

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



Developed by the National Institutes of Health, the Centers for Disease Control and Prevention, and the HIV Medicine Association of 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)

How to Cite the Adult and Adolescent Opportunistic Infection Guidelines:

Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. National Institutes of Health, Centers for Disease Control and Prevention, HIV Medicine Association, and Infectious Diseases Society of America. Available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection>. Accessed (insert date) [include page numbers, table number, etc., if applicable].

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 for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*

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 by relevant outside reviewers before the document is altered. Major revisions within the last six months are as follows:

January 18, 2023

Hepatitis C Virus

- Added criteria to identify patients who are eligible for a simplified hepatitis C virus (HCV) treatment approach.
- Provided treatment regimens with an updated recommendation for the use of simplified, pan-genotypic regimens.
- Added a table of drug interactions between common antiretroviral and recommended HCV treatment regimens.

September 28, 2022

Monkeypox

- Added links to useful government and professional association websites.

September 7, 2022

Hepatitis B Virus

- Updated the information on vaccines to recommend a double-dose recombinant hepatitis B vaccine and to include as an alternative the recombinant HBsAg vaccine conjugated to CpG 1018 (Heplisav-B).
- Emphasized avoidance of dolutegravir/lamivudine (3TC) for antiretroviral therapy for people who are HBsAg positive because 3TC is the only active drug against hepatitis B virus in this regimen.

Immunization

- Harmonized recommendations for the hepatitis B vaccine with the updated Hepatitis B Virus section (see above).

- Noted that two new pneumococcal conjugate vaccines are now preferred for protection against invasive pneumococcal disease: PCV15 (given in series with PPSV23) and PCV20 (given as a single vaccine).
- Recommended the recombinant herpes zoster vaccine (RZV) for all individuals with HIV who are 18 years and older rather than 50 years and older.

August 1, 2022

Monkeypox

- Added a brief statement about monkeypox with a link to information from the Centers for Disease Control and Prevention (CDC).
- Information about monkeypox as an HIV-related opportunistic infection will be added to this guideline as relevant data emerge.

Introduction

Updated: June 9, 2022

Reviewed: January 11, 2023

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*, toxoplasma encephalitis, cytomegalovirus retinitis, cryptococcal meningitis, tuberculosis, disseminated *Mycobacterium avium* complex (MAC) disease, and pneumococcal respiratory disease, as well as certain cancers such as Kaposi sarcoma and central nervous system lymphoma, have been hallmarks of AIDS. These OIs, and many more, 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 manifestation of AIDS.⁴

Starting in the late 1980s, the use of chemoprophylaxis, immunization, and better strategies for managing OIs improved quality of life and lengthened survival of people with HIV.⁵ Early antiretroviral drugs and treatment strategies added further benefit.⁶ However, the introduction of highly effective combination ART in the mid-1990s has most profoundly reduced OI-related morbidity and mortality in people with HIV.⁷⁻¹³

Despite the availability of multiple safe, effective, and simple ART regimens that, when used widely, have led to corresponding population-level declines in the incidence of OIs,^{11,14,15} the Centers for Disease Control and Prevention (CDC) estimates that more than 13% of people with HIV are unaware of their HIV infection and that 34% of Americans who are aware of their HIV infection are not effectively virally suppressed.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 thus preventing or substantially reducing the incidence of HIV related OIs, remains challenging for three main reasons:

- *Not all HIV infections are diagnosed, and once diagnosed many persons have already experienced substantial immunosuppression.* CDC estimates that in 2019, among those with diagnosed HIV, approximately 20% had a CD4 T lymphocyte (CD4) cell count <200 cells/mm³ (or <14%) at the time of diagnosis.¹⁶
- *Not all persons with diagnosed HIV receive timely continuous HIV care or are prescribed ART.* CDC estimates that in 2019, 81% of people with newly diagnosed HIV had been linked to care within 1 month. Among people with HIV, only 58% were adequately engaged in continuous care.¹⁶
- *Not all persons greater than 13 years old treated for HIV achieve durable viral suppression.* CDC estimates that in 2019, only 68% of persons had durable viral suppression within 6 months of HIV diagnosis.¹⁷ Causes for the suboptimal response to treatment include poor adherence, unfavorable pharmacokinetics, or unexplained biologic factors.^{18,19}

Thus, some people with HIV infection will continue to present with an OI as the sentinel event leading to a diagnosis of HIV infection or present with an OI as a complication of unsuccessful viral suppression.¹⁷

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.²⁰⁻²⁶

When certain OIs occur—most notably tuberculosis and syphilis—they can increase plasma viral load,²⁷⁻³¹ which both accelerates HIV progression and increases the risk of HIV transmission if patients are not virally suppressed by ART.

Thus, 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.³² 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 1993.³³ 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 CDC, and the HIV Medicine Association of the Infectious Diseases Society of America (HIVMA/IDSA) now jointly co-sponsor these guidelines,^{1,34,35} which have been published in peer-reviewed journals and/or the MMWR in 1997, 1999, and 2002.³⁵⁻⁴⁴ Since 2009, the 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.

Data regarding the use of these guidelines demonstrate that the document is a valuable reference for HIV health care providers. In 2021, there were approximately 417,000 page views of the online version of the guidelines, and approximately 19,600 PDF downloads.

All guideline recommendations regarding therapy and prevention are rated in terms of the quality of supporting evidence; comments about diagnosis are not rated. These ratings allow readers to assess the relative importance of each recommendation. This document focuses on adults and adolescents; recommendations for children with HIV can be found in separate documents on the [Clinicalinfo](#) website.

These guidelines are intended for clinicians, other health care providers, patients 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.

Snapshot of Guidelines Development Process

These guidelines were prepared by the OI Working Group under the auspices of the NIH 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. Briefly, co-editors who are selected and appointed by their respective agencies or organizations (i.e., NIH, CDC, IDSA) convene OI-specific working groups of clinicians and scientists with subject matter expertise in those specific

OIs. The co-editors appoint a leader for each working group. The working groups review in real time the relevant literature published since the last review of the guidelines and, if indicated, propose revised recommendations, which are then presented to the co-editors and other working group leaders. The co-editors and working group leaders have a teleconference quarterly to determine changes in each section that are indicated. The co-editors also convene a meeting with panel members each year to review progress and set an agenda for the coming year. Final guidelines revisions posted on the Clinicalinfo website may include additional changes made by the co-editors under the advisement of OARAC.

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-editors who represent the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Disease Society of America (HIVMA/IDSA), plus Panel members with expertise in HIV clinical care, infectious disease management, and research. Co-editors are appointed by their respective agencies or organizations. Panel members are selected from government, academia, and the health care community by the co-editors and assigned to a working group for one or more of the guideline sections based on the member's area of subject matter expertise. Each working group is chaired by a Panel member selected by the co-chairs. 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-editors 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-editors 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-editors strive to ensure that 50% or more of the members of each working group have no conflicts of interest.
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 NIH Office of AIDS Research Advisory Council (OARAC). See Appendix B: Panel Roster and Financial Disclosures .
Funding source	The 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. Panel members of each working group are responsible for identifying relevant literature, conducting a systematic comprehensive review of that literature, and proposing updates to the guidelines based on the literature review.

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. Aspects of evidence that are considered include but are not necessarily limited to the type of study (e.g., case series, prospective cohort, randomized controlled trial), 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-editors and subject matter experts at CDC 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-editors and reviewed by OAR and CDC 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 infection. These guidelines are also available on the Clinicalinfo website.
Update plan	Each working group leader and the co-editors 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; by new information regarding indications or dosing; by new safety or efficacy data; or by other information that may affect prevention and treatment of HIV-related OIs. In the event of new data of clinical importance, the Panel may post an interim announcement on the Clinicalinfo website pending update of the guidelines with the appropriate changes.

How to Use the Information in these Guidelines

Recommendations in this report address:

1. Preventing exposure to opportunistic pathogens;
2. Preventing disease;
3. Discontinuing primary prophylaxis after immune reconstitution;
4. Treating disease;
5. When to start ART in the setting of an acute OI;
6. Monitoring for adverse effects (including immune reconstitution inflammatory syndrome [IRIS]);
7. Managing treatment failure;
8. Preventing disease recurrence (secondary prophylaxis or chronic maintenance therapy);
9. Discontinuing secondary prophylaxis or chronic maintenance therapy after immune reconstitution; and
10. 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. In cases where there are no data for the prevention or treatment of an OI 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.

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

This document also includes tables in each section pertinent to the prevention and treatment of the OI(s) in that section, as well as seven summary tables at the end of the document (Tables 1–7) and a figure of the latest Advisory Committee of Immunization Practices immunization recommendations adapted to adults and adolescents with HIV.

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. Palella FJ, Jr., Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998;338(13):853-860. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9516219>.
6. 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>.
7. 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>.
8. 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>.
9. 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>.
10. 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>.
11. 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>.

12. 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>.
13. 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>.
14. 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>.
15. 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>.
16. Centers for Disease Control and Prevention. HIV surveillance report: diagnoses of HIV infection in the United States and dependent areas, 2019. 2021. Available at: <http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html>. Accessed: April 1, 2022.
17. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2019. 2021. Available at: <https://www.cdc.gov/hiv/pdf/library/reports/surveillance/cdc-hiv-surveillance-report-vol-26-no-2.pdf>. Accessed: April 1, 2022.
18. Panel on Antiretroviral Guidelines for Adults and Adolescents. Limitations to treatment safety and efficacy. *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV*. 2022. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines>.
19. 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>.
20. 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>.
21. 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>.
22. 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>.
23. 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>.
 24. 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>.
 25. 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>.
 26. 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>.
 27. 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>.
 28. 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>.
 29. 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>.
 30. 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>.
 31. 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>.
 32. 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>.
 33. 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>.
34. 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>.
 35. 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>.
 36. 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>.
 37. 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>.
 38. Kaplan JE, Masur H, Holmes KK, USPHS, 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>.
 39. 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>.
 40. 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>.
 41. 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>.
 42. 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>.
 43. 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>.

44. Antiretroviral therapy and medical management of pediatric HIV infection and 1997 USPHS/IDSA report on the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *Pediatrics*. 1998;102(4 Pt 2):999-1085. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9826994>.

Bacterial Enteric Infections

Updated: April 12, 2022

Reviewed: January 11, 2023

Epidemiology

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 decline among people with HIV when treated with antiretroviral therapy (ART).¹⁻⁷ The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) count⁵ and is greatest in individuals with clinical AIDS or CD4 counts <200 cells/mm³. The bacteria most frequently isolated by culture from adults with HIV in the United States are *Salmonella* (particularly *Salmonella enterica* serotypes Typhimurium and Enteritidis), *Shigella*, and *Campylobacter*. Diarrheagenic *Escherichia coli*, particularly enteroaggregative *E. coli*, may contribute to the burden of diarrheal disease,⁸ but their role is understood poorly because diagnosis remains a research-only test. *Clostridioides difficile*-associated infection (CDI) is common in people with HIV; data⁹ suggest that low CD4 count (<50 cells/mm³) is an independent disease risk factor in addition to traditional risk factors, such as exposure to a health care facility or to antibiotics. Incidence of community-onset CDI is increasing, and health care providers also should consider CDI in the evaluation of outpatient diarrheal illnesses in people with HIV. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in people with HIV. Other enteric infections that may cause diarrhea—such as *Mycobacterium avium* complex (MAC) and cytomegalovirus—are discussed elsewhere in these guidelines.

As with bacterial enteric infections in HIV-uninfected persons, the probable source for most bacterial enteric infections in people with HIV is ingestion of contaminated food or water.³ Sexual activity with the potential for direct or indirect fecal-oral exposure also increases risk of infections, especially with *Shigella*¹⁰ and *Campylobacter*.¹¹ HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase the risk of enteric bacterial infections.

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.¹²⁻¹⁵

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.^{1,3,4,16} Relapses in infection with *Salmonella* and other Gram-negative bacterial enteric pathogens after appropriate treatment have been well documented in people with HIV.¹⁷⁻¹⁹

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (i.e., ingestion of contaminated food or water, sexual history or other fecal-oral exposures, 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, 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]). Although stool molecular methods rapidly diagnose enteric infections, stool cultures are required to obtain phenotypic antibiotic sensitivity testing for isolated enteric pathogens. Thus, the Centers for Disease Control and Prevention recommends reflex stool cultures and antibiotic sensitivity testing for specimens with positive CIDT reports given increasing resistance detected in enteric bacterial infections.²⁰ 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.

Other infections for which people with HIV are at risk, albeit at a lower rate, are non-*jejuni*, non-*coli* *Campylobacter* species—such as *C. fetus*, *C. upsaliensis*, and *C. lari*—and the enterohepatic *Helicobacter* spp. (*H. cinaedi* 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. Patient populations at risk for *C. difficile* diarrhea include patients 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/mm³, those taking acid-suppressive medications, and those with moderate-to-severe community-acquired diarrhea.²¹ Only patients with diarrhea (defined as three or more loose stools in 24 hours) should be tested for *C. difficile* to limit detection of asymptomatic colonization, and only stool samples that take the shape of the container (i.e., diarrheal) should be tested for *C. difficile* toxin B. 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. EIAs suffer from low sensitivity, whereas polymerase chain reaction (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.²² Based on the criteria above (i.e., patient 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 (SHEA) guidelines for *C. difficile* infection 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.²³

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). Some sexually transmitted rectal infections (e.g., proctitis due to lymphogranuloma venereum, *Neisseria gonorrhoeae*, or *Treponema pallidum*) can produce symptoms similar to colitis due to *Salmonella*, *Shigella*, and *Campylobacter* spp. infection. If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, [diagnostic evaluation for STIs](#) with anoscopy, culture, and biopsy and NAATs should be considered.

Preventing Exposure

Multiple epidemiologic exposures can place people at risk of 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/mm³ or a history of AIDS-defining illness²⁴ are at the greatest risk of enteric illnesses⁵; however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Individuals 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 after potential contact with human feces (e.g., through defecation, cleaning feces from infants, contact with a person who has diarrhea), after handling pets or other animals, after gardening or other contact with soil, before preparing food and eating, and before and after sex (**AIII**). People with HIV should avoid unprotected sex practices—such as anal sex and oral-anal contact—that could result in oral exposure to feces and, in addition to handwashing, they should be advised to use barriers—such as [dental dams](#)—during sex to reduce exposures when possible (**AIII**). Avoiding sex while any partner has diarrhea may further reduce risk of transmission.

Preventing Disease

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 with rifaximin, azithromycin, or fluoroquinolones can be considered—such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration (**CIII**).²⁵ Because of toxicities associated with fluoroquinolone use (e.g., *C. difficile* infection, tendinitis) and the risk for antibiotic resistance, use of fluoroquinolones for prophylaxis is discouraged.

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 (**BIII**). For pregnant people, azithromycin would be the preferred agent for prophylaxis (**BIII**). Risk of toxicity should be considered before prophylaxis with TMP-SMX is

initiated solely because of travel. Clinicians should be aware of new concerns about fluoroquinolone safety.²⁶

Treating Disease

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 (**BIII**). The effectiveness and safety of probiotics or antimotility agents have not been studied adequately in people with HIV who have diarrheal illnesses.²⁷ Antimotility agents should be avoided if concern about inflammatory diarrhea, including CDI, exists (**BIII**).

After obtaining stool samples for diagnostic evaluation, 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/mm³ who have had 1 day 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 5 days, [**BIII**]) may be indicated in people with HIV and CD4 counts of 200 to 500 cells/mm³ who have diarrhea severe enough to compromise quality of life or ability to work. Patients with advanced HIV disease (i.e., CD4 counts <200 cells/mm³ or concomitant AIDS-defining illness) and clinically severe diarrhea (i.e., six or more 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 diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment. Empiric therapy with ciprofloxacin is acceptable, particularly if the infection is not associated with international travel (**AIII**). In patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when clinical judgment indicates severity of disease, hospitalization and treatment with IV antibiotic therapy should be considered. In this scenario, IV ceftriaxone or IV cefotaxime are alternative antibiotic therapies (**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 can be considered in the differential diagnosis.

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.^{28,29} 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.³⁰⁻³⁴

Pathogen-Specific Therapy

***Salmonella* spp.**

Immunocompetent hosts who do not have HIV often do not require 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 7 times compared to people who do not have HIV.^{1,35}

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone (**AIII**). Ciprofloxacin is the preferred agent³⁶ (**AIII**). Other fluoroquinolones—such as levofloxacin and moxifloxacin—likely would be effective in treating salmonellosis in people with HIV, but they have not been well evaluated in clinical studies (**BIII**). Depending on antibiotic susceptibility, alternatives to the fluoroquinolones might include TMP-SMX or expanded-spectrum cephalosporins, such as ceftriaxone or cefotaxime (**BIII**).

The optimal duration of therapy for HIV-related *Salmonella* infection has not been defined. For patients with CD4 counts ≥ 200 cells/mm³ who have mild gastroenteritis without bacteremia, 7 to 14 days of treatment is reasonable. For the same patients with bacteremia, 14 days is appropriate provided clearance of bacteremia is documented. Longer treatment is suggested if bacteremia persists or if the infection is complicated; that is, if metastatic foci are present (**BIII**). For patients with advanced HIV disease (CD4 count < 200 cells/mm³), 2 to 6 weeks of antibiotics is often recommended (**CII**).³⁷

People with HIV and *Salmonella* bacteremia, which typically occurs in those with advanced HIV disease, should be monitored clinically for recurrence after treatment (**BIII**). Recurrence may present as bacteremia or as an anatomically localized infection, including intra-abdominal, 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/mm³ 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,³⁸ and HIV suppression with ART appears to decrease the risk of recurrent illnesses.³⁹

In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts > 200 cells/mm³, secondary prophylaxis for salmonellosis probably can be discontinued (**CII**).⁷ Clinicians also should be aware that recurrence may indicate development of antimicrobial resistance during therapy.

***Shigella* spp.**

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/mm³ whose diarrhea resolves before culture confirmation of *Shigella* infection. When treatment is offered, antibiotic selection should be guided by the results of antibiotic susceptibility testing.³⁶

The recommended treatment for shigellosis is a fluoroquinolone, preferably ciprofloxacin, for 7 to 10 days (**AIII**) with levofloxacin or moxifloxacin serving as alternatives (**BIII**). Although current Clinical and Laboratory Standards Institute criteria categorize *Shigella* isolates with ciprofloxacin minimum inhibitory concentration (MIC) 0.12 to 1 ug/mL as fluoroquinolone susceptible, these isolates may harbor plasmid-mediated resistance genes. Until the clinical significance of these findings can be determined, fluoroquinolones should be used to treat only isolates with MIC <0.12 ug/mL.⁴⁰

Ciprofloxacin-resistant *S. sonnei* and *S. flexneri* have been reported in the United States and 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.³⁴ Depending on antibiotic susceptibilities, alternative agents might include TMP-SMX (7–10 days) or azithromycin (5 days) (**BIII**). Azithromycin has not been evaluated in people with HIV and shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.⁴⁰

Azithromycin susceptibility testing, however, is not widely available in clinical laboratories but can be performed by many state public health laboratories. An estimated 36% of *Shigella* spp. isolated among the general U.S. population in 2018 was resistant to azithromycin, and azithromycin-resistant *Shigella* spp. infections in MSM with HIV have been reported recently.^{41–44} Treatment for patients with *Shigella* bacteremia is less well defined, but extending treatment to at least 14 days is reasonable (**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/mm³, in which case, extending antimicrobial therapy for up to 6 weeks is reasonable (**BIII**). As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent shigellosis.

***Campylobacter* spp.**

The optimal treatment of campylobacteriosis in people with HIV is defined poorly. Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended (**BIII**). Rates of resistance to antimicrobial agents differ by *Campylobacter* species. 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% of isolates were resistant to fluoroquinolones, and 13.3% were resistant to azithromycin.⁴⁴

For patients with mild disease and CD4 counts >200 cells/mm³, some clinicians opt to withhold therapy 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 a reasonable approach (**BIII**). Azithromycin has not been evaluated in people with HIV and campylobacteriosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.²⁸ 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**). Azithromycin is **not recommended** for treatment of *Campylobacter* bacteremia (**AIII**). Adding a second active agent—such as an aminoglycoside—may be prudent in these patients to limit the emergence of antibiotic resistance (**BIII**). Antibiotic choice should be guided by antibiotic susceptibility tests. 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 patients with CD4 counts <200 cells/mm³. 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.

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. 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^{23,45} and should be consulted for further information.

Treatment of an Initial Episode of CDI

Four randomized clinical trials all conducted in the general population (two identical studies with ~60% hospitalized patients; two studies restricted to hospitalized patients)⁴⁶⁻⁴⁹ 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).⁴⁵ Fidaxomicin was equivalent to oral vancomycin in initial clinical cure, serious adverse events and all-cause mortality. Given these data, the 2021 IDSA CDI guidelines update⁴⁵ for adults suggests treatment with fidaxomicin (**AI**), rather than oral vancomycin, for initial CDI (see the table below) whether CDI is severe or nonsevere. Fidaxomicin remains very expensive but should be considered in people with HIV and CDI, if available. 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.^{50,51} Thus, metronidazole is to be considered as an alternative drug for CDI therapy only if access to either fidaxomicin or vancomycin is limited (see the table below) and CDI is nonsevere (white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL) (**CI**).²³

Treatment of Recurrent CDI

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.^{23,45} 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,⁴⁶⁻⁴⁹ the 2021 IDSA CDI guidelines update⁴⁵ suggests treatment of adults with recurrent CDI with fidaxomicin (**AI**), rather than oral vancomycin (see the table below). 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 episode, 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 (**AI**).

Bezlotoxumab (FDA approved in 2016) 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 guidelines update suggests use of bezlotoxumab as a co-intervention along with vancomycin as the SOC antibiotic in patients with a history of CDI in the last 6 months and/or other risk factors for recurrence (**CI**).⁴⁵ However, data on the benefit of bezlotoxumab therapy when fidaxomicin is used as the SOC antibiotic are limited (**CIII**). 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 (**CIII**).⁵² However, it is important to

note that complications of FMT, including transmission of enteric pathogens and antibiotic-resistant bacteria with deaths, have been reported.⁵³ FMT for treatment of recurrent CDI may be considered after three total CDI episodes (initial and two recurrent CDI episodes) (**CIII**).^{23,45} The effect of ART on recurrence of CDI is unknown but, similar to other enteric infections, ART initiation should follow standard guidelines (see the Special Considerations with Regard to Starting ART section below).

Special Considerations with Regard to Starting ART

ART initiation should follow standard guidelines. The presence of an enteric infection should not delay ART initiation (**BIII**). 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 IRIS)

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 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.

Observational studies suggest that plasma drug concentrations in people with HIV may be decreased as a result of diarrhea or malabsorption.⁵⁴ 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. 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 (IRIS) has not been described in association with treatment for 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

The diagnosis of bacterial enteric infection in pregnant people with HIV is the same as in people who are not pregnant and should be managed the same, 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**).⁵⁵ Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating

quinolone use in pregnant people did not find an increased risk of birth defects or musculoskeletal abnormalities.⁵⁶⁻⁵⁸ Thus, quinolones can be used for bacterial enteric infections in pregnant people with HIV if indicated by susceptibility testing or failure of first-line therapy, as listed above **(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)**.⁵⁹⁻⁶¹ However, a recent review of potential risks related to TMP-SMX use cites the low quality of current data and supports the use of TMP-SMX in pregnant people with HIV as clinically indicated.⁶² 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, these can be used in pregnancy as in nonpregnant individuals. Limited data are available on the risks of vancomycin use during pregnancy; however, 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,⁶³ it should be noted that with intravenous use, vancomycin readily crosses the placenta.⁶⁴ 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.⁶⁴ A recent review of metronidazole use in pregnancy for treatment of trichomoniasis or bacterial vaginosis found no increase in risk of birth defects.⁶⁵ Studies on the use of metronidazole for CDI in pregnancy were not found.

Recommendations for Preventing and Treating Bacterial Enteric Infections
Preventing Bacterial Enteric Illness
<ul style="list-style-type: none"> 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, azithromycin, or fluoroquinolones can be considered (CIII). Because of toxicity associated with fluoroquinolone use (e.g., bacterial resistance, CDI, tendinitis), use of fluoroquinolones for prophylaxis is discouraged. For patients already on TMP-SMX for prophylaxis against <i>Pneumocystis</i> pneumonia, TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to rifaximin, azithromycin, or fluoroquinolones (BIII). For pregnant people, azithromycin is the preferred agent for prophylaxis (BIII).
General Considerations When Managing Patients with Bacterial Enteric Infections
<ul style="list-style-type: none"> 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 will facilitate antibiotic susceptibility testing among these patients. Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/mm³. 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. 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 count 200–500 cells/mm³, with diarrhea severe enough to compromise quality of life or ability to work

Preferred Therapy

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

For people with advanced HIV (CD4 count <200 cells/mm³ or concomitant AIDS-defining illnesses) and clinically severe diarrhea (≥6 liquid stools/day or bloody stool and/or accompanying fever or chills)

Preferred Therapy

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

Alternative Therapy

- Ceftriaxone IV 1 g every 24 hours **(BIII)**, or
- Cefotaxime IV 1 g every 8 hours **(BIII)**

Note: 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 reasonable.

IV antibiotic therapy with hospitalization should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, blood pressure instability, and/or when clinical judgment indicates severity of disease.

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.

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.

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 7-fold) compared with people without HIV **(AIII)**.

Preferred Therapy for Salmonella Gastroenteritis with or Without Bacteremia

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

Alternative Therapy

- Levofloxacin 750 mg (PO or IV) every 24 hours **(BIII)**, or
- Moxifloxacin 400 mg (PO or IV) every 24 hours **(BIII)**

Alternatives to fluoroquinolone may include one of the following:

- Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) every 12 hours **(BIII)**, or
- Ceftriaxone IV 1 g every 24 hours **(BIII)**, or
- Cefotaxime IV 1 g every 8 hours **(BIII)**

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count >200 cells/mm³: 7–14 days **(BIII)**
- If CD4 count <200 cells/mm³, particularly if the primary illness was severe: 2–6 weeks **(BIII)**

Duration of Therapy for Gastroenteritis with Bacteremia

- If CD4 count >200 cells/mm³: 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/mm³: 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.

Some experts recommend secondary prophylaxis for the following:

- Patients with recurrent bacteremia, or
- Patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm³ and severe diarrhea **(BIII)**

When to Stop Secondary Prophylaxis

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm³ **(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/mm³ whose diarrhea resolves before culture confirmation of *Shigella* infection **(CIII)**.

Preferred Therapy

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours if MIC <0.12 ug/mL (see Note) **(AIII)**

Alternative Therapy (Depending on Susceptibility Results)

- Levofloxacin 750 mg (PO or IV) every 24 hours **(BIII)**, or
- Moxifloxacin (PO or IV) 400 mg every 24 hours **(BIII)**, or
- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV every 12 hours **(BIII)**, or
- Azithromycin 500 mg PO daily for 5 days **(BIII)** (Note: azithromycin is **not recommended** for *Shigella* bacteremia **[AIII]**)

Duration of Therapy

- Gastroenteritis: 7–10 days **(AIII)** (except azithromycin, treat for 5 days)
- Bacteremia: ≥14 days **(BIII)**
- Recurrent infections: up to 6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy

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

Note: Increased resistance of *Shigella* to fluoroquinolones is occurring globally and in the United States. Avoid treating *Shigella* with fluoroquinolones if ciprofloxacin MIC is ≥ 0.12 ug/mL even if the laboratory identifies the isolate as sensitive. Many *Shigella* strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of *Shigella* isolates from individuals with HIV should be performed routinely. Azithromycin susceptibility testing is not widely available in clinical laboratories but can be performed by many state public health laboratories.

Treating Campylobacteriosis

- Optimal treatment is defined poorly.
- The rate of fluoroquinolone resistance in the United States is increasing (28.5% resistance in 2018 among *C. jejuni* isolates).
- Antimicrobial therapy should be modified based on susceptibility reports.

Mild Disease if CD4 Count >200 cells/mm³

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

Mild to Moderate Disease

Preferred Therapy

- Azithromycin 500 mg PO daily for 5 days (**BIII**) (**Not recommended** for bacteremia [**AIII**]), or
- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days (**BIII**) (if susceptible)

Alternative Therapy (Depending on Susceptibility Results)

- Levofloxacin 750 mg PO or IV every 24 hours (**BIII**), or
- Moxifloxacin 400 mg PO or IV every 24 hours (**BIII**)

Bacteremia

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (**BIII**) plus an aminoglycoside (**BIII**) in bacteremic patients to limit the emergence of antibiotic resistance

Duration of Therapy

- Gastroenteritis: 7–10 days, except for 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**)

Treating *Clostridioides difficile*-associated Infection (CDI)

Preferred Therapy (Severe or Nonsevere CDI)*

- Fidaxomicin 200 mg (PO) 2 times per day for 10 days (**AI**)
- Vancomycin 125 mg (PO) 4 times per day for 10 days (**AI**)
- For severe, life-threatening CDI, see text and references for additional information.

*Alternative Therapy for Nonsevere CDI**

- If fidaxomicin or vancomycin access is limited and if CDI is nonsevere, outpatient disease: metronidazole 500 mg PO 3 times per day for 10 days **(CII)**.

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

Recurrent CDI

- Treatment is the same as in patients without HIV infection (see text and references). Use of bezlotoxumab **(CIII)** or FMT **(CIII)** may be successful and safe to treat recurrent CDI in people with HIV although recent concerns have been raised (discussed in text).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CDI = *Clostridioides difficile*-associated infection; FMT = fecal microbiota therapy; IV = intravenously; MIC = minimum inhibitory concentration; PCR = polymerase chain reaction; PO = orally; TMP-SMX = trimethoprim-sulfamethoxazole

* 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

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.

References

1. 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>.
2. Sorvillo FJ, Lieb LE, Waterman SH. Incidence of campylobacteriosis among patients with AIDS in Los Angeles County. *J Acquir Immune Defic Syndr*. 1991;4(6):598-602. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2023099>.
3. 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>.
4. Nelson MR, Shanson DC, Hawkins DA, Gazzard BG. Salmonella, Campylobacter and Shigella in HIV-seropositive patients. *AIDS*. 1992;6(12):1495-1498. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1362879>.
5. 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>.
6. Wilcox CM, Saag MS. Gastrointestinal complications of HIV infection: changing priorities in the HAART era. *Gut*. 2008;57(6):861-870. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18203808>.
7. 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>.
8. 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>.
9. 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>.
10. 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>.
11. 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>.
12. Snijders F, Kuijper EJ, de Wever B, van der Hoek L, Danner SA, Dankert J. Prevalence of Campylobacter-associated diarrhea among patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1997;24(6):1107-1113. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9195065>.

13. 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>.
14. Tee W, Mijch A, Wright E, Yung A. Emergence of multidrug resistance in Campylobacter jejuni isolates from three patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21(3):634-638. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8527556>.
15. Meier PA, Dooley DP, Jorgensen JH, Sanders CC, Huang WM, Patterson JE. Development of quinolone-resistant Campylobacter fetus bacteremia in human immunodeficiency virus-infected patients. *J Infect Dis*. 1998;177(4):951-954. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9534967>.
16. 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>.
17. 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>.
18. Mayer KH, Hanson E. Recurrent salmonella infection with a single strain in the acquired immunodeficiency syndrome. confirmation by plasmid fingerprinting. *Diagn Microbiol Infect Dis*. 1986;4(1):71-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3510806>.
19. Rubino S, Spanu L, Mannazzu M, et al. Molecular typing of non-typhoid Salmonella strains isolated from HIV-infected patients with recurrent salmonellosis. *AIDS*. 1999;13(1):137-139. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10207558>.
20. 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>.
21. 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>.
22. Brecher SM, Novak-Weekley SM, Nagy E. Laboratory diagnosis of Clostridium difficile infections: there is light at the end of the colon. *Clin Infect Dis*. 2013;57(8):1175-1181. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23788237>.
23. 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>.
24. 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>.

25. Advice for travelers. *Med Lett Drugs Ther.* 2019;61(1582):153-160. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31599872>.
26. 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>.
27. 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>.
28. 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>.
29. 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>.
30. Lubbert C, Straube L, Stein C, et al. Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae in international travelers returning to Germany. *Int J Med Microbiol.* 2015;305(1):148-156. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25547265>.
31. 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>.
32. Johnning A, Kristiansson E, Angelin M, et al. Quinolone resistance mutations in the faecal microbiota of Swedish travellers to India. *BMC Microbiol.* 2015;15:235. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26498929>.
33. 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>.
34. 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.
35. 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>.
36. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis.* 2001;32(3):331-351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11170940>.

37. 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>.
38. Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Recomm Rep*. 1992;41(RR-17):1-19. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1361652>.
39. 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>.
40. 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>.
41. 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>.
42. 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>.
43. 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>.
44. Centers for Disease Control and Prevention. National Antimicrobial Resistance Monitoring System (NARMS) Now: Human Data. 2021. Available at: <https://wwwn.cdc.gov/narmsnow/>.
45. 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>.
46. 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>.
47. 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>.
48. 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>.

49. 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>.
50. 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>.
51. 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>.
52. 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>.
53. 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>.
54. 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>.
55. 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>.
56. 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>.
57. Schaefer C, Amoura-Elfant 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>.
58. 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>.
59. 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>.
60. 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>.

61. 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>.
62. 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>.
63. 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>.
64. 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>.
65. 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

Updated: June 11, 2021

Reviewed: January 11, 2023

Epidemiology

Bartonella species cause infections that include cat scratch disease (CSD), 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 (<https://www.bacterio.net/genus/bartonella>);¹⁴ *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/mm³. In patients with HIV, bartonellosis is often a chronic illness, lasting for months to more than a year, with bacillary angiomatosis (BA) lesions and intermittent bacteremia. Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in patients 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. Control of cat flea infestation and avoidance of 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/mm³ 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 (<https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10486>) and is available at some state health laboratories. In addition, several private laboratories offer serological testing, but the performance characteristics of these tests have not been validated for patients 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 resolution⁸ 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 chocolate agar), and they have 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, polymerase chain reaction (PCR) amplification methods (using universal and/or specific primers) for tissue samples are increasingly available through private laboratories, as well as the CDC (<https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10365>) and may aid in diagnosis of *Bartonella* in freshly biopsied tissue samples (such as BA skin lesions, lymph node biopsies, cardiac valves, or other vascular lesions) or whole blood.^{8,10} 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.

