased volume of distribution or impaired oral absorption might require a dose increase to achieve therapeutic concentrations.

Therapeutic drug monitoring (TDM), if available and appropriate, allows the clinician to make informed, individualized decisions in complicated scenarios, leading to dose adjustments that are more precise than those based on estimated CrCl or eGFR. When TDM is desired, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution. Drugs in this table that are used for the prevention or treatment of opportunistic infections and that are known to have assays (for clinical and/or research purposes) available within the United States and typically in Europe include the following:

- Acyclovir
- Amikacin
- Ciprofloxacin
- Clarithromycin
- Cycloserine
- Emtricitabine
- Ethambutol
- Ethionamide
- Famciclovir
- Fluconazole
- Flucytosine
- Ganciclovir
- Levofloxacin
- Posaconazole
- Pyrazinamide
- Quinine
- Rifabutin
- Tenofovir
- Trimethoprim
- Valacyclovir
- Voriconazole

Note: The dosing recommendations provided for people on hemodialysis (HD) specifically apply to those receiving intermittent HD several times weekly. Guidance for other forms of renal replacement therapy (RRT), such as peritoneal dialysis or continuous RRT, is beyond the scope of these guidelines. Given the complexities of drug dosing in people receiving other forms of RRT, clinicians should consult specialists and consider TDM to ensure optimal management.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Acyclovir *For IV acyclovir, administer IV fluid hydration to reduce the risk of nephrotoxicity.*	IV Dose for Serious HSV Infections • 5 mg/kg IV every 8 hours IV Dose for Serious VZV Infections or HSV Encephalitis • 10 mg/kg IV every 8 hours	26–50	100% of dose IV every 12 hours
		10–25	100% of dose IV every 24 hours
		<10 or HD	50% of dose IV every 24 hours For people on HD, administer dose after HD on dialysis days.
	PO Dose for Herpes Zoster: 800 mg PO five times per day	10–25	800 mg PO every 8 hours
		<10 or HD	800 mg PO every 12 hours For people on HD, administer dose after HD on dialysis days.
Amikacin *Administer IV fluid hydration to reduce the risk of nephrotoxicity.*	For Mycobacterial Infections: • 15 mg/kg IV per day • Target peak concentration 35–45 mcg/mL; target trough concentration <5 mcg/mL *or* • 25 mg/kg IV three times per week • Target peak concentration 65–80 mcg/mL; target trough concentration <5 mcg/mL	<60 or HD Use with caution in people with renal insufficiency and ototoxicity.	Perform TDM to adjust dose and interval as needed to attain target concentrations. Doses likely needed only 2–3 times per week. Consider consulting local pharmacokinetic dosing services if available. For people on HD, administer dose after HD on dialysis days.
Cidofovir *Administer IV fluid hydration and oral probenecid to reduce the risk of nephrotoxicity (see Table 2 for dosing instructions).*	5 mg/kg IV on Day 0, repeat 5 mg/kg IV dose on Day 7, then 5 mg/kg IV every 2 weeks	Pretreatment SCr >1.5 mg/dL *or* CrCl ≤55 mL/min *or* Urine protein ≥100 mg/dL (≥2+ proteinuria)	Cidofovir is not recommended unless benefits outweigh risks. See "Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis" for recommendations on renal dose adjustments.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
		If SCr increases by 0.3–0.4 mg/dL above baseline	Decrease to 3 mg/kg IV per dose.
		If SCr increases by ≥0.5 mg/dL above baseline *or* ≥3+ proteinuria	Discontinue therapy.
Ciprofloxacin	500–750 mg PO every 12 hours *or* 400 mg IV every 8–12 hours	30–50	500–750 mg PO every 12 hours *or* 400 mg IV every 12 hours
		<30	250–500 mg PO every 24 hours *or* 400 mg IV every 24 hours
		HD	250–500 mg PO every 24 hours *or* 200–400 mg IV every 24 hours; administer dose after HD on dialysis days.
Clarithromycin	500 mg PO every 12 hours	30–60	Usual dose unless used with an HIV PI or with COBI, then reduce dose by 50% (or consider using azithromycin as alternative).
		<30 or HD	250 mg PO twice daily *or* 500 mg PO once daily If used with an HIV PI or COBI, reduce dose by 75% (or consider using azithromycin as alternative).