In summary, diagnosis of bartonellosis may require multiple testing modalities, including serologic testing (which is the most accessible test, and helpful both for diagnosis and subsequent monitoring, when positive), histopathology, and 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/mm³), 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**). Patients 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**). Patients 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. Patients who are homeless or in marginal housing should be informed that body louse infestation can be associated with serious illness and provided with appropriate measures to eradicate body lice, if present (**AII**). Regardless of CD4 count, patients with HIV and solid organ transplantation may be at risk of developing more severe *Bartonella* infections, similar to transplant recipients without HIV.¹¹

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

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 reports¹² 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**).¹³

Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis (**AII**).¹⁴ Quinolones and trimethoprim-sulfamethoxazole (TMP-SMX) have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended (**AIII**).

Special Consideration with Regard to Starting ART

The potential exists for immune reconstitution inflammatory syndrome (IRIS) in association with bartonellosis and antiretroviral therapy (ART) in persons with HIV. In ART-naïve 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**).

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

Because of the propensity for relapse of *Bartonella* infection, patients should have anti-*Bartonella* IgG antibody titers checked at the time of diagnosis (diluted to endpoint) and, if positive, should be followed with sequential titers every 6 to 8 weeks during treatment, preferably until 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 (ARV) 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 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 3–4 months of therapy and when the CD4 count remains >200 cells/mm³ on effective ART for ≥ 6 months (**CIII**).⁸ Some specialists would discontinue therapy only if the *Bartonella* titers also have decreased 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.

The approach to diagnosis of *Bartonella* infections in pregnant women is the same as in non-pregnant women. 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 ceftizoxime¹⁵ or ceftriaxone, may have efficacy against *Bartonella* in pregnant women with HIV, 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).

Recommendations for Treating *Bartonella* Infections

Preferred Therapy

For Cat Scratch Disease, 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)

For Infections Involving the CNS

- Doxycycline 100 mg PO or IV every 12 hours +/- rifampin 300 mg PO or IV every 12 hours (AIII)

For Confirmed Bartonella Endocarditis

- (Doxycycline 100 mg IV q12h + 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
- (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) (second line due to potential gentamicin nephrotoxicity as glomerulonephritis frequently complicates *Bartonella* endocarditis)

For Other Severe Infections (Multifocal Disease or with Clinical Decompensation)

- Doxycycline 100 mg PO or IV q12h + rifampin 300 mg PO or IV every 12 hours (BIII), or
- Erythromycin 500 mg PO or IV q6h + rifampin 300 mg PO or IV every 12 hours (BIII)

Note: IV therapy may be needed initially (AIII)

Alternative Therapy for Bartonella Infections (Not for 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

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/mm³ (AIII)

Indications for Discontinuing Long-Term Suppressive Therapy (CIII)

- Received at least 3–4 months of treatment; and
- CD4 count > 200 cells/mm³ for at least 6 months
- Some specialists would discontinue therapy only if *Bartonella* titers have also decreased by fourfold (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 section](#) for dosing recommendations).
- In pregnancy, erythromycin or an alternative macrolide should be used as first-line therapy (**AIII**) rather than doxycycline due to toxicity profile; third-generation cephalosporins may have efficacy but are second line.

Key to Abbreviations: +/- = with or without; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; IV = intravenously; PO = orally; q(n)h = every n hours

References

1. Rose SR, Koehler JE. Chapter 236: Bartonella, including cat-scratch disease. In: Bennett JE, Dolin R, Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Disease*. 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;337:1876-1883. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9407154>.
3. Koehler JE, Glaser CA, Tappero JW. Rochalimaea henselae infection. A new zoonosis with the domestic cat as reservoir. *JAMA*. 1994;271:531-535. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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;37:559-566. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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;51:131-40. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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;13:909-920. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2802010>.
7. Regnery RL, Olson JG, Perkins BA, Bibb W. Serological response to "Rochalimaea henselae" antigen in suspected cat-scratch disease. *Lancet*. 1992;339:1443-1445. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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;53:2773-2776. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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;32:1492-1494. Available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC264025/>.
10. Dumler JS, Carroll KC, Patel R. *Bartonella*. In: Carroll KC, Pfaller MA, Landry M, et al, eds. *Manual of Clinical Microbiology*. 12th ed. Washington, DC: American Society for Microbiology; 2019.
11. Psarros G, Riddell J 4th, 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;91:111-121. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22391473>.
12. Guerra LG, Neira CJ, Boman D, et al. Rapid response of AIDS-related bacillary angiomatosis to azithromycin. *Clin Infect Dis*. 1993;17:264-266. Available at <https://www.ncbi.nlm.nih.gov/pubmed/8399879>.

13. 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;24:254-260. Available at <https://www.ncbi.nlm.nih.gov/pubmed/27885316>.
14. 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;109:449-55. Available at <https://pubmed.ncbi.nlm.nih.gov/3415105>.
15. Riley LE, Tuomala RE. Bacillary angiomatosis in a pregnant patient with acquired immunodeficiency syndrome. *Obstet Gynecol*. 1992;79:818-819. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1565376>.

Candidiasis (Mucocutaneous)

Updated: May 26, 2020

Reviewed: January 11, 2023

Epidemiology

Oropharyngeal and esophageal candidiasis are common in patients with HIV infection.^{1,2} The vast majority of such infections are caused by *Candida albicans*, *although infections caused by non-C. albicans species have also been reported in recent years worldwide.*³⁻⁶ The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm³, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.^{1,2} In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy, adult women and does not suggest HIV infection. The advent of antiretroviral therapy (ART) has led to a dramatic decline in the prevalence of oropharyngeal and esophageal candidiasis and a marked diminution in cases of refractory disease.

Fluconazole (or azole) resistance is predominantly the consequence of previous exposure to fluconazole (or other azoles), particularly repeated and long-term exposure.⁷⁻⁹ In this setting, the vast majority of cases relate to acquisition of *C. albicans* resistance; however, prior exposure to azole therapy has also been associated with a gradual emergence of non-*C. albicans* species, particularly *Candida glabrata*, as a cause of refractory mucosal candidiasis in patients with advanced immunosuppression and low CD4 counts.^{7,10}

Clinical Manifestations

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, oropharyngeal mucosa, or tongue surface. Lesions can be easily 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 patients with HIV who have oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in patients 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 women with HIV infection, Candida vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In women with advanced immunosuppression, episodes may be more severe and recur more frequently. In contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common and when it occurs, it is uncommonly refractory to azole therapy unless caused by non-C. albicans species.

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.

The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy, or visualization of lesions plus fungal smear or brushings without histopathologic examination. 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 the 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.

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

Data from prospective controlled trials indicate that fluconazole can reduce the risk of mucosal disease (i.e., oropharyngeal, esophageal, and vulvovaginal disease) in patients with advanced HIV.¹¹⁻¹⁴ However, 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. Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* strains and introduce significant drug-drug interactions. In addition, long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII)**. Administration of ART and immune restoration is an effective means to prevent disease.

Treating Disease

Oropharyngeal Candidiasis

Oral fluconazole is as effective as or superior to topical therapy for oropharyngeal candidiasis. In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Moreover, oral therapy has the additional benefit over topical regimens in being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy (**AI**). One to 2 weeks of therapy is recommended for oropharyngeal candidiasis; 2 to 3 weeks of therapy is recommended for esophageal disease.¹⁵

Using topical agents to treat oropharyngeal candidiasis reduces systemic drug exposure, diminishes the risk of drug-drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. Unfavorable taste and multiple daily dosing, such as in the cases of clotrimazole and nystatin, may lead to decreased tolerability of topical therapy. 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.¹⁶ Nystatin suspension or pastilles four times daily remains an additional alternative (**BI**).¹⁷ Topical, low-concentration gentian violet (0.00165%) applied twice daily may be an alternative, well-tolerated (i.e., without mucosal staining), and cost-effective regimen to nystatin suspension (**BI**).¹⁸

Itraconazole oral solution for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated (**BI**).¹⁷ Posaconazole oral suspension¹⁹ is also as effective as fluconazole and generally better tolerated than itraconazole solution, although both posaconazole and itraconazole have more drug-drug interactions than fluconazole (**BI**). Both antifungals are alternatives to oral fluconazole, although few situations require that these drugs be used in preference to fluconazole solely to treat mucosal candidiasis. In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.¹⁹ A new solid oral delayed-release tablet formulation of posaconazole, which exhibits less variable absorption than the oral suspension, is now available.²⁰ Whether it offers any advantage for the treatment of oropharyngeal candidiasis is unknown, and it currently is indicated only for prophylaxis of invasive *Aspergillus* and *Candida* infections.²¹ 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 (**AI**). However, patients with severe symptoms initially may have difficulty swallowing oral drugs. As with oropharyngeal candidiasis, itraconazole capsules for esophageal candidiasis are less effective than fluconazole because of variable absorption (**CII**). A 2-week course of the newer triazole isavuconazole, given orally at an initial loading dose of 200 mg, followed by 50 mg once daily; or a loading dose of 400 mg followed by 100 mg once daily; or 400 mg once weekly, is also as effective as fluconazole for uncomplicated esophageal candidiasis (**BI**); 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.²² Voriconazole, amphotericin B (either deoxycholate or lipid formulations), and the echinocandins caspofungin, micafungin, and anidulafungin all effectively treat esophageal candidiasis (**BI**); however, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.^{23,24} Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis (**AI**). Although infection with other pathogens (e.g., cytomegalovirus, herpes simplex virus that causes esophagitis) 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, endoscopy is recommended to identify different causes of esophagitis or drug-resistant *Candida* (**AII**).

Vulvovaginal Candidiasis

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

- Oral fluconazole (**AII**)
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) (**AII**)
- Itraconazole oral solution (**BII**)

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for ≥ 7 days (**AII**). For more information, see the [Vulvovaginal Candidiasis](#) section in the [Sexually Transmitted Diseases 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 patients with mucocutaneous candidiasis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed.

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

For most patients 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 patients 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. Periodic monitoring of liver function studies should be considered if azole therapy is anticipated for >21 days, especially in patients with other hepatic comorbidities (**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.

Immune reconstitution inflammatory syndrome (IRIS) with ART has not yet been reported for mucocutaneous candidiasis in patients with HIV infection. Indeed, ART is associated with a markedly reduced incidence of candidiasis.

Managing Treatment Failure

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis after 7 to 14 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of patients with HIV infection who have oral or esophageal candidiasis, typically those with CD4 counts <50 cells/mm³ and who have received multiple courses of azole antifungals.⁸ Confirmatory culture and, in the case of esophageal candidiasis, endoscopy are necessary to confirm 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 patients with azole-refractory oropharyngeal or esophageal candidiasis (**AI**).²⁵ Again, although the

new solid delayed-release tablet formulation of posaconazole has been recently made 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 patients with fluconazole-refractory mucosal candidiasis (**BII**).¹⁷ If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin (**BII**), caspofungin (**BII**), micafungin (**BII**), or voriconazole (**BII**).

IV amphotericin B is usually effective for treating refractory disease (**BII**). Both amphotericin B deoxycholate and the lipid preparations of amphotericin B have been used successfully (**BII**). Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension four times daily) is sometimes effective in patients whose oropharyngeal candidiasis does not respond to itraconazole (**BII**), but this product is not commercially available in the United States.

Preventing Recurrence

When to Start Secondary Prophylaxis

A randomized clinical trial¹⁴ in patients with HIV infection with CD4 counts <150 cells/mm³ 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 groups among those receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) for recurrent oropharyngeal or vulvovaginal candidiasis **is not recommended** by most HIV specialists unless patients have frequent or severe recurrences (**BIII**) 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 either oropharyngeal (**BI**), esophageal (**BI**), or vulvovaginal (**BII**) candidiasis.¹¹⁻¹³ Oral posaconazole twice daily is also effective for esophageal candidiasis (**BII**).²⁶ The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in patients with HIV infection who are severely immunocompromised. Several important factors should be considered when making the decision to use secondary prophylaxis. These factors include the effect of recurrences on the patient's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events, and, most importantly, drug-drug interactions.²⁷

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

When to Stop Secondary Prophylaxis

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/mm³ following initiation of ART (**AIII**).

Special Considerations During Pregnancy

Pregnancy increases the risk of vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same in pregnant women as in those who are not pregnant.

Topical therapy is preferable for treatment of oral candidiasis in pregnancy, but is essential for vulvovaginal candidiasis, especially during the first trimester. 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.²⁸⁻³² 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.³³ 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.³⁰ A report from a national cohort register in Denmark found an increased hazard ratio (HR) of 1.48 (95% CI, 1.23–1.77) for spontaneous pregnancy loss with any exposure to oral fluconazole from 7 to 22 weeks of pregnancy compared to unexposed, matched controls.³¹ An increased HR of 1.47 (95% CI, 1.22–1.77) 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; CI 95%, 1.89–8.90) 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 candidal infections (**AIII**). Neonates born to women receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Itraconazole at high doses has been shown to be teratogenic in animals, but the metabolic mechanism accounting for these defects is not present in humans, so the data supporting this finding may not be applicable to human pregnancy. Case series in humans do not suggest an increased risk of birth defects with itraconazole,³⁴ 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. 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. 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.³⁵ Human data are not available for these drugs, thus their use in human pregnancy **is not recommended (AIII)**.

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** in women with HIV who become pregnant (**AIII**).

Recommendations for Treating Mucosal Candidiasis

Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 Days)

Preferred Therapy

- Fluconazole 100 mg PO once daily **(AI)**

Alternative Therapy

- One 10-mg clotrimazole troche PO five times a day **(BI)**, *or*
- 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 product label for more detailed application instructions. **(BI)**, *or*
- Itraconazole oral solution 200 mg PO daily **(BI)**, *or*
- Posaconazole oral suspension 400 mg PO twice daily for 1 day, then 400 mg daily **(BI)**, *or*
- Nystatin suspension 4–6 mL four times daily or 1–2 flavored pastilles four to five times daily **(BII)**, *or*
- Gentian violet (0.00165%) topical application twice daily **(BI)**

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

Note: Systemic antifungals are required for effective treatment of esophageal candidiasis **(AI)**.

Preferred Therapy

- Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)**, *or*
- Itraconazole oral solution 200 mg PO daily **(AI)**

Alternative Therapy

- Voriconazole 200 mg PO or IV twice daily **(BI)**, *or*
- Isavuconazole 200 mg PO as a loading dose, followed by isavuconazole 50 mg PO daily **(BI)**, *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*
- Caspofungin 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)**, *or*
- Amphotericin B deoxycholate 0.6 mg/kg IV daily **(BI)**, *or*
- Lipid formulation of amphotericin B 3–4 mg/kg IV daily **(BIII)**

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

Uncomplicated Vulvovaginal Candidiasis

Preferred Therapy

- Oral fluconazole 150 mg for one dose **(AII)**, *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)**

Alternative Therapy

- Itraconazole oral solution 200 mg PO daily for 3–7 days **(BII)**

- For azole-refractory *Candida glabrata* vaginitis, boric acid 600 mg vaginal suppository once daily for 14 days (BII)

Note: Severe or recurrent vaginitis should be treated with oral fluconazole (100–200 mg) or topical antifungals for ≥7 days (AII).

Chronic Suppressive Therapy

- Chronic suppressive therapy is usually not recommended unless patients have frequent or severe recurrences (BIII).
- If used, it is reasonable to discontinue therapy if CD4 count >200 cells/mm³ (AIII).

If 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)
- Posaconazole oral suspension 400 mg PO twice daily (BII)

Vulvovaginal Candidiasis

- Fluconazole 150 mg PO once weekly (BII)

Other Considerations

- Chronic or prolonged use of azoles might promote development of resistance.
- Systemic azoles may have **significant** drug-drug interactions with ARV drugs and other drugs for treatment of OIs; refer to [Table 4](#) for dosing recommendations. Consider TDM if prolonged use is indicated.

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; IV = intravenous; OI = opportunistic infection; PO = orally; TDM = therapeutic drug monitoring

References

1. 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>.
2. 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>.
3. 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>.
4. 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>.
5. 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>.
6. Clark-Ordóñez I, Callejas-Negrete OA, Arechiga-Carvajal ET, Mourino-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>.
7. 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>.
8. 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>.
9. 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>.
10. 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>.
11. 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>.

12. 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 Bein 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>.
13. 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>.
14. 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>.
15. 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>.
16. 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>.
17. 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>.
18. Mukherjee PK, Chen H, Patton LL, et al. Topical gentian violet compared with nystatin oral suspension for the treatment of oropharyngeal candidiasis in HIV-1-infected participants. *AIDS*. 2017;31(1):81-88. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27677161>.
19. 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>.
20. 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>.
21. Corporation MSD. Posaconazole package insert. 2014. Accessed March 15, 2014. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022003s018s020,0205053s002s004,0205596s001s003lbl.pdf.
22. 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>.
23. 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>.
 24. 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>.
 25. 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>.
 26. 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>.
 27. 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>.
 28. 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>.
 29. 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>.
 30. 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>.
 31. 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>.
 32. 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>.
 33. 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>.

34. 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>.
35. 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>.

Epidemiology

Chagas disease (American trypanosomiasis) is caused by the protozoan parasite *Trypanosoma cruzi*, and transmitted to humans by infected triatomine 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 The hematophagous triatomine vectors defecate during or immediately after feeding on a person. The parasite is present in large numbers in the feces of infected bugs, and enters the human body through the bite wound, or through the intact conjunctiva or other mucous membrane.

Vector-borne transmission occurs only in the Americas, where an estimated 8 to 10 million people have Chagas disease.⁵ 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, and large-scale migration has brought infected individuals to cities both within and outside of Latin America.^{4,6,7}

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.⁸⁻¹⁰ However, the risk of vector-borne infection within the United States appears to be very low, probably because of better housing conditions and less efficient vectors.¹¹ *T. cruzi* also can 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.^{12,13} Currently an estimated 90% of the U.S. blood supply is screened.

For these reasons, the vast majority of the estimated 300,000 individuals in the United States with Chagas disease are thought to be immigrants who acquired the infection while living in endemic areas in Latin America.¹⁴ In patients chronically infected with *T. cruzi* as a result of prior infection, profound immunosuppression (e.g., due to advanced HIV disease) may lead to reactivation disease characterized by parasitemia, associated with increased intracellular parasite replication and lack of immunological control of the infection.¹⁵⁻¹⁷

Clinical Manifestations

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 Romana'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 etiologic treatment, *T. cruzi* infection passes into the chronic phase.^{2,18}

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 them will progress to clinically evident Chagas disease, most commonly cardiomyopathy.^{2,18} 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.^{4,19} Over time, the disease may progress to higher-grade heart block and complex ventricular arrhythmias. In patients with more advanced cardiomyopathy, congestive heart failure, ventricular aneurysm, and complete heart block are poor prognostic signs, associated with high rates of short-term mortality, including sudden death.²⁰ Chagas digestive disease is much less common than cardiomyopathy, and seen predominantly in infected patients

in parts of Brazil and Bolivia.²¹ 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, usually detectable by microscopy, and can occur in the settings of immunosuppressive therapy to prevent transplant rejection and cancer chemotherapy, as well as in HIV-infected patients.^{16,22-26} Even in the absence of symptoms, patients with chronic Chagas disease who are HIV-co-infected have significantly higher levels of *T. cruzi* parasitemia than their immunocompetent counterparts.²⁵ Most cases of clinically apparent reactivation occur in patients with CD4 T lymphocyte cell counts <200 cells/mm³, a history of prior opportunistic infections, or both.¹⁶

The clinical features of reactivated Chagas disease in patients with HIV infection 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).^{15,16,27,28} The presentation may be confused with central nervous system (CNS) toxoplasmosis and should be considered in the differential diagnosis of AIDS patients with CNS symptoms or mass lesions on imaging. The second most frequently reported manifestation of reactivation in HIV-infected patients 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.^{16,29} Less frequent manifestations of reactivation include skin lesions, erythema nodosum, and parasitic invasion of the peritoneum, stomach or intestine.^{16,29}

Diagnosis

Most patients infected with Chagas disease, including those in the United States, are in the chronic phase and typically unaware of their infection. Screening for infection in patients 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 HIV-infected patients 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) are used in parallel to improve the accuracy. 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.^{30,31} Data suggest that the sensitivity of serological assays varies by geographical location, possibly because of *T. cruzi* strain differences and resulting antibody responses.^{32,33} Options for *T. cruzi* serological testing in the United States include diagnostic ELISA kits based on parasite lysate or recombinant antigens.^{30,34} In general, polymerase chain reaction (PCR) is not a useful diagnostic test for chronic *T. cruzi* infection. The sensitivity is highly variable and depends on patient characteristics as well as PCR primers and methods.^{35,36}

In HIV-infected patients with epidemiologic risk factors for Chagas disease, co-infection with *T. cruzi* and reactivation disease should be considered in the differential diagnosis of CNS mass lesions, meningoencephalitis, arrhythmias or heart failure.^{16,26,27} The imaging pattern of brain chagoma is similar to that of cerebral toxoplasmosis, although chagomas tend to be larger than Toxoplasma lesions.^{17,27,28} 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) shows a mild pleocytosis (lymphocyte predominance), increased protein, and *T. cruzi* trypomastigotes.^{16,17,27,28} In a case series that included 15 HIV and *T. cruzi*-co-infected patients with clinical meningoencephalitis, trypomastigotes were visualized in CSF in 85%.^{15,16,27,28}

A definitive diagnosis of re-activation is established by identification of the parasite or its products in tissue, such as on brain biopsy, in CSF or in blood.¹⁶ Circulating parasites are rarely detected microscopically in immunocompetent patients with chronic Chagas disease or in HIV-co-infected patients in the absence of reactivation.²⁵ If observed in an HIV-*T. cruzi*-co-infected patient, circulating parasites suggest reactivation and the need for treatment. Blood concentration techniques, such as capillary centrifugation, can improve sensitivity.³⁷ In centrifuged blood, *T. cruzi* trypomastigotes are found just above the buffy coat. Centrifugation and microscopic examination of CSF also can be employed for patients with suspected CNS Chagas disease. 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.

Conventional PCR is not useful for diagnosing re-activation, because the method can yield a positive result in chronic *T. cruzi* infection in the absence of re-activation.^{35,36} However, quantitative PCR assays (real-time PCR) performed on serial blood specimens that show rising parasite numbers over time provide the earliest and most sensitive indicator of reactivation.^{38,39} 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.⁴⁰

Preventing Exposure

Travelers to endemic countries may be at risk for 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 constructed of adobe brick, mud, or thatch.⁴¹ 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.⁴²

Most blood products in the United States are screened routinely for *T. cruzi* but screening is not universal in the United States or in others areas, including parts of Latin America.⁴³

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

Clinical manifestations of Chagas disease in HIV-positive patients usually represent reactivation and not acute infection with *T. cruzi*. All HIV-infected patients with epidemiologic risk factors for Chagas disease should be tested for antibody to *T. cruzi* to detect latent infection.¹⁸ A single course of treatment with benznidazole or nifurtimox can be considered for *T. cruzi*-infected individuals who have not been previously treated and who do not have advanced Chagas cardiomyopathy (**CIII**). 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.^{31,44} Although direct data are lacking, optimization of antiretroviral therapy (ART) may help prevent Chagas reactivation in co-infected patients (**BIII**). Most symptomatic reactivation cases have occurred in patients who were not taking ART.¹⁶

Treating Disease

Chemotherapy for Chagas disease with benznidazole or nifurtimox is effective in reducing parasitemia and preventing clinical manifestations or slowing progression in patients with acute, early-chronic, and re-activated disease.^{44,45} These drugs have limited efficacy, however, in achieving parasitological cure. Consultation with a specialist should be sought. Benznidazole (5 to 8 mg/kg/day for 30 to 60 days) is the initial treatment most commonly recommended (**BIII**). Nifurtimox (8 to 10 mg/kg/day, administered for 90 to 120 days) is an alternative (**CIII**). The duration of therapy with either of these agents has not been studied in patients co-infected with HIV. Mortality is high for symptomatic reactivated *T. cruzi* infection,

even in patients who receive chemotherapy.^{16,27} Limited data suggest that early recognition and treatment of reactivation may improve prognosis.¹⁶

Benznidazole is approved by FDA for use in children 2–12 years of age and is commercially available at <http://www.benznidazoletablets.com/en/>. Nifurtimox is not currently FDA approved and is available from the Centers for Disease Control and Prevention (CDC) Drug Service for use under an investigational protocol. Consultations and nifurtimox requests should be addressed to Division of Parasitic Diseases and Malaria Public Inquiries line (404-718-4745); parasites@cdc.gov, the CDC Drug Service (404-639-3670), and for emergencies after business hours, on weekends, and federal holidays through the CDC Emergency Operations Center (770-488-7100).

Special Considerations with Regard to Starting Antiretroviral Therapy

As with other parasite infections that localize in the CNS, the decision to initiate antiretroviral therapy (ART) must be carefully considered in HIV-infected patients with 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 as soon as their CNS disease is clinically stable (AIII).

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

Patients undergoing treatment should be monitored closely because both benznidazole and nifurtimox are associated with significant toxicities.⁴⁶ Benznidazole causes peripheral neuropathy, rash, and granulocytopenia. Nifurtimox causes anorexia, nausea, vomiting, abdominal pain and weight loss, restlessness, tremors, and peripheral neuropathy. The adverse effects of both drugs wane when the drugs are discontinued.

As stated above, no reports are available regarding *T. cruzi* infection and IRIS.

Managing Treatment Failure

Although no efficacy data are available, retreatment with benznidazole or nifurtimox is recommended for HIV-infected patients with *T. cruzi* reactivation who fail to respond or who relapse after initial antitrypanosomal therapy (AIII). A publication documents a single case of a *T. cruzi*-infected patient on immunosuppressive therapy for systemic lupus erythematosus who had a good response to posaconazole after failure of benznidazole treatment; failure of benznidazole and response to posaconazole were documented by real-time PCR assays in serial specimens.⁴⁷ However, the results of a randomized clinical trial comparing the efficacy and safety of low and high dose posaconazole to that of benznidazole demonstrated that posaconazole was not efficacious for treatment of chronic Chagas disease.⁴⁸

Preventing Recurrence

Patients with HIV infection are at risk for recurrent or relapsing clinical manifestations because of intermittent reactivation of chronic infection.¹⁶ The drugs 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 HIV-infected patients is limited, expert advice should be sought.⁴⁵ Whether secondary prophylaxis or chronic maintenance therapy should be used in HIV-infected patients with latent Chagas disease is unclear, particularly when potent ART is used.

Special Considerations During Pregnancy

As recommended for all individuals with epidemiological risk of Chagas disease, screening of pregnant women who have lived in endemic areas should be considered to identify maternal infection and possible risk of infection in their offspring. In pregnant women in areas where the disease is endemic in Latin America, the seroprevalence of *T. cruzi* infection can be as high as 30%.^{14,49} In the United States, a 1999 study of 3,765 pregnant women in Houston, Texas, confirmed antibody to *T. cruzi* in 0.4% of Hispanic women and 0.1% of

non-Hispanic women and a 2013 study of 4,000 predominantly Hispanic women in the same city found 0.25% with confirmed infection.^{50,51}

From 1% to 10% of infants of *T. cruzi*-infected mothers are born with acute *T. cruzi* infection.^{14,49} Most congenital *T. cruzi* infections are asymptomatic or cause non-specific signs; laboratory screening is required for detection of these cases. Studies from the 1980s suggest that congenital transmission of *T. cruzi* may increase the risk of spontaneous abortion, stillbirth, and low birthweight.⁵² 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.⁴⁹ Limited data suggest that the rate of congenital transmission is higher for HIV-infected women than in immunocompetent mothers.^{16,53} Infants co-infected with HIV and *T. cruzi* also may be more likely to have symptoms, especially neurologic symptoms.^{54,55}

Minimal data are available on 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.^{56,57} Benznidazole crosses the placenta in rats and covalently binds to fetal proteins.⁵⁸ Because of the toxicity and limited experience with use of these drugs in pregnancy, treatment of acute *T. cruzi* infection in pregnant women 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. For HIV-infected pregnant women with symptomatic reactivation of *T. cruzi* infection, ART should be initiated (**AIII**) as initial treatment. Two cases of treatment of Chagas disease in pregnancy with benznidazole have been reported. One report was of an acute infection with treatment continued for the first few weeks of an subsequently diagnosed pregnancy, with normal infant outcome,⁵⁹ and one was of treatment of an HIV-infected woman with severe immunosuppression with Chagasic encephalitis in the third trimester of pregnancy.⁶⁰ The infant was small for gestational age but otherwise healthy and without evidence of *T. cruzi* infection. All infants born to *T. cruzi*-infected women should undergo appropriate testing for congenitally acquired *T. cruzi* infection and be treated promptly if infection is confirmed.^{14,61}

Recommendations for Preventing and Treating Chagas Disease (American Trypanosomiasis)

Preventing Clinical Disease

Indication

- Individuals with epidemic risk factors for Chagas disease and tested positive for antibody to *T. cruzi*, have not been previously treated, and do not have advanced Chagas cardiomyopathy.
 - A single course of benznidazole or nifurtimox can be considered (doses and duration same as for treatment of disease) (**CIII**). However, the efficacy of this therapy is suboptimal, and treated patients are still at risk of reactivation.
 - Initiation or optimization of ART may prevent reactivation of Chagas disease (**BIII**)

Treating Chagas Disease

Note: Treatment is effective in reducing parasitemia and preventing clinical manifestation or slowing progression in patients with acute, early-chronic, and re-activated disease. They have limited efficacy, however, in achieving parasitological cure.

Preferred Therapy for Acute, Early Chronic, and Re-Activated Disease:

- Benznidazole 5–8 mg/kg/day PO in 2 divided doses for 30–60 days (**BIII**) (commercially available at <http://www.benznidazoletablets.com/en/>).

Alternative Therapy

- Nifurtimox 8–10 mg/kg/day PO for 90–120 days (**CIII**) (not commercially available in the United States. Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100)

Note:

- Optimal duration of therapy has not been studied in HIV-infected patients.
- Initiation or optimization of ART in patients undergoing treatment for Chagas disease, once the patient is clinically stable (**AIII**)
- Even with treatment, mortality is high in patients with symptomatic reactivation.

Key to Acronyms: ART = antiretroviral therapy; CDC = Centers for Disease Control and Prevention; PO = orally

References

1. Bittencourt AL. Congenital Chagas disease. *Am J Dis Child*. Jan 1976;130(1):97-103. Available at <http://www.ncbi.nlm.nih.gov/pubmed/813519>.
2. Maguire J. Trypanosomiasis. In: Gorbach S. BJ, Blacklow, N; ed. *Infectious Diseases*: Lippincott, Williams & Wilkins; 2004:2327-2334.
3. Benchimol Barbosa PR. The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks. *Int J Cardiol*. Sep 10 2006;112(1):132-133. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16600406>.
4. Rassi A, Jr., Rassi A, Marin-Neto JA. Chagas disease. *Lancet*. Apr 17 2010;375(9723):1388-1402. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20399979>.
5. Organización Panamericana de la Salud. Estimación cuantitativa de la enfermedad de Chagas en las Américas. Montevideo, Uruguay, Organización Panamericana de la Salud. 2006.
6. Gascon J, Bern C, Pinazo MJ. Chagas disease in Spain, the United States and other non-endemic countries. *Acta Trop*. Jul-Aug 2010;115(1-2):22-27. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19646412>.
7. Moncayo A. Chagas disease: current epidemiological trends after the interruption of vectorial and transfusional transmission in the Southern Cone countries. *Mem Inst Oswaldo Cruz*. Jul 2003;98(5):577-591. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12973523>.
8. Dorn PL, Perniciaro L, Yabsley MJ, et al. Autochthonous transmission of *Trypanosoma cruzi*, Louisiana. *Emerg Infect Dis*. Apr 2007;13(4):605-607. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17553277>.
9. Herwaldt BL, Grijalva MJ, Newsome AL, et al. Use of polymerase chain reaction to diagnose the fifth reported US case of autochthonous transmission of *Trypanosoma cruzi*, in Tennessee, 1998. *J Infect Dis*. Jan 2000;181(1):395-399. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10608796>.
10. Kjos SA, Snowden KF, Craig TM, Lewis B, Ronald N, Olson JK. Distribution and characterization of canine Chagas disease in Texas. *Vet Parasitol*. Apr 15 2008;152(3-4):249-256. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18255233>.
11. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2860516>.
12. Centers for Disease C, Prevention. Blood donor screening for chagas disease--United States, 2006-2007. *MMWR Morb Mortal Wkly Rep*. Feb 23 2007;56(7):141-143. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17318113>.
13. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. *Curr Opin Infect Dis*. Oct 2008;21(5):476-482. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18725796>.
14. Bern C, Verastegui M, Gilman RH, et al. Congenital *Trypanosoma cruzi* transmission in Santa Cruz, Bolivia. *Clin Infect Dis*. Dec 1 2009;49(11):1667-1674. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19877966>.
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*. Mar 1994;50(3):261-268. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Jan 2007;101(1):31-50. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17244408>.
17. Vaidian AK, Weiss LM, Tanowitz HB. Chagas' disease and AIDS. *Kinetoplastid Biol Dis*. May 13 2004;3(1):2. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15142278>.
18. Committee WHOE. Control of Chagas disease. *World Health Organ Tech Rep Ser*. 2002;905:i-vi, 1-109, back cover. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12092045>.
19. Rassi A, Jr., Rassi A, Little WC. Chagas' heart disease. *Clin Cardiol*. Dec 2000;23(12):883-889. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11129673>.
20. Rassi A, Jr., Rassi SG, Rassi A. Sudden death in Chagas' disease. *Arq Bras Cardiol*. Jan 2001;76(1):75-96. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11175486>.
21. de Oliveira RB, Troncon LE, Dantas RO, Menghelli UG. Gastrointestinal manifestations of Chagas' disease. *Am J Gastroenterol*. Jun 1998;93(6):884-889. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9647012>.
22. Campos SV, Strabelli TM, Amato Neto V, et al. Risk factors for Chagas' disease reactivation after heart transplantation. *J Heart Lung Transplant*. Jun 2008;27(6):597-602. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18503957>.