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
Cycloserine	10–15 mg/kg/day PO in two divided doses (maximum 1,000 mg/day); start at 250 mg once daily and increase dose per tolerability. Target peak concentration 20–35 mcg/mL	30–80	Usual dose; consider TDM and monitor for toxicities.	
		<30 or HD	250 mg once daily or 500 mg three times per week Perform TDM and adjust dose accordingly. Monitor for toxicities. Use with caution in people with ESRD who are not on dialysis.	
Emtricitabine[a] (FTC) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for ARV FDC products containing FTC.	One 200 mg capsule PO once daily *or* 240 mg solution PO once daily	CrCl^ or eGFR# (mL/min)	Oral Capsules	Oral Solution
		15–29 (see footnote[b])	200 mg every 72 hours	80 mg every 24 hours
		<15	200 mg every 96 hours	60 mg every 24 hours
		HD (administer dose after HD on dialysis days)	No dose adjustment necessary.	No dose adjustment necessary.
Emtricitabine/ Tenofovir Alafenamide (FTC/TAF) (FDC Trade Name: Descovy) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for other ARV FDC products containing FTC/TAF.	One tablet (FTC 200 mg/TAF 25 mg) PO once daily	15–29	Coformulated tablet is not recommended. See footnote[b] for more information.	
		<15	Coformulated tablet is not recommended.	
		HD	One tablet daily; on dialysis days, administer dose after HD.	
Emtricitabine/ Tenofovir		30–49	One tablet PO every 48 hours (monitor for worsening renal function or consider switching to TAF)	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
Disoproxil Fumarate (FTC/TDF) (FDC Trade Name: Truvada) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for other ARV FDC products containing FTC/TDF.	One tablet (FTC 200 mg/TDF 300 mg) PO once daily	<30 or HD	Do not use coformulated tablet. Use formulation for each component drug and adjust dose according to recommendations for the individual drugs.	
Entecavir	Usual Dose: 0.5 mg PO once daily For Treatment of 3TC-Refractory HBV or for Decompensated Liver Disease: 1 mg PO once daily	CrCl^ or eGFR# (mL/min)	Usual Renal Dose Adjustment	3TC-Refractory or Decompensated Liver Disease
		30 to <50	• 0.25 mg PO once daily, *or* • 0.5 mg PO every 48 hours	• 0.5 mg PO once daily, *or* • 1 mg PO every 48 hours
		10 to <30	• 0.15 mg PO once daily, *or* • 0.5 mg PO every 72 hours	• 0.3 mg PO once daily, *or* • 1 mg PO every 72 hours
		<10 or HD (for people on HD, administer dose after HD on dialysis days.)	• 0.05 mg PO once daily, *or* • 0.5 mg PO once every 7 days	• 0.1 mg PO once daily, *or* • 1 mg PO once every 7 days
Ethambutol	For MAI: 15 mg/kg PO daily For MTB: 15–25 mg/kg PO daily (See the *Mycobacterium tuberculosis* section for additional MTB dosing recommendations.)	<30 or HD	For MAI: 15 mg/kg PO three times weekly For MTB: 15–25 mg/kg PO three times weekly For people on HD, administer dose after HD. Perform TDM to guide optimal dosing.	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Ethionamide	15–20 mg/kg PO daily (usually 250–500 mg PO once or twice daily)	<30 or HD	250–500 mg PO once daily Consider TDM.
Famciclovir	For Herpes Zoster: 500 mg PO every 8 hours For HSV: 500 mg PO every 12 hours	40–59	500 mg PO every 12 hours
		20–39	500 mg PO every 24 hours
		<20	250 mg PO every 24 hours
		HD	250 mg PO only on HD days; administer dose after HD.
Fluconazole	200–1,200 mg PO or IV every 24 hours (dose and route of administration depends on type of OI)	≤50	Administer 100% of the indication-specific initial dose, then adjust maintenance doses to 50% of dose every 24 hours.
		HD	Administer 100% of the indication-specific initial dose, then adjust maintenance doses to full dose three times per week after HD.
Flucytosine	25 mg/kg PO every 6 hours TDM is recommended to guide optimal dosing (target peak serum concentration 2 hours after dose: 25–100 mcg/mL). If TDM is not possible, monitor CBC twice weekly.	21–40	25 mg/kg PO every 12 hours
		10–20	25 mg/kg PO every 24 hours
		<10	25 mg/kg PO every 48 hours
		HD	25–50 mg/kg PO every 48–72 hours; administer dose after HD.
Foscarnet *Administer IV fluid hydration to reduce the risk of nephrotoxicity.*	Induction Therapy for CMV Infection: 180 mg/kg/day IV in two divided doses Maintenance Therapy for CMV Infection or for Treatment of HSV Infections: 90–120 mg/kg IV once daily	Dosage adjustment needed according to calculated CrCl/kg; consult product label for dosing table.	Dosage adjustment needed according to calculated CrCl/kg; consult product label for dosing table.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
Ganciclovir	Induction Therapy: 5 mg/kg IV every 12 hours	50–69	2.5 mg/kg IV every 12 hours	
		25–49	2.5 mg/kg IV every 24 hours	
		10–24	1.25 mg/kg IV every 24 hours	
		<10 or HD	1.25 mg/kg IV three times per week For people on HD, administer dose after HD.	
	Maintenance Therapy: 5 mg/kg IV every 24 hours	50–69	2.5 mg/kg IV every 24 hours	
		25–49	1.25 mg/kg IV every 24 hours	
		10–24	0.625 mg/kg IV every 24 hours	
		<10 or HD	0.625 mg/kg IV three times per week. For people on HD, administer dose after HD.	
Lamivudine (3TC) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for ARV FDC products containing 3TC.	300 mg PO every 24 hours See footnote[d] for more information on alternative dosing.	CrCl^ or eGFR# (mL/min)	Epivir Label[c]	Alternative Dose
		15–29	150 mg PO once, then 100 mg PO every 24 hours	100–150 mg every 24 hours
		5–14	150 mg PO once, then 50 mg PO every 24 hours	100–150 mg every 24 hours
		<5 or HD (for people on HD, administer dose after HD on dialysis days)	50 mg PO once, then 25 mg PO every 24 hours	100–150 mg every 24 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
Lamivudine/ Tenofovir Disoproxil Fumarate (3TC/TDF) (FDC Trade Name: Cimduo) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for other ARV FDC products containing 3TC/TDF.	One tablet (3TC 300 mg/TDF 300 mg) PO once daily	<50 or HD	Coformulated tablet is not recommended.	
Levofloxacin	500 mg (low dose) or 750–1,000 mg (high dose) IV or PO daily Dose can be adjusted based on serum concentrations	CrCl^ or eGFR# (mL/min)	Low Dose	High Dose
		20–49	500 mg once, then 250 mg every 24 hours, IV or PO	750 mg every 48 hours IV or PO
		<20 or HD (for people on HD, administer dose after HD on dialysis days)	500 mg once, then 250 mg every 48 hours, IV or PO	750 mg once, then 500 mg every 48 hours, IV or PO
Paromomycin	500 mg PO every 6 hours	<10 or HD	Minimal systemic absorption. No dosage adjustment necessary but monitor for worsening renal function and ototoxicity in people with ESRD.	
Penicillin G (Potassium or Sodium)	Neurosyphilis, Ocular Syphilis, or Otosyphilis • 3–4 million units IV every 4 hours, *or* • 18–24 million units IV daily as continuous infusion	10–50	2–3 million units IV every 4 hours *or* 12–18 million units IV as continuous infusion	
		<10	2 million units IV every 4–6 hours *or* 8–12 million units IV as continuous infusion	
		HD	2 million units IV every 4–6 hours *or* 8 million units IV as continuous infusion	
Pentamidine	4 mg/kg IV every 24 hours May reduce dose to 3 mg/kg IV daily in the event of toxicities.	<10 or HD	4 mg/kg IV every 48 hours	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Posaconazole	IV: 300 mg twice daily on Day 1; then 300 mg once daily Delayed-Release Tablet: 300 mg (three 100 mg delayed-release tablets) PO once daily Oral Suspension: 400 mg PO twice daily	<50 or HD	The manufacturer recommends that IV posaconazole be avoided because of potential toxicity due to accumulation of SBECD (vehicle of IV product), unless benefits outweigh risks. An observational study did not find worsening in renal function in people with CrCl <50 ml/min given SBECD. Switch people with CrCl <50 mL/min to oral posaconazole when feasible. No dosage adjustment of oral dose in people with renal insufficiency. Higher variability in serum concentrations observed in people with CrCl <20 mL/min. Perform posaconazole TDM (target trough concentration >1.25 mcg/mL for treatment).
Pyrazinamide	See the *Mycobacterium tuberculosis* section for weight-based dosing guidelines.	<30 or HD	25–35 mg/kg/dose three times per week For people on HD, administer dose after HD. Perform TDM to guide optimal dosing.
Quinine Sulfate	650 mg salt (524 mg base) PO every 8 hours	<10 or HD	650 mg once, then 325 mg PO every 12 hours
Rifabutin	5 mg/kg PO daily (usually 300 mg PO daily) See the *Mycobacterium tuberculosis* section and Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage adjustment based on interactions with ARVs.	<30	Perform rifabutin TDM. If rifabutin-associated neutropenia is suspected, consider 50% of dose once daily.
Streptomycin	15 mg/kg IM or IV every 24 hours *or* 25 mg/kg IM or IV three times per week	Use with caution in people with renal insufficiency.	TDM is no longer available. Consider an alternative aminoglycoside, as clinically appropriate. If used: 15 mg/kg two to three times weekly. Administer dose after HD.
Sulfadiazine *Administer oral or IV fluid hydration to reduce the risk for nephrotoxicity.*	1,000–1,500 mg PO every 6 hours (1,500 mg every 6 hours for people >60 kg)	≤50 or HD	No data. Use alternative anti-toxoplasma therapy.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Tecovirimat	IV *35 to <120 kg* • 200 mg every 12 hours *≥120 kg* • 300 mg every 12 hours	30–89	No dosage adjustment necessary. Use with caution because of potential accumulation of hydroxypropyl-β-cyclodextrin.
		<30	Contraindicated because of potential accumulation of hydroxypropyl-β-cyclodextrin. Note: IV formulation may be considered in people with CrCl <30 only if drug absorption via enteral administration is expected to be problematic based on an individual risk–benefit assessment in consultation with CDC. In these circumstances, use with caution and monitor renal function continuously. Switch to the oral formulation as soon as possible.
	PO *40 to <120 kg* • 600 mg every 12 hours *≥120 kg* • 600 mg every 8 hours	Any eGFR	No dosage adjustment necessary.
Tenofovir Alafenamide (TAF) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for ARV FDC products containing TAF.	25 mg PO daily	<15	Not recommended
		HD	No dosage adjustment necessary. Administer dose after HD on dialysis days.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Tenofovir Disoproxil Fumarate (TDF) Note: Please refer to Appendix B in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations for ARV FDC products containing TDF.	300 mg PO daily	30–49	300 mg PO every 48 hours (consider switching to TAF for treatment of HBV)
		10–29	300 mg PO every 72–96 hours (consider switching to alternative agent for treatment of HBV)
		<10	Not recommended
		HD	300 mg PO once weekly; administer dose after dialysis.
Trimethoprim/ Sulfamethoxazole (TMP-SMX) *Encourage oral hydration when using oral TMP-SMX.*	For PCP Treatment: • 5 mg/kg (of TMP component) IV every 6–8 hours, *or* • Two TMP-SMX DS tablets PO every 8 hours	15–30	5 mg/kg (TMP) IV every 12 hours, or two TMP-SMX DS tablets PO every 12 hours
		<15	5 mg/kg (TMP) IV every 24 hours, or one TMP-SMX DS tablet PO every 12 hours (or two TMP-SMX DS tablets every 24 hours)
		HD	5 mg/kg (TMP) IV every 24 hours, or two TMP-SMX DS tablets PO daily; on dialysis days, administer dose after HD. Consider TDM to optimize therapy (target TMP concentrations: 5–8 mcg/mL).
	For PCP Prophylaxis: • One TMP-SMX DS tablet PO daily, *or* • One TMP-SMX DS tablet PO three times per week, *or* • One TMP-SMX SS tablet PO daily	15–30	Reduce dose by 50% (e.g., 1 SS tablet PO daily).
		<15 or HD	Reduce dose by 50% or use alternative agent. For people on HD, administer dose after HD on dialysis days.
	For TE Treatment: 5 mg/kg (TMP component) IV or PO every 12 hours	15–30	5 mg/kg (TMP component) IV or PO every 24 hours
		<15 or HD	5 mg/kg (TMP component) IV or PO every 24 hours or use alternative agent. For people on HD, administer dose after HD on dialysis days).
	For TE Chronic Maintenance Therapy: • One TMP-SMX DS tablet twice daily, *or* • One TMP-SMX DS tablet daily	15–30	Reduce dose by 50%.
		<15 or HD	Reduce dose by 50% or use alternative agent. For people on HD, administer dose after HD on dialysis days).