23. Kohl S, Pickering LK, Frankel LS, Yaeger RG. Reactivation of Chagas' disease during therapy of acute lymphocytic leukemia. *Cancer*. Sep 1 1982;50(5):827-828. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6807527>.
24. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989-1996. *Clin Infect Dis*. Sep 1999;29(3):561-567. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10530448>.
25. Sartori AM, Neto JE, Nunes EV, et al. Trypanosoma cruzi parasitemia in chronic Chagas disease: comparison between human immunodeficiency virus (HIV)-positive and HIV-negative patients. *J Infect Dis*. Sep 15 2002;186(6):872-875. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12198628>.
26. 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*. Nov 1998;59(5):784-786. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9840598>.
27. 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*. Nov 2008;12(6):587-592. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18337139>.
28. 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*. May 2009;9(5):324-330. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19393962>.
29. 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*. Dec 1997;25(6):1397-1400. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9431385>.
30. Leiby DA, Wendel S, Takaoka DT, Fachini RM, Oliveira LC, Tibbals MA. Serologic testing for Trypanosoma cruzi: comparison of radioimmunoprecipitation assay with commercially available indirect immunofluorescence assay, indirect hemagglutination assay, and enzyme-linked immunosorbent assay kits. *J Clin Microbiol*. Feb 2000;38(2):639-642. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10655360>.
31. Tarleton RL, Reithinger R, Urbina JA, Kitron U, Gurtler RE. The challenges of Chagas Disease-- grim outlook or glimmer of hope. *PLoS Med*. Dec 2007;4(12):e332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18162039>.
32. 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*. Nov 2008;79(5):755-759. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18981518>.
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*. Mar 2009;80(3):410-415. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19270291>.
34. Gorlin J, Rossmann S, Robertson G, et al. Evaluation of a new Trypanosoma cruzi antibody assay for blood donor screening. *Transfusion*. Mar 2008;48(3):531-540. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Mar-Apr 1996;90(2):129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8761570>.
36. Wincker P, Telleria J, Bosseno MF, et al. PCR-based diagnosis for Chagas' disease in Bolivian children living in an active transmission area: comparison with conventional serological and parasitological diagnosis. *Parasitology*. Apr 1997;114 (Pt 4):367-373. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9107023>.
37. Feilij H, Muller L, Gonzalez Cappa SM. Direct micromethod for diagnosis of acute and congenital Chagas' disease. *J Clin Microbiol*. Aug 1983;18(2):327-330. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6413530>.
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 <http://www.ncbi.nlm.nih.gov/pubmed/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*. Nov 2000;19(11):1114-1117. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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 <http://www.ncbi.nlm.nih.gov/pubmed/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*. Nov 1978;27(6):1116-1122. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Mar 2003;68(3):307-311. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12685636>.
 43. Schmunis GA, Cruz JR. Safety of the blood supply in Latin America. *Clin Microbiol Rev*. Jan 2005;18(1):12-29. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15653816>.
 44. Rodriques Coura J, de Castro SL. A critical review on Chagas disease chemotherapy. *Mem Inst Oswaldo Cruz*. Jan 2002;97(1):3-24. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11992141>.
 45. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of chagas disease in the United States: a systematic review. *JAMA*. Nov 14 2007;298(18):2171-2181. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18000201>.
 46. Castro JA, de Mecca MM, Bartel LC. Toxic side effects of drugs used to treat Chagas' disease (American trypanosomiasis). *Hum Exp Toxicol*. Aug 2006;25(8):471-479. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16937919>.
 47. Pinazo MJ, Espinosa G, Gallego M, Lopez-Chejade PL, Urbina JA, Gascon J. Successful treatment with posaconazole of a patient with chronic Chagas disease and systemic lupus erythematosus. *Am J Trop Med Hyg*. Apr 2010;82(4):583-587. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20348503>.
 48. Molina I, Gomez i Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazole for chronic Chagas' disease. *N Engl J Med*. May 15 2014;370(20):1899-1908. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24827034>.
 49. 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*. Feb 2004;70(2):201-209. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14993634>.
 50. Di Pentima MC, Hwang LY, Skeeter CM, Edwards MS. Prevalence of antibody to *Trypanosoma cruzi* in pregnant Hispanic women in Houston. *Clin Infect Dis*. Jun 1999;28(6):1281-1285. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10451166>.
 51. Edwards MS, Rench MA, Charles TW, et al. Perinatal Screening for Chagas Disease in Southern Texas. *J Ped Infect Dis*. 2015;4(1):67. Available at <http://jpid.oxfordjournals.org/content/early/2013/10/03/jpid.pit056.1.full>.
 52. Bittencourt AL. Possible risk factors for vertical transmission of Chagas' disease. *Rev Inst Med Trop Sao Paulo*. Sep-Oct 1992;34(5):403-408. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1342103>.
 53. 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*. Mar-Apr 2009;42(2):107-109. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19448923>.
 54. Freilij H, Altcheh J. Congenital Chagas' disease: diagnostic and clinical aspects. *Clin Infect Dis*. Sep 1995;21(3):551-555. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8527542>.
 55. Freilij H, Altcheh J, Muchnik G. Perinatal human immunodeficiency virus infection and congenital Chagas' disease. *Pediatr Infect Dis J*. Feb 1995;14(2):161-162. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7746707>.
 56. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Assessment of cytogenetic damage in chagasic children treated with benznidazole. *Mutat Res*. Oct 1988;206(2):217-220. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3140001>.
 57. Gorla NB, Ledesma OS, Barbieri GP, Larripa IB. Thirteenfold increase of chromosomal aberrations non-randomly distributed in chagasic children treated with nifurtimox. *Mutat Res*. Oct 1989;224(2):263-267. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2507913>.
 58. 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*. Nov 1984;272(1):17-23. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6440493>.
 59. 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*. May-Jun 2014;47(3):397-400. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25075496>.
 60. 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 <http://www.ncbi.nlm.nih.gov/pubmed/23965334>.
 61. Oliveira I, Torrico F, Munoz J, Gascon J. Congenital transmission of Chagas disease: a clinical approach. *Expert Rev Anti Infect Ther*. Aug 2010;8(8):945-956. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20695749>.

Coccidioidomycosis

Updated: February 16, 2021

Reviewed: January 11, 2023

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, these areas include the lower San Joaquin Valley and other arid regions in southern California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas.² Several cases of coccidioidomycosis in individuals who acquired the infection in eastern Washington state have been reported. One of these cases was phylogenetically linked to local *Coccidioides immitis* isolates.² These observations suggest that the coccidioidal endemic range may be expanding.

The risk of developing symptomatic coccidioidomycosis after infection is increased in patients with HIV who have CD4 T lymphocyte (CD4) counts <250 cells/mm³, those who are not virologically suppressed, or those who have AIDS.³ The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).^{4,5}

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 patients with HIV, lack of viral suppression and CD4 count <250 cells/mm³ are associated with increased severity of the presentation of coccidioidomycosis.⁷

Focal pneumonia is most common in patients with CD4 counts ≥ 250 cells/mm³. Focal pneumonia can be difficult to distinguish from a bacterial community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.^{7,8} However, coccidioidomycosis may present with hilar or 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. mediastinal adenopathy, upper lobe infiltrates, nodules, and peripheral blood eosinophilia—all of which are uncommon in bacterial pneumonia and should make one think of coccidioidomycosis, particularly in patients who reside in, previously resided in, or have travelled to a known endemic area.

Diffuse pneumonia and extrathoracic disease usually occur in more 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 and serological tests are frequently negative at presentation.

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.

Elevated coccidioidal antibody titers even without symptoms can indicate risk of subsequent symptomatic disease in patients with advanced HIV. A study conducted prior to the advent of potent ART described 13 patients with HIV who had CD4 counts <350 cells/mm³ and positive coccidioidal serologic tests without an anatomic site of infection. Five patients subsequently developed clinical illness when their median CD4 count fell to 10 cells/mm³.¹⁰

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 spherules on histopathological examination of infected tissue confirms 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* spp. grow relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a non-pigmented mold may be observed in as few as 3 to 7 days and can be confirmed as *Coccidioides* by gene probe. *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 that *Coccidioides* spp. may be present, and 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 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, and negative serology cannot be used to rule out disease. Repeat testing every 1-2 weeks should be considered if the patient is ill and the diagnosis has not been established. Patients with past coccidioidal infection and without disease activity usually have negative serological tests. Screening with an enzyme immunoassay (EIA) for IgM and IgG antibody is recommended. It 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. A lateral flow assay (LFA) recently has become available but 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 in samples from individuals with active coccidioidomycosis. The assay is most useful in diagnosing extrathoracic disseminated coccidioidomycosis. A recent study suggests that detection of coccidioidal antigen in CSF has a very high sensitivity and specificity for diagnosing coccidioidal meningitis.¹⁶

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 not Food and Drug Administration (FDA)-approved nor tested in patients with HIV.¹⁷

Preventing Exposure

Individuals 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, and they should stay inside during dust storms (**BIII**). No evidence indicates that gardening in cultivated soil in the coccidioidal endemic region increases the risk of acquiring coccidioidomycosis.

Preventing Disease

Preventing Coccidioidomycosis
Primary antifungal prophylaxis for individuals with negative serologic tests for <i>Coccidioides</i> is not recommended (AIII) except for the following indications: Indication for Primary Prophylaxis <ul style="list-style-type: none">• New positive IgM and/or IgG test for <i>Coccidioides</i>; and• No sign of active coccidioidomycosis; and• CD4 count <250 cells/mm³ Preferred Therapy <ul style="list-style-type: none">• Fluconazole 400 mg PO once daily (AIII) Discontinuation of Primary Prophylaxis <ul style="list-style-type: none">• CD4 count ≥250 cells/mm³ with virologic suppression on ART (BIII)• Close clinical follow-up is recommended (BIII)

Key: CD4 = CD4 T lymphocyte cell; 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 patients with HIV with low CD4 counts who live in regions in which *Coccidioides* spp. are endemic,⁴ and it **is not recommended (AIII)**. Yearly or twice-yearly serological testing for coccidioidomycosis is reasonable for serologically negative individuals with HIV who live in endemic areas. 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 immunodiffusion technique are recommended. In patients who have CD4 counts <250 cells/mm³ and who previously tested negative for *Coccidioides*, a new positive serology test suggests possible active disease¹⁰ and should prompt further clinical evaluation. If no signs, symptoms, or laboratory abnormalities compatible with active coccidioidomycosis are identified, antifungal therapy with fluconazole 400 mg daily is recommended for those with a new positive serological test and CD4 counts <250 cells/mm³ (**AIII**). This regimen should be continued until the CD4 count is ≥250 cells/mm³ and virological suppression is documented (**BIII**). For those with CD4 counts already ≥250/mm³ and with viral suppression on antiretrovirals, close clinical follow-up without antifungal therapy is recommended (**BIII**). For asymptomatic patients who have not lived in or travelled to endemic regions, routine testing does not appear useful and **should not be performed (AIII)**.

Treating Disease

Treating Coccidioidomycosis
<p>Treating Mild-to-Moderate Pulmonary Infections</p> <p><i>Indications for Treatment</i></p> <ul style="list-style-type: none"> • Patients who have clinically mild infection, such as focal pneumonia; • Patients with positive coccidioidal serologies but with mild or without clinical illness. <p><i>Preferred Therapy</i></p> <ul style="list-style-type: none"> • Fluconazole 400 mg PO once daily (AII), or • Itraconazole 200 mg PO three times daily for 3 days then twice daily (AII) <p><i>Alternative Therapy (For Patients Who Failed to Respond to Fluconazole or Itraconazole)</i></p> <ul style="list-style-type: none"> • Voriconazole loading dose of 400 mg twice daily for the first day followed by 200 mg PO twice daily (BIII); or • Posaconazole (extended-release tablet) 300 mg PO twice daily for the first day and then 300 mg daily (BIII) <p>Treating Severe Pulmonary or Extrapulmonary Infection (Except Meningitis)</p> <p><i>Preferred Therapy</i></p> <ul style="list-style-type: none"> • Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), or • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII) • Use until clinical improvement, then switch to triazole (BIII). <p><i>Alternative Therapy</i></p> <ul style="list-style-type: none"> • Some specialists recommend combining amphotericin B with a triazole (fluconazole or itraconazole 400mg daily) and continue the triazole once amphotericin B is stopped (CIII). <p>Treatment for Meningeal Infections (Consultation with a Specialist Is Advised)</p> <p><i>Preferred Therapy</i></p> <ul style="list-style-type: none"> • Fluconazole 400–800 mg IV or PO once daily (AII) <p><i>Alternative Therapy</i></p> <ul style="list-style-type: none"> • 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 once daily after a loading dose (CIII), or • Isavuconazole 372 mg every 8 hr for 6 doses, then 372 mg daily (CIII). • Intrathecal amphotericin B (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. <p>Treatment in Pregnancy</p> <ul style="list-style-type: none"> • Azole antifungal agents are contraindicated and should be avoided in the first trimester of pregnancy because of potential teratogenic effect and risk of spontaneous abortion (AIII). • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII), or

<ul style="list-style-type: none"> • Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII)
Discontinuing Therapy
<p>Focal Coccidioidal Pneumonia, Therapy Can Be Stopped If (AII)</p> <ul style="list-style-type: none"> • Clinically responded to 3 to 6 months of antifungal therapy, <i>and</i> • CD4 count ≥ 250 cells/mm³, <i>and</i> • Virologic suppression on ARVs, <i>and</i> • Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology. <p>Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis</p> <ul style="list-style-type: none"> • Relapse can occur in 25% to 33% of patients without HIV and can occur in patients with HIV who have CD4 count >250 cells/mm³. • Therapy duration is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts (BIII). <p>Coccidioidal Meningitis</p> <ul style="list-style-type: none"> • Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong (AII).
Other Considerations
<ul style="list-style-type: none"> • Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy. • 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 Adult and Adolescent Antiretroviral Guidelines DDI Tables list these interactions and recommend dosage adjustments where feasible.

Key: ARVs = antiretrovirals; CD4 = CD4 T lymphocyte cell; CSF = cerebrospinal fluid; DDI = drug–drug interaction; IV = intravenous; PO = orally

Treatment of mild-to-moderate pulmonary coccidioidal infection: Therapy with a triazole antifungal agent given orally 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**).^{18,19} Itraconazole is preferred for those who have bone or joint disease (**AI**).²⁰ Serum itraconazole concentrations should be measured after the drug reaches steady state at 2 weeks to ensure adequate absorption. Target serum concentration (the sum of the parent itraconazole and hydroxyl itraconazole metabolite levels) is at least >1 mcg/mL and preferably >2 mcg/mL.

Data to support clinical efficacy for treatment with posaconazole^{21,22} and voriconazole are limited, but these agents are useful for patients who do not respond to fluconazole or itraconazole (**BIII**). Voriconazole is given as a loading dose of 400 mg twice daily 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 mcg/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 (**BIII**),²² but the current extended-release tablet formulation of posaconazole at a dosage of 300 mg twice daily for the first day, then 300mg once daily is better tolerated by patients and provides more reliable serum concentrations. Recently, a

syndrome of mineralocorticoid excess manifesting as hypertension with hypokalemia was reported in some patients taking posaconazole.²³ Monitoring of blood pressure and serum potassium levels is appropriate in patients taking posaconazole.

No data have been published on the use of the antifungal isavuconazole for coccidioidomycosis in patients with HIV. Among nine patients with pulmonary disease without HIV, initial therapy with isavuconazole resulted in complete or partial treatment success in five patients (56%).²⁴

All triazole antifungals have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents and other anti-infective agents. [Drug–drug interaction \(DDI\) tables](#) in the Adult and Adolescent ARV Guidelines 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**).¹⁹ 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 anecdotal reports²⁵ from studies that used lipid formulations of amphotericin B for the treatment of coccidioidomycosis. Lipid formulations are likely to be as effective as the deoxycholate formulation and should be considered as equivalent alternative 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 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**).¹⁹

Treatment of patients with coccidioidal meningitis: Treatment of coccidioidal meningitis requires consultation with a specialist (**AIII**). Intravenous amphotericin B alone is ineffective as treatment for coccidioidal meningitis. Treatment with a triazole antifungal is recommended. Fluconazole (400 to 800 mg daily) is the preferred regimen (**AII**),^{18,26} but itraconazole 400 to 600 mg daily also has been successfully used (**BII**).²⁷ Therapy with voriconazole (**BIII**),²⁸⁻³⁰ posaconazole (**CII**),^{22,31} and isavuconazole (**CII**) has been described in individual cases and has been successful.³² Despite appropriate antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B is recommended (**AIII**). 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, and this titer 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 patients with HIV and coccidioidomycosis.³³⁻³⁵ In general, delaying initiation of ART while treating coccidioidomycosis **is not recommended (AIII)**. Conversely, a recent case series³⁶ and a single case report³⁷ suggested that, in highly immunosuppressed patients (i.e., CD4 counts <100 cells/mm³) with disseminated disease, clinical

decline may occur with initiation of ART. These findings suggest that 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 disease (**BIII**). However, delay may not prevent IRIS, as reported in at least one patient with disseminated disease, who had received treatment with fluconazole for 28 days but who still had worsening symptoms within a week after starting ART.³⁸ Close monitoring for clinical worsening, particularly if meningitis is present, is essential when treating highly immunosuppressed people who have HIV and who have disseminated coccidioidomycosis.¹³

Managing Treatment Failure

Serum drug concentrations should be checked in patients with severe coccidioidomycosis who do not respond to treatment with itraconazole. In 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**) and voriconazole (**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 [DDI tables in the Adult and Adolescent Antiretroviral Guidelines](#)). Posaconazole and isavuconazole have fewer known drug interactions with antiretrovirals than voriconazole. In certain situations, surgical intervention may be indicated.¹⁸

Therapy After Immune Reconstitution

Patients with peripheral blood CD4 count ≥ 250 cells/mm³ appear capable of maintaining their coccidioidal-specific cellular immune response.³⁹ Moreover, a prospective study has demonstrated that coccidioidomycosis is less severe in those with lower HIV RNA and higher CD4 counts.⁵ Given these facts, in patients with HIV who have undetectable HIV RNA on potent ART and who have CD4 count ≥ 250 cells/mm³, 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 and 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. For patients with detectable HIV viremia or CD4 count < 250 cells/mm³, 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 nonmeningeal disseminated coccidioidomycosis^{40,41} and may occur in people with HIV who have CD4 counts ≥ 250 cells/mm³ and are virologically suppressed on antiretrovirals.^{1,36} During and after coccidioidomycosis therapy, patients should have serial chest radiographs and coccidioidal serology tests every 3 to 6 months. Relapses have been reported in $\geq 80\%$ of patients with meningitis in whom triazoles have been discontinued.⁴² Therefore, therapy for coccidioidal meningitis should be continued for life (**AII**).

Special Considerations During Pregnancy

Women are generally at lower risk than men for severe coccidioidomycosis, and disease does not appear to reactivate or worsen in women with prior coccidioidomycosis during pregnancy. However, when coccidioidomycosis is acquired during the second or third trimester of pregnancy, the infection is more likely to be severe and disseminated.⁴³

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.⁴⁴

A recent systematic review and meta-analysis of cohort or case control studies (n = 6 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 (odds ratio 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. One registry-based cohort study (included in the systematic review)^{5,37} and a more recent large population-based case-control study⁴⁵ specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

A nationwide cohort study in Denmark reported that the risk of spontaneous abortion was greater in women exposed to oral fluconazole in pregnancy than in women who had not been exposed or those with topical azole exposure only.⁴⁶ A cohort study using Swedish and Norwegian registry data (n = 1,485,316 pregnancies) found no association between fluconazole use in pregnancy and risk of stillbirth or neonatal death.⁴⁷ Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short-term exposure. Responding to the reported birth defects, the FDA has changed the pregnancy category for fluconazole from C to D for any use other than a single 150 mg dose of fluconazole to treat vaginal candidiasis.⁴⁸ Although cases of birth defects in infants exposed to itraconazole have been reported, prospective cohort studies of >300 women with first trimester exposure did not show an increased risk of malformation.^{49,50} However, in general, all azole antifungals **should be avoided** during the first trimester of pregnancy (**BIII**). One problematic area is coccidioidal meningitis, for which the only alternative treatment to triazole antifungals is IV or intrathecal amphotericin B. In such situations, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the mother, the infectious diseases consultant, and the obstetrician.⁴³ Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies; for voriconazole, these occurred at doses lower than recommended for humans; however, adequately controlled studies in humans have not been conducted. Therefore, use of voriconazole and posaconazole **should be avoided** in pregnancy, especially in the first trimester (**AIII**).

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. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. One study suggested that the treatment regimen for women who develop coccidioidomycosis in the second or third trimester can be similar to that for nonpregnant women with coccidioidomycosis (**CIII**).¹⁸

References

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. 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. 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>.
4. 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>.
5. 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>.
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. 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. 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. 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. 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. 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. 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. 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. 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. 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. 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>.
17. 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>.
18. Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guideline for the treatment of coccidioidomycosis. Infectious Diseases Society of America. *Clin Infect Dis.* 2000;30(4):658-661. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10770727>.
19. 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>.
20. 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>.
21. 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>.
22. 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>.
23. 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>.
24. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27169478>.
 25. Stewart ER, Eldridge ML, McHardy I, Cohen SH, Thompson GR, 3rd. Liposomal Amphotericin B as Monotherapy in Relapsed Coccidioidal Meningitis. *Mycopathologia*. 2018;183(3):619-622. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29340909>.
 26. 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>.
 27. 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>.
 28. 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>.
 29. 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>.
 30. 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>.
 31. 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>.
 32. 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>.
 33. 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>.
 34. 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>.

35. Tribble 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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/>.
40. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med*. 1990;89(3):282-290. Available at: <https://pubmed.ncbi.nlm.nih.gov/2168126/>.
41. 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/>.
42. 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/>.
43. 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/>.
44. 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/>.
45. 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/>.
46. 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/>.

47. 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/>.
48. U.S. Food and Drug Administration. FDA Drug Safety Communication: Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants. 2011. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-use-long-term-high-dose-diflucan-fluconazole-during-pregnancy-may-be>.
49. 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://pubmed.ncbi.nlm.nih.gov/19338381/>.
50. 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://pubmed.ncbi.nlm.nih.gov/10992182/>.

Community-Acquired Pneumonia

Updated: September 7, 2022

Reviewed: January 11, 2023

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/mm³, 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 obesity⁴, 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/mm³) 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/mm³, but even those with counts > 500 cells/mm³, 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/mm³), 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/mm³, radiographic progression of disease, and presence of shock.⁵⁹ In that study, multilobar infiltrates, cavitory 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/mm³), 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/mm³ (and especially if <100 cells/mm³) 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 12 hours 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 study⁸¹ 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/mm³.⁸⁴ 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/mm³ 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/mm³ 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/mm³ while on ART **(BIII)**. Clinical evidence supporting use of PPSV23 in persons with CD4 counts <200 cells/mm³ 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)**. For pregnant people with HIV, administer inactivated influenza or recombinant vaccine 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/mm³) 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 criteria⁶⁷ 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/mm³ was associated with an increased risk of death.¹⁰¹ This led to the suggestion to hospitalize CAP patients with CD4 counts <200 cells/mm³ 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 ($>38^{\circ}\text{C}$ or $<35^{\circ}\text{C}$), 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 CAP⁶⁷ 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 \geq 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 shock⁶⁷ 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 Guidelines¹²⁰ 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/mm³ 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 telavancin 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 Telavancin 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/mm³ should receive a dose of PPSV23 at least 8 weeks later **(AI)**. While individuals with HIV with CD4 counts <200 cells/mm³ 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/mm³ while on ART **(BIII)**. Clinical evidence supporting use of PPSV23 in persons with CD4 counts <200 cells/mm³ 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).

Recommendations for Preventing and Treating Community-Acquired Pneumonia

- 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).
- For pregnant people with HIV, administer inactivated influenza or recombinant vaccine 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, Naucier 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 Modiyangi 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/loi80120_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, Naucle 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-Elfant 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

Updated: July 1, 2021

Reviewed: January 11, 2023

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 Pacific Northwest. Before the era of effective antiretroviral therapy (ART), approximately 5% to 8% of patients with HIV in high-income countries had disseminated cryptococcosis.¹ In a surveillance study in the late 1990s, people with HIV who developed cryptococcosis were severely immunosuppressed and had limited access to routine HIV medical care.² Current 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 HIV⁴ are observed in those who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm³. The incidence of the disease has declined substantially among people treated with ART.⁴

Clinical Manifestations

In people with HIV, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache slowly developing over many weeks, with a median onset of 2 weeks after infection.¹ Classic meningeal symptoms and signs—such as neck stiffness and photophobia—occur in only one-quarter to one-third of patients. Some patients experience encephalopathic symptoms—such as lethargy, altered mentation, personality changes, and memory loss—that are usually a result of increased intracranial pressure (ICP). Among people presenting with cryptococcal meningitis shortly after initiating ART, the symptom onset can be more acute, likely related to unmasking immune reconstitution inflammatory syndrome (IRIS).⁵

Cryptococcosis usually is disseminated when diagnosed in a patient with HIV. In spite of widespread disseminated disease, patients with HIV may manifest few symptoms suggesting a disseminated infection. Any organ can be involved, and 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

Analysis of cerebrospinal fluid (CSF) generally demonstrates mildly elevated protein levels, low-to-normal glucose concentrations, and a variable presence of pleocytosis consisting mostly of lymphocytes. Some patients with HIV have very few CSF inflammatory cells. A Gram stain or an India ink preparation, if available, may demonstrate numerous yeast forms. In patients with HIV and cryptococcal meningitis, the opening pressure in the CSF may be elevated, with pressures ≥ 25 cm H₂O occurring in 60% to 80% of patients.^{6,7}

Cryptococcal disease can be diagnosed by culture, CSF microscopy, cryptococcal antigen (CrAg) detection, or CSF polymerase chain reaction (PCR). In patients with HIV-related cryptococcal meningitis, approximately 50% of blood cultures will be positive, and approximately 80% of CSF cultures will be positive. Visible *Cryptococcus* colonies on a Sabouraud dextrose agar plate 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.⁸

CSF CrAg is usually positive in patients with cryptococcal meningoencephalitis; however, early meningitis can present with negative CSF studies and positive CrAg in blood only.⁹ Thus, serum CrAg testing always should be performed in an immunocompromised individual with an unknown central nervous system (CNS) disorder.⁹ Serum CrAg is positive in both meningeal and non-meningeal cryptococcal infections and may be present weeks to months before symptom onset.¹⁰

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 Food and Drug Administration (FDA). It is a useful initial screening tool to diagnose cryptococcosis in patients with HIV when applied to serum or plasma,^{8,11} 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 patient with HIV, when serum CrAg LFA titers are $\geq 1:160$, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are $\geq 1:640$, disseminated and/or CNS involvement should be assumed, regardless of CSF test results.^{12,13} 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.

In 2016, the BioFire FilmArray Meningitis/Encephalitis Panel PCR assay (Biofire Diagnostics, Salt Lake City, UT) 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.¹⁴⁻¹⁶ False negative results have been noted to occur when there is a low burden of organisms; in one study, when there were <100 CFU/mL, the sensitivity of the PCR test fell to 50%.¹⁴ 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.¹⁷ 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).¹⁴

Preventing Exposure

Cryptococcus is ubiquitous in the environment. 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.

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/mm³, the prevalence of cryptococcal antigenemia—a harbinger of disease—was 2.9%, and for those with CD4 counts ≤ 50 cells/mm³, the prevalence was 4.3%.¹⁸ 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 ≤ 100 cells/mm³ and particularly in those with CD4 counts ≤ 50 cells/mm³ (**AII**). A positive test generally should prompt CSF evaluation for CNS infection (**BIII**), particularly when the serum LFA titer is $\geq 1:160$ (**AII**).¹³

Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients with HIV^{19,20} who have CD4 counts < 100 cells/mm³.^{19,21} 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 survival benefit associated with prophylaxis, possibility of drug-drug interactions, potential development of antifungal drug resistance, and costs (**BII**).

Treating Disease

Treatment consists of three phases: induction, consolidation, and maintenance.

Induction Treatment

For induction treatment of cryptococcal meningitis and other forms of extrapulmonary cryptococcosis, an amphotericin B formulation given intravenously, in combination with oral flucytosine, is recommended (**AI**). Historically, amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily has been the preferred formulation of the drug. However, evidence that lipid formulations of amphotericin B are effective for cryptococcosis is growing, particularly in patients who experience clinically significant kidney dysfunction during therapy or who are likely to develop acute kidney injury. 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 efficacy for all three regimens; however, less nephrotoxicity was observed among those receiving the 3 mg/kg daily liposomal amphotericin B regimen.²⁰ Additional data from animal models and a phase 2 trial in humans, show that single-dose liposomal amphotericin B at a dose of 10 mg/kg has similar rates of CSF yeast clearance and less toxicity than 14 days of amphotericin B deoxycholate.²²

The preferred regimen for primary induction therapy for patients with normal renal function is 2 weeks of an amphotericin B formulation once daily plus flucytosine 25 mg/kg four times daily (**AI**).^{23,24} Based on available clinical trial data and clinical experience, liposomal amphotericin B, at a dose of 3 to 4 mg/kg daily, is the favored formulation (**AI**).

Amphotericin B deoxycholate at a dose of 0.7 to 1.0 mg/kg daily is equally effective and can be used if the costs of lipid formulations are prohibitive and/or interruption of induction therapy because of kidney damage is unlikely (**AI**).

The noncomparative CLEAR study demonstrated a 58% response rate in patients with HIV who were treated with amphotericin B lipid complex at a mean dose of 4.4 mg/kg daily.²⁵ Thus,

amphotericin B lipid complex at a dose of 5 mg/kg daily can be used as an alternative amphotericin B formulation although fewer data are available to support its use **(BII)**.

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 postdose after three to five doses have been administered. Peak serum concentrations should be between 25 mg/L and 100 mg/L.¹⁶ Renal function should be monitored closely and the flucytosine dose adjusted accordingly for patients with renal impairment. The dose of flucytosine should be reduced by 50% for every 50% decline in creatinine clearance. The addition of flucytosine to the amphotericin B regimen during acute treatment is associated with more rapid sterilization of CSF and survival benefit.^{23,26-28} A randomized clinical trial also 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.²⁹ Adjunctive fluconazole 800 to 1,200 mg per day plus amphotericin B has been used in the absence of flucytosine, but adjunctive flucytosine has a survival advantage over adjunctive fluconazole and is preferred **(AI)**.²⁴ Amphotericin B deoxycholate alone or with fluconazole at a dose of 800 to 1,200 mg daily **(BI)** or lipid-formulation amphotericin B alone **(BI)** or with fluconazole at a dose of 800 to 1,200 mg daily **(BIII)** may be viable options in some circumstances, but they are less preferable alternatives than lipid-formulation amphotericin B plus flucytosine.²⁴

Fluconazole (1,200 mg daily) plus flucytosine is also a potential alternative to amphotericin B regimens **(BII)**. Some experts would use 800 mg fluconazole daily with flucytosine **(BIII)**.^{24,30} Fluconazole alone, based on studies assessing early fungicidal activity, is inferior to amphotericin B for induction therapy^{31,32} and is recommended only for patients who cannot tolerate or who do not respond to standard treatment. If fluconazole alone is used for primary induction therapy, the starting daily dose should be 1,200 mg **(CI)**.³³

The duration of induction therapy historically has been 2 weeks. In a multicenter clinical trial that evaluated 10-week outcomes of treatment of cryptococcal meningitis in 721 African adults with HIV, 1 week of amphotericin B deoxycholate therapy was shown to be noninferior to 2 weeks,²⁴ and at 1 year, follow-up of 236 patients from this treatment trial showed continued noninferiority of the 1-week regimen compared with the 2-week regimen.³⁴ Thus, in resource-limited settings, 1 week of amphotericin B deoxycholate with flucytosine followed by high-dose fluconazole is now preferred **(BIII)**.³⁵ However, in high-resource settings where the less toxic liposomal or other lipid amphotericin B formulations is used and a greater capacity to provide supportive care to mitigate amphotericin B toxicities exists, 2 weeks of induction amphotericin B combination therapy is recommended **(AI)**.

Consolidation Treatment

A lumbar puncture and repeat CSF culture should be performed after 2 weeks of induction therapy. At that point, 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 frequently 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)**.^{36,37} 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 (**AI**). 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 therapy noted breakthrough infection during consolidation.²³ 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 patients with cryptococcal meningitis increases linearly with increasing doses of the drug.^{29,31} A phase 2 trial of treatment with either 400 mg or 800 mg fluconazole found that relapses were more frequent in patients receiving 400 mg fluconazole.³⁸ In clinically stable patients, 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**).³⁹

For patients who have completed 2 weeks of induction therapy, but have not improved clinically or remain clinically unstable, continuation of amphotericin B plus flucytosine is recommended until the CSF cultures are confirmed to be negative (**BIII**). For patients who have improved clinically, but whose CSF remains culture positive after 2 weeks of induction therapy, the fluconazole dose should be increased to 1,200 mg per day and another lumbar puncture should be performed 2 weeks later (**BIII**). For all patients with CSF cultures positive at Week 2, the duration of consolidation therapy should be 8 weeks from the time the CSF cultures are negative (**AI**).^{23,26,40}

An alternative approach for outpatients who are not ill enough to be hospitalized but still have positive CSF cultures after completing 2 weeks of induction therapy is to continue flucytosine for an additional 2 weeks together with fluconazole at a dose of 1,200 mg per day before starting single-drug consolidation therapy.

Itraconazole can be used as an alternative therapy for consolidation (**CI**), but it is clearly inferior to fluconazole.⁴⁰ 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 use of these extended-spectrum triazole antifungals for treatment of refractory cases, with success rates of approximately 50%.⁴¹⁻⁴³ Currently, the role of posaconazole, voriconazole, and isavuconazole in the initial management of cryptococcosis has not been established in randomized clinical trials, and these agents are **not recommended** for consolidation or maintenance therapy (**AIII**). Echinocandins have no activity against *Cryptococcus* spp. and **are not recommended** for clinical management of cryptococcosis (**AII**).

Maintenance Treatment

Fluconazole 200 mg per day is used for maintenance treatment and continue until at least one year from initiation of antifungal therapy (**AI**) (see the Preventing Recurrence section below).⁴⁴

Treatment of Non-CNS 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 to moderate symptoms and only focal pulmonary infiltrates, treatment with fluconazole 400 to 800 mg per day for 10 weeks followed by 200 mg daily for a total of 6 months combined with effective ART is recommended (**BIII**).²⁶

Patients with isolated or asymptomatic cryptococcal antigenemia without meningitis and low serum CrAg titers (i.e., $\leq 1:320$ using LFA) can be treated in a similar fashion as patients with mild to moderate symptoms and only focal pulmonary cryptococcosis with fluconazole 400 to 800 mg per

day (**BIII**). If the serum CrAg titer by LFA is $\geq 1:640$ (or $\geq 1:160$ 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 patients should be treated the same as patients with cryptococcal meningitis (**BIII**).¹³ All patients with asymptomatic cryptococcal antigenemia should have their CSF sampled to rule out CNS disease. If serum CrAg titers are $\geq 1:640$ with the LFA test and a CSF sample is not available, CNS involvement should be assumed regardless of CSF culture results or clinical signs or symptoms, and the patient should be treated as detailed above for CNS disease (**AII**).^{12,13,45}

Special Considerations with Regard to Starting ART

Unlike with other opportunistic infections, ART initiation generally is deferred for 4 to 6 weeks after antifungal agents are started (**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 8 days) after the diagnosis of meningitis with patients for whom ART was delayed for 4 to 6 weeks (median 35 days) after diagnosis.⁴⁶ 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% versus 30%, $P = 0.03$). This increase was most pronounced during the first 8 to 30 days of 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 of deaths in the early ART group was likely attributable to paradoxical IRIS.⁴⁷

Most experts aim to start ART after 4 to 6 weeks of antifungal therapy; however, individual patient factors may alter this timing. In general, ensuring that the patient's CSF cultures are sterile before starting ART will reduce the risk of IRIS.⁴⁸ 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). For non-CNS cryptococcosis, for which the risk of IRIS appears to be lower, the optimal time to begin ART and 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 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 H₂O in the lateral decubitus position.^{6,23} In a large clinical trial in patients with AIDS and cryptococcal meningitis, increased ICP was associated with 93% of deaths during the first 2 weeks of antifungal therapy and 40% of deaths during weeks 3 to 10.⁶ In another clinical trial, patients with HIV-associated cryptococcal meningitis 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.⁴⁹ 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 patients with cryptococcal meningitis at the time of diagnosis. However, in routine practice, CSF opening pressure frequently is not measured. Among patients in whom CSF opening pressure was not measured initially, a repeat lumbar puncture should be performed with measurement of opening pressure. For patients with ongoing headaches, a repeat lumbar puncture should be performed with urgency, and among those without headaches, a repeat lumbar puncture should be considered strongly within 48 hours of the initial procedure.⁴⁹ Measures to decrease ICP should be used for all patients with 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 at least halves the opening pressure or normalizes the pressure to <20 cm H₂O.^{49,50} 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 daily until symptoms and signs consistently improve and opening pressure normalizes to <20 cm H₂O (**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 patients who are relatively asymptomatic or who had a baseline CSF opening pressure of <20 cm H₂O, (**BII**).⁴⁹ This second lumbar puncture can be especially useful if the initial opening pressure was not measured (**AII**). ICP can be a dynamic process that changes over time.

CSF shunting through a lumbar drain or ventriculostomy should be considered for patients 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 decrease in ICP (**AI**).⁵¹ 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 decrease killing of *Cryptococcus*, and was associated with more adverse events.⁵² 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**).

Patients treated with amphotericin B formulations should be monitored for nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 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 infusion reactions (**CIII**), but scant data exist to support these practices. Meperidine (25–50 mg titrated during infusion) is effective for preventing and treating amphotericin B–associated 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 amphotericin B formulation (**AII**).⁵³

In patients receiving flucytosine, dosage should be adjusted based on changes in creatinine clearance and can be guided by flucytosine levels. Peak serum flucytosine levels 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)**.²⁴ Flucytosine is associated with concentration-dependent bone marrow toxicity. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities.

Common side effects of higher dose fluconazole therapy can include dry skin (17% of patients) and alopecia (16% of patients).⁵⁴ Increased liver transaminases or alkaline phosphatase are relatively rare with fluconazole 400 to 800 mg use, with only 1 to 2% having values >5 times the upper limit of normal.⁴⁶ For people who have difficulty tolerating higher fluconazole doses, it appears safe to reduce the consolidation therapy fluconazole dose to 400 mg per day after initiation of ART **(BII)**.³⁹

Immune Reconstitution Inflammatory Syndrome

An estimated 10 to 30% of people with HIV who have cryptococcal meningitis experience IRIS after initiation or re-initiation of effective ART.^{55,56} Patients with HIV who have cryptococcal IRIS are more likely to be ART naive and have less CSF inflammation on initial presentation.⁵⁷ 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)**.^{46,58} 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,^{57,59} whereas treatment failure is associated with continued positive cultures. The primary microbiological criterion for treatment failure is a CSF culture that yields *Cryptococcus*; 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 predicting sterile CSF cultures and can be diagnostically useful to distinguish paradoxical IRIS with a negative CSF PCR from culture-positive relapse with a positive CSF PCR.¹⁴

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 is appropriate, such as restarting amphotericin B therapy or increasing the fluconazole dose to 1,200 mg per day **(BIII)**. In patients 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 **(BIII)**; precise data-driven management strategies have not been developed. Serum C-reactive protein (CRP) is generally elevated at the time IRIS develops;⁶⁰ CRP will decrease with corticosteroid therapy if IRIS is present and can be used to monitor IRIS resolution. At hospital discharge, restarting fluconazole therapy at consolidation therapy doses to be continued for 8 weeks is recommended **(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.⁶¹ 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 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.⁶² 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 $\mu\text{g/mL}$ are considered not fully susceptible.^{63,64}

Optimal therapy for patients with treatment failure has not been established. Patients who do not respond to induction with fluconazole monotherapy should be switched to amphotericin B, with or without flucytosine. Those initially treated with an amphotericin B formulation should remain on this agent until clinical response occurs. In this setting, liposomal amphotericin B (4–6 mg/kg daily) or amphotericin B lipid complex (5 mg/kg daily) is better tolerated and has greater efficacy than the deoxycholate formulation^{20,65,66} 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 $\mu\text{g/mL}$ MIC for fluconazole) some experts would recommend adjunctive weekly amphotericin B administration during consolidation therapy (**BIII**).⁶⁴ Higher doses of fluconazole (i.e., 1,200 mg per day) in combination with flucytosine 25 mg/kg 4 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, but they offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates high-level fluconazole resistance. Most clinical failures are not due to antifungal drug resistance, but rather result from inadequate induction therapy, nonadherence, drug interactions that decrease the serum concentrations of fluconazole (e.g., with rifampin), or the development of paradoxical IRIS.

Preventing Recurrence

When to Start Maintenance Therapy

Patients 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 (**CI**).⁴⁰ One study demonstrated that only 70% of patients receiving fluconazole 200 mg per day achieved therapeutic concentrations of fluconazole in plasma when the fluconazole MIC was ≥ 8 $\mu\text{g/mL}$, and only 30% when the MIC was 16 $\mu\text{g/mL}$.⁶⁴ For patients in whom susceptibility studies have been performed and the fluconazole MIC is ≥ 8 $\mu\text{g/mL}$, some experts recommend that the fluconazole dose be increased to 400 mg per day (**BIII**). Failure to administer secondary prophylaxis for an entire year is the most common reason for subsequent relapse of cryptococcal disease.⁶⁷

When to Stop Maintenance Therapy

Only a few patients have been evaluated for relapse after successful antifungal therapy for cryptococcosis and discontinuation of maintenance therapy while on ART. 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/mm³, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.⁶⁸ A prospective, randomized study of 60 patients 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/mm³ with a sustained undetectable HIV RNA level for 3 months on potent ART.⁶⁹ Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated opportunistic infections, it is reasonable to discontinue maintenance therapy after at least 1 year from initiation of antifungal therapy, in patients whose CD4 counts are >100 cells/mm³ with undetectable viral loads on ART **(BII)**.⁷⁰ Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/mm³ **(AIII)**.

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections in individuals who are pregnant is similar to that in individuals who are not pregnant. Treatment should be initiated promptly after a diagnosis is confirmed. It should be emphasized that initiating antifungal therapy during the postpartum period is associated with an increased risk of IRIS.⁷¹

Lipid formulations of amphotericin B are preferred for the initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in patients who are pregnant. Extensive clinical experience with amphotericin B has not documented teratogenicity. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

In animal studies, flucytosine is teratogenic; experience in humans is limited to case reports and small series. Therefore, flucytosine use should be considered only when the benefits outweigh the risks to the fetus and only in the third trimester **(AIII)**.

Fluconazole is teratogenic 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 through or beyond the first trimester of pregnancy.⁷² A recent systematic review and meta-analysis of cohort or case-control studies reporting fetal outcomes after exposure to fluconazole in the first trimester of pregnancy analyzed more than 16,000 exposures and found an association with increased risk of heart defects and spontaneous abortion; exposure to a fluconazole dose ≥150 mg was associated with an increase in overall congenital malformations.⁷³ One registry-based cohort study included in the systematic review⁷⁴ and a more recent large population-based case-control study⁷⁵ specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

A nationwide cohort study in Denmark also found that exposure to oral fluconazole during pregnancy was associated with an increased risk of spontaneous abortion compared with unexposed pregnancies or those with topical azole exposure only.⁷⁶ 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.⁷⁷ 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 [FDA classified fluconazole as pregnancy category D for any use other than a single dose of fluconazole 150 mg to treat vaginal candidiasis](#). Use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh the risks. For pregnant women, amphotericin B should be continued throughout the first trimester. After induction therapy, weekly amphotericin B has been used for consolidation therapy for women who are pregnant throughout the first trimester.⁷¹ After the first trimester, switching to oral fluconazole 200 mg per day may be considered if appropriate clinically.

In a case series of 12 pregnant Ugandan women with cryptococcal meningitis who received amphotericin B deoxycholate 0.7 to 1 mg/kg induction therapy, maternal mortality was 25%.⁷¹ Stillbirths and miscarriages were common during the initial maternal hospitalization with only 33% (4 live births out of 12 pregnancies) fetal survival.⁷¹ Consolidation therapy comprised weekly amphotericin during the first trimester and fluconazole thereafter. With life-threatening cryptococcal disease, fetal demise is common even without fluconazole exposure.⁷¹

Although case reports of birth defects in infants exposed to itraconazole exist, prospective cohort studies of >300 women with first-trimester exposure did not show an increased risk of fetal malformation.^{78,79} However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy (**BIII**). 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 (**AIII**).

Recommendations for Treating Cryptococcosis

Treating Cryptococcal Meningitis

Treatment consists of three phases: induction, consolidation, and maintenance therapy.

Induction Therapy (Duration of Therapy: 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens

- Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day **(AI)**, *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day **(AI)**—if cost is an issue and the risk of renal dysfunction is low.

Note: Flucytosine dose should be adjusted in renal impairment (see [Table 6](#)).

Alternative Regimens

- Amphotericin B lipid complex 5 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day **(BII)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV once daily plus fluconazole 800–1,200 mg PO or IV once daily **(BIII)**; *or*
- Fluconazole 1,200 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day **(BII)**; *or*
- Fluconazole 800 mg PO or IV once daily plus flucytosine 25 mg/kg PO four times a day **(BIII)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily plus fluconazole 800–1,200 mg PO or IV once daily **(BI)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV once daily alone **(BI)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily alone **(BI)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 1 week followed by fluconazole 1,200 mg PO once daily **(BIII)**; *or*
- Fluconazole 1,200 mg PO or IV once daily alone **(CI)**

If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative **(BIII)**.

Consolidation Therapy (Duration of Therapy: ≥8 Weeks, Followed by Maintenance Therapy)

Preferred Regimen

- Fluconazole 800 mg PO once daily **(AI)**
- For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily **(AII)**
- If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, increase fluconazole dose to 1,200mg and perform LP 2 weeks later **(BIII)**; duration of consolidation therapy should be 8 weeks from the time of negative CSF culture **(AI)**.

Maintenance Therapy

Preferred Regimen

- Fluconazole 200 mg PO once daily for ≥1 year from initiation of antifungal therapy **(AI)**—see below for recommendation on when to stop maintenance therapy

Stopping Maintenance Therapy

If the Following Criteria Are Fulfilled (BII)

- At least 1 year from initiation of antifungal therapy, *and*
- Patient remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥ 100 cells/mm³ and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy

- If CD4 count declines to ≤ 100 cells/mm³ (AIII)

Treating Non-CNS Extrapulmonary, Diffuse Pulmonary Disease, or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer $\geq 1:640$)

- Same treatment as for CNS disease (BIII)

Treating Non-CNS Focal Pulmonary Disease or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer $\leq 1:320$)

- Fluconazole 400 to 800 mg PO daily for 10 weeks followed by fluconazole 200 mg daily for a total of 6 months (BIII)

Other Considerations

- Addition of flucytosine to an amphotericin B-based regimen has been associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival.
- When flucytosine is used, serum concentrations (if TDM available) should be monitored 2 hours postdose, after 3–5 doses have been administered, and drug concentration should be between 25 and 100 mg/L. Alternatively, if flucytosine levels cannot be measured, at least twice weekly complete blood counts may be used to monitor for cytopenias.
- 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).
- Typical duration of induction therapy is 2 weeks. In the setting of severe amphotericin B–induced toxicity, at least 1 week of amphotericin B deoxycholate was noninferior to 2 weeks of amphotericin B deoxycholate (BIII).²⁴
- Corticosteroids should not be used routinely during induction therapy unless used for management of IRIS (AI).
- Corticosteroids and mannitol are ineffective in reducing ICP and **are not recommended (AIII)**.
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. [Table 4](#) lists these interactions and recommends dosage adjustments where feasible.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; LFA = lateral flow assay; LP = lumbar puncture; PO = orally; TDM = therapeutic drug monitoring

References

1. Aberg J, WG. P. Cryptococcosis. In: Secondary Aberg J, WG. P, ed^eds. Subsidiary Aberg J, WG. P, trans. Secondary Cryptococcosis. Vol. ed. New York, NY: Churcill 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12627365
3. Rajasingham R, Smith RM, Park BJ, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *Lancet Infect Dis*. 2017;17(8):873-881. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28483415>.
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: <http://www.ncbi.nlm.nih.gov/pubmed/23457543>.
5. 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.ncbi.nlm.nih.gov/pubmed/30094292>.
6. 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.ncbi.nlm.nih.gov/pubmed/10619732>.
7. 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://www.ncbi.nlm.nih.gov/pubmed/19279443>.
8. 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.ncbi.nlm.nih.gov/pubmed/24378231>.
9. 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.ncbi.nlm.nih.gov/pubmed/30256903>.
10. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11953469>.
11. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8075272>.
12. 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.ncbi.nlm.nih.gov/pubmed/29020172>.
 13. 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.ncbi.nlm.nih.gov/pubmed/30257903>.
 14. 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.ncbi.nlm.nih.gov/pubmed/26711635>.
 15. 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.ncbi.nlm.nih.gov/pubmed/26719436>.
 16. 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.ncbi.nlm.nih.gov/pubmed/27335149>.
 17. 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/>
 18. 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.ncbi.nlm.nih.gov/pubmed/25422390>.
 19. 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>.
 20. 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.ncbi.nlm.nih.gov/pubmed/20536366>.
 21. 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>.
22. 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.ncbi.nlm.nih.gov/pubmed/29945252>.
 23. 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.ncbi.nlm.nih.gov/pubmed/9203426>.
 24. 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.ncbi.nlm.nih.gov/pubmed/29539274>.
 25. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15809927>.
 26. 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10770733.
 27. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O, French Cryptococcosis Study G. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med*. 2007;4(2):e21. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17284154>.
 28. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O, French Cryptococcosis Study G. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. *PLoS One*. 2008;3(8):e2870. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18682846>.
 29. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23550668>.
 30. 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: <http://www.ncbi.nlm.nih.gov/pubmed/7803641>.
 31. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naïve or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis*. 2007;45(1):76-80. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17554704.

32. 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18990067.
33. Nussbaum JC, Jackson A, Namarika D, et al. Combination flucytosine and high-dose fluconazole compared with fluconazole monotherapy for the treatment of cryptococcal meningitis: a randomized trial in Malawi. *Clin Infect Dis*. 2010;50(3):338-344. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20038244>.
34. 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.ncbi.nlm.nih.gov/pubmed/31155650>.
35. World Health Organization. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. 2018. Available at: <https://www.who.int/publications/i/item/9789241550277>
36. 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.ncbi.nlm.nih.gov/pubmed/24065327>.
37. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11590483>.
38. 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.ncbi.nlm.nih.gov/pubmed/19441980>.
39. 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.ncbi.nlm.nih.gov/pubmed/26716103>.
40. 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10064246.
41. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12715306>.

42. Pituitum 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: <http://www.ncbi.nlm.nih.gov/pubmed/16135526>.
43. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27169478>.
44. 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=1538722.
45. Faini D, Kalinsuma 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.ncbi.nlm.nih.gov/pubmed/30422904>.
46. Boulware DR, Mehta 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: <http://www.ncbi.nlm.nih.gov/pubmed/24963568>.
47. 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.ncbi.nlm.nih.gov/pubmed/25651842>.
48. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23525034>.
49. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25057102>.
50. 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.ncbi.nlm.nih.gov/pubmed/9473014>.
51. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12203177>.
52. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26863355>.

53. 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>.
54. Davis MR, Nguyen MH, Donnelley MA, Thompson 3rd GR. Tolerability of long-term fluconazole therapy. *J Antimicrob Chemother*. 2019;74(3):768-771. Available at: <https://pubmed.ncbi.nlm.nih.gov/30535104/>
55. 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15825000.
56. 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>.
57. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20677939>.
58. 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.ncbi.nlm.nih.gov/pubmed/23525034>.
59. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21029993>.
60. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21253011>.
61. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21534892>.
62. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11600357>.
63. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8838190>.
64. 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.ncbi.nlm.nih.gov/pubmed/31420668>.
 65. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9342068>.
 66. Chen SC, Australasian Society for Infectious Diseases Mycoses Interest 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: <http://www.ncbi.nlm.nih.gov/pubmed/11801583>.
 67. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20526411>.
 68. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12186514>.
 69. Vibhagool A, Sungkanuparph S, Moonsikapun 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: <http://www.ncbi.nlm.nih.gov/pubmed/12746781>.
 70. 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: <http://www.ncbi.nlm.nih.gov/pubmed/14765351>.
 71. 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.ncbi.nlm.nih.gov/pubmed/31689712>.
 72. 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>.
 73. 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.ncbi.nlm.nih.gov/pubmed/31446677>.

74. 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.ncbi.nlm.nih.gov/pubmed/23984730>.
75. 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.ncbi.nlm.nih.gov/pubmed/26640069>.
76. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26746458>.
77. 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>.
78. 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>.
79. 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>.

Cryptosporidiosis

Updated: January 18, 2023

Reviewed: January 18, 2023

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 cell (CD4) counts <100 cells/mm³—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis.¹ The three species that most commonly infect humans are *Cryptosporidium hominis*, *Cryptosporidium parvum*, and *Cryptosporidium 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 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 recreational water sources—such as swimming pools and lakes—and public water supplies 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 diagnosis 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 the different ways that *Cryptosporidium* can be transmitted (**BIII**). Modes of transmission include direct contact with people, including diapered children, and animals infected with *Cryptosporidium*; swallowing contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Scrupulous handwashing can reduce the risk of diarrhea in individuals with HIV, including diarrhea caused by *Cryptosporidium*.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/mm³—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 persons 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

Because chronic cryptosporidiosis occurs primarily in people with HIV with advanced immunodeficiency, initiation of ART before they become severely immunosuppressed should prevent this 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 travelers' 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

In the setting of severe immune suppression, ART with immune restoration to a CD4 count >100 cells/mm³ usually leads to resolution of clinical cryptosporidiosis¹⁹⁻²² 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 the oral or intravenous route are important. Stool volume in patients with 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 (ERCP) 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 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/mm³ 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 was not confirmed, however, 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/mm³, 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 non-absorbable 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 extra-intestinal 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

Rehydration and initiation of ART are the mainstays of initial treatment of cryptosporidiosis during pregnancy, as they are in non-pregnant people (**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

Recommendations for Preventing and Managing Cryptosporidiosis

Preventing Chronic Cryptosporidiosis

- Because chronic cryptosporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease **(AII)**.

Managing Cryptosporidiosis

Preferred Management Strategies

- Aggressive oral and/or IV rehydration and replacement of electrolyte loss **(AIII)**, and
- Symptomatic treatment of diarrhea with antimotility agents **(AIII)**; tincture of opium may be more effective than loperamide **(CIII)**, and
- People with HIV not taking ART should initiate ART to achieve immune restoration to CD4 count >100 cells/mm³ **(AII)**.

Consider

- 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
- 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

Other Considerations

- Because diarrhea can cause lactase deficiency, patients should avoid milk products **(CIII)**.

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

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. 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: Bennett JE, Dolin R, and Blaser MJ, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 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) (Last updated September 10, 2015; last reviewed January 11, 2023)

Epidemiology

Isosporiasis, also known as cystoisosporiasis, occurs worldwide but predominantly in tropical and subtropical regions. Immunocompromised patients, including those who are HIV-infected, are at increased risk for chronic, debilitating illness.¹⁻⁷ Although *Isospora* (*Cystoisospora*) *belli* completes its life cycle in humans, the oocysts shed in the feces of infected individuals must mature (sporulate) outside the host, in the environment, to become infective. On the basis of limited data, the maturation process is completed in approximately 1 to 2 days but might occur more rapidly in some settings.² 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.

Clinical Manifestations

The most common manifestation 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, particularly in immunocompromised patients, resulting in severe dehydration, electrolyte abnormalities such as hypokalemia, weight loss, and malabsorption.⁶⁻¹² Acalculous cholecystitis/cholangiopathy^{2,13-15} and reactive arthritis¹⁶ also have been reported.

Diagnosis

Typically, infection is diagnosed by detecting *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 patients 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 UV fluorescence microscopy, under which they autofluoresce.^{2,17} Infection also can be diagnosed by detecting oocysts in duodenal aspirates/mucus or developmental stages of the parasite in intestinal biopsy specimens.^{2,10} Extraintestinal infection, such as in the biliary tract, lymph nodes, spleen, and liver, has been documented in postmortem examinations of HIV-infected patients.^{2,18-20}

Preventing Exposure

Because *I. belli* is acquired by ingesting infected water or food, avoiding potentially contaminated food or water in isosporiasis-endemic areas may help prevent infection.

Preventing Disease

In some settings, chemoprophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis.^{1,3,4,21} In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment).¹ In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm³.³ After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis 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 isosporiasis was lower in patients with versus without a history of *Pneumocystis pneumonia*—indirect evidence of a protective effect from use of TMP-SMX for *Pneumocystis pneumonia*.⁴ Insufficient evidence is available, however, to support a general recommendation for primary prophylaxis for isosporiasis per se, especially for U.S. travelers in isosporiasis-endemic areas.

Treating Disease

Clinical management includes fluid and electrolyte support for dehydrated patients and nutritional supplementation for malnourished patients (**AIII**). TMP-SMX is the antimicrobial agent of choice for treatment of isosporiasis (**AI**). It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails (**AIII**).

Three studies in HIV-infected patients in Haiti have demonstrated the effectiveness of various treatment regimens of TMP-SMX.^{6,7,22} The patients were not receiving ART, and laboratory indicators of immunodeficiency (such as CD4 cell counts) were not specified. On the basis of 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**).²³ In another study, TMP-SMX (160/800 mg) administered twice daily was also effective (**BI**).²² Although published experience using two daily doses of TMP-SMX (160/800 mg) is limited, one approach would be to start with this regimen but to increase the daily dose and the duration of therapy (up to 3–4 weeks)^{6,10} if symptoms worsen or persist (**BIII**). Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption.

Limited data suggest that therapy with pyrimethamine–sulfadiazine and pyrimethamine–sulfadoxine may be effective.^{2,9,10,24–26} However, the combination of pyrimethamine plus sulfadoxine is not typically recommended for use in the United States (**CIII**); it has been associated with an increased risk of severe cutaneous reactions, including Stevens-Johnson syndrome,²⁷ and pyrimethamine and sulfadoxine clear slowly from the body after therapy is discontinued.

Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.^{3,28,29} Pyrimethamine (50–75 mg/day) plus leucovorin (10–25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients (**BIII**).

The author panel has issued a statement on the availability of pyrimethamine. For more information, please visit <https://aidsinfo.nih.gov/news/1604/notice-of-availability-of-pyrimethamine>.

Special Considerations with Regard to Starting ART

Only limited data address the utility of ART in the setting of *Isospora* and HIV co-infection.^{3,14,21} Immune reconstitution with ART may result in fewer relapses of isosporiasis, and no cases of immune reconstitution inflammatory syndrome (IRIS) have been reported. Therefore, the potential benefits of ART likely outweigh the risks. For patients with isosporiasis who otherwise fulfill criteria for ART, TMP-SMX therapy and ART can be started simultaneously; there is no known reason to defer initiation of ART other than the potential for poor ART absorption (**AIII**).

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

Patients should be monitored for clinical response and adverse events. In HIV-infected patients, TMP-SMX therapy is commonly associated with side effects, such as rash, fever, leukopenia, thrombocytopenia, and elevated transaminase levels. IRIS has not been described.

Managing Treatment Failure

If symptoms worsen or persist despite approximately 5 to 7 days of TMP-SMX therapy, the possibilities of noncompliance, malabsorption, and concurrent infections/enteropathies should be considered; the TMP-SMX regimen (daily dose, duration, and mode of administration) also should be reevaluated. For patients with documented sulfa intolerance or in whom treatment fails, use of a potential alternative agent (typically pyrimethamine) should be considered. Ciprofloxacin is a second-line agent (**CI**). On the basis of limited data from a randomized, controlled trial in Haiti, ciprofloxacin (500 mg twice daily for 7 days) is less effective than TMP-SMX but may have modest activity against *I. belli*.²²

Unsubstantiated or mixed data are available for albendazole,²⁹⁻³¹ nitazoxanide,^{32,33} doxycycline,³⁴ the macrolides roxithromycin and spiramycin,^{25,35,36} and the veterinary anticoccidial agent diclazuril (**CIII**).^{37,38} Limited data suggest that drugs such as metronidazole, quinacrine, iodoquinol, paromomycin, and furazolidone are ineffective.^{8,25,26,28,35,37} Apparent or partial responses, if noted, may be attributable to treatment of concomitant infections or to nonspecific effects.

Preventing Recurrence

Patients with CD4 cell counts <200 cells/mm³ should receive secondary prophylaxis (chronic maintenance therapy) with TMP-SMX, which is also protective against *Pneumocystis jirovecii* and *Toxoplasma gondii* infections (**AI**). In 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, relapses rapidly responded to retreatment, and secondary prophylaxis decreased the risk of relapse.^{6,7,22} In a randomized, placebo-controlled trial, no symptomatic recurrences were noted in patients who received maintenance therapy with thrice-weekly TMP-SMX (160/800 mg) (**AI**).⁷ Daily TMP-SMX (160/800 mg) and thrice-weekly TMP-SMX (320/1600 mg) have been effective (**BIII**);^{5,10} however, clinical and parasitologic relapses despite maintenance TMP-SMX therapy and ART have been reported.¹⁴

In sulfa-intolerant patients, pyrimethamine (25 mg/day) with leucovorin (5–10 mg/day) has been used (**BIII**).²⁸ On the basis of limited data, ciprofloxacin (500 mg thrice weekly) is considered a second-line alternative (**CI**).²²

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 patients without evidence of active *I. belli* infection who have a sustained increase in the CD4 cell count to levels >200 cells/mm³ for >6 months after initiation of ART (**BIII**).

Special Considerations During Pregnancy

TMP-SMX is the agent of choice for primary treatment and secondary prophylaxis in pregnant women, as it is in persons who are not pregnant. Although first-trimester exposure to trimethoprim has been associated with a small increased risk of birth defects,³⁹⁻⁴² TMP-SMX therapy should be provided in the setting of maternal symptomatic *I. belli* infection. Because of 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**). Although pyrimethamine has been associated with birth defects in animals, limited human data have not suggested an increased risk of defects.⁴³ Human data about the use of ciprofloxacin during several hundred pregnancies have not suggested an increased risk of birth defects or cartilage abnormalities.⁴⁴

Recommendations for Treating *Isospora belli* Infection

Treating *Isospora belli* Infection

General Management Considerations:

- Fluid and electrolyte support in patients with dehydration (**AIII**)
- Nutritional supplementation for malnourished patients (**AIII**)

Preferred Therapy for Acute Infection:

- TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days (**AII**), or
- TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days (**BI**)
- One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist (**BIII**)
- IV therapy for patients with potential or documented malabsorption

Alternative Therapy For Acute Infection (For Patients with Sulfa Intolerance):

- Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily (**BIII**), or
- Ciprofloxacin 500 mg PO BID for 7 days (**CI**)

Chronic Maintenance Therapy (Secondary Prophylaxis)

(In Patients with CD4 Count $<200/\text{mm}^3$)

Preferred Therapy:

- TMP-SMX (160 mg/800 mg) PO 3 times weekly (**AI**)

Alternative Therapy:

- TMP-SMX (160 mg/800 mg) PO daily (**BIII**), or
- TMP-SMX (320 mg/1600 mg) PO 3 times weekly (**BIII**), or
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (**BIII**)
- Ciprofloxacin 500 mg PO 3 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 *I. belli* infection (**BIII**)

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole

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*. May 1 1999;353(9163):1463-1468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10232311>.
2. Lindsay DS, Dubey JP, Blagburn BL. Biology of *Isospora* spp. from humans, nonhuman primates, and domestic animals. *Clin Microbiol Rev*. Jan 1997;10(1):19-34. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Mar 2007;8(2):124-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Dec 1995;53(6):656-659. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Aug 2003;69(2):217-222. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Jul 10 1986;315(2):87-90. Available at <http://>

www.ncbi.nlm.nih.gov/pubmed/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*. Apr 20 1989;320(16):1044-1047. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2927483>.
8. Forthal DN, Guest SS. *Isospora belli* enteritis in three homosexual men. *Am J Trop Med Hyg*. Nov 1984;33(6):1060-1064. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6507724>.
9. 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*. Feb 1985;26(2):179-187. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4038492>.
10. 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*. Nov 1984;33(6):1065-1072. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6334448>.
11. Bialek R, Overkamp D, Rettig I, Knobloch J. Case report: Nitazoxanide treatment failure in chronic isosporiasis. *Am J Trop Med Hyg*. Aug 2001;65(2):94-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11508398>.
12. Williams DT, Smith RS, Mallon WK. Severe hypokalemia, paralysis, and AIDS-associated *Isospora belli* diarrhea. *J Emerg Med*. Dec 2011;41(6):e129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18993015>.
13. 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*. Nov 1 1994;121(9):663-664. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7944075>.
14. 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*. Feb 2008;9(2):126-130. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18257775>.
15. Walther Z, Topazian MD. *Isospora* cholangiopathy: case study with histologic characterization and molecular confirmation. *Hum Pathol*. Sep 2009;40(9):1342-1346. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19447468>.
16. Gonzalez-Dominguez J, Roldan R, Villanueva JL, Kindelan JM, Jurado R, Torre-Cisneros J. *Isospora belli* reactive arthritis in a patient with AIDS. *Annals of the rheumatic diseases*. Sep 1994;53(9):618-619. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7979603>.
17. 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*. Sep 2002;67(3):304-305. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12408672>.
18. 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. *The Journal of eukaryotic microbiology*. 2003;50 Suppl:682-684. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14736218>.
19. Restrepo C, Macher AM, Radany EH. Disseminated extraintestinal isosporiasis in a patient with acquired immune deficiency syndrome. *Am J Clin Pathol*. Apr 1987;87(4):536-542. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3826017>.
20. Bernard E, Del Giudice P, Carles M, et al. Disseminated isosporiasis in an AIDS patient. *Eur J Clin Microbiol Infect Dis*. Sep 1997;16(9):699-701. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9352268>.
21. 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*. Jun 2009;80(6):1060-1064. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19478276>.
22. 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*. Jun 6 2000;132(11):885-888. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10836915>.
23. Guerrant RL, Van Gilder T, Steiner TS, et al. Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis*. Feb 1 2001;32(3):331-351. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11170940>.
24. Mojon M, Coudert J, E.O. dL. Serious isosporosis by *Isospora belli*: a case report treated by Fansidar [Abstract]. *Southeast Asian J Trop Med Public Health*. 12:449-500. 1981.
25. Ebrahimzadeh A, Bottone EJ. Persistent diarrhea caused by *Isospora belli*: therapeutic response to pyrimethamine and

- sulfadiazine. *Diagn Microbiol Infect Dis*. Oct 1996;26(2):87-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8985661>.
26. Trier JS, Moxey PC, Schimmel EM, Robles E. Chronic intestinal coccidiosis in man: intestinal morphology and response to treatment. *Gastroenterology*. May 1974;66(5):923-935. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4826994>.
 27. Navin TR, Miller KD, Satriale RF, Lobel HO. Adverse reactions associated with pyrimethamine-sulfadoxine prophylaxis for *Pneumocystis carinii* infections in AIDS. *Lancet*. Jun 8 1985;1(8441):1332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2860516>.
 28. Weiss LM, Perlman DC, Sherman J, Tanowitz H, Wittner M. *Isospora belli* infection: treatment with pyrimethamine. *Ann Intern Med*. Sep 15 1988;109(6):474-475. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3261956>.
 29. Jongwutiwes S, Sampatanukul P, Putaporntip C. Recurrent isosporiasis over a decade in an immunocompetent host successfully treated with pyrimethamine. *Scandinavian journal of infectious diseases*. 2002;34(11):859-862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12578164>.
 30. 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*. Sep 1996;10(11):1301-1302. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8883600>.
 31. Zulu I, Veitch A, Sianongo S, et al. Albendazole chemotherapy for AIDS-related diarrhoea in Zambia--clinical, parasitological and mucosal responses. *Alimentary pharmacology & therapeutics*. 2002; 16(3):595-601. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11876715.
 32. 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*. Nov-Dec 1997;91(6):701-703. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9580117>.
 33. 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*. Jun 1997;56(6):637-639. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9230795>.
 34. Meyohas MC, Capella F, Poirot JL, et al. [Treatment with doxycycline and nifuroxazide of *Isospora belli* infection in AIDS]. *Pathologie-biologie*. Jun 1990;38(5 (Pt 2)):589-591. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2385457>.
 35. Gaska JA, Tietze KJ, Cosgrove EM. Unsuccessful treatment of enteritis due to *Isospora belli* with spiramycin: a case report. *J Infect Dis*. Dec 1985;152(6):1336-1338. Available at <http://www.ncbi.nlm.nih.gov/pubmed/4067332>.
 36. Musey KL, Chidiac C, Beaucaire G, Houriez S, Fourrier A. Effectiveness of roxithromycin for treating *Isospora belli* infection. *J Infect Dis*. Sep 1988;158(3):646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3411149>.
 37. Limson-Pobre RN, Merrick S, Gruen D, Soave R. Use of diclazuril for the treatment of isosporiasis in patients with AIDS. *Clin Infect Dis*. Jan 1995;20(1):201-202. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7727660>.
 38. Kayembe K, Desmet P, Henry MC, Stoffels P. Diclazuril for *Isospora belli* infection in AIDS. *Lancet*. Jun 17 1989;1(8651):1397-1398. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2567420>.
 39. Czeizel AE, Rockenbauer M, Sorensen HT, Olsen J. The teratogenic risk of trimethoprim-sulfonamides: a population based case-control study. *Reprod Toxicol*. Nov-Dec 2001;15(6):637-646. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11738517>.
 40. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Folic acid antagonists during pregnancy and the risk of birth defects. *N Engl J Med*. Nov 30 2000;343(22):1608-1614. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11096168>.
 41. Hernandez-Diaz S, Werler MM, Walker AM, Mitchell AA. Neural tube defects in relation to use of folic acid antagonists during pregnancy. *American journal of epidemiology*. May 15 2001;153(10):961-968. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11384952>.
 42. 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? *Sexually transmitted infections*. Dec 2001;77(6):441-443. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11714944>.
 43. 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*. Jul-Aug 2001;95(4):424-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11579889>.
 44. 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*. May 2006;107(5):1120-1138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16648419>.