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
	For Toxoplasmosis Primary Prophylaxis: One TMP-SMX DS tablet PO daily	15–30	Reduce dose by 50%.	
		<15 or HD	Reduce dose by 50% or use alternative agent. For people on HD, administer dose after HD on dialysis days.	
Valacyclovir *Encourage oral fluid hydration to reduce the risk for nephrotoxicity.*	For Herpes Zoster: 1 g PO three times daily	30–49	1 g PO every 12 hours	
		10–29	1 g PO every 24 hours	
		<10 or HD	500 mg PO every 24 hours For people on HD, administer dose after HD on dialysis days).	
	For HSV Treatment: 1 g PO twice daily For HSV Chronic Suppressive Therapy: 500 mg PO twice daily	30–49	No dosage adjustment necessary.	
		10–29	For Treatment: 1 g PO every 24 hours For Suppressive Therapy: 500 mg PO every 24 hours	
		<10 or HD	500 mg PO every 24 hours For people on HD, administer dose after HD on dialysis days).	
Valganciclovir *Encourage oral fluid hydration to reduce the risk for nephrotoxicity.*	Induction Therapy: 900 mg PO twice daily Maintenance Therapy: 900 mg PO once daily	CrCl^ or eGFR# (mL/min)	Induction	Maintenance
		40–59	450 mg PO twice daily	450 mg PO daily
		26–39	450 mg PO daily	450 mg PO every 48 hours
		10–25	450 mg PO every 48 hours	450 mg PO twice weekly

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR[#] (mL/min)	Dose	
		<10 or HD (for people on HD, administer dose after HD on dialysis days)	Not recommended Use IV ganciclovir. May consider: • 200 mg (oral powder for solution) PO three times per week If oral powder formulation is not available, consider: • 450 mg (tablet) PO three times weekly	Not recommended Use IV ganciclovir. May consider: • 100 mg (oral powder for solution) PO three times per week If oral powder formulation is not available, consider: • 450 mg (tablet) PO twice weekly
Voriconazole	6 mg/kg IV every 12 hours for two doses, then 4 mg/kg IV every 12 hours *or* 200–300 mg PO every 12 hours	<50 or HD	IV voriconazole is not recommended by the manufacturer for CrCl <50 ml/min because of potential toxicity from accumulation of SBECD (vehicle of IV product). Observational studies did not find worsening in renal function in people with CrCl <50 ml/min. Switch people with CrCl <50 ml/min or on HD to oral voriconazole when feasible. No need for dosage adjustment when the oral dose is used. Perform TDM to adjust dose.	

[a] The prescribing information for emtricitabine (Emtriva) recommends adjusting doses for people with CrCl 30–49 mL/min and for people on hemodialysis. However, the prescribing information for certain FDC products that contain emtricitabine (including Descovy, Biktarvy, Genvoya, and Odefsey) recommends that the standard dose (emtricitabine 200 mg) can be given once daily in these individuals (for people on HD, administer dose after HD on dialysis days). The recommendations in this table incorporate the dosing guidance from the FDC products.

[b] To allow people to remain on certain TAF-containing FDC products, some clinicians may use full-dose, daily emtricitabine in people with CrCl 15–29 mL/min who are not on HD. For more information, see the Adult and Adolescent Antiretroviral Guidelines.

[c] The prescribing information for lamivudine (Epivir) recommends dosage adjustment from 300 mg once daily to 150 mg once daily for people with CrCl 30–49 mL/min. However, the prescribing information for certain FDC products that contain lamivudine (including Dovato and Triumeq) recommends no dose adjustment for CrCl 30–49 mL/min. The recommendations in this table incorporate the dosing guidance from the FDC products.

[d] Clinicians may consider using the nearest available lamivudine tablet strength (100 mg or 150 mg) to avoid the need for 3TC oral solution, thereby simplifying regimens and facilitating adherence. Some clinicians may use full-dose 3TC to allow people to remain on certain FDC antiretroviral products. For more information, see the Adult and Adolescent Antiretroviral Guidelines.

^ CrCl based on the Cockroft-Gault formula can be determined using this CrCl calculator. Please refer to the drug's prescribing information and to the National Institute of Diabetes and Digestive and Kidney Diseases Determining Drug Dosing in Adults with Chronic Kidney Disease page for a discussion on using CrCl based on the Cockcroft-Gault equation versus eGFR.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Adults With Renal Insufficiency

[#] eGFR based on the 2021 CKD-EPI equation can be determined using this eGFR calculator. Please refer to the drug's prescribing information and to the National Institute of Diabetes and Digestive and Kidney Diseases Determining Drug Dosing in Adults With Chronic Kidney Disease page for a discussion on using CrCl based on the Cockcroft-Gault equation versus eGFR.

Key: 3TC = lamivudine; ARV = antiretroviral; CBC = complete blood count; CDC = Centers for Disease Control and Prevention; CMV = cytomegalovirus; COBI = cobicistat; CrCl = creatinine clearance; DS = double strength; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; HD = hemodialysis; HSV = herpes simplex virus; IM = intramuscular; IV = intravenous; MAI = *Mycobacterium avium intracellulare;* MTB = *Mycobacterium tuberculosis*; OI = opportunistic infection; PCP = *Pneumocystis* pneumonia; PI = protease inhibitor; PO = orally; SCr = serum creatinine; SBECD = sulfobutylether cyclodextrin; SS = single strength; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TE = *Toxoplasma gondii* encephalitis TMP-SMX = trimethoprim-sulfamethoxazole; VZV = varicella zoster virus

Appendix A. List of Abbreviations (Last updated May 7, 2013; last reviewed January 8, 2025)

Acronym/Abbreviation	Definition
ABGs	arterial blood gases
ACTG	AIDS Clinical Trials Group
AFB	acid-fact bacilli
AIN	anal intraepithelial neoplasia
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
ARV	antiretroviral
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	atypical squamous cells—cannot exclude high grade cervical squamous intraepithelial lesion
ASC-US	atypical squamous cells of uncertain significance
AST	serum aspartate aminotransferase
AUC	area under the curve
BA	bacillary angiomatosis
BAL	bronchoalveolar lavage
BID	twice a day
BIW	twice a week
CAP	community-acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CD4	CD4 T lymphocyte cell
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile*-associated infection
CES-D	Center for Epidemiologic Studies Depression Scale
CFU	colony-forming unit
CIA	chemiluminescence immunoassays
CIN	cervical intraepithelial neoplasia
C_{max}	maximum concentration
C_{min}	minimum concentration
CMV	cytomegalovirus
CNS	central nervous system
CPE	central nervous system penetration effectiveness
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CT	computed tomography