Cytomegalovirus Disease (Last updated July 1, 2021; last reviewed January 11, 2023)

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 with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV experiencing reactivation of latent infection. Infection with a novel strain also may occur.

End-organ disease caused by CMV occurs in patients with HIV and advanced immunosuppression, typically those with CD4+ T lymphocyte cell (CD4) counts <50 cells/mm³ who are not receiving, adherent to, or responding to antiretroviral therapy (ART).¹⁻³ Among those treated with ART who have achieved virologic control, a new diagnosis of CMV end-organ disease is exceedingly rare.

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis, the most common CMV end-organ disease in such patients.¹⁻³ The incidence of new cases of CMV end-organ disease has declined by $\geq 95\%$ with the advent of potent ART.^{4,5} For those 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 immune recovery sufficient to warrant discontinuation of anti-CMV therapy (i.e., CD4+ counts >100 cells/mm³) relapse of the retinitis occurs at a rate of 0.03/person-year and has been documented⁶ at CD4 counts as high as 1,250 cells/mm³. Therefore, regardless of whether or not anti-CMV therapy is continued, regular ophthalmologic follow-up is needed.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in people with HIV. It occurs as unilateral disease in two-thirds of patients at presentation, but disease ultimately progresses to bilateral in most patients in the absence of therapy or immune recovery.⁶ In patients with unilateral CMV retinitis and CD4 count <50 cells/mm³, rates of contralateral disease approach those of the prepotent ART era.⁶

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. The characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage. 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. There will be little inflammation of the vitreous humor unless immune recovery with ART occurs.¹ 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 over a period of no longer than 6 months. Movement of lesion borders occurs at variable rates in different directions,⁷ causing a characteristic “brushfire” pattern, with their granular, leading edges advancing before an atrophic gliotic scar.⁸

Colitis occurs in 5% to 10% of patients with AIDS and CMV end-organ disease.² The most frequent clinical manifestations are weight loss, fever, anorexia, abdominal pain, diarrhea, and malaise. In the colon, and especially in the cecum, CMV can cause perforation and present as an acute abdomen. Computed tomography may show colonic thickening or a colonic mass that may be mistaken for malignancy or other opportunistic infections (OI). Hemorrhage and perforation can be life-threatening complications.

Esophagitis occurs in a small percentage of patients with AIDS who experience CMV end-organ disease and causes odynophagia, nausea, and occasionally midepigastic or retrosternal discomfort as well as fever.

CMV pneumonitis is uncommon in people with HIV, which is in contrast to other conditions with severe immunosuppression, such as solid organ and stem-cell transplant patients. CMV is detected frequently in the bronchoalveolar lavage (BAL) using DNA-specific polymerase chain reaction (PCR), but is a bystander most of the time and should trigger a search for a more likely causative pathogen. CMV PCR from the BAL has not been shown to have diagnostic value in people with HIV.

CMV neurologic disease includes dementia, ventriculoencephalitis, and polyradiculomyelopathies.⁹ Patients with dementia caused by CMV encephalitis typically have lethargy or confusion in the presence or absence of fever. Cerebrospinal fluid (CSF) 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. Patients 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 of computed tomography or magnetic resonance images is highly suggestive of CMV ventriculoencephalitis, rather than HIV-associated neurocognitive disorder. CMV polyradiculomyelopathy or transverse myelitis causes a Guillain-Barre-like syndrome characterized by radicular back pain, urinary retention, and progressive bilateral leg weakness. Clinical symptoms usually progress over several weeks to include loss of bowel and bladder control and flaccid paraplegia. A spastic myelopathy has been reported, and sacral paresthesia can occur. The CSF in CMV polyradiculopathy usually demonstrates neutrophilic pleocytosis (usually 100 to 200 neutrophils/ μ L and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Diagnosis

The diagnosis of CMV end-organ disease is typically made on the basis of the clinical presentation and, when possible, evidence of the virus in tissue. CMV retinitis usually is diagnosed based on recognition of characteristic retinal changes observed through a dilated pupil during an ophthalmoscopic examination performed by an experienced ophthalmologist. Diagnosis in that setting has a 95% positive predictive value. 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 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, in 77% of relapsed retinitis, and in 23% of quiescent retinitis.¹⁰ 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 usually is 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.^{2,11} Similarly, CMV esophagitis is diagnosed by 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.² The number of inclusion bodies in specimens varies from many inclusion bodies to rare or isolated inclusion bodies. Immunohistochemistry also may be used to detect CMV in tissue. Culturing CMV, or detection of CMV DNA by PCR, from a biopsy or cells brushed from the colon or the esophagus is insufficient to establish the diagnosis of CMV colitis or esophagitis in the absence of histopathologic changes, because a substantial number of patients with low CD4 cell counts may shed CMV and have positive cultures in the absence of clinical disease.¹²

The diagnosis of CMV pneumonitis requires consistent clinical and radiological findings (i.e.,

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.¹³ Detection of CMV in the lungs in the absence of these criteria typically represents shedding, rather than clinical disease.

CMV neurologic disease is diagnosed on the basis of a compatible clinical syndrome and the presence of CMV in CSF or brain tissue, most often evaluated with PCR.^{3,14,15} Blood tests to detect CMV by antigen detection, culture, or PCR are not recommended for diagnosis of CMV end-organ disease because of their poor positive predictive value in people with advanced AIDS.¹⁶ CMV viremia can be detected by PCR, antigen assays, or culture and is often present in endorgan disease. A negative serum or plasma PCR assay does not rule out CMV end-organ disease. CMV viremia may be present in the absence of end-organ disease in people with HIV with low CD4 cell counts.^{9,12–15,17} Monitoring for CMV viremia is not recommended.

The presence of serum antibodies to CMV, in and of itself, 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 (IgG) antibody level indicates that CMV is unlikely to be the cause of the disease process.

Preventing Exposure

Although CMV infection is common in the general population, geographic, socioeconomic, and racial and ethnic differences exist in CMV prevalence.¹⁰ In the National Health and Nutrition Examination Survey (NHANES) 1999–2004, CMV seropositivity was associated with older age, female sex, foreign birthplace, and markers of socioeconomic status, such as low household income and education and high household crowding. Some people with HIV may belong to groups with relatively low seroprevalence rates for CMV and, therefore, cannot be presumed to be seropositive. Adolescents and adults with HIV should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms used during sexual contact reduce the risk of exposure to CMV, as well as other sexually transmitted pathogens (**AII**).

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count >100 cells/mm³ (**BI**). A randomized, placebo-controlled trial addressed whether valganciclovir (the current standard oral agent for treatment of CMV disease) in addition to ART might reduce CMV end-organ disease in AIDS patients at high risk (CD4 count <100 cells/mm³ and CMV viremia detected by plasma CMV DNA PCR assay).¹⁸ This study failed to show a benefit for such preventive therapy; 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**).

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. Patients who have a low CD4 cell count (<100 cells/mm³) and are not on ART should be made aware of the implications of increased floaters in the eye and be advised to assess their visual acuity regularly using simple techniques, such as reading newsprint. Development of floaters or changes in visual acuity should prompt an urgent referral to ophthalmology (**AIII**). In the premodern ART era, some specialists recommended ophthalmologic examinations every 3 to 4 months for patients with CD4+ cells <50 cells/mm³, because up to one-half of early CMV retinitis was asymptomatic (**CIII**). However, with the decline in CMV incidence in the modern ART era, the value of this recommendation is unknown. Some clinicians do recommend a baseline ophthalmologic exam for people with HIV with CD4 <100 cells/mm³ (**CIII**).

Treating Disease

The therapeutic approach to CMV retinitis should be individualized based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and possibly the location of lesions (**AIII**). CMV retinitis should ideally be treated with the active participation of an ophthalmologist who is familiar with the diagnosis and management of this retinal disease (**AIII**).

Oral valganciclovir (**AI**), intravenous (IV) ganciclovir (**AI**), or IV ganciclovir induction followed by oral valganciclovir maintenance (**AI**) are first-line therapies for treating CMV retinitis. Although IV foscarnet (**BI**), and IV cidofovir (**CI**) are also effective treatments for CMV retinitis, substantial toxicities, including nephrotoxicity, make these less-preferred options.^{8,19–26} Systemic therapy has been documented to reduce CMV involvement of the contralateral eye,¹⁹ to reduce CMV visceral disease, and to improve survival.^{20,27} Given the evident benefits of systemic anti-CMV therapy, treatment regimens for CMV retinitis should include a systemic component. Few trials have compared regimen efficacy during the past 15 years. None of the listed regimens has been proven in a clinical trial to have superior efficacy related to protecting vision. Therefore, clinical judgment must be used when choosing a regimen.^{21–25}

When systemic therapy is indicated, most clinicians will prescribe IV ganciclovir (**AI**) or oral valganciclovir (**AI**) for an induction period lasting a minimum of 14 to 21 days, with the duration determined by clinical response based on retinal examination. Many prefer the IV formulation when retinitis is more central and sight-threatening or when adequate gastrointestinal (GI) absorption is a concern. In such cases, the patient's transition to oral valganciclovir can be considered when there is evidence of clinical response. In cases where toxicity of ganciclovir and valganciclovir (i.e., severe cytopenias) is a concern and there is not renal insufficiency, or when ganciclovir-resistant CMV is a concern, IV foscarnet may be used (**BI**). IV cidofovir is rarely used, unless there is the need to avoid both ganciclovir and foscarnet (**CI**). Cidofovir administration is complicated by the need to co-administer IV fluid hydration and probenecid to counter the nephrotoxicity of the drug. In addition, IV cidofovir is associated with increased risk of immune recovery uveitis, hypotony, and neutropenia.²⁸

In the presence of immediately sight-threatening lesions (those within 1,500 microns of the fovea or optic disc) at presentation (**AIII**), some clinicians will supplement 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 (**AIII**). Injections are continued on a weekly basis until lesion inactivity is achieved, at which time systemic treatment alone is considered to be adequate for maintenance therapy. The recommendation to supplement systemic therapy with intravitreal injections is based on 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,¹⁹ such injections can be complicated by bacterial or fungal infections, hemorrhage, or retinal detachment. Repeated intravitreal injections of ganciclovir or of foscarnet alone have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series,²⁹ but this strategy should be reserved for those individuals who cannot be treated systemically. Intravitreal cidofovir is associated with hypotony and uveitis—and a substantially increased risk of immune recovery uveitis—and should be avoided (**AIII**).³⁰

For patients without sight-threatening lesions, oral valganciclovir alone often is adequate (**AI**). The ganciclovir implant, a surgically implanted reservoir of ganciclovir that lasts for approximately 6 months, is no longer manufactured.

Treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery, is beneficial (**AII**). Ocular complications, such as immune recovery uveitis (IRU) and retinal detachment, are related to lesion size, so minimizing lesion size with anti-CMV therapy until immune recovery is sufficient to control the retinitis is logical. Furthermore, evidence from both the pre-ART and ART eras demonstrate that specific anti-CMV therapy decreases mortality among immune-compromised patients with CMV retinitis.^{12,20,26,31}

For patients who have colitis or esophagitis, many HIV specialists recommend anti-CMV therapy for 21 to 42 days **(CII)** or until signs and symptoms have resolved. IV ganciclovir generally is the therapy of choice and can be switched to oral valganciclovir once the patient can tolerate and absorb oral medications **(BI)**. Foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment-limiting or in cases of ganciclovir-resistant virus **(BIII)**. Oral valganciclovir can be used in patients with mild disease **(BIII)**.

Experience treating well-documented CMV pneumonia in patients with HIV infection is limited and anecdotal. Treatment with IV ganciclovir or, alternatively, with foscarnet, is logical **(CIII)**. The optimal duration of therapy and the role of oral valganciclovir have not been established.

Therapy for well-documented neurologic disease also has not been extensively studied. Given the poor outcomes in many patients with CMV-related neurologic disease, some experts would initiate therapy with both IV ganciclovir and IV foscarnet, despite the substantial toxicities associated with such an approach **(CIII)**. The optimal duration of therapy and the role of oral valganciclovir have not been established.

Special Considerations with Regard to Starting Antiretroviral Therapy

Immune reconstitution inflammatory syndrome (IRIS) from CMV may occur in patients who have active retinitis and those who have had CMV retinitis in the recent or distant past. One study demonstrated a substantial increase in immune reconstitution uveitis (IRU) in association with immediate, as opposed to deferred initiation of ART (71% vs. 31%).³² 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). 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. Several trials have demonstrated benefits of early versus delayed ART, including reduced risk of mortality, reduced AIDS progression, and shorter time to viral suppression.^{33–36} Only one study has evaluated the benefits of early ART during treatment of an active OI, and it included few participants with CMV disease.³⁴

As CMV replication usually declines within 1 to 2 weeks after anti-CMV therapy is initiated, most experts would initiate ART no later than 1 to 2 weeks after starting anti-CMV therapy for retinitis, esophagitis, colitis, or other end-organ diseases caused by CMV **(CIII)**. IRIS is a particular concern with any neurologic disease, including CMV encephalitis, ventriculitis, and radiculitis. In these cases, however, most experts would not defer initiation of ART for more than 2 weeks, although clinical judgment based on individual cases is needed **(CIII)**.

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

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 **(CIII)**. The purpose of such examinations is to evaluate efficacy of treatment, identify second eye involvement in cases of unilateral disease, and detect IRU or such complications 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 patients who have experienced immune recovery (CD4+ count >100 cells/mm³ for ≥3 months), the frequency of ophthalmologic follow-up can be decreased to every 3 months, but clinicians should be aware that lesion reactivation and retinal complications still occasionally occur in patients with immune reconstitution.

Adverse effects of ganciclovir/valganciclovir include anemia, neutropenia, thrombocytopenia, nausea, diarrhea, and renal dysfunction. Ganciclovir-related neutropenia often can be reversed with granulocyte colony stimulating factor (G-CSF).^{33,34} In patients receiving ganciclovir or valganciclovir,

complete blood counts and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy (**AIII**). Adverse effects of foscarnet include nephrotoxicity and electrolyte abnormalities; seizures that occur characteristically in the context of renal insufficiency; and anemia. Genital ulcers also can occur during foscarnet administration in those who are incontinent to urine due to the toxic effects of excreted drug on exposed skin. Foscarnet often is given in the inpatient setting because of the intensity of monitoring and need for hydration. For patients receiving foscarnet in the outpatient setting, serum electrolytes (including potassium, magnesium, calcium, and phosphorus) and renal function should be measured at least twice weekly during induction and at least weekly during maintenance therapy. Complete blood counts should be monitored weekly (**AIII**).

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 prehydration and oral probenecid before cidofovir administration. In patients receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion. Drug administration is contraindicated if renal dysfunction or substantial proteinuria is detected. 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.

As noted previously, patients with CMV retinitis must have careful ophthalmologic monitoring to detect and manage the wide range of complications related to CMV, the drugs used to treat CMV, and IRIS. IRU, an ocular form of IRIS presumed to be an adverse immunologic reaction to CMV, is characterized by inflammation in the anterior chamber or vitreous body in the setting of immune recovery after initiation of ART. IRU usually is observed in patients with a substantial rise in CD4 cell count in the first 4 to 12 weeks after initiation of ART.^{28,35–38} The estimated incidence of IRU is 0.02/person-year after immune recovery.³⁹ Ocular complications of IRU include macular edema and 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 some type of corticosteroid therapy. The benefit of anti-CMV therapy is unclear.^{35,40} Many experts would use both corticosteroids and anti-CMV therapy (**CIII**). Data are insufficient on 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. When oral corticosteroids are used, a short course rather than chronic therapy usually is recommended (**BIII**).⁴¹ IRU can occur months or years after successful treatment of CMV retinitis in patients with a history of CMV retinitis who subsequently start taking ART or have such therapy optimized.

People with advanced HIV remain at risk for development of CMV retinitis prior to immune reconstitution, even after initiation of ART.^{42,43} Development of CMV retinitis in the setting of recent ART initiation should be treated with systemic anti-CMV therapy, similar to any patient with CMV retinitis, and the same ART regimen should be continued (**AI**). Corticosteroids are not recommended (**AIII**). In addition, in the absence of uveitis, corticosteroids should not be used in patients undergoing treatment for CMV retinitis who have worsening of retinitis upon ART initiation. In this situation, anti-CMV therapy and ART regimens should be continued (**AIII**).

Managing Treatment Failure

Failure of therapy for CMV retinitis or reactivation of lesions is most likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART.⁴⁴ Treatment failure

also may be a result of inadequate anti-CMV drug levels in the eye, CMV drug resistance, or nonadherence. 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.^{40,45,46}

When reactivation of lesions occurs in patients receiving maintenance therapy, retinitis usually can be controlled with re-induction of the same drug used for maintenance followed by re-institution of maintenance therapy (**BIII**).⁴⁷ Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy and for patients with continued progression or multiple reactivations of retinitis (**CIII**).⁴⁷ This drug combination, however, is associated with substantial toxicity.

Drug resistance can occur in patients receiving long-term anti-CMV therapy.^{48–51} Drug resistance rates of approximately 25% per person-year were reported in the pre-ART era^{48,52,53} for ganciclovir, foscarnet, and cidofovir.^{48,49} In the ART era, the rate of resistance appears to be lower (approximately 5% per person-year).⁵⁴ 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.^{50,55–59} 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 cidofovir⁵⁷ and occasionally to foscarnet.⁵⁸ Although early CMV disease progression typically is not a result of drug resistance, late CMV reactivation may be. By themselves, peripheral blood CMV viral load measurements have poor positive predictive value for treatment failure.

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.^{60–62} 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.⁶² Circulating CMV in blood and vitreous fluid have identical UL97 sequences in more than 90% of cases;⁶³ therefore, evaluating the blood for resistance is reasonable, and detection of resistance in the blood or urine correlates with clinical behavior of the retinitis in most cases.⁶⁴ 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.⁶⁵ Many clinicians will treat ganciclovir-resistant CMV with a series of intravitreal injections of foscarnet and/or IV foscarnet or cidofovir (**CIII**).

Preventing Recurrence

When to Start Maintenance Therapy

After induction therapy for CMV retinitis, chronic maintenance therapy should be continued,^{9,14,19,22,66} until immune reconstitution occurs as a result of ART (**AI**). Maintenance therapy is started after induction has achieved control of retinitis, as evidenced by resolved or markedly reduced retinal lesion opacity, indicating virus inactivity. Although several regimens are effective for chronic suppression—including parenteral ganciclovir, parenteral foscarnet, and parenteral cidofovir—oral valganciclovir may be the easiest and least toxic to administer to an outpatient population, provided that GI absorption is adequate. Systemic therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred.

The choice of regimen (i.e., which drug[s] and whether given intravitreally, orally, or intravenously) should be made in consultation with an ophthalmologist. Considerations should include the anatomic location of the retinal lesion; vision in the contralateral eye; and a patient's immunologic and virologic status, comorbidities, concomitant medications, and response to ART.

After resolution of the acute CMV syndrome and initiation of effective ART, chronic mainte-

nance therapy is not routinely recommended for CMV GI disease, pneumonitis, and central nervous system disease unless there is concurrent retinitis, there have already been recurrent infections, or severe disease was present initially (**BII**).

When to Stop Maintenance Therapy

Maintenance therapy can be discontinued safely in adults and adolescents with CMV retinitis whose lesions have been treated for at least 3 to 6 months and are inactive and who have had sustained (i.e., 3–6 months) increases in CD4 cell counts to >100 cells/mm³ in response to ART (**AII**).^{4,67–73} Such decisions should be made in consultation with an ophthalmologist. A 3% reactivation rate is reported in patients whose anti-CMV therapy has been discontinued for immune recovery, and no level of CD4 cell count is absolutely safe (reactivations have been reported at CD4 cell counts of 1,250 cells/mm³). Therefore, in all patients for whom anti-CMV maintenance therapy has been discontinued, ophthalmologic monitoring for early detection of CMV relapse and for IRU should be performed at least every 3 months and periodically after immune reconstitution (**AIII**). Monitoring CMV viral load in blood has poor positive predictive value for relapse of retinitis and, therefore, is not recommended (**AII**).¹⁶

Reactivation of CMV retinitis occurs frequently in patients whose CD4 cell counts have decreased to <50 cells/mm³ and whose anti-CMV maintenance therapies have been discontinued.⁷⁴ Therefore, reinstitution of maintenance therapy should occur when the CD4 cell count has decreased to <100 cells/mm³ (**AIII**).

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for nonpregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant people with HIV (**AIII**). For retinal disease, use of intravitreal injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs (**BIII**). Systemic antiviral therapy should then be started after the first trimester. For life-threatening indications, treatment with systemic antiviral therapy during the first trimester may be necessary.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.^{75–77} However, safe use in all trimesters of human pregnancy after organ transplantation and in other patient populations has been reported.^{75–79}

Foscarnet is associated with an increase in skeletal anomalies or variants in rats and rabbits. No experience with use early in human pregnancy has been reported. A single case report of use in the third trimester described normal infant outcome.⁸⁰ Because toxicity of foscarnet is primarily renal, weekly monitoring of amniotic fluid volumes by ultrasound is recommended after 20 weeks of gestation to detect oligohydramnios if foscarnet is used.

Cidofovir is embryotoxic and teratogenic (i.e., meningomyelocele and skeletal abnormalities) among rats and rabbits. No experience with use of cidofovir in human pregnancy has been reported; use in pregnancy is not recommended (**AIII**).

On the basis of limited data, toxicity reports, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy (**BIII**). The fetus should be monitored by fetal-movement counting in the third trimester and by periodic ultrasound monitoring after 20 weeks of gestation to look for evidence of hydrops fetalis indicating substantial anemia. No data exist to support use of pooled or CMV-specific intravenous immunoglobulin in this clinical situation.

Primary infection, reactivation, and reinfection with a different strain of CMV during pregnancy (non-primary infection)⁸¹ all can lead to *in utero* transmission and congenital CMV. Maternal ART in pregnancy 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.⁸² Recent studies indicate the prevalence of congenital CMV among infants in the United States who are exposed to HIV is 1.2% to 1.3%.⁸³ Risk factors for congenital CMV include mothers with CD4+ <200 cells/mm³, mothers with urinary CMV shedding,⁸⁴ and HIV transmission to infants. Maternal CMV and infant congenital CMV also have been associated with increased risk of HIV perinatal transmission in pregnant women with HIV who have not received antenatal ART.⁸⁵

In women diagnosed with primary CMV infection in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation (**CIII**). In studies in HIV-uninfected populations, 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).⁸⁶ Any ultrasound findings suspicious for congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis. 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.⁸⁷

If fetal CMV infection is confirmed, no standard therapy exists for *in utero* treatment. Available clinical studies support the possible effectiveness and safety of CMV hyperimmune globulin in pregnancy for prevention or treatment of congenital CMV.^{88,89} A nonrandomized trial of CMV hyperimmune globulin in women not infected with HIV with primary CMV infection in pregnancy found decreased incidence of having a symptomatic newborn at birth⁹⁰ and regression of fetal cerebral abnormalities;⁹¹ however, a well-designed, prospective, randomized, placebo-controlled study with relatively large sample size subsequently found no benefit of CMV hyperimmune globulin in pregnant women.^{88,92,93} A second randomized clinical trial that planned to enroll 800 patients with primary CMV infection at <24 weeks gestation was stopped for futility after enrollment of 399 participants when a planned interim analysis suggested that complete enrollment would not provide a significant outcome.⁹³

Routine screening for CMV infection in pregnancy is not recommended in the absence of effective *in utero* therapy. Treatment of asymptomatic maternal CMV infection during pregnancy solely to prevent infant infection is not indicated (**AIII**).

Recommendations for Treating Cytomegalovirus Infections

Preventing CMV Disease

- CMV end-organ disease is best prevented by using ART to maintain CD4+ count >100 cells/mm³.

Managing CMV Retinitis

- The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications; prior exposure to anti-CMV drugs; and on the location of lesions (**AIII**).
- Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reducing CMV visceral disease, and improving survival, treatment should include systemic therapy whenever feasible.

Initial Therapy Followed by Chronic Maintenance Therapy—For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea)

Preferred Therapy

- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV daily (**AI**), *or*
- Ganciclovir 5 mg/kg IV q12h for 14–21 days, then valganciclovir 900 mg PO daily (**AI**), *or*
- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily (**AI**); *or* with or without
- Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) repeat weekly until lesion inactivity is achieved. This is to provide higher intraocular levels of drug and faster control of the infection until steady-state intraocular ganciclovir concentrations are achieved. (**AIII**)
 - **Note:** IV ganciclovir can be switched to oral valganciclovir if the patient is clinically improving and there are no concerns about gastrointestinal absorption.

Alternative Therapy

- Intravitreal injections as listed above (**AIII**); plus one of the following systemic therapies:
 - Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h (**BI**), *or*
 - Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week 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) (**CI**). Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/dL, a calculated creatinine clearance ≤5 mL/min or a urine protein ≥100 mg/dL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised
- **Note:** This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.

For Peripheral Lesions

- Valganciclovir 900 mg PO q12h for 14–21 days, then 900 mg once daily (**AI**) for the first 3–6 months until ART-induced immune recovery (**AII**).

IRU

- Minimizing lesion size by treating all CMV retinitis lesions until there is immune recovery may reduce the incidence of IRU (**BII**).
- IRU might develop in the setting of immune reconstitution.

Treatment of IRU

- Pericardial or intravitreal corticosteroid or a short course of systemic steroid (**BIII**).

Stopping Chronic Maintenance Therapy for CMV Retinitis

- CMV treatment for at least 3–6 months, and lesions are inactive, and with CD4+ count >100 cells/mm³ for 3–6 months in response to ART (**AII**).
- Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of CD4 cell count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring.
- Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution (**AIII**).

Reinstituting Chronic Maintenance for CMV Retinitis

- CD4 count <100 cells/mm³ (**AIII**).

<p>Managing CMV Esophagitis or Colitis</p> <ul style="list-style-type: none"> Doses are the same as for CMV retinitis. <p><i>Preferred Therapy</i></p> <ul style="list-style-type: none"> Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy (BI). <p><i>Alternative Therapy</i></p> <ul style="list-style-type: none"> Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h (BIII)—for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance; <i>or</i> Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption (BIII); <i>or</i> <p><i>Duration of Anti-CMV Therapy</i></p> <ul style="list-style-type: none"> 21–42 days or until signs and symptoms have resolved (CII). <p>Note: Maintenance therapy is usually not necessary, but should be considered after relapses (BII).</p>
<p>Managing Well-Documented CMV Pneumonitis</p> <ul style="list-style-type: none"> Doses are the same as for CMV retinitis. Treatment experience for CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (CIII). The role of oral valganciclovir has not been established. The optimal duration of therapy has not been established.
<p>Managing CMV Neurological Disease</p> <ul style="list-style-type: none"> Doses are the same as for CMV retinitis. <u>Treatment should be initiated promptly.</u> Combination of ganciclovir IV plus foscarnet IV to stabilize disease and maximize response (CIII). Optimal duration of therapy has not been established. The role of oral valganciclovir has not been established. Optimize ART to achieve viral suppression and immune reconstitution (BIII).

Key to Acronyms: ART = antiretroviral therapy; BID = twice a day; CMV = cytomegalovirus; IRU = immune recovery uveitis; PO = orally; IV = intravenously; q(n)h = every “n” hours

References

- 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>.
- 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>.
- 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>.
- 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>.
- 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>.
- 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>.
- 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>.

8. 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>.
9. Arribas JR, Clifford DB, Fichtenbaum CJ, Commings 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>.
10. 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>.
11. 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>.
12. 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>.
13. 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>.
14. 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>.
15. 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>.
16. 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>.
17. 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>.
18. 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>.
19. 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>.
20. 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>.
21. Studies of Ocular Complications of AIDS Research Group, AIDS Clinical Trial Group. 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>.

22. 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>.
23. 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>.
24. 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>.
25. 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>.
26. 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>.
27. Jabs DA, Ahuja A, Van Natta M, Dunn JP, Yeh S, Studies of the Ocular Complications of AIDS Research Group. 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>.
28. 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>.
29. Young S, Morlet N, Besen G, et al. High-dose (2,000-microgram) intravitreal ganciclovir in the treatment of cytomegalovirus retinitis. *Ophthalmology*. 1998;105(8):1404-1410. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9709750>.
30. Taskintuna I, Rahhal FM, Rao NA, et al. Adverse events and autopsy findings after intravitreal 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>.
31. 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>.
32. 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>.
33. 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>.

34. 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>.
35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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>.
40. 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>.
41. Morrison VL, Kozak I, LaBree LD, Azen SP, Kayicioglu OO, Freeman WR. Intravitreal triamcinolone acetate for the treatment of immune recovery uveitis macular edema. *Ophthalmology*. 2007;114(2):334-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17270681>.
42. 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>.
43. Jabs DA, Van Natta ML, Holland GN, Danis R, Studies of the Ocular Complications of AIDS Research Group. 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>.
44. 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>.
45. Kuppermann BD, Quiceno JJ, 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>.
46. Arevalo JF, Gonzalez C, Capparelli EV, et al. Intravitreal 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>.

47. 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>.
48. 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>.
49. 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>.
50. 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>.
51. 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>.
52. 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>.
53. 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>.
54. Martin BK, Ricks MO, Forman MS, Jabs DA, Cytomegalovirus Retinitis and Viral Resistance Study Group. 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>.
55. 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>.
56. 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>.
57. 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>.
58. 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>.
59. 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>.

60. 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>.
61. Vitracene Study Group. Randomized dose-comparison studies of intravitreal 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>.
62. Jabs DA, Martin BK, Ricks MO, Forman MS, Cytomegalovirus Retinitis and Viral Resistance Study Group. 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>.
63. 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>.
64. 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>.
65. Jabs DA, Martin BK, Forman MS, Cytomegalovirus Retinitis and Viral Resistance Study Group. 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>.
66. AIDS Clinical Trials Group. Studies of ocular complications of AIDS Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 1. Rationale, design, and methods. *Control Clin Trials*. 1992;13(1):22-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1315661>.
67. 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>.
68. 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>.
69. 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>.
70. 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>.
71. 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>.