CYP3A4	Cytochrome P450 3A4
DAAs	direct acting antiviral agents
DOT	directly observed therapy
DS	double strength
EDTA	ethylenediaminetetraacetic acid
EIAs	enzyme immunoassays
EM	erythema multiforme
FDA	Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody absorbed
g	gram
G6PD	Glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HPA	hypothalamic-pituitary-adrenal
HPV	human papillomavirus
HSIL	high grade cervical squamous intraepithelial lesion
HSV	herpes simplex virus
HSV-1	herpes simplex virus 1
HSV-2	herpes simplex virus 2
ICP	intracranial pressure
ICU	intensive care unit
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assays
IM	intramuscular
IND	investigational new drug
IRIS	immune reconstitution inflammatory syndrome
IRU	immune recovery uveitis
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	JC virus
KS	Kaposi Sarcoma
LEEP	loop electrosurgical excision procedure
LP	lumbar puncture
LSIL	low grade squamous intraepithelial lesion

LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MAI	*Mycobacterium avium intracellulare*
MCD	multicentric Castleman's disease
MDR TB	multi-drug-resistant tuberculosis
mg	milligram
mmHg	millimeters of mercury
MSM	men who have sex with men
MTB	*Mycobacterium tuberculosis*
NAA	nucleic acid amplification
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drugs
NVP	nevirapine
OI	opportunistic infection
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PEL	primary effusion lymphoma
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	orally
PORN	Progressive Outer Retinal Necrosis
PPV	polysaccharide vaccine
PSI	pneumonia severity index
q(n)h	every "n" hours
qAM	every morning
QID	four times a day
qPM	every evening
RPR	rapid plasma reagin
RVR	rapid virological response
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SQ	subcutaneous
SS	single strength
STD	sexually transmitted disease
SVR	sustained virologic response
TB	tuberculosis
TDM	therapeutic drug monitoring
TE	*Toxoplasma* encephalitis

TEN	toxic epidermal necrolysis
TID	three times daily
TIW	three times weekly
TP-PA	*T. pallidum* particle agglutination
TST	tuberculin skin test
ULN	upper limit of normal
VAIN	vaginal intra-epithelial neoplasia
VDRL	Venereal Disease Research Laboratory
VIII	vestibulocochlear
VIN	vulvar intraepithelial neoplasia
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

Abbreviation	**Drug Name**
3TC	lamivudine
5-FU	fluorouracil
ATV/r	ritonavir-boosted atazanavir
BCA	bichloroacetic acid
BOC	boceprevir
COBI	cobicistat
ddA-TP	dideoxyadenosine triphosphate
ddI	didanosine
DHA	dihydroartemisinin
EFV	efavirenz
EMB	ethambutol
EVG	elvitegravir
FTC	emtricitabine
INH	isoniazid
MVC	maraviroc
PCV13	13-valent pneumococcal conjugate vaccine
PegIFN	peginterferon alfa
PI	protease inhibitor
PPV23	23-valent pneumococcal polysaccharides vaccine
PZA	pyrazinamide
RAL	raltegravir
RBV	ribavirin
RFB	rifabutin
RIF	rifampin

RPT	rifapentine
SMX	sulfamethoxazole
TCA	trichloroacetic acid
TDF	tenofovir disoproxil fumarate
TMP	trimethoprim
TMP-SMX	trimethoprim-sulfamethoxazole
TVR	telaprevir
ZDV	zidovudine

Appendix B. Panel Roster and Financial Disclosures

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			Company	Relationship
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Note: Members are required to update disclosures annually and to notify guideline staff of any relevant changes in status during the interim.

Appendix B. Panel Roster and Financial Disclosures

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			Company	Relationship
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			ViiV Healthcare Gilead Sciences	Research Support

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Appendix B. Panel Roster and Financial Disclosures

Bacterial Enteric Infections

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Carolyn Alonso	*Harvard Medical School; Beth Israel Deaconess Medical Center*	Bacterial Enteric Infections	Clinical Care Options	Honoraria
			DSM Pfizer	Advisory Board
			Merck	Research Support
			Ferring	Travel Support
Anna Bowen	*Centers for Disease Control and Prevention*	Bacterial Enteric Infections	None	N/A
Paul Pham	*The Johns Hopkins University School of Medicine: Westview Urgent Care Medi Center*	Section Review Group Bacterial Enteric Infections	Novo Nordisk	Stockholder
Jennifer Spicer	*Emory University School of Medicine*	Bacterial Enteric Infections	None	N/A
Brian Zanoni*	*Emory University School of Medicine*	Bacterial Enteric Infections	Accordant Health Services	Consultant

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Bartonellosis

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Nesli Basgoz	*Harvard Medical School*	Bartonellosis	None	N/A
Carl Boodman	*University of Manitoba, Canada*	Bartonellosis	Research Foundation Flanders-Fonds de Recherche du Québec European Society of Clinical Microbiology and Infectious Diseases Canadian Institute of Health Research fellowship Clinical Investigator Program (University of Manitoba)	Research Support
			European Union (doctoral mobility grant)	Travel Support
			International Diagnostics Network/Global Health CPD	Consultant
James Kirby	*Harvard Medical School; Beth Israel Deaconess Medical Center*	Bartonellosis	None	N/A
Jane Koehler	*University of California, San Francisco School of Medicine*	Bartonellosis	None	N/A
Grace Marx	*Centers for Disease Control and Prevention*	Bartonellosis	None	N/A
Stacey Rose*	*Baylor College of Medicine*	Bartonellosis	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Candidiasis

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Melissa Johnson	*Duke University School of Medicine*	Candidiasis	Scynexis	Research Support
			Biomeme	Patent
Michail Lionakis	*National Institutes of Health*	Candidiasis	None	N/A
Jeniel Nett*	*University of Wisconsin–Madison School of Medicine and Public Health*	Candidiasis	None	N/A
Jack Sobel	*Wayne State University School of Medicine*	Candidiasis	Mycovia Pharmaceuticals	Consultant

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Community-Acquired Pneumonia