72. 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>.
73. 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>.
74. 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>.
75. 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>.
76. 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>.
77. 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>.
78. 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>.
79. 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>.
80. 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>.
81. 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>.
82. 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>.
83. Purswani MU, Russell JS, Dietrich M, et al. Birth prevalence of congenital cytomegalovirus infection in HIV-exposed uninfected children in the era of combination antiretroviral therapy. *J Pediatr*. 2020;216:82-87.e82. Available at: <https://www.sciencedirect.com/science/article/pii/S0022347619311618?via%3Dihub>.
84. 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/](https://pubmed.ncbi.nlm.nih.gov/28369278/).

85. 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/>.
86. Society for Maternal-Fetal M, 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>.
87. Tanimura K, Yamada H. Potential biomarker 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#>.
88. 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/>.
89. Nigro G, Adler SP. 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/>.
90. 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>.
91. 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>.
92. 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>.
93. Hughes B. LB17. Randomized trial to prevent congenital cytomegalovirus (CMV). *Open Forum Infect Dis*. 2019;6:S1000-S1001. Available at: https://academic.oup.com/ofid/article/6/Supplement_2/S1000/5603805.

Hepatitis B Virus Infection

Updated: September 7, 2022

Reviewed: January 11, 2023

Epidemiology

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide.¹⁻⁵ Globally and in North America, approximately 10% of people with HIV have evidence of chronic HBV infection.⁶⁻⁸

Transmission routes vary geographically, with perinatal and early-childhood exposures responsible for most HBV transmission in higher-prevalence regions.⁹ 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 is becoming prevalent due to the increasing foreign-born population.¹⁰ Although the general modes of transmission are similar to those of HIV, HBV is transmitted more efficiently than HIV.^{1,2} The risk of progression to chronic HBV infection decreases with age and is 90% among those with HBV infection before 1 year of age, 25% to 50% among those with HBV infection between 1 year and 5 years of age, and <5% among those infected with HBV as adults.^{10,11} People with HIV are at increased risk for developing chronic HBV infection.¹² Genotypes of HBV (A–J) have been identified, and their geographic distributions differ.¹³ Genotype A is most common among people with HBV infection in North America and Western Europe and genotypes B and C among people with HBV infection in Asia.¹⁴

Clinical Manifestations

Acute HBV infection is asymptomatic in approximately 70% of persons infected; <1% of people with HBV infection develop fulminant hepatic failure.^{3,15} When symptoms manifest, they may include right upper quadrant abdominal pain, nausea, vomiting, fever, and arthralgias with or without jaundice. HBV has an average incubation period of 90 days (range 60–150 days) from exposure to onset of jaundice and 60 days (range 40–90 days) from exposure to onset of abnormal liver enzymes. 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 develop cirrhosis, hepatocellular carcinoma (HCC), or liver failure, and up to 25% of people will die prematurely from complications of chronic HBV infection.¹⁶

Diagnosis

The Centers for Disease Control and Prevention, the United States Preventive Services Taskforce, and the American Association for the Study of Liver Disease (AASLD) recommend testing people with HIV for chronic HBV infection.¹⁷⁻¹⁹ Initial testing should include serologic testing for HBV surface antigen (HBsAg), HBV core antibody (anti-HBc total), and HBV surface antibody (anti-HBs) (**AI**). In acute infection, HBsAg can be detected 4 weeks (range 1–9 weeks) after exposure, and anti-HBc immunoglobulin M is usually detectable at the onset of symptoms.

Chronic HBV infection is defined as persistent HBsAg detected on two occasions at least 6 months apart.¹⁹ 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 serum HBV DNA and

persistent or fluctuating alanine transaminase (ALT) elevations.¹⁹ People whose past infection has resolved are HBsAg-negative with positive anti-HBs and/or anti-HBc, although covalently closed circular DNA (cccDNA) may remain in hepatocyte nuclei.^{3,20} With cccDNA in hepatocyte nuclei, a patient with severe immune suppression—such as seen with anti-CD20 therapy or after stem cell transplant—may become serum HBsAg-positive again with HBV viremia.^{21,22}

The presence of an isolated anti-HBc test result usually signifies infection with HBV in the past with subsequent loss of anti-HBs and occurs in 7% to 19% of people with HIV.²³⁻²⁷ Incidence of HBV viremia among people with HIV and isolated anti-HBc ranges from 1% to 36%.^{23,25,28-30} The clinical significance of isolated anti-HBc is unknown,^{23,27,30-32} but in people with HIV, it may indicate chronic or, more likely, resolved HBV infection.^{26,33,34} In a low-prevalence country—such as the United States—isolated anti-HBc also may represent a false-positive result.^{26,33,35,36} People with HIV—particularly those with underlying hepatitis C virus (HCV) coinfection—have a higher frequency of isolated anti-HBc.^{26,37,38}

Diagnosing HBV Disease Progression and the Role of Assessment of Liver Fibrosis

Compared with people with HBV monoinfection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.³⁹ Among people with HBV monoinfection, HBV DNA suppression, anti-HBe seroconversion (to anti-HBe-seronegativity), HBsAg loss, and acquisition of anti-HBs are all associated with a decreased incidence of cirrhosis, HCC,⁴⁰⁻⁴² and improved survival.⁴³⁻⁴⁶ In comparison, people with HIV/HBV coinfection are usually more likely to have detectable HBeAg,^{39,47} lower rates of seroconversion to anti-HBe, and increased risk of HCC and liver-related mortality and morbidity.^{48,49}

Chronic HBV infection is a dynamic disease with a number of phases that are associated with either active or inactive chronic hepatitis and include the following: the immune-tolerant phase (normal ALT [upper limits of normal 19–25 U/L for women and 29–33 U/L for men], HBeAg-positive, high HBV DNA), the immune active phase (HBeAg-positive or -negative, detectable HBV DNA, elevated ALT), and the inactive hepatitis B phase (HBeAg-negative, anti-HBe-positive, low or undetectable HBV DNA, normal ALT).¹⁹ Duration of disease phases is different in those who acquire infection as neonates or young children than in those who acquire infection as adults. The immune tolerant phase occurs primarily among perinatally infected persons. Clinicians should be knowledgeable about these phases among people with HBV monoinfection to determine who needs treatment and who should be monitored (see the [AASLD 2018 Hepatitis B Guidance](#)). In HIV/HBV coinfection, monitoring and treatment also are focused on the simultaneous treatment of both viruses.

People with anti-HBe seroconversion and HBeAg loss usually transition into the inactive hepatitis B phase.¹⁶ This transition can be spontaneous or associated with effective HBV treatment. In some instances, increased levels of ALT may precede a decline in HBV DNA that is accompanied by anti-HBe seroconversion—that is, loss of HBeAg and development of anti-HBe.⁵⁰ However, such spontaneous HBeAg conversion rates appear to be lower among people with HIV/HBV coinfection than among people with HBV monoinfection. People in the inactive state remain at risk of reactivation of HBV infection and development of HCC, but the risk is lower than for people with active HBV replication. In any patient, the reemergence of abnormal liver enzyme tests may reflect HBeAg-negative chronic HBV disease, a result of mutations in the basal core and precore promoter regions of the virus.¹⁶ Although people who are HBeAg-negative usually have lower levels of HBV DNA, they experience unrelenting but fluctuating disease progression, with changing HBV DNA

levels.⁵¹ People in the inactive phase still require HBeAg, ALT, and HBV DNA monitoring. Persistent low-level serum ALT abnormalities may be associated with significant liver disease, although normal ALT levels also may be seen in the setting of cirrhosis.⁵¹

When chronic HBV infection is diagnosed, patients should be linked to care and have a complete history and physical examination for signs of cirrhosis or HCC. In addition, clinicians should perform HBV serologic 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), and anti-hepatitis A virus—to determine the need for vaccination, abdominal ultrasound, and liver fibrosis assessments at the initial visit and monitor these every 6 to 12 months.³ People with chronic HBV infection are at increased risk of HCC; therefore, HCC surveillance every 6 months is required for people who are cirrhotic 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.⁵² People with HIV/HBV coinfection are at increased risk of HCC,⁵³ and some experts recommend screening people who have HIV/HBV coinfection and are older than 40 years of age for HCC. Assessment of the patient's liver fibrosis stage is important. Increasing evidence indicates that noninvasive methods (i.e., elastography and serum markers) to evaluate liver fibrosis can be used to determine fibrosis in HBV infection.⁵⁴ The decision to perform a liver biopsy should be individualized, but the procedure is rarely necessary.³

Preventing Exposure

HBV infection is transmitted primarily through percutaneous or mucosal exposure to infectious blood or body fluids. Therefore, people with HIV should be counseled about transmission risks for HBV infection and encouraged to avoid behaviors associated with such transmission (**AIII**). Such counseling should emphasize sexual transmission and the risks associated with sharing needles and syringes, unregulated tattooing, or body piercing.

Preventing Disease

All family members and sexual contacts of people with HBV infection should be tested, and all susceptible contacts should receive hepatitis B (HepB) vaccine regardless of whether they have HIV (**AII**). HepB vaccination is the most effective way to prevent HBV infection and its consequences. All people with HIV who are susceptible to HBV infection should receive HepB vaccination with one of the available vaccines (see below) (**AII**) or with the combined hepatitis A (HepA) and HepB vaccine (Twinrix®) (**AII**).

All people with HIV should be screened for HBV infection, and screening should include HBsAg, anti-HBs, and anti-HBc.^{17,18,51} A patient who is seropositive for anti-HBc and anti-HBs has resolved infection and does not need vaccination. Similarly, the presence of anti-HBs alone at levels ≥ 10 mIU/mL after completion of the vaccine series is consistent with seroprotection,⁵⁵ and no further vaccinations are required.⁵⁶ The interpretation is less clear among people with the isolated anti-HBc pattern (HBsAg-negative, anti-HBc-positive, anti-HBs-negative). Aside from false-positive results, this pattern may signify infection in the distant past with subsequent loss of anti-HBs.⁵⁷ Most people with HIV with isolated anti-HBc are HBV DNA-negative and not immune to HBV infection³⁸; therefore, routinely checking HBV DNA is not recommended. However, such people should be vaccinated with one standard dose of HepB vaccine, 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 HepB vaccine should be completed and followed by anti-HBs testing **(BII)**.⁵⁸ 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.⁵⁸ 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)**.

Available adult single-antigen HepB vaccines include two recombinant HBsAg vaccines (Engerix-B® and Recombivax-HB®) and a recombinant HBsAg vaccine conjugated to a cytosine phosphoguanine oligonucleotide (CpG 1018) adjuvant, which is a toll-like receptor 9 agonist (Heplisav-B®). The magnitude and duration of immunogenicity to HepB vaccination with the recombinant vaccines in adults with HIV are significantly lower than in healthy adults who are HIV seronegative.^{56,59-61} Factors associated with poor response to recombinant vaccines include low CD4 T lymphocyte cell (CD4) counts,^{59,62-67} presence of detectable HIV RNA,^{63,67,68} coinfection with HCV, occult HBV infection, and the general health status of the host.^{25,38,69-73} Although vaccine response is better when CD4 counts are >350 cells/mm³, vaccination should not be deferred until CD4 counts increase to >350 cells/mm³ because some people with HIV with CD4 counts <350 cells/mm³ do respond to vaccination **(AII)**.

If the recombinant vaccine three-dose series is given to people with HIV, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) recommends double-dose vaccine as the primary series, because a recent meta-analysis of 10 studies of people with HIV demonstrated that compared to a single dose, a double dose 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 **(AII)**.⁷⁴

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 PLWH who received the HepB vaccine, those with anti-HBs ≥ 10 mIU/mL were less likely to develop acute HBV infection compared to those who did not achieve that level (5% vs 11%, hazard ratio 0.51; 95% CI 0.3–1.0).⁷⁵ In addition, among those who were acutely HBV infected, 0% of those with anti-HBs ≥ 10 mIU/mL developed chronic infection compared to 35% of those with anti-HBs <10 mIU/mL ($P = 0.02$).

Because of waning immunity, some experts would check anti-HBs annually and a booster dose would be given if levels fall below 10mIU/mL, particularly if patients have on going risk factors for acquiring HBV and are not receiving tenofovir.

Among people with HIV who did not respond (anti-HBs titers <10 mIU/mL) to a primary three-dose vaccine series with a single-dose recombinant vaccine, 25% to 50% responded to an additional vaccine dose, and 44% to 100% responded to a three-dose revaccination series.⁷⁶⁻⁷⁹ As a result, people with HIV who do not respond to a complete HepB vaccination series with one of the recombinant vaccines should be revaccinated with three double doses or with Heplisav-B **(BIII)**,⁵⁶ although some specialists might delay revaccination until antiretroviral therapy (ART) results in a sustained increase in CD4 count **(CIII)**. Two randomized controlled trials have shown that giving four double doses of the recombinant vaccine produces higher anti-HBs titers than three doses of single-dose vaccine,^{80,81} and one study also showed a higher overall response rate.⁸¹ Some specialists consider that this approach—four doses—improves immunologic response in people with HIV either as an initial vaccination schedule or among people who are non-responders. However, whether

vaccination with a schedule of four double doses is superior to four single doses or three double doses is still unclear.

In four randomized-controlled trials, a regimen of two doses of [Heplisav-B®](#) was superior to three doses of Engerix-B® in people without HIV.⁸²⁻⁸⁴ In the largest trial, the protection rate was 95% for Heplisav-B® and 81% for Engerix-B®.⁸⁴ An increase in the number of cardiovascular events was observed in the Heplisav-B® group that was not statistically significant. A study of the safety and efficacy of Heplisav-B® in people with HIV is underway. If a two-dose vaccine is preferred, Heplisav-B® is an option (**CIII**). If Heplisav-B® is used, the vaccine should not be interchanged with either of the other recombinant vaccines for the second dose.

[Recommendations](#) provided by the Advisory Committee on Immunization Practices state that the two-dose vaccine series is appropriate only when both doses are Heplisav-B®. In other situations, three total doses of vaccine should be given.

Preventing Other Liver Diseases

HepA vaccination is recommended for all people who are hepatitis A virus (HAV) antibody-negative and have chronic liver disease,³ for people who are injection and non-injection drug users, and for men who have sex with men (**AIII**). Among people with HIV with CD4 counts <200 cells/mm³, responses to the HepA vaccine are reduced.^{85,86} Antibody response should be assessed 1 month after vaccination is complete. If anti-HAV immunoglobulin G (IgG) is negative, people should be revaccinated when their CD4 count is >200 cells/mm³ (**BIII**).

People with chronic HBV infection should be advised to avoid alcohol consumption (**AIII**).

Treating Disease

The ultimate treatment goals in HIV/HBV coinfection are the same as for HBV monoinfection: to prevent disease progression and to reduce HBV-related morbidity and mortality. People with HIV/HBV coinfection should receive tenofovir disoproxil fumarate (TDF)- or tenofovir alafenamide (TAF)-based ART.

Special Considerations with Regard to Starting ART

Preferred Regimen

The U.S. Department of Health and Human Services [Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV](#) (Adult and Adolescent Antiretroviral Guidelines) recommend the fixed-dose coformulations of TDF/(emtricitabine [FTC] or lamivudine [3TC]), TAF/FTC, or abacavir/3TC as nucleoside reverse transcriptase inhibitor (NRTI) regimen backbones for most ART-naïve people regardless of CD4 count.⁸⁷ Because both tenofovir and (FTC or 3TC) have anti-HBV activity, the tenofovir combinations are also the treatment of choice for people with HIV/HBV coinfection (**AIII**) regardless of CD4 count (**AI**) and HBV DNA level (**AIII**) (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 log₁₀ declines in HBV DNA levels.⁸⁸⁻⁹³ TDF and TAF have a high genetic barrier for development of resistance mutations (**AI**).^{3,94}

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 TDF/FTC can be considered. Among people with a CrCl 30 to 59 mL/min, a TAF/FTC regimen is preferred. Currently approved 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 (**BIII**). Renally dosed TDF also can be used if recovery of renal function is unlikely (**BIII**). If renally dosed TDF is used, then the CrCl needs to be monitored carefully. 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.⁹⁵ Among people with HBV monoinfection, 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 ($P < .0001$). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ($P = .004$).^{96,97}

Chronic administration of 3TC or FTC as the only active drug against HBV **should be avoided** because of the high rate of selection of HBV drug-resistance mutations (**AI**).

People receiving ART should continue HBV therapy indefinitely (**BIII**) because relapses after response can occur, particularly in those with lower CD4 counts.³ Additionally, discontinuation of nucleos(t)ide analogue therapy is associated with an HBV flare in approximately 30% of cases,^{98,99} with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.^{59,100-102} In addition, switching to the one-pill regimen of dolutegravir/3TC should be avoided because 3TC is then the only active drug against HBV. If anti-HBV therapy and ART must be discontinued, transaminase levels should be monitored every 6 weeks for 3 months and every 3 to 6 months thereafter. 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,¹⁰³⁻¹⁰⁵ attempts should be made to treat both hepatitis viruses, if feasible. If ART is administered, then anti-HBV therapy must be included as part of the regimen (as above) and anti-HCV therapy can be introduced as needed (see [Hepatitis C Virus](#)) (**CIII**). 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**).¹⁰⁶⁻¹⁰⁹

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 HBV infection and HIV, co-treatment is essential and recommended.⁸⁷ Few options exist that can be used for treatment of HBV alone in a patient with HIV/HBV coinfection. Anti-HBV therapy must not be given in the absence of a fully suppressive ART regimen (**AII**). Only pegylated interferon (IFN)-alfa-2a monotherapy may be

considered for people with HIV/HBV coinfection who are not receiving ART and who meet criteria for anti-HBV therapy as described in the [AASLD 2018 Hepatitis B Guidance \(CIII\)](#).¹⁹

Regimens That Are Not Recommended

Tenofovir (TDF and TAF), entecavir, 3TC, FTC, and telbivudine **should not be used alone** in the absence of a fully suppressive ART regimen because of the development of HIV drug resistance mutations (**AI**).^{110,111} Other anti-HBV treatment regimens include adefovir in combination with 3TC or FTC in addition to a fully suppressive ART regimen^{93,112,113}; 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 does not recommend this regimen for people with HIV/HBV coinfection (**AI**).

Monitoring of Response to Therapy and Adverse Events

To prevent emergence of drug-resistant variants and evaluate response for people on nucleos(t)ide analogues, treatment response should be monitored by testing for HBV DNA at 3- to 6-month intervals (**AI**). Treatment responses are defined as the following:

- Primary non-response: HBV DNA $<1 \log_{10}$ decline at 12 weeks.¹¹⁴
- Complete virologic response: undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.¹¹⁵
- Partial virologic response: $\geq 1 \log_{10}$ decline, but still detectable HBV DNA at 24 weeks.¹¹⁵
- Maintained virologic response: response that continues while on therapy.¹¹⁵
- Sustained virologic response: one that is still present 6 months after stopping therapy.¹¹⁵

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 noninvasive markers; 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; however, this desirable serologic response is uncommon ($<1\%$ of HBsAg-positive people per year).³

Adverse Events

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both are more frequent among people with HIV who have underlying renal insufficiency, are older, or have been treated with TDF for prolonged periods.¹¹⁶ These biochemical changes are usually reversible when TDF is discontinued or changed to TAF.¹¹⁷

Electrolytes and serum creatinine levels should be evaluated at baseline and every 3 to 6 months, with urinalysis 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.¹¹⁷ All nucleos(t)ides must be dose adjusted for renal

dysfunction (see package insert), and TAF with FTC or 3TC is not recommended for people with CrCl <30 mL/min unless they are on hemodialysis (**AI**).

TAF has been associated with weight gain among people with HIV but has not been studied in HBV mono-infection.

Entecavir-associated lactic acidosis is uncommon but has been reported among people with HBV mono-infection with advanced cirrhosis.¹¹⁸

Major toxicities of IFN- α (pegylated or standard) are flu-like symptoms—such as fatigue, pyrexia, myalgia, and headache—and psychiatric reactions, including depression, insomnia, irritability, and anxiety. Other common reactions are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus.

Immune Reconstitution Inflammatory Syndrome (IRIS)

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,”¹¹⁹ which constitutes 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.^{120,121} 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**).¹¹⁷

Flares are worse among people with more severe liver disease, especially those with cirrhosis.¹²² Distinguishing between drug-induced liver injury or other causes of hepatitis (acute hepatitis caused by HAV, HCV, hepatitis D virus [HDV], hepatitis E virus [HEV], 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, aspartate aminotransferase) and the presence of HBV or HCV coinfection before initiation of ART. In HIV/HBV coinfection, baseline elevated HBV DNA levels are predictive of hepatotoxicity.¹²³⁻¹²⁶ However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80% to 90%) people with HIV/HBV coinfection do not have ART-associated hepatotoxicity,¹²⁷ 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.^{128,129} 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. However, the development of jaundice is associated with severe morbidity and mortality, and the offending drug(s) should be discontinued (**AIII**).¹³⁰

The major problem in managing ALT flares is distinguishing between drug-induced liver injury and HBV reactivation, IRIS, emergence of HBV drug resistance, and HBeAg seroconversion. In drug-induced liver injury, determining the offending medication also can be challenging. A review of the

medication history and testing for serum HBV DNA, HBeAg, HIV RNA, and CD4 count can help distinguish between these possibilities. Liver histology also may help to differentiate drug toxicity (e.g., increased eosinophils) from viral hepatitis (e.g., portal inflammation). If the flare is severe or HBV drug resistance is suspected, then consultation with a hepatologist is recommended. Other causes of abnormal liver tests should be considered, including use of drugs or alcohol, other viral hepatitis infections (HAV, HCV, HDV, and HEV), and nonalcoholic fatty liver disease.

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogues is defined as primary non-response (HBV DNA $<1 \log_{10}$ decline) after 12 weeks 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 patient is on 3TC/FTC monotherapy or to non-adherence to therapy.³ 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 non-adherence and drug resistance, evaluating people with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.¹³¹ 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.¹³²

3TC (or FTC) monotherapy for HBV infection leads to emergence of drug-resistant HBV, which increases with time on treatment; therefore, it **should not be used** as the sole anti-HBV drug in an ART regimen (**AII**). The rate of development of 3TC-resistance is approximately 20% per year among people with HIV/HBV coinfection treated with 3TC alone.¹³³ If 3TC resistance is suspected or documented, TDF or TAF should be added to the ART regimen (**BIII**).¹³⁴⁻¹³⁶ Because people with 3TC-resistant HBV will have cross-resistance to the other L-nucleosides (telbivudine, FTC), and partial resistance to entecavir, those agents **should not be used** among people found to have 3TC-resistant HBV (**AI**).¹³⁷ All nucleoside analogs must be dose adjusted for renal insufficiency per package insert guidelines and [Table 6](#).

If treatment failure occurs on entecavir, the only rational choice is replacement with TDF or TAF (with or without FTC) because of the cross-resistance that occurs with L-nucleosides (telbivudine, 3TC, FTC) (**AI**).

People whose HBV infection initially fails to respond to pegylated IFN-alfa can be given nucleos(t)ide analogue 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.³ Thus, in a patient 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.¹³⁸ Nonetheless, people on drugs that are less potent or that have a lower barrier to resistance—such as adefovir or L-nucleosides—who have partial virologic responses ($<2 \log_{10}$ drop in HBV DNA levels from baseline at 24 weeks) should be switched to a more potent regimen—such as tenofovir with FTC or entecavir (if on adefovir)—because of the risk of development of drug resistance to the initial therapy **(BII)**.

Special Considerations for Treating End-Stage Liver Disease

People with HIV/HBV coinfection who have end-stage liver disease should be managed as a person with HBV monoinfection 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 nucleoside analogs are safe and efficacious **(AI)**.^{133,139,140} All people with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).^{141,142} 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 norfloxacin (400 mg/day), ciprofloxacin (750 mg/week), or trimethoprim-sulfamethoxazole (one doubled-strength tablet/day) **(AI)**.¹⁴³

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 [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 non-absorbable disaccharides—such as lactulose—and/or non-absorbable antibiotics, such as rifaximin.³

People with HBV-related cirrhosis are at increased risk of HCC¹⁴⁴ and should have imaging studies performed every 6 months, as recommended in HBV monoinfection **(AI)**.³ Choice of imaging (ultrasound, computed tomography, or magnetic resonance imaging) depends upon the expertise of the imaging center and whether the patient has cirrhosis. Usually, ultrasound is the initial preferred imaging modality.³ HCC can occur without cirrhosis in HBV infection, and HIV/HBV coinfection appears to increase the risk of HBV-associated HCC,¹⁴⁵ but more frequent surveillance in HIV/HBV coinfection has not been studied, and so cannot be recommended given insufficient evidence. 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.¹⁴⁶ Because transplantation does not cure HBV infection, post-transplant hepatitis B immune globulin (HBIG) and HBV treatment is required **(AII)**.

Preventing Recurrence

As previously indicated, most people should continue HBV therapy (with the exception of pegylated IFN- α) 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.¹⁰⁰⁻¹⁰²

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 HIV-negative people with HBsAg-positive/anti-HBc-positive disease receiving immunomodulatory therapy is well described.^{147,148} Even among people with HBsAg-negative/anti-HBc-positive disease, HBV reactivation occurs in 8% to 18% of people receiving anti-cancer drugs¹⁴⁹ and 1.7% of people receiving rheumatologic disease drugs.¹⁵⁰

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 Special Considerations with Regard to Starting ART above). The optimal approach for those people with HBsAg-negative/anti-HBc-positive disease is unknown. However, because TDF or TAF plus FTC 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 cannot be used as part of their HIV regimen, these patients 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 is preferred if HBV DNA is detectable or if immunosuppression is more severe, such as with anti-CD20 antibodies (**AII**).¹⁵¹ 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**).¹⁹

Special Considerations During Pregnancy

Pregnant people with HIV should be screened for HBV infection, and coinfection with HBV may be first diagnosed at this time (**AI**).¹⁵² People with HIV should be tested for HBsAg during each pregnancy, preferably in the first trimester, even if vaccinated or tested previously.¹⁵² Those who are both HBsAg-negative/anti-HBs-negative should be offered vaccination against HBV. Pregnant persons with chronic HBV infection who have not already received the HepA vaccine series should be screened for immunity to HAV infection. If they screen negative for anti-HAV IgG, they should receive the HepA vaccine series (**AIII**).¹⁵³ Treatment of symptomatic acute HBV infection during pregnancy should be supportive, with special attention given to maintaining blood glucose levels and normal clotting status. Risk of pre-term labor and delivery may increase with acute HBV infection. High maternal HBV DNA levels correlate strongly with perinatal HBV transmission, including failures of HBV passive-active immunoprophylaxis.¹⁵⁴⁻¹⁵⁷ 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.

ART—including drugs active against both HIV and HBV—is recommended for all people with HIV/HBV coinfection, including pregnant people (**AIII**). TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant people with chronic HBV infection (**AIII**).¹⁵³ A person with HBV/HIV coinfection who becomes pregnant while virally suppressed on an antiretroviral regimen that includes TAF can be offered the choice of continuing TAF or switching from TAF to TDF (**BIII**).¹⁵⁸ Several other antiviral agents have activity against HBV, including entecavir, adefovir, and telbivudine. However, these drugs have not been well evaluated in

pregnancy, with too few exposures to assess overall risk. They **are currently not recommended** for pregnant people with HBV/HIV coinfection.¹⁵⁸ Once HBV therapy with nucleos(t)ide analogs and ART is initiated in people with HIV/HBV coinfection, treatment should be continued indefinitely.

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). As of January 2018, 5,008 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 has been well tolerated by pregnant women and is a recommended NRTI for use in pregnancy (**AI**).¹⁵³ Similarly, no increase in birth defects has been noted in 2,785 cases of first-trimester exposure to FTC. FTC is a recommended NRTI and is used commonly in pregnancy (**BI**).¹⁵⁹ A total of 3,535 cases of first-trimester exposure to tenofovir have been reported to the Antiretroviral Pregnancy Registry with no increase in birth defects noted.¹⁵⁸

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, but the evidence is mixed; the role of concomitant medications and other cofactors and/or confounders requires further investigation.¹⁵³

Several other ART agents with activity against HBV—including adefovir and telbivudine—have been evaluated and found not to be teratogenic in animals, but experience with these agents in the first trimester of human pregnancy is limited. These drugs could be included in a regimen during pregnancy if other options are inappropriate and if the benefits are thought to outweigh the risks. Each of these agents should be administered only in combination with a fully suppressive ART regimen because of the risk of development of ART drug resistance. Entecavir was associated with skeletal anomalies in rats and rabbits, but only at high, maternally toxic doses (see package insert). Data on the use of entecavir and adefovir in human pregnancy are not available. Telbivudine given to pregnant people who were HBV-seropositive/HIV-seronegative during the second and third trimester was well tolerated, with no birth defects observed.¹⁶⁰

IFN-alfa formulations are not recommended for use in pregnancy. Although these agents are not teratogenic, they are abortifacient at high doses in monkeys and **should not be used** in pregnant people because of their direct antigrowth and antiproliferative effects (**AI**).¹⁶¹

Infants born to people 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 month and 6 months of age, respectively (**AI**). Infants who weigh <2,000 g at birth should receive 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).

Recommendations for Preventing and Treating Hepatitis B Virus Infection

Preventing HBV Infection

Indications for HepB Vaccination

- People without chronic HBV infection and without immunity to HBV infection (anti-HBs <10 mIU/mL) **(AII)**.
- People with isolated anti-HBc **(BII)**. Recommend one standard dose of HepB vaccine followed by anti-HBs at 1–2 months. If the titer is >100 mIU/mL, no further vaccination is needed, but if the titer is <100 mIU/mL, a complete series of HepB vaccine should be completed, followed by anti-HBs testing **(BII)**. If anti-HBs quantitative titer is not available, then recommend a complete HepB vaccine series followed by qualitative anti-HBs testing **(BII)**.
- Although vaccine response is better in patients with CD4 >350 cells/mm³, vaccination should not be deferred in patients with a lower CD4 count because some people with CD4 <350 cells/mm³ do respond to vaccination **(AII)**.

Vaccination Schedule

- HepB vaccine IM (Engerix-B® 40 mcg or Recombivax HB® 20 mcg) at 0, 1, and 6 months (double dose, three-dose series) **(AII)**; *or*
- Combined HepA and HepB vaccine (Twinrix®) 1 mL IM as a three-dose series (at 0, 1, and 6 months) **(AII)**; *or*
- Vaccine conjugated to CpG (Heplisav-B®) IM at 0 and 1 months **(CIII)**—a two-dose series can be used only when both doses given are Heplisav-B®.
- Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series.

For Vaccine Non-Responders

- Revaccinate with a second double-dose, three-dose recombinant HBV vaccine series **(BII)**. Some experts consider that a double-dose four-dose vaccine series of recombinant hepatitis B vaccine (Engerix-B® 40 mcg or Recombivax® 20 mcg at 0, 1, 2, and 6 months) may produce a better immunologic response, but this approach has not been demonstrated to be superior to a double dose, three-dose series; *or*
- Revaccinate with two-dose series of HepBCpG (Heplisav-B®) **(BIII)**.
- For people with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a CD4 count ≥200 is achieved and sustained with ART **(CIII)**.

Treating HBV Infection

Indication for Therapy

- For all people with HIV/HBV coinfection, regardless of CD4 count and HBV DNA level **(AIII)**, therapy should be selected to treat both HIV and HBV infections **(AIII)**.

Preferred Therapy (CrCl ≥60 mL/min)

- The ART regimen must include two drugs active against HBV, preferably with [TDF 300 mg plus (FTC 200 mg or 3TC 300 mg)] or [TAF (10 or 25 mg)^a plus FTC 200 mg] PO once daily **(AII)**.

Recommendations for Preventing and Treating Hepatitis B Virus Infection

Preferred Therapy (CrCl 30–59 mL/min)

- The ART regimen must 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 or TAF), *or*
- ART with renally dose-adjusted TDF and FTC can be used **(BIII)** when recovery of renal function is unlikely (see [Table 6](#) for dosing recommendation for TDF and FTC or 3TC for people with renal impairment). Guidance for TAF use in people with CrCl <30 is not yet established.

Preferred Therapy (Receiving HD)

- (TDF or TAF) plus (FTC or 3TC) can be used. Refer to [Table 6](#) for dosing recommendation.

Duration of Therapy

- People on treatment for HBV and HIV should receive therapy indefinitely **(BIII)**.

Alternative Therapy

For Persons Not on ART

- Anti-HBV therapy is indicated for all those who meet criteria for treatment according to the [AASLD 2018 Hepatitis B Guidance](#).
- Peg-IFN-alfa 2a 180 mcg SQ once weekly for 48 weeks **(CIII)**, *or*
- Peg-IFN-alfa 2b 1.5 mcg/kg SQ once weekly for 48 weeks **(CIII)**
- Anti-HBV drugs—such as 3TC, FTC, TAF, TDF, entecavir, adefovir, and telbivudine—must **not** be given in the absence of a fully suppressive ART regimen to avoid selection of drug-resistant HIV **(AII)**.

Other Considerations

- HepA vaccination is recommended for all people who are HAV antibody–negative and have chronic liver disease, are men who have sex with men, or are injection drug users **(AIII)**.
- Antibody response to HepA vaccine should be assessed 1 month after completion of vaccination series. If anti-HAV IgG is negative, people should be revaccinated when the CD4 count is >200 cells/mm³ **(BIII)**.
- 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.
- 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 **(AIII)**.
- If anti-HBV therapy must be discontinued, serum transaminase levels should be monitored every 6 weeks for 3 months, then every 3 to 6 months thereafter.
- If a hepatic flare occurs after drug discontinuation, HBV therapy should be reinstituted because it can be potentially lifesaving **(AIII)**.

Recommendations for Preventing and Treating Hepatitis B Virus Infection

- If immunosuppressive therapy is given, HBV reactivation can occur. For people who are HBsAg-positive, treatment for HBV infection should be administered **(AII)**. People with isolated anti-HBc can either be monitored or be given prophylaxis to prevent reactivation depending on the degree of immunosuppression and whether HBV DNA is detectable **(AII)**.