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Engi Attia	*University of Washington School of Medicine*	Community-Acquired Pneumonia	None	N/A
Kristina Crothers	*University of Washington School of Medicine*	Community-Acquired Pneumonia *Pneumocystis* Pneumonia	None	N/A
Miwako Kobayashi	*Centers for Disease Control and Prevention*	Community-Acquired Pneumonia	None	N/A
Ioannis Konstantinidis	University of Pittsburgh Medical Center	Community-Acquired Pneumonia	None	N/A
Michael Niederman	*NewYork-Presbyterian/ Weill Cornell Medicine Medical Center*	Community-Acquired Pneumonia	Merck	Scientific Advisory Board
			GSK	Data and Safety Monitoring Board
			Boehringer-Ingelheim	Research Support (paid to institution)
			Merck	Consultant
Maria Rodriguez-Barradas *	*Michael E. DeBakey Department of Veterans Affairs Medical Center; Baylor College of Medicine*	Community-Acquired Pneumonia	None	N/A
Jerry Zifodya	*Tulane School of Medicine*	Community-Acquired Pneumonia	Firland Foundation Wetmore Foundation	Research Support

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Cryptosporidiosis/Microsporidiosis

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Mahalia Desruisseaux	*Yale School of Medicine*	Cryptosporidiosis/ Microsporidiosis Geographic Opportunistic Infections	None	N/A
Timothy Hatlen	*University of California, Los Angeles David Geffen School of Medicine*	Cryptosporidiosis/ Microsporidiosis	None	N/A
Michele Hlavsa	*Centers for Disease Control and Prevention*	Cryptosporidiosis/ Microsporidiosis	None	N/A
Nagalingeswaran Kumarasamy	*The Warren Alpert Medical School of Brown University*	Cryptosporidiosis/ Microsporidiosis	Indian Council of Medical Research World Health Organization Unitaid amfAR	Research Support
Honorine Ward	*Tufts University School of Medicine*	Cryptosporidiosis/ Microsporidiosis	None	N/A
Louis Weiss*	*Albert Einstein College of Medicine*	Cryptosporidiosis/ Microsporidiosis	None	N/A
Clinton White	*The University of Texas Medical Branch*	Cryptosporidiosis/ Microsporidiosis	None	N/A
Lihua Xiao	*Centers for Disease Control and Prevention*	Cryptosporidiosis/ Microsporidiosis	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Geographic Opportunistic Infections (Chagas Disease, Cystoisosporiasis, Leishmaniasis, Malaria, Talaromycosis)

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Naomi Aronson	*F. Edward Hébert School of Medicine at Uniformed Services University*	Geographic Opportunistic Infections	None	N/A
Johanna Daily	*Albert Einstein College of Medicine, Weiler Hospital*	Geographic Opportunistic Infections	None	N/A
Mahalia Desruisseaux	*Yale School of Medicine*	Cryptosporidiosis/ Microsporidiosis Geographic Opportunistic Infections	None	N/A
Thuy Le	*Duke University School of Medicine*	Geographic Opportunistic Infections	Gilead Sciences	Research Support (paid to institution)
Rogelio López-Vélez	*Ramón y Cajal Health Research Institute, Ramón y Cajal University Hospital*	Geographic Opportunistic Infections	None	N/A
Rojelio Mejia	*Baylor College of Medicine*	Geographic Opportunistic Infections	IC-Medtech	Research Support
			Roche/GenMark	Advisory Board
Edward Mitre*	*F. Edward Hébert School of Medicine at Uniformed Services University*	Geographic Opportunistic Infections	None	N/A
Susan Montgomery	*Centers for Disease Control and Prevention*	Geographic Opportunistic Infections	None	N/A
Sunil Parikh	*Yale School of Public Health*	Geographic Opportunistic Infections	Medincell	Scientific Advisory Board
			Kainomyx	Consultant
Adrienne Showler	*National Institute of Allergy and Infectious Diseases*	Geographic Opportunistic Infections	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Hepatitis B Virus

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Debika Bhattacharya	*University of California, Los Angeles David Geffen School of Medicine*	Hepatitis B Virus	Gilead Sciences	Research Support (paid to institution)
Claudia Hawkins	*Northwestern University Feinberg School of Medicine*	Hepatitis B Virus	None	N/A
Min Kim	*Centers for Disease Control and Prevention*	Hepatitis B Virus	None	N/A
Kristen Marks	*Weill Cornell Medicine*	Hepatitis B Virus	Gilead Sciences	Consultant
			Immorna Novo Nordisk	Data and Safety Monitoring Board
			Viiv Healthcare	Research Support (paid to institution)
Chloe Thio*	*The Johns Hopkins University School of Medicine*	Hepatitis B Virus	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Hepatitis C Virus

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Meena Bansal	*Icahn School of Medicine at Mount Sinai*	Hepatitis C Virus	Pfizer Histoindex Siemens	Travel Support
			The Kinetix Group Madrigal Pfizer mBIOTA CurveBio GSK Fibrinostics Boeheringer-Ingelheim Merck NOVO Nordisk Boston Pharma	Consultant
Greer Burkholder	*The University of Alabama at Birmingham Marnix E. Heersink School of Medicine*	Hepatitis C Virus	Merck Foundation Cepheid	Research Support
Emily Cartwright	*Centers for Disease Control and Prevention*	Hepatitis C Virus	None	N/A
Arthur Kim	*Harvard Medical School*	Hepatitis C Virus	Shionogi, Inc	Data and Safety Monitoring Board
Nina Kim	*University of Washington School of Medicine and School of Public Health*	Hepatitis C Virus	Gilead Sciences (FOCUS Grant)	Research Support (paid to institution)
Kristen Marks	*Weill Cornell Medicine*	Hepatitis C Virus	Gilead Sciences	Consultant
			Immorna Novo Norodisk	Data and Safety Monitoring Board

			Viiv	Research Support (paid to institution)
Susanna Naggie	*Duke University School of Medicine*	Hepatitis C Virus	Bristol Myers Squibb/PRA 9	Event Adjudication Committee
			Vir Biotechnology	Advisory Board
			Vir Biotechnology	Stockholder
			Clinical Infectious Diseases	Deputy Editor
Merceditas Villanueva*	*Yale School of Medicine*	Hepatitis C Virus	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Herpes (HHV-8/CMV)

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Gary Holland	*University of California, Los Angeles David Geffen School of Medicine*	Herpes (HHV-8/CMV) Herpes (HSV/VZV)	None	N/A
Christine Johnston	*University of Washington School of Medicine*	Herpes (HHV-8/CMV) Herpes (HSV/VZV)	GSK Pfizer Assembly Biosciences Oxymo Aicuris	Consultant
			GSK Moderna Gilead	Research Support
			HIV Vaccine Trials	Data and Safety Monitoring Board
Warren Phipps*	*University of Washington School of Medicine*	Herpes (HHV-8/CMV)	None	N/A
Ramya Ramaswami	*National Institutes of Health*	Herpes (HHV-8/CMV)	Celgene/Bristol Myers Squibb EMD Serono Merck Sobi/CTI BioPharma PDS Biotech Eli Lilly	Research Support
Shannon Ross	*The University of Alabama at Birmingham Marnix E. Heersink School of Medicine*	Herpes (HHV-8/CMV) Herpes (HSV/VZV)	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Herpes (HSV/VZV)

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Gary Holland	*University of California, Los Angeles David Geffen School of Medicine*	Herpes (HHV-8/CMV) Herpes (HSV/VZV)	None	N/A
Christine Johnston	*University of Washington School of Medicine*	Herpes (HHV-8/CMV) Herpes (HSV/VZV)	GSK Pfizer Assembly Biosciences Oxymo Aicuris	Consultant
			GSK Moderna	Research Support
			HIV Vaccine Trials	Data and Safety Monitoring Board
Andrew Karaba	*The Johns Hopkins University School of Medicine*	Herpes (HSV/VZV)	Hologic, Inc.	Consultant
Poonam Mathur	*University of Washington School of Medicine*	Herpes (HSV/VZV)	None	N/A
Shannon Ross	*The University of Alabama at Birmingham Marnix E. Heersink School of Medicine*	Herpes (HHV-8/CMV) Herpes (HSV/VZV)	None	N/A
Sarah Schmalzle*	*Baltimore County Department of Health*	Herpes (HSV/VZV)	None	N/A

* Section Group Lead

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Human Papillomavirus

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Susan Cu-Uvin	*The Warren Alpert Medical School of Brown University*	Human Papillomavirus	AIDS Malignancy Consortium	Data and Safety Monitoring Board
Grant Ellsworth*	*Weill Cornell Medical College*	Human Papillomavirus	Merck	Research Support (paid to institution)
Andrea Lisco	*National Institutes of Health*	Human Papillomavirus	Merck	Other—Support under Merck Investigator Studies for clinical trial
			NeoImmuneTech	Research Support
Lauri Markowitz	*Centers for Disease Control and Prevention*	Human Papillomavirus	None	N/A
L. Stewart Massad	*Washington University School of Medicine in St. Louis*	Human Papillomavirus	Merck	Consultant
Anna-Barbara Moscicki	*University of California, Los Angeles David Geffen School of Medicine*	Human Papillomavirus	Merck	Advisory Board
Joel Palefsky	*University of California, San Francisco School of Medicine*	Human Papillomavirus	Merck GSK Abbott	Consultant
			Roche Molecular Diagnostics Merck GSK Abbott	Honoraria
			Roche Molecular Diagnostics Atila Biosystems Hologic	Research Support
Elizabeth Stier	*Boston University Medical Campus*	Human Papillomavirus	None	N/A
John Weiser	*Centers for Disease Control and Prevention*	Human Papillomavirus	None	N/A

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
John Winters	*Icahn School of Medicine at Mount Sinai*	Human Papillomavirus	None	N/A

* Section Group Lead

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Immunizations

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Meagan Deming	*University of Maryland School of Medicine*	Immunizations	CEPI	Research Support
Shireesha Dhanireddy	*University of Washington School of Medicine*	Leadership Immunizations	None	N/A
Philip Peters	*Centers for Disease Control and Prevention*	Immunizations	None	N/A
Daniel Solomon*	*Harvard Medical School*	Immunizations	None	N/A
Jennifer Whitaker	*Baylor College of Medicine*	Immunizations	Pfizer	Research Support

* Section Group Lead

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Invasive Mycoses

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
John Baddley	*University of Maryland School of Medicine*	Invasive Mycoses	None	N/A
David Boulware	*University of Minnesota Medical School*	Invasive Mycoses	None	N/A
Marisa Miceli	*University of Michigan Medical School*	Invasive Mycoses	Scynexis F2G AN2 Therapeutics Pulmocide	Research Support (paid to institution)
			Scynexis	Data and Safety Monitoring Board
John Perfect*	*Duke University School of Medicine*	Invasive Mycoses	None	N/A
George R. Thompson	*University of California, Davis Medical Center*	Invasive Mycoses	Astellas Pharma Basilea GSK Melinta Mundipharma Cidara Therapeutics F2G	Scientific Advisory Board
			Pfizer	Data and Safety Management Board
			Astellas Pharma Basilea GSK Melinta Mundipharma Cidara Therapeutics F2G	Research Support

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Mpox

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
John Brooks	*Atlanta, GA*	Leadership Mpox	None	N/A
Chase Cannon	*University of Washington*	Mpox	Roche Diagnostics	Consultant
			Hologic	Research Support
Emily Heil	*University of Maryland School of Pharmacy*	Mpox Pharmacology	Wolters Kluwer	Consultant
Jesse O'Shea*	*Centers for Disease Control and Prevention*	Mpox	None	N/A
Agam Rao	*Centers for Disease Control and Prevention*	Mpox	None	N/A
Boghuma Kabisen Titanji	*Emory University School of Medicine*	Mpox	None	N/A
Jason Zucker	*Columbia University Vagelos College of Physicians and Surgeons*	Mpox	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Mycobacterium avium Complex