^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.

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: 3TC = lamivudine; AASLD = American Association for the Study of Liver Disease; anti-HBc = HBV core antibody; anti-HBs = antibody to hepatitis B surface antigen; ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CpG = cytosine phosphoguanine; CrCl = creatinine clearance; FTC = emtricitabine; HAV = hepatitis A virus; HBsAg = HBV surface antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HD = hemodialysis; HepA = hepatitis A; HepB = hepatitis B; IFN = interferon; IgG = immunoglobulin G; IM = intramuscular; mIU/mL = milli-international units per milliliter; PO = orally; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

References

1. Lee WM. Hepatitis B virus infection. *N Engl J Med*. 1997;337(24):1733-1745. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9392700>.
2. Levine OS, Vlahov D, Koehler J, Cohn S, Spronk AM, Nelson KE. Seroepidemiology of hepatitis B virus in a population of injecting drug users: association with drug injection patterns. *Am J Epidemiol*. 1995;142(3):331-341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7631637>.
3. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016;63(1):261-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26566064>.
4. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26231459>.
5. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;385(9963):117-171. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25530442>.
6. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol*. 2006;44(1 Suppl): S6-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16352363>.
7. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology*. 2009;49(5 Suppl):S138-145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19399813>.
8. Kourtis AP, Bulters M, Hu DJ, Jamieson DJ. HIV-HBV coinfection—a global challenge. *N Engl J Med*. 2012;366(19):1749-1752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22571198>.
9. 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.ncbi.nlm.nih.gov/pubmed/31266615>.
10. 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>.
11. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med*. 1975;292(15):771-774. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1113797>.
12. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis*. 1995;20(4):992-1000. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7795104>.

13. Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. *World J Gastroenterol*. 2014;20(18):5427-5434. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24833873>.
14. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23749665>.
15. 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: <http://www.ncbi.nlm.nih.gov/pubmed/1348798>.
16. McMahon BJ. The natural history of chronic hepatitis B virus infection. *Hepatology*. 2009;49(5 Suppl):S45-55. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19399792>.
17. Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep*. 2008;57(RR-8):1-20. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18802412>.
18. LeFevre ML, U. S. Preventive Services Task Force. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2014;161(1):58-66. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24863637>.
19. 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://www.ncbi.nlm.nih.gov/pubmed/29405329>.
20. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28200098>.
21. Mitka M. FDA: increased HBV reactivation risk with ofatumumab or rituximab. *JAMA*. 2013;310(16):1664. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24150447>.
22. Seto WK, Chan TS, Hwang YY, et al. Hepatitis B reactivation in occult viral carriers undergoing hematopoietic stem cell transplantation: a prospective study. *Hepatology*. 2017;65(5):1451-1461. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28027590>.
23. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18977722>.
24. Tien PC, Kovacs A, Bacchetti P, et al. Association between syphilis, antibodies to herpes simplex virus type 2, and recreational drug use and hepatitis B virus infection in the Women's Interagency HIV Study. *Clin Infect Dis*. 2004;39(9):1363-1370. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15494914>.

25. Shire NJ, Rouster SD, Rajjicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2004;36(3):869-875. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15213572>.
26. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23090927>.
27. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26829660>.
28. 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 US women. *J Infect Dis*. 2007;195(10):1437-1442. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17436223>.
29. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15714424>.
30. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16816553>.
31. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18486540>.
32. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17712758>.
33. Grob P, Jilg W, Bornhak H, et al. Serological pattern "anti-HBc alone": report on a workshop. *J Med Virol*. 2000;62(4):450-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11074473>.
34. Ponde RA, Cardoso DD, Ferro MO. The underlying mechanisms for the 'anti-HBc alone' serological profile. *Arch Virol*. 2010;155(2):149-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20091193>.
35. Hofer M, Joller-Jemelka HI, Grob PJ, Luthy R, Opravil M. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis*. 1998;17(1):6-13. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9512175>.

36. Juhl D, Knobloch JKM, Görg S, Hennig H. Comparison of two test strategies for clarification of reactive results for anti-HBc in blood donors. *Transfus Med Hemother*. 2016;43(1):37-43. Available at: <https://pubmed.ncbi.nlm.nih.gov/27022321>.
37. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15809901>.
38. 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: <http://www.ncbi.nlm.nih.gov/pubmed/14615664>.
39. Colin JF, Cazals-Hatem D, Lioriot MA, et al. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology*. 1999;29(4):1306-1310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10094979>.
40. Harris RA, Chen G, Lin WY, Shen FM, London WT, Evans AA. Spontaneous clearance of high-titer serum HBV DNA and risk of hepatocellular carcinoma in a Chinese population. *Cancer Causes Control*. 2003;14(10):995-1000. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14750539>.
41. Iloeje UH, Yang HI, Su J, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology*. 2006;130(3):678-686. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16530509>.
42. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA*. 2006;295(1):65-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16391218>.
43. Fattovich G, Olivari N, Pasino M, D'Onofrio M, Martone E, Donato F. Long-term outcome of chronic hepatitis B in Caucasian patients: mortality after 25 years. *Gut*. 2008;57(1):84-90. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17715267>.
44. Hsu YS, Chien RN, Yeh CT, et al. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology*. 2002;35(6):1522-1527. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12029639>.
45. Niederau C, Heintges T, Lange S, et al. Long-term follow-up of HBeAg-positive patients treated with interferon alfa for chronic hepatitis B. *N Engl J Med*. 1996;334(22):1422-1427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8618580>.
46. Lau DT, Everhart J, Kleiner DE, et al. Long-term follow-up of patients with chronic hepatitis B treated with interferon alfa. *Gastroenterology*. 1997;113(5):1660-1667. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9352870>.
47. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9108941>.

48. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12493258>.
49. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17692986>.
50. McMahon BJ. Natural history of chronic hepatitis B. *Clin Liver Dis*. 2010;14(3):381-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20638020>.
51. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology*. 2009;50(3):661-662. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19714720>.
52. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011;53(3):1020-1022. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21374666>.
53. Wandeler G, Maunon E, Atkinson A, et al. Incidence of hepatocellular carcinoma in HIV/HBV-coinfected patients on tenofovir therapy: relevance for screening strategies. *Journal of Hepatology*. 2019;71(2):274-280. Available at: <https://www.sciencedirect.com/science/article/pii/S0168827819302260?via%3Dihub>.
54. Singh S, Muir AJ, Dieterich DT, Falck-Ytter YT. American Gastroenterological Association Institute technical review on the role of elastography in chronic liver diseases. *Gastroenterology*. 2017;152(6):1544-1577. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28442120>.
55. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med*. 1986;315(4):209-214. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2941687>.
56. Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. *MMWR Recomm Rep*. 2006;55(RR-16):1-33; quiz CE31-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17159833>.
57. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23532480>.
58. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26768256>.
59. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10649616>.
60. 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: <http://www.ncbi.nlm.nih.gov/pubmed/2143776>.
 61. Tayal SC, Sankar KN. Impaired response to recombinant hepatitis B vaccine in asymptomatic HIV-infected individuals. *AIDS*. 1994;8(4):558-559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7912087>.
 62. Fonseca MO, Pang LW, de Paula Cavaleiro 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: <http://www.ncbi.nlm.nih.gov/pubmed/15780739>.
 63. Veiga AP, Casseb J, Duarte AJ. Humoral response to hepatitis B vaccination and its relationship with T CD45RA+ (naïve) and CD45RO+ (memory) subsets in HIV-1-infected subjects. *Vaccine*. 2006;24(49-50):7124-7128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16884833>.
 64. 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: <http://www.ncbi.nlm.nih.gov/pubmed/1532609>.
 65. 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: <http://www.ncbi.nlm.nih.gov/pubmed/1535502>.
 66. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15531038>.
 67. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15156488>.
 68. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16142673>.
 69. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10534727>.
 70. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10613751>.

71. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15067070>.
72. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11967322>.
73. Auffermann-Gretzinger S, Keffe 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: <http://www.ncbi.nlm.nih.gov/pubmed/11342445>.
74. 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>.
75. 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.ncbi.nlm.nih.gov/pubmed/19487908>.
76. Clemens R, Sanger R, Kruppenbacher J, et al. Booster immunization of low- and non-responders after a standard three dose hepatitis B vaccine schedule—results of a post-marketing surveillance. *Vaccine.* 1997;15(4):349-352. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9141203>.
77. Craven DE, Awdeh ZL, Kunches LM, et al. Nonresponsiveness to hepatitis B vaccine in health care workers: results of revaccination and genetic typings. *Ann Intern Med.* 1986;105(3):356-360. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2943202>.
78. Goldwater PN. Randomized, comparative trial of 20 micrograms vs. 40 micrograms Engerix B vaccine in hepatitis B vaccine non-responders. *Vaccine.* 1997;15(4):353-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9141204>.
79. Kim MJ, Nafziger AN, Harro CD, et al. Revaccination of healthy nonresponders with hepatitis B vaccine and prediction of seroprotection response. *Vaccine.* 2003;21(11-12):1174-1179. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12559795>.
80. Chaiklang K, Wipasa J, Chaiwarith R, Praparattanapan J, Supparatpinyo K. Comparison of immunogenicity and safety of four doses and four double doses vs. standard doses of hepatitis B vaccination in HIV-infected adults: a randomized, controlled trial. *PLoS One.* 2013;8(11):e80409. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24265819>.
81. Launay O, van der Vliet D, Rosenberg AR, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs. standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA.* 2011;305(14):1432-1440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21486976>.
82. Halperin SA, Ward B, Cooper C, et al. Comparison of safety and immunogenicity of two doses of investigational hepatitis B virus surface antigen co-administered with an

- immunostimulatory phosphorothioate oligodeoxyribonucleotide and three doses of a licensed hepatitis B vaccine in healthy adults 18-55 years of age. *Vaccine*. 2012;30(15):2556-2563. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22326642>.
83. Heyward WL, Kyle M, Blumenau J, et al. Immunogenicity and safety of an investigational hepatitis B vaccine with a Toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40-70 years of age. *Vaccine*. 2013;31(46):5300-5305. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23727002>.
 84. Jackson S, Lentino J, Kopp J, et al. Immunogenicity of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant compared with a licensed hepatitis B vaccine in adults. *Vaccine*. 2018;36(5):668-674. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29289383>.
 85. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19617848>.
 86. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16271546>.
 87. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2021. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines>.
 88. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12143063>.
 89. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12441815>.
 90. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12447773>.
 91. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12478090>.
 92. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12519935>.

93. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17058225>.
94. 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.ncbi.nlm.nih.gov/pubmed/27753684>.
95. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27171740>.
96. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28404092>.
97. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28404091>.
98. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20216301>.
99. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18795964>.
100. Bessesen M, Ives D, Condeay 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: <http://www.ncbi.nlm.nih.gov/pubmed/10452630>.
101. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10723980>.
102. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11023772>.
103. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10969344>.

104. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15577625>.
105. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9455792>.
106. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26082511>.
107. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26297529>.
108. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26967675>.
109. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26215390>.
110. 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.ncbi.nlm.nih.gov/pubmed/17582071>.
111. Koziel MJ, Peters MG. Viral hepatitis in HIV infection. *N Engl J Med*. 2007;356(14):1445-1454. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17409326>.
112. 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.ncbi.nlm.nih.gov/pubmed/11551579>.
113. 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.ncbi.nlm.nih.gov/pubmed/19043923>.
114. European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol*. 2017;67(2):370-398. Available at: <https://pubmed.ncbi.nlm.nih.gov/28427875>.
115. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22436845>.

116. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25259702>.
117. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26627107>.
118. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19937695>.
119. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17112628>.
120. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15206064>.
121. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11997718>.
122. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19231993>.
123. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18276600>.
124. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26848975>.
125. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18937580>.
126. 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.ncbi.nlm.nih.gov/pubmed/10632283>.
127. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15577540>.
 128. 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: <http://www.ncbi.nlm.nih.gov/pubmed/14562855>.
 129. 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-naïve HCV-HIV-coinfected patients: lopinavir-ritonavir versus nelfinavir. *Clin Infect Dis*. 2005;41(8):1186-1195. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16163639>.
 130. Reuben A. Hy's law. *Hepatology*. 2004;39(2):574-578. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14768020>.
 131. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17596850>.
 132. 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>.
 133. 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.ncbi.nlm.nih.gov/pubmed/10534354>.
 134. 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 coinfecting individuals. *AIDS*. 2009;23(13):1707-1715. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19584701>.
 135. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19780875>.
 136. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17983801>.

137. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25320730>.
138. 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: <http://www.ncbi.nlm.nih.gov/pubmed/22005002>.
139. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9654535>.
140. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10528035>.
141. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23463403>.
142. Runyon BA, Practice Guidelines Committee, 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: <http://www.ncbi.nlm.nih.gov/pubmed/14999706>.
143. 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: <http://www.ncbi.nlm.nih.gov/pubmed/7887554>.
144. Di Bisceglie AM. Hepatitis C and hepatocellular carcinoma. *Hepatology*. 1997;26(3 Suppl 1):34S-38S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9305661>.
145. Salmon-Ceron D, Rosenthal E, Lewden C, et al. Emerging role of hepatocellular carcinoma among liver-related causes of deaths in HIV-infected patients: the French national Mortalité 2005 study. *J Hepatol*. 2009;50(4):736-745. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19231018>.
146. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16352366>.
147. 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.ncbi.nlm.nih.gov/pubmed/14724827>.

148. 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.ncbi.nlm.nih.gov/pubmed/24164839>.
149. 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.ncbi.nlm.nih.gov/pubmed/23775967>.
150. 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.ncbi.nlm.nih.gov/pubmed/26420955>.
151. 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.ncbi.nlm.nih.gov/pubmed/25447850>.
152. 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>.
153. 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. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines>.
154. del Canho R, Grosheide PM, Schalm SW, de Vries RR, Heijtkink 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: <http://www.ncbi.nlm.nih.gov/pubmed/8051386>.
155. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9675462>.
156. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19413519>.
157. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24862434>.
158. Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Hepatitis B virus/HIV coinfection. Available at: <https://clinicalinfo.hiv.gov/en/guidelines/perinatal/hepatitis-b-virushiv-coinfection?view=full>.

159. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry international interim report for 1 January 1989 through 31 January 2012. Wilmington, NC: Registry Coordinating Center; 2012. Available at: <http://www.apregistry.com>.
160. Han GR, Jiang HX, Wang CM, et al. Long-term safety and efficacy of telbivudine in infants born to mothers treated during the second or third trimesters of pregnancy. *J Viral Hepat*. 2017;24(6):514-521. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28039902>.
161. Boskovic R, Wide R, Wolpin J, Bauer DJ, Koren G. The reproductive effects of beta interferon therapy in pregnancy: a longitudinal cohort. *Neurology*. 2005;65(6):807-811. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16186517>.

Hepatitis C Virus Infection

Updated: January 18, 2023

Reviewed: January 18, 2023

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 States¹⁰ 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,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/mm³). Further, coinfecting 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 immunosuppression⁶¹ (CD4 cell count <200 cells/mm³). 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 alpha-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, coinfecting 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-naïve 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 the inclusion of people with HIV in 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-naïve, 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-naïve 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-naïve 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 exposure⁹⁴; 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-naïve 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.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 infection¹⁰¹; 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

Pregnant individuals, including those with HIV, should be tested for HCV infection to allow appropriate management for the mothers during 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 to pregnant people with HCV infection than ever before^{111,112}; thus, universal screening for pregnant people 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 For the pregnant person, 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), 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 coinfecting 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 coinfecting 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 coinfecting 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-coinfecting 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 coinfecting 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 coinfecting 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, Kottlil S, et al. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfecting 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-naïve 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, Hulleger 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. Degasperis 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](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 Disease (Last updated May 26, 2020; last reviewed January 11, 2023)

Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common. Among persons aged 14 to 49 years in the United States, the HSV-1 seroprevalence is 47.8%, and the HSV-2 seroprevalence is 11.9%.¹ While most cases of recurrent genital herpes are due to HSV-2, over the past decade, HSV-1 has become an increasing cause of first-episode genital herpes, causing up to 70% of infections in some populations, such as young adult women and men who have sex with men.² Approximately 70% of persons with HIV are HSV-2 seropositive, and 95% are seropositive for either HSV-1 or HSV-2.³ HSV-2 infection increases the risk of HIV acquisition two- to three-fold,^{4,5} and in coinfecting patients, HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions.⁶

Clinical Manifestations

Oral 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 patients is 5 days to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is typically caused by HSV-2 and is the most common manifestation of HSV-2 infection. Increasingly, first-episode genital herpes is caused by HSV-1 and is indistinguishable from HSV-2 infection, although recurrences and viral shedding occur less often with genital HSV-1 infection. Typical genital mucosal or skin lesions evolve through stages of papule, 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, mon pubis, thighs). Local symptoms might include a sensory prodrome consisting of pain and pruritus. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.⁷ These classic manifestations occur in some patients, 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 persons with CD4 T lymphocyte (CD4) cell counts <200 cells/mm³ than in those with higher CD4 counts.^{8,9} An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but recurrences and viral shedding occur less often with genital HSV-1 infection.

HSV is a significant cause of proctitis in men with HIV infection who have sex with men and may not be associated with external anal ulcers.¹⁰ In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 counts <100 cells/mm³ and also may be associated with acyclovir-resistant HSV.¹¹ In addition, atypical presentations such as hypertrophic genital HSV,^{12,13} which mimics neoplasia and requires biopsy for diagnosis, may be seen in persons with HIV infection.

The manifestations of non-mucosal HSV infections (e.g., HSV keratitis, HSV encephalitis, HSV hepatitis, herpetic whitlow) are similar to those observed in HIV-seronegative individuals. Disseminated HSV infection is rare, even in profoundly immunosuppressed patients. HSV retinitis manifests as acute retinal necrosis, which can lead rapidly to loss of vision.

Diagnosis

Because mucosal HSV infections cannot be diagnosed accurately by clinical examination, a laboratory diagnosis of all suspected HSV mucosal infections should be pursued.¹⁴ HSV DNA polymerase chain

reaction (PCR), and viral culture are preferred methods for diagnosis of mucocutaneous lesions potentially caused by HSV. PCR is the most sensitive method of diagnosis. HSV detected in genital lesions should be typed as HSV-1 or HSV-2. The frequency of recurrences is greater for HSV-2 than for HSV-1, and therefore knowledge of viral type is helpful for counseling purposes.

Type-specific serologic assays are commercially available and can be used for diagnosis of HSV-2 infection in asymptomatic individuals or those with atypical lesions. Type-specific serologic screening for HSV-2 for persons with HIV infection can be considered. However, providers should be aware that there are some important limitations of currently available serologic tests. In particular, false positive HSV-2 serologic test results occur with the enzyme immunoassay antibody tests, particularly at low index values (1.1–3.5).^{15–17} In such situations, confirmatory testing with a second serologic test is recommended in the 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Disease Treatment Guidelines.¹⁸ A diagnosis of HSV-2 should be accompanied by counseling that includes discussion of the risk of transmitting infection to sex partners. Guidelines for counseling are provided in the 2015 CDC Sexually Transmitted Disease Treatment Guidelines.¹⁸ Serologic screening for HSV-1 infection **is not recommended**.

Preventing Exposure

Although most people with HIV also have HSV-1 and HSV-2 infections, it is important to prevent HSV-2 acquisition in those who do not have HSV-2. Persons with HIV who are HSV-2 seronegative should consider asking their partners to be tested using HSV type-specific serology before initiating sexual activity because disclosure of HSV-2 in heterosexual HIV-negative, HSV-2-discordant couples was associated with reduced risk of transmission of HSV-2 **(BII)**.¹⁹ Consistent use of latex condoms reduced HSV-2 acquisition among heterosexual couples, and their use should be encouraged to prevent transmission of HSV-2 and other sexually transmitted pathogens **(AII)**.^{20,21}

Sexual transmission of HSV most often occurs during episodes of asymptomatic viral shedding. However, persons with HIV should specifically avoid sexual contact with partners who have overt genital or orolabial herpetic lesions **(AII)**.

In HSV-2 seropositive persons who have symptomatic genital herpes but not HIV, suppressive antiviral therapy (e.g., valacyclovir 500 mg once daily) reduced HSV-2 transmission to susceptible heterosexual partners by 48%.²² However, in HIV-1/HSV-2-seropositive persons not on antiretroviral therapy (ART), suppressive acyclovir (400 mg twice daily) did not prevent HSV-2 transmission to HSV-2 seronegative partners.²³ Suppressive anti-HSV therapy to prevent HSV-2 transmission to susceptible partners **is not recommended** for persons with HIV/HSV-2 coinfection who are not on ART **(AI)**. There are no data available regarding 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 persons without HIV.^{24–26} However, HSV-2 seronegative persons with HIV on TDF-containing ART regimens are at similar risk of acquiring HSV-2 as those on non-TDF containing ART regimens, suggesting that TDF is not effective in preventing HSV-2 acquisition in persons with HIV infection.²⁷ The dose, duration, timing, and efficacy of anti-HSV prophylaxis after known or suspected exposure to HSV has not been evaluated. No vaccine for prevention of HSV infection is available. Some studies have shown that medical male circumcision (MMC) decreased the risk of HSV-2 acquisition in African men without HIV,^{28,29} and may be associated with decreased risk of HSV-2 transmission to female partners.³⁰ However, MMC 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

Patients 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 effective for suppressive and episodic therapy. Valacyclovir is the prodrug of acyclovir, and has improved oral bioavailability, with decreased dosing frequency, compared to acyclovir. 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 (GUD) when initiating ART.³¹ Episodic treatment for individual recurrences of GUD does not influence the natural history of genital HSV-2 infection.

Patients with orolabial HSV lesions can be treated with oral acyclovir, valacyclovir, or famciclovir for 5 days to 10 days (**AIII**). First episodes of genital HSV should be treated with oral acyclovir, valacyclovir, or famciclovir for 7 days 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 (**AIII**).^{11,32} Once the lesions begin to regress, patients can be switched to oral antiviral therapy. Therapy should be continued until the lesions have completely healed. Although disseminated disease due to HSV is rare in persons with HIV, HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by varicella-zoster virus.

Special Considerations with Regard to Starting Antiretroviral Therapy

Orolabial and genital HSV should not influence the decision on when to start ART in persons 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 coinfecting persons. In such cases, suppressive anti-HSV therapy can be considered. The frequency and severity of clinical episodes of genital herpes is often reduced in individuals after immune reconstitution on ART. However, immune reconstitution does not reduce the frequency of genital HSV shedding.³³

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 patients receiving episodic or suppressive HSV therapy unless they have advanced renal impairment. However, for patients receiving high-dose IV acyclovir, monitoring of renal function, and dose adjustment as necessary, are recommended at initiation of treatment and once or twice weekly for the duration of treatment.

HSV-2 shedding and GUD can increase in the first 6 months after initiation of ART, particularly in those with low CD4 counts.^{34,35} 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).³⁶

Managing Treatment Failure

Treatment failure due to acyclovir resistance should be suspected if herpes-related lesions do not begin to resolve within 7 days to 10 days after initiation of anti-HSV therapy. In persons with suspected acyclovir-resistant HSV, viral culture of the lesion should be performed, and if virus is isolated, susceptibility testing done to confirm drug resistance (**AII**).³⁷ Phenotypic testing of viral isolates has been the gold standard method for assessing HSV resistance; genotypic testing is not yet available.

The treatment of choice for acyclovir-resistant HSV is IV foscarnet (**AI**).^{38,39} IV cidofovir is a potential alternative (**CIII**). A novel agent, the helicase-primase inhibitor pritelivir, is currently being tested in clinical trials for treatment of acyclovir-resistant herpes in immunocompromised persons (*ClinicalTrials.gov* Identifier: [NCT03073967](https://clinicaltrials.gov/ct2/show/study/NCT03073967)). There is an Expanded Access Program available for oral pritelivir in these populations; for more information see [AiCuris Pritelivir Early Access website](#). Topical trifluridine, foscarnet,

cidofovir, and imiquimod also have been used successfully to treat external lesions, although prolonged application for 21 days to 28 days or longer may be required (**CIII**).⁴⁰⁻⁴⁴

Preventing Recurrence

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences of HSV lesions and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences (**AI**).^{14,45} Suppressive therapy for HSV may be continued indefinitely, without regard to improved CD4 count, although the need for continued therapy should be addressed on an annual basis, particularly if immune reconstitution has occurred (**BIII**). Persons starting ART with CD4 counts <250 cells/mm³ have an increased risk of HSV-2 shedding and GUD in the first 6 months on ART. Suppressive acyclovir decreases the risk of GUD nearly 60%, and may be recommended for persons with CD4 counts <250 cells/mm³ starting ART (**BI**).

In persons with HIV not on ART, suppressive anti-HSV therapy also results in a decrease in HIV RNA levels in plasma, anal, and genital secretions, and in a lower risk of HIV progression.⁴⁶ However, antiviral regimens for herpes do not decrease the risk of HIV transmission to sexual partners, and should not be used in place of ART to delay HIV progression.⁴⁷ In persons who are taking ART, suppressive HSV antivirals do not delay HIV progression, improve CD4 recovery, or decrease markers of systemic inflammation^{48,49} and are not useful for these ends (**AI**).

Although there is no data specific to persons with HIV, in hematopoietic stem cell recipients, the risk of developing acyclovir-resistant HSV was lower with daily suppressive acyclovir therapy than with episodic therapy.⁵⁰

Special Considerations During Pregnancy

Laboratory testing to diagnose mucocutaneous HSV infections is the same for pregnant women as for non-pregnant women. Episodic therapy for first-episode HSV disease and for recurrences can be offered during pregnancy. Visceral disease following HSV acquisition is more likely to occur during pregnancy and can be fatal. Acyclovir is the antiviral drug with the most reported experience in pregnancy and appears to be safe, particularly during the second and third trimesters (**AIII**).⁵¹ One recent case-control study suggested a higher risk of gastroschisis associated with both genital herpes and acyclovir use during the first trimester of pregnancy.⁵² The use of valacyclovir and famciclovir during pregnancy has been described, and the antiviral drugs also appear to be safe and well tolerated during the third trimester.⁵³ Given its simplified dosing schedule valacyclovir is an option for treatment and suppressive therapy during pregnancy (**CIII**).

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of neonatal HSV transmission in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV infection late in pregnancy. However, when HSV transmission does occur, the adverse sequelae for the neonate can be very significant. The predominant risk for neonatal HSV transmission is maternal genital shedding of HSV at delivery. Cesarean delivery is recommended for women with a genital herpes prodrome or visible HSV genital lesions at the onset of labor (**BII**).¹⁴ Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and reduces the need for cesarean delivery for recurrent HSV in HIV-seronegative women⁵⁴ and is likely to have similar efficacy in women with HIV infection. However, neonatal HSV disease has been reported in infants born to women treated with antenatal suppressive antiviral therapy.⁵⁵ Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 weeks' gestation for pregnant women with recurrences of genital herpes during pregnancy (**BII**).⁵⁶ Suppressive therapy for women who are seropositive for HSV-2 but no history of genital lesions **is not recommended**. Maternal genital herpes was a risk factor for perinatal HIV transmission in the era preceding availability of ART.⁵⁷ Whether HSV facilitates HIV transmission in pregnant women on ART is unknown.

Recommendations for Treating Herpes Simplex Virus Infections

Note: Compared to acyclovir, valacyclovir has improved bioavailability and requires less frequent dosing.

Treating 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)**

Treating 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)**

Treating Severe Mucocutaneous HSV Infections (AIII)

- For initial therapy, acyclovir 5 mg/kg IV every 8 hours
- After lesions begin to regress, change to oral therapy as above.
- Continue treatment until lesions have completely healed.

Chronic Suppressive Therapy

Indications:

- For patients with severe recurrences **(AI)**, *or*
- Patients who want to minimize the frequency of recurrences **(AI)**, including pregnant women, *or*
- To reduce the risk of genital ulcer disease in patients with CD4 counts <250 cells/mm³ who are starting ART **(BI)**

Treatment:

- Valacyclovir 500 mg PO twice a day **(AI)**, *or*
- Famciclovir 500 mg PO twice a day **(AI)**, *or*
- Acyclovir 400 mg PO twice a day **(AI)**
- Evaluate ongoing need for suppressive therapy annually.

For Acyclovir-Resistant Mucocutaneous HSV Infections

Preferred Therapy:

- IV Foscarnet 80–120 mg/kg/day in 2–3 divided doses until clinical response **(AI)**

Alternative Therapy (Duration: ≥21–28 Days, Based on Clinical Response) **(CIII)**:

- IV cidofovir 5 mg/kg once weekly, *or*
- Topical trifluridine 1% three times a day, *or*
- Topical cidofovir 1% gel once daily, *or*
- Topical imiquimod 5% cream three times a week, *or*
- Topical foscarnet 1% five times a day

Notes:

- 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.
- An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection; for more information see [AiCuris Pritelivir Early Access website](#).

Key: ART = antiretroviral therapy; HSV = herpes simplex virus; IV = intravenously; PO = orally

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. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA*. 2006;296(8):964–973. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16926356>.
4. 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>.
5. 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>.
6. 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>.
7. 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>.
8. 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>.
9. 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>.
10. 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>.
11. 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>.
12. 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>.
13. 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>.
14. Workowski KA, Berman S, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–110. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21160459>.
15. 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>.
16. 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>.
17. 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>.
18. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. 2015;64(RR-03):1–137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26042815>.
19. 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>.

20. Wald A, Langenberg AG, Krantz E, et al. The relationship between condom use and herpes simplex virus acquisition. *Ann Intern Med*. 2005;143(10):707-713. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16287791>.
21. 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>.
22. 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>.
23. 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 coinfecting persons: a randomized controlled trial. *J Infect Dis*. 2013;208(9):1366-1374. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23901094>.
24. 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>.
25. 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>.
26. 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>.
27. 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>.
28. 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>.
29. 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>.
30. 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>.
31. Keating TM, Kurth AE, Wald A, Kahle EM, Barash EA, Buskin SE. Clinical burden of herpes simplex virus disease in people with human immunodeficiency virus. *Sex Transm Dis*. 2012;39(5):372-376. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22504602>.
32. 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>.
33. 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>.
34. 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>.
35. 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>.
36. 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>.
37. Balfour HH Jr. Antiviral drugs. *N Engl J Med*. 1999;340(16):1255-1268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10210711>.
38. Safran 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>.

39. 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>.
40. 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>.
41. Perkins N, Nisbet M, Thomas M. Topical imiquimod treatment of aciclovir-resistant herpes simplex disease: case series and literature review. *Sex Transm Infect*. 2011;87(4):292-295. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21406577>.
42. Lateef F, Don PC, Kaufmann M, White SM, Weinberg JM. Treatment of acyclovir-resistant, foscarnet-unresponsive HSV infection with topical cidofovir in a child with AIDS. *Arch Dermatol*. 1998;134(9):1169-1170. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9762047>.
43. Kessler HA, Hurwitz S, Farthing C, et al. Pilot study of topical trifluridine for the treatment of acyclovir-resistant mucocutaneous herpes simplex disease in patients with AIDS (ACTG 172). AIDS Clinical Trials Group. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;12(2):147-152. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8680885>.
44. Javalay 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>.
45. 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>.
46. 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>.
47. Celum C, Wald A, Lingappa JR, et al. Acyclovir and transmission of HIV-1 from persons infected with HIV-1 and HSV-2. *N Engl J Med*. 2010;362(5):427-439. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20089951>.
48. 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>.
49. 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>.
50. 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>.
51. 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>.
52. 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>.
53. 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>.
54. Sheffield JS, Hollier LM, Hill JB, Stuart GS, Wendel GD. Acyclovir prophylaxis to prevent herpes simplex virus recurrence at delivery: a systematic review. *Obstet Gynecol*. 2003;102(6):1396-1403. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14662233>.
55. 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>.
56. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 117: Gynecologic care for women with human immunodeficiency virus. *Obstet Gynecol*. 2010;116(6):1492-1509. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21099636>.
57. 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

Updated: September 13, 2019

Reviewed: January 11, 2023

Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma 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. Histoplasmosis is also found in Latin America and the Caribbean and less commonly in other parts of the world. In endemic areas, the annual incidence rate may approach 5% among individuals with HIV. A CD4 T lymphocyte (CD4) count <150 cells/mm³ is associated with an increased risk of symptomatic illness in people with HIV.^{1,2}

Histoplasmosis is acquired by 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 reactivation of a quiescent focal infection acquired years early; this is the presumed mechanism for disease occurrence in nonendemic areas.

Clinical Manifestations

In patients with HIV, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough, chest pain, and dyspnea occur in approximately 50% of patients.^{1,3} Central nervous system (CNS), gastrointestinal (GI), and cutaneous manifestations occur in a smaller percentage of patients. Approximately 10% of patients experience shock and multi-organ failure. Patients with CNS histoplasmosis typically experience fever and headache, and if brain involvement is present, seizures, focal neurological deficits, and changes in mental status.⁴ GI disease usually manifests as diarrhea, fever, abdominal pain, and weight loss.⁵ In a case series of patients with AIDS in Panama, diarrhea was seen in 50% of the patients with histoplasmosis.⁶ For patients with CD4 counts >300 cells/mm³, histoplasmosis is often limited to the respiratory tract and usually presents with cough, pleuritic chest pain, and fever.

Diagnosis

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated and acute pulmonary histoplasmosis⁷ but is insensitive for chronic forms of pulmonary infection. In a study using a newer quantitative assay, *Histoplasma* antigen was detected in 100% of urine samples and 92% of serum samples from people with AIDS and disseminated histoplasmosis.⁸ Antigen detection in bronchoalveolar lavage fluid may also be useful method for diagnosis of pulmonary histoplasmosis.⁹ In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by white blood cells, and histopathological examination of biopsy material from involved tissues often demonstrate the characteristic 2 to 4 μ m in diameter budding yeast cells.

H. capsulatum can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions, or from samples from other involved sites in $>85\%$ of patients with AIDS and disseminated histoplasmosis, but the organism requires several weeks to grow.¹⁰ Serologic tests are

less useful than antigen assays in patients with AIDS and disseminated histoplasmosis but may be helpful in patients with pulmonary disease who have reasonably intact immune responses.^{10,11}

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.⁴ In a recent review of CNS histoplasmosis that included patients with HIV infection, cultures were positive in 38% of patients.¹² *Histoplasma* antigen can be detected in CSF in a far greater number of cases, and antibodies against *H. capsulatum* are seen in approximately one-half of cases.¹² A positive antigen or antibody test result from CSF is diagnostic for histoplasmosis. In cases in which none of these specific tests is 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

Individuals 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 <150 cells/mm³ should avoid 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 old buildings; and exploring caves.

Preventing Disease

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis, although not mortality, in patients who have advanced HIV and who live in areas in which histoplasmosis is highly endemic.¹³ Some experts would give prophylaxis with itraconazole at a dose of 200 mg daily to patients with CD4 counts <150 cells/mm³ who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) (**BI**).

If used, primary prophylaxis can be discontinued in patients on antiretroviral therapy (ART) once CD4 counts are ≥ 150 cells/mm³ for 6 months and HIV-1 viral load is undetectable (**BIII**). Prophylaxis should be restarted if the patient's CD4 count falls to <150 cells/mm³ (**BIII**).

Treating Disease

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily); the liposomal formulation induced a more rapid and complete response, lowered mortality rates, and reduced toxicity.¹⁴ Based on these findings, patients with moderately severe to severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for ≥ 2 weeks or until they clinically improve (**AI**). Amphotericin B lipid complex (5 mg/kg daily) can be used if cost is a concern or patient cannot tolerate liposomal amphotericin B (**AIII**).

Step-down therapy to oral itraconazole, 200 mg three times a day for 3 days, and then 200 mg two times a day, should be given for ≥ 12 months (**AII**).¹⁵ 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, random serum levels of itraconazole should

be measured 2 weeks after the start of therapy. A serum level of 1 to 2 µg/mL is recommended, and the number and severity of adverse events increase when levels are ≥ 4 µg/mL.¹⁶

In patients with less severe disseminated histoplasmosis, oral itraconazole, 200 mg three times daily for 3 days followed by 200 mg twice daily, is appropriate initial therapy (**AII**).^{15,17} 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, but it is less well tolerated than the capsule formulation. The capsule formulation should be given with food and cannot be used when the patient requires gastric acid inhibiting drugs. A new formulation of itraconazole, SUBA-itraconazole, has improved absorption and may prove useful in treating histoplasmosis; however, this agent cannot be recommended, pending further data on its use for this purpose.

The management of acute pulmonary histoplasmosis in a patient with HIV who has a CD4 count >300 cells/mm³ is the same as for an immunocompetent patient (**AIII**).¹⁵

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dosage of 5 mg/kg IV daily for 4 to 6 weeks (**AIII**). This initial IV therapy should be followed by maintenance therapy with oral itraconazole at a dose of 200 mg two or three times daily for ≥ 12 months and until resolution of abnormal CSF findings (**AIII**).¹⁵

Oral posaconazole and voriconazole have been reported to be effective in treating histoplasmosis in a small number of patients with AIDS or other immunosuppressive conditions¹⁸⁻²¹ and may be reasonable alternatives for patients who are only moderately ill and intolerant of itraconazole and for those who have *Histoplasma* meningitis and require long-term antifungal therapy (**BIII**). If voriconazole is used, trough serum levels should be measured after 5 days of therapy with a goal of achieving a concentration of 2 to 5 µg/mL. Concentrations are highly variable among different patients and over time, within a given patient. Concentrations can vary because of absorption issues and drug-drug interactions. Neurotoxicity and hepatotoxicity are associated with serum levels >5 µg/mL, but individual patients can experience adverse effects with lower serum levels. Posaconazole serum levels should be measured after 5 days of therapy to ensure adequate absorption, with a goal of achieving a concentration >1 µg/mL.

Fluconazole is less effective than itraconazole for treatment of histoplasmosis, but has been shown to be moderately effective at a dose of fluconazole 800 mg daily. At this dose, fluconazole may be a reasonable alternative for those intolerant of itraconazole and for long-term therapy for *Histoplasma* meningitis (**CII**).²² Isavuconazole has been used in too few patients with histoplasmosis to be recommended at this time. 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 response to therapy. A rise in antigen level suggests relapse.

Individuals with HIV diagnosed with histoplasmosis should be started on ART as soon as possible after initiating antifungal therapy (**AIII**). Immune reconstitution inflammatory syndrome (IRIS) has been uncommonly reported in patients with HIV who have histoplasmosis.^{23,24} ART should, therefore, not be withheld because of concern for the possible development of IRIS (**AIII**).

All triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. [Table 4](#) lists these interactions and recommendations for dosage adjustments, where feasible.

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 reasonable alternatives for patients intolerant of itraconazole who are only moderately ill (**BIII**);¹⁸⁻²¹ fluconazole at a dose of 800 mg daily also can be used (**CII**).²² Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or protease inhibitors. Posaconazole has fewer known drug interactions with ART medications than voriconazole.

Prevention of Relapse

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered to patients with severe disseminated infection or CNS infection (**AIII**) and after re-induction therapy to those whose disease relapsed despite initial receipt of appropriate therapy (**BIII**). Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.^{25,26} The role of voriconazole or posaconazole has not been evaluated in sufficiently powered studies.

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that it was safe to discontinue itraconazole treatment for histoplasmosis in patients who had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum or urine antigen <4.1 units, and CD4 counts ≥ 150 cells/mm³; and had been on ART for 6 months.²⁵ 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 meet the criteria described above, have a serum or urine antigen below the limit of quantification in ng/mL (current terminology that replaces the term “units”), and have an undetectable viral load (**AI**). Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm³ (**BIII**).²⁵

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis in pregnant patients. Extensive clinical experience with amphotericin B has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of >300 women with first trimester exposure did not show an increased risk of congenital malformation.^{27,28} However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy (**BIII**). Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses ≥ 400 mg/day throughout or beyond the first trimester of pregnancy.²⁹ Although several cohort studies 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.^{30,31} On the basis of the reported birth defects, the Food and Drug Administration has changed the pregnancy category for fluconazole for any use other than a single, low dose for treatment of vaginal candidiasis from category C to category D (see the FDA Drug Safety Communication).

In animals, voriconazole (at doses lower than recommended human doses) and posaconazole are teratogenic and embryotoxic. There are no adequately controlled studies of these drugs in humans. Use of voriconazole and posaconazole **should be avoided** in pregnancy, especially in the first trimester (**AIII**).

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections

Preventing First Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis

- CD4 count <150 cells/mm³ and at high risk because of occupational exposure or residence in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**

Preferred Therapy

- Itraconazole 200 mg PO once daily **(BI)**

Criteria for Discontinuing Primary Prophylaxis (BIII)

- Patient on ART, and
- CD4 count ≥150 cells/mm³, and
- Undetectable HIV-1 viral load for 6 months

Indication for Restarting Primary Prophylaxis

- CD4 count <150 cells/mm³ **(BIII)**

Treating Moderately Severe to Severe Disseminated Disease

Induction Therapy

Preferred Therapy

- Liposomal amphotericin B at 3 mg/kg IV daily **(AI)**

Alternative Therapy

- Amphotericin B lipid complex at 5 mg/kg IV daily **(AIII)**

Duration

- For ≥2 weeks or until clinically improved

Maintenance Therapy

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then two times a day for ≥12 months **(AII)**, with dosage adjustment based on interactions with ART and itraconazole serum concentration

Treating Less Severe Disseminated Disease

Induction and Maintenance Therapy

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day for ≥12 months **(AII)**, with dose adjustment based on interactions with ART and itraconazole serum concentration

Alternative Therapy

- **Note:** These recommendations are based on limited clinical data for patients who are intolerant to itraconazole and who are only moderately ill.
- Posaconazole, extended release tablet 300 mg PO twice daily for 1 day, then 300 mg PO once daily **(BIII)**

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII)
- Fluconazole 800 mg PO once daily (CII)

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks)

- Liposomal amphotericin B 5 mg/kg IV daily (AIII)

Maintenance Therapy

- Itraconazole 200 mg PO two or three times a day for ≥ 12 months and until resolution of abnormal CSF findings with dosage adjustment based on interactions with ART and itraconazole serum concentration (AIII)

Alternative Therapy

- **Note:** These recommendations are based on limited clinical data for patients intolerant to itraconazole.
- Voriconazole 400 mg PO two times a day for 1 day, then 200 mg PO two times a day (BIII)
- Posaconazole 300 mg extended release tablet PO twice daily for 1 day, then 300 mg PO once daily (BIII)
- Fluconazole 800 mg PO once daily (CII)

Long Term Suppressive Therapy

Indications

- Severe disseminated or CNS infection after completing ≥ 12 months of treatment (AIII), and
- Relapse despite appropriate initial therapy (BIII)

Preferred Therapy

- Itraconazole 200 mg PO once daily (AIII)

Alternative Therapy

- Posaconazole 300 mg extended release tablet PO once daily (BIII)
- Voriconazole 200 mg PO twice daily (BIII)
- Fluconazole 400 mg PO once daily (CII)

Criteria for Discontinuing Long Term Suppressive Therapy (AI)

- Received azole treatment for >1 year, and
- Negative fungal blood cultures, and
- Serum or urine *Histoplasma* antigen below the level of quantification, and
- Have an undetectable HIV viral load, and
- CD4 count >150 cells/mm³ for ≥ 6 months in response to ART

Indication for Restarting Secondary Prophylaxis

- CD4 count <150 cells/mm³ (BII)

Other Considerations

- Itraconazole serum concentrations should be measured in all patients after 2 weeks of therapy (time it usually takes to reach 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 to 2 µg/mL. Concentrations >4 µg/mL are associated with increased frequency and severity of adverse effects.

- Itraconazole oral solution is preferred over the capsule formulation because of improved absorption but is less well tolerated. However, it is not necessary to use the oral solution if itraconazole concentration is >1.0 µg/mL with the capsule formulation.
- Voriconazole trough serum levels should be measured after 5 days of therapy (time it usually takes to reach steady state) with a goal of achieving a concentration of 2 to 5 ug/mL. Levels are highly variable among patients, and for individual patients, levels can vary because of drug-drug interactions. Neurotoxicity and hepatotoxicity are associated with serum levels >5 ug/mL, but individual patients can experience adverse effects with lower serum levels.
- Trough posaconazole serum levels should be measured after 5 days of therapy (time it usually takes to reach steady state) to ensure adequate absorption, with a goal of achieving a concentration >1 ug/mL.
- Acute pulmonary histoplasmosis in patients with HIV with CD4 count >300 cells/mm³ 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. [Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines](#) lists these interactions and recommends dosage adjustments where feasible.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, CSF = cerebrospinal fluid; CYP = cytochrome P450; IV = intravenous; PI = protease inhibitor; PO = orally

References

1. 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>.
2. 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>.
3. 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>.
4. 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>.
5. 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>.
6. 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>.
7. Swartzentruber S, Rhodes L, Kurkjian K, et al. Diagnosis of acute pulmonary histoplasmosis by antigen detection. *Clin Infect Dis*. 2009;49(12):1878-1882. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19911965>.
8. 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>.
9. 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>.
10. 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>.
11. 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>.

12. 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>.
13. 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>.
14. 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>.
15. 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>.
16. 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>.
17. 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>.
18. 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>.
19. 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>.
20. 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>.
21. 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>.
22. 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>.

23. 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>.
24. Breton G, Adle-Biasette 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>.
25. 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>.
26. Hecht FM, Wheat J, Korzun AH, et al. Itraconazole maintenance treatment for histoplasmosis in AIDS: a prospective, multicenter trial. *Journal of acquired immune deficiency syndromes and human retrovirology : official publication of the International Retrovirology Association*. 1997;16(2):100-107. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9358104>.
27. 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>.
28. 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>.
29. 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>.
30. Norgaard 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>.
31. 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>.

Human Herpesvirus-8 Disease

Updated: May 29, 2018

Reviewed: January 11, 2023

Epidemiology

The seroprevalence of human herpesvirus-8 (HHV-8)—also known as Kaposi sarcoma-associated herpesvirus (KSHV)—varies worldwide and is estimated to be 1% to 5% in the general U.S. population^{1,2} compared with 10% to 20% in certain Mediterranean countries and 30% to 80% in parts of sub-Saharan Africa.³ In the United States, men who have sex with men (MSM) and persons with HIV infection are at increased risk for HHV-8 infection. Among MSM without HIV infection, the seroprevalence ranges from 13% to 20% and HHV-8 seroprevalence increases to 30% to 35% among MSM with HIV infection.⁴⁻⁶ Injection drug use may also be a risk factor for HHV-8 seropositivity,⁷ although this association has not been consistently observed.⁸

HHV-8 is etiologically associated with all forms of Kaposi sarcoma (KS) including classic, endemic, transplant-related, and AIDS-related, as well as rare neoplastic disorders (primary effusion lymphoma [PEL] and solid organ variants) and the lymphoproliferative disorder known as multicentric Castleman's disease (MCD). Although the precise pathogenesis for these tumors remains unclear, infection with HHV-8 precedes their development.⁹ Patients who are HHV-8 seropositive and exhibit HHV-8 viremia are at increased risk (approximately nine-fold) for developing KS relative to those without HHV-8 viremia.¹⁰ HHV-8 viremia typically accompanies symptomatic episodes of multicentric Castleman's disease.¹¹

The overall prevalence of KS in the U.S. was as high as 30% among patients with AIDS prior to the advent of effective antiretroviral therapy (ART).¹² The incidence of KS rose steeply in the United States between 1981 and 1987 and subsequently gradually declined.¹³ Reasons for this reduction in KS incidence prior to the widespread availability of ART include the deaths of patients with advanced AIDS who were most susceptible to KS, and the increasing use by individuals with HIV of antiviral drugs that may have had activity against HHV-8 (zidovudine for the treatment of HIV; ganciclovir, foscarnet, and cidofovir use for treatment of CMV disease).¹⁴ Supporting the latter hypothesis, observational studies indicate that patients receiving ganciclovir or foscarnet (but not acyclovir) develop KS at a reduced rate.¹⁵⁻¹⁸ A more marked reduction in KS incidence occurred beginning in 1996, shortly after the introduction of protease inhibitor-containing ART in the U.S. Despite these declines, KS is among the most common cancers among the AIDS population in the U.S.,¹⁹ and HIV infection increases the risk of KS several thousand fold even in the ART era.²⁰ Notably, KS is a common cancer in many countries in sub-Saharan Africa,²¹ fueled in part by the HIV pandemic, and incidence has not declined in regions of sub-Saharan Africa where ART coverage is increasing but incomplete.^{22,23} PEL and MCD remain rare relative to KS.^{24,25}

KS and PEL are described most frequently among individuals with HIV exhibiting advanced immunosuppression (CD4 T lymphocyte [CD4] cell counts <200 cells/mm³), although they may occur at any CD4 cell count. Recent reports of KS occurring at higher CD4 cell counts in the United States^{26,27} suggest that clinicians caring for patients with HIV should be vigilant for the clinical manifestations of KS in patients at risk of HHV-8 infection, regardless of CD4 cell count. MCD may arise at any CD4 cell count.

Clinical Manifestations

Most individuals latently infected with HHV-8 are asymptomatic.²⁸ Immunocompetent children and organ transplant recipients infected with HHV-8 may develop a primary infection syndrome consisting of fever, rash, lymphadenopathy, bone marrow failure, and occasional rapid progression to KS.^{29,30} KS manifestations vary

widely, but most patients have nontender, hyperpigmented, macular or nodular skin lesions. Oral lesions occur in approximately one-third of patients³¹ and are predictors of pulmonary involvement and less favorable treatment outcomes.³²⁻³⁴ Lymphatic involvement is also common and may lead to debilitating lower extremity edema. Involvement of internal viscera occurs in up to 50% of cases and may be difficult to diagnose. Patients with visceral involvement may be asymptomatic, or manifest with shortness of breath, painless rectal bleeding or melena, and other non-specific pulmonary and gastrointestinal symptoms.³⁵⁻⁴⁰

PEL characteristically presents with effusions isolated within the pleural, pericardial, or abdominal cavities,⁴¹ but mass lesions and “extracavitary” disease within skin, hematopoietic organs, and the gastrointestinal tract have been described.⁴²⁻⁴⁴ MCD routinely manifests with systemic symptoms including fever and night sweats, and findings on examination including generalized adenopathy, fever and hepatosplenomegaly.^{24,45} MCD may mimic other inflammatory conditions including sepsis, with hypotension, clinical evidence of a systemic inflammatory response, and progression to multi-organ failure.^{24,46,47}

Another HHV-8- associated condition, the KSHV inflammatory cytokine syndrome (KICS), has been more recently described.⁴⁸⁻⁵⁰ Patients with this syndrome display MCD-like inflammatory symptoms, but do not have pathological findings of MCD. Patients with KICS are frequently critically ill and demonstrate marked elevations in IL-6 and IL-10, as well as high plasma HHV-8 viral loads. KICS may contribute to the inflammatory symptoms seen in some patients with severe KS or PEL, and there may be significant clinical overlap between these conditions.

Diagnosis

The diagnoses of KS, MCD and PEL depend on cytologic and immunologic cell markers, as well as histology. Clinical diagnosis alone is not sufficient for KS, and tissue examination is needed to confirm the diagnosis.^{51,52} Confirmation of these diagnoses is achieved through immunohistochemical staining of tumors with antibodies recognizing the HHV-8-encoded latency-associated nuclear antigen (LANA).^{53,54} While not commercially available, diagnoses may also be confirmed utilizing polymerase chain reaction (PCR) to identify HHV-8 DNA within tumor tissue.^{53,54} Use of serologic testing for HHV-8 antibodies is currently not indicated for either diagnostic testing or routine screening for HHV-8-related illnesses due to lack of standardization and poor sensitivity and specificity of these assays.⁵⁵ In addition, use of PCR to quantify HHV-8 in the peripheral blood has no established role in the diagnosis of KS, MCD, or PEL.¹¹

HHV-8 Transmission/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.^{4,28,56} In a study of 50 HHV-8-infected MSM in the U.S., HHV-8 was detected by PCR in the saliva of 39% of participants and on more than 35% of days on which samples were obtained.⁴ HHV-8 shedding is also common among persons in sub-Saharan Africa. Among HHV-8-infected adults without KS in Uganda, 22% had HHV-8 DNA detected in saliva and 3% in genital secretions; HHV-8 was also detected in saliva of 68% of commercial sex workers in Kenya.^{57,58} 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. HHV-8 transmission through blood transfusion has been reported in Uganda, where HHV-8 is endemic;⁵⁹ however, studies from the U.S. and Western Europe have not found evidence to support HHV-8 transmission through blood transfusion.^{60,61}

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

Despite observational evidence supporting a role for anti-HHV-8 therapy in preventing the development of KS, the toxicity of current anti-HHV-8 treatments outweighs the potential use for prophylaxis (**AIII**). Because strong risk factors for the development of KS in HIV-positive individuals include both low CD4-positive T cell count⁶² and uncontrolled viremia,⁶³ early initiation of ART is likely to be the most effective measure for the prevention of KS (**AII**). Although epidemiologic data are somewhat conflicting, there are no antiretroviral agents which have proven clearly superior for the prevention of KS.⁶⁰⁻⁶⁵ Therefore, specific classes of ART for prevention of KS or other HHV-8-associated illnesses are not recommended (**AII**).

Treating Disease

KS: Chemotherapy, in combination with ART, should be administered to patients with visceral involvement (**AI**) and is likely to be a useful adjunctive therapy in individuals with disseminated cutaneous KS (**BIII**).⁶⁴⁻⁶⁷ Liposomal doxorubicin and paclitaxel exhibit comparable response rates and progression-free survival, although liposomal doxorubicin exhibits less high-grade toxicity relative to paclitaxel and is, therefore, generally preferred as first-line therapy (**AI**).⁶⁴ Paclitaxel has proven effective with relapse following treatment failure with liposomal doxorubicin.⁶⁷ Importantly, concurrent use of corticosteroids in patients with KS should be either avoided or used with caution and under close observation, given the potential for exacerbation of life-threatening disease, as well as an association between the use of corticosteroids and development of KS (**AIII**).⁶⁸⁻⁷⁰ KS arising in the setting of organ transplantation is related to the use of corticosteroids and other non-targeted immunosuppressives, especially in geographic areas of high HHV-8 seroprevalence.⁷¹ Transplant-associated KS may be effectively treated or avoided with use of immunosuppressive regimens which include drugs that inhibit the mammalian target of rapamycin (mTOR) such as rapamycin and sirolimus.⁷¹⁻⁷³

The antiviral agents ganciclovir, foscarnet, and cidofovir exhibit *in vitro* activity against HHV-8.^{74,75} Available data indicate that antivirals have limited efficacy for the treatment of KS (ganciclovir and cidofovir)^{76,77} and HHV-8-associated hemophagocytosis (foscarnet).^{78,79} Therefore, antiviral agents with activity against HHV-8 are not recommended for KS treatment (**AII**).

PEL: Chemotherapy, in combination with ART, should be administered to patients with PEL (**AIII**), although, given its rarity, there are limited data available from longitudinal observational series or 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, and the combination of infusional etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) demonstrated superior survival relative to CHOP in one pooled analysis (**BII**).^{80,81} Rituximab may be considered for rare CD20-positive cases of PEL (**CIII**), and dose-adjusted EPOCH (DA-EPOCH) may be beneficial for some patients (**CIII**).^{82,83} Antiviral agents, including valganciclovir or zidovudine, may also be used as adjunctive therapies, but available data are limited for this approach and additive toxicities may limit their utility (**CIII**).⁸⁴⁻⁸⁶

MCD: There are no standardized treatments for MCD, but several treatment regimens have been utilized. The use of either IV ganciclovir or oral valganciclovir are options for treatment of MCD (**CII**). A 3-week course of twice-daily IV ganciclovir or oral valganciclovir was associated with remissions in MCD in one report,⁸⁷ and a combination of valganciclovir and high-dose zidovudine has led to durable clinical remissions (**CII**).⁸⁸

Rituximab has also emerged as an important adjunctive treatment for MCD **(CII)**,^{89,90} although up to one-third of patients receiving rituximab may have subsequent exacerbations or emergence of KS.^{91,92} For patients with concurrent diagnoses of KS and MCD, use of both rituximab and liposomal doxorubicin is recommended **(BII)**.⁴⁵ Therapeutic monoclonal antibodies targeting either interleukin-6 (IL-6) or the IL-6 receptor have also proven effective for some patients with MCD and may be utilized in some situations **(BII)**.⁹³⁻⁹⁵ At this time, there is insufficient evidence to recommend monitoring IL-6 levels for diagnostic or prognostic purposes. Although corticosteroids are potentially 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)**.⁶⁸⁻⁷⁰

Detailed recommendations for the treatment of HHV-8 malignancies (including chemotherapy and radiation therapy) are beyond the scope of these guidelines. Treatment should be undertaken in consultation with an experienced specialist with appropriate guidance from both oncology and infectious disease specialists **(AIII)**. Preferred ART to be given concurrently with chemotherapy for HHV-8 malignancies should be chosen to minimize drug-drug interactions and additive toxicities.

Special Considerations When Starting Antiretroviral Therapy

Early initiation of ART may prevent incident KS and PEL.^{74,96} ART that suppresses HIV replication should be administered to all patients with HIV and KS **(AII)**, PEL **(AIII)**, or MCD **(AIII)**, although insufficient evidence exists to support using one ART regimen over another.

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

Immune reconstitution inflammatory syndrome (IRIS) may occur among HHV-8-infected patients initiating ART.

KS: KS-IRIS is characterized by either first presentation of KS (“unmasking”), or paradoxical worsening of pre-existing KS following ART initiation, and can be associated with significant morbidity and mortality.⁹⁷ Studies in the U.S. and Europe reveal that KS is the most commonly reported form of IRIS, occurring in 6% to 34% of KS patients with HIV who are initiating ART.^{98,99} In sub-Saharan Africa, exacerbations of KS compatible with KS-IRIS have been reported in 18% to 61% of adults initiating ART treatment.¹⁰⁰⁻¹⁰² Risk factors for developing KS-IRIS include advanced KS tumor stage (T1), pre-treatment HIV viral load >5 log₁₀ copies/mL, detectable pre-treatment plasma HHV-8, and initiation of ART alone without concurrent chemotherapy.⁹⁷ Treatment of KS-IRIS includes systemic chemotherapy and supportive measures. Steroids are strongly discouraged for management of KS-IRIS, as corticosteroid therapy has been associated with exacerbation of pre-existing KS in persons with HIV **(AIII)**.^{70,103}

PEL: No data exist on the frequency with which initiation of ART complicates the course of primary effusion lymphoma.

MCD: A small number of patients with HIV-associated MCD have experienced clinical decompensation upon initiation of ART.^{104,105}

Although neither the incidence nor predictors of HHV-8-associated IRIS are well-described, suppression of HIV replication and immune reconstitution are key components of therapy, and initiation of ART should not be delayed **(AIII)**.

Preventing Recurrence

Effective suppression of HIV replication with ART in patients with HIV and KS may prevent KS progression or occurrence of new lesions. Because KS is an AIDS-defining cancer, ART is indicated for all patients with active KS **(AII)**. Suppression of HIV replication to prevent recurrence is also recommended for patients with MCD **(AIII)** as well as those with 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 11.6% among pregnant women from 4 other U.S. cities.¹⁰⁶ Pregnancy does not appear to affect the prevalence of antibodies to HHV-8 or the antibody levels,¹⁰⁷ although levels of HHV-8 DNA in the peripheral blood may increase late in pregnancy.¹⁰⁸ HHV-8 seropositivity does not appear to influence pregnancy outcome. Routine screening for HHV-8 by PCR or serology is not indicated for pregnant women with HIV **(AIII)**. Antiviral therapy for 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 between the obstetrician, infectious disease specialist, and oncologist. With limited disease, treatment may be deferred until after delivery.¹⁰⁹

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.¹¹⁰⁻¹¹³ Perinatal transmission of HHV-8 occurs infrequently. Evidence supporting vertical transmission during pregnancy or the intrapartum period includes cases of KS occurring in the infant shortly after birth,^{114,115} higher risk for transmission with higher maternal antibody titer (and, by inference, higher maternal levels of HHV-8),¹¹⁶ and detection of similar strains of HHV-8 DNA by PCR in specimens drawn at birth from HHV-8-seropositive mothers and their infants.¹¹⁷ Data indicate increased mortality through age 24 months among infants with HIV born to HHV-8-seropositive mothers compared with HHV-8-seronegative mothers,^{114-116,118-123} 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 compared with HHV-8 antibody-negative women.¹¹⁸⁻¹²³

Recommendations for Preventing and Treating HHV-8 Diseases—Kaposi Sarcoma (KS), Primary Effusion Lymphoma (PEL), Multicentric Castleman’s Disease (MCD)

Preventing development of KS:

- Since low CD4 cell count and uncontrolled HIV viremia are strong risk factors of KS, early initiation of ART is likely to be the most effective measure for the prevention of KS **(AII)**

Mild-to-Moderate KS (localized involvement of skin and/or lymph nodes)¹:

- Initiation or optimization of ART **(AII)**

Advanced KS (visceral and/or disseminated cutaneous disease)¹:

- Chemotherapy (*in consultation with specialist*) + ART [visceral KS **(AI)** or widely-disseminated cutaneous KS **(BIII)**].
- Liposomal doxorubicin is preferred first-line chemotherapy **(A1)**
- Avoid use of corticosteroids in patients with KS, including those with KS-IRIS, given the potential for exacerbation of life-threatening disease **(AIII)**
- Antiviral agents with activity against HHV-8 are not recommended for KS treatment **(AIII)**.

PEL:

- Chemotherapy (*in consultation with a specialist*) **(AIII)** + ART **(AIII)**
- Oral valganciclovir or IV ganciclovir can be used as adjunctive therapy **(CIII)**

MCD:

All patients with MCD should receive ART **(AIII)** in conjunction with one of the therapies listed below.

Therapy Options (in consultation with a specialist, and depending on HIV/HHV-8 status, presence of organ failure, and refractory nature of disease):

- IV ganciclovir (or oral valganciclovir) +/- high dose zidovudine **(CII)**
- Rituximab +/- prednisone **(CII)**
- For patients with concurrent KS and MCD – rituximab + liposomal doxorubicin **(BII)**
- Monoclonal antibody targeting IL-6 or IL-6 receptor **(BII)**
- Corticosteroids are potentially effective as adjunctive therapy, but should be used with caution or avoided, especially in patients with concurrent KS. **(AIII)**

Other Considerations:

- Patients who receive rituximab or corticosteroids for treatment of MCD may experience subsequent exacerbation or emergence of KS

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenously; KS = Kaposi sarcoma; MCD = multicentric Castleman’s disease; PEL = primary effusion lymphoma; PO = orally; q(n)h = every “n” hours

¹ The commonly used AIDS Clinical Trials Group (ACTG) KS Staging Classification uses T(Tumor), Immune(I), and Systemic illness (S) criteria to classify patients into “Good Risk” and “Poor Risk” categories (ref Krown, JCO, 1989). “Good Risk” tumor stage criteria are used by some specialists to correspond with mild-to-moderate KS.

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: <http://www.ncbi.nlm.nih.gov/pubmed/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: <http://www.ncbi.nlm.nih.gov/pubmed/12519435>.
3. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20143397>.
4. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11070101>.
5. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D. The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. *Nat Med*. 1996;2(8):918-924. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8705863>.
6. Gao SJ, Kingsley L, Li M, et al. KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. *Nat Med*. 1996;2(8):925-928. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8705864>.
7. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11228278>.
8. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12085330>.
9. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8657239>.
10. Lennette ET, Blackbourn DJ, Levy JA. Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. *Lancet*. 1996;348(9031):858-861. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8826812>.
11. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10979949>.
12. Beral V. The epidemiology of cancer in AIDS patients. *AIDS*. 1991;5 Suppl 2:S99-103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1845066>.

13. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12189223>.
14. Casper C. Defining a role for antiviral drugs in the treatment of persons with HHV-8 infection. *Herpes.* 2006;13(2):42-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16895654>.
15. 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>.
16. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with human immunodeficiency virus infection: a meta-analysis of randomized individual patient data. *J Infect Dis.* 1998;178(2):349-359. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9697714>.
17. Mocroft A, Youle M, Gazzard B, Morcinek J, Halai R, Phillips AN. Anti-herpesvirus treatment and risk of Kaposi's sarcoma in HIV infection. Royal Free/Chelsea and Westminster Hospitals Collaborative Group. *AIDS.* 1996;10(10):1101-1105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8874626>.
18. Glesby MJ, Hoover DR, Weng S, et al. Use of antiherpes drugs and the risk of Kaposi's sarcoma: data from the Multicenter AIDS Cohort Study. *J Infect Dis.* 1996;173(6):1477-1480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8648224>.
19. Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. *J Natl Cancer Inst.* 2011;103(9):753-762. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21483021>.
20. 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>.
21. North AB, South CD. Cancer Incidence in Antarctica (2003-2007). In: Secondary North AB, South CD, eds. Subsidiary North AB, South CD, trans. Secondary Cancer Incidence in Antarctica (2003-2007). Vol. ed. Lyon: International Agency for Research on Cancer; 2013.
22. Casper C. The increasing burden of HIV-associated malignancies in resource-limited regions. *Annu Rev Med.* 2011;62:157-170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20868276>.
23. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25844696>.
24. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15801951>.
25. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25843728>.

26. Maurer T, Ponte M, Leslie K. HIV-associated Kaposi's sarcoma with a high CD4 count and a low viral load. *N Engl J Med*. 2007;357(13):1352-1353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17898112>.
27. Mani D, Neil N, Israel R, Aboulafia DM. A retrospective analysis of AIDS-associated Kaposi's sarcoma in patients with undetectable HIV viral loads and CD4 counts greater than 300 cells/mm(3). *J Int Assoc Physicians AIDS Care (Chic)*. 2009;8(5):279-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19721098>.
28. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17152006>.
29. Andreoni M, Sarmati L, Nicastrì E, et al. Primary human herpesvirus 8 infection in immunocompetent children. *JAMA*. 2002;287(10):1295-1300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11886321>.
30. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11070102>.
31. Nichols CM, Flaitz CM, Hicks MJ. Treating Kaposi's lesions in the HIV-infected patient. *J Am Dent Assoc*. 1993;124(11):78-84. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8227776>.
32. Reichart PA. Oral manifestations in HIV infection: fungal and bacterial infections, Kaposi's sarcoma. *Med Microbiol Immunol*. 2003;192(3):165-169. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12684760>.
33. Rohrmus B, Thoma-Greber EM, Bogner JR, Rocken M. Outlook in oral and cutaneous Kaposi's sarcoma. *Lancet*. 2000;356(9248):2160. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11191549>.
34. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11077385>.
35. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21103057>.
36. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26839780>.
37. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26261737>.
38. Buchbinder A, Friedman-Kien AE. Clinical aspects of epidemic Kaposi's sarcoma. *Cancer Surv*. 1991;10:39-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1821322>.

39. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12062994>.
40. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16185232>.
41. Patel S, Xiao P. Primary effusion lymphoma. *Arch Pathol Lab Med*. 2013;137(8):1152-1154. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23899073>.
42. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24917369>.
43. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25389336>.
44. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26407759>.
45. 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: <http://www.ncbi.nlm.nih.gov/pubmed/25331113>.
46. Soumerai JD, Sohani AR, Abramson JS. Diagnosis and management of Castleman disease. *Cancer