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Constance Benson*	*University of California, San Diego School of Medicine*	Leadership *Mycobacterium avium* Complex	Gilead Sciences BioMerieux	Research Support (paid to institution)
			ViiV	Data and Safety Monitoring Board
Lauren Collins	*Emory University School of Medicine*	*Mycobacterium avium* Complex	None	N/A
Timothy Hatlen	*University of California, Los Angeles David Geffen School of Medicine* *Harbor-UCLA Medical Center*	Cryptosporidiosis/ Microsporidiosis *Mycobacterium avium* Complex	None	N/A
Maura Manion	*National Institutes of Health*	*Mycobacterium avium* Complex	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Mycobacterium tuberculosis

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
James Brust*	*Albert Einstein College of Medicine*	*Mycobacterium tuberculosis*	None	N/A
Kelly Dooley	*Vanderbilt University School of Medicine*	*Mycobacterium tuberculosis*	None	N/A
Neela Goswami	*Centers for Disease Control and Prevention*	*Mycobacterium tuberculosis*	None	N/A
Scott Heysell	*University of Virginia School of Medicine*	*Mycobacterium tuberculosis*	None	N/A
Jyoti Mathad	*NewYork-Presbyterian/Weill Cornell Medicine*	*Mycobacterium tuberculosis*	None	N/A
Graeme Meintjes	*University of Cape Town, South Africa, Faculty of Health Sciences*	*Mycobacterium tuberculosis*	Otsuka Pharmaceutical	Data and Safety Monitoring Board
Sarita Shah	*Emory University School of Medicine*	*Mycobacterium tuberculosis*	None	N/A
Timothy Sterling	*Vanderbilt University Medical Center*	*Mycobacterium tuberculosis*	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Pneumocystis Pneumonia

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Kristina Crothers	*University of Washington School of Medicine*	Community-Acquired Pneumonia *Pneumocystis* Pneumonia	None	N/A
Jannik Helweg-Larsen	*Rigshospitalet, Copenhagen University, Denmark*	*Pneumocystis* Pneumonia	None	N/A
Aley Kalapila	*Emory University School of Medicine*	*Pneumocystis* Pneumonia	The Body Pro	Honoraria
Joseph Kovacs*	*National Institutes of Health*	*Pneumocystis* Pneumonia *Toxoplasma gondii*	Matinas Merck	Research Support
Alison Morris	*University of Pittsburgh School of Medicine*	*Pneumocystis* Pneumonia	Pfitzer	Research Support
			AstraZeneca	Travel Support
Sean Wasserman	*University of Cape Town, South Africa, Faculty of Health Sciences*	*Pneumocystis* Pneumonia	None	N/A

* Section Group Lead

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Pregnancy

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Jean Anderson	*The Johns Hopkins University School of Medicine*	Pregnancy	None	N/A
Katherine Bunge	*UPMC Magee-Womens Hospital*	Pregnancy	None	N/A
Karley Dutra	*Medical University of South Carolina*	Pregnancy	None	N/A
Oluwatosin Goje	*Cleveland Clinic Lerner College of Medicine*	Pregnancy	Elsevier Merck	Editorial Board
Erica Hardy	*Warren Alpert Medical School of Brown University*	Pregnancy	None	N/A
Sylvia LaCourse*	*University of Washington School of Medicine and School of Public Health*	Pregnancy	Merck	Research Support (paid to institution)
			Merck	Travel Support
Gweneth Lazenby	*Medical University of South Carolina*	Pregnancy	None	N/A
Anna Powell	*The Johns Hopkins University School of Medicine*	Pregnancy	Cepheid	Consultant
Rodney Wright	*Albert Einstein College of Medicine*	Pregnancy	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Syphilis

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Laura Bachmann	*Centers for Disease Control and Prevention*	Syphilis	None	N/A
Khalil Ghanem	*The Johns Hopkins University School of Medicine*	Syphilis	None	N/A
Matthew Hamill	*The Johns Hopkins University School of Medicine*	Syphilis	Chembio Diagnostics, Inc.	Honoraria
			Cepheid Chembio Diagnostics, Inc. Roche Diagnostics	Other
Edward W. Hook	*The University of Alabama at Birmingham Marnix E. Heersink School of Medicine*	Syphilis	Visby Diagnostics Global Antibiotic Research and Development Program INNOVIA Therapeutics	Scientific Advisory Board
			Global Antibiotic Research and Development Program	Research Support
			Global Antibiotic Research and Development Program	Consultant
Arlene Sena	*The University of North Carolina at Chapel Hill School of Medicine*	Syphilis	Hologic	Speakers Bureau
			Entasis	Advisory Board
Irene Stafford	*The University of Texas Health Science Center at Houston, McGovern Medical School*	Syphilis	None	N/A
Susan Tuddenham*	*The Johns Hopkins University School of Medicine*	Syphilis	None	N/A
Kimberly Workowski	*Emory University School of Medicine*	Syphilis	Gilead Abbvie Acuris	Research Support

* Section Group Lead

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Toxoplasma gondii

Member	Institution	Panel Section Group(s)	Financial Disclosure	
			Company	Relationship
Sarita Boyd	*U.S. Food and Drug Administration*	*Toxoplasma gondii*	None	N/A
Joseph Kovacs*	*National Institutes of Health*	*Pneumocystis* Pneumonia *Toxoplasma gondii*	Martinas Merck	Research Support
Janaki Kuruppu	*National Institutes of Health*	*Toxoplasma gondii*	None	N/A
Leon Lai	*MedStar Washington Hospital Center*	*Toxoplasma gondii*	None	N/A
Jose M. Miro	*Hospital Clinic de Barcelona–IDIBAPS, University of Barcelona, Spain*	*Toxoplasma gondii*	None	N/A
Daniel Podzamczer	*Fight AIDS and Infectious Diseases Foundation, Hospital Germans Trias i Pujol, Badalona, Spain*	*Toxoplasma gondii*	ViiV Healthcare	Research Support
Bryan R. Smith	*National Institutes of Health*	*Toxoplasma gondii*	None	N/A

* Section Group Lead

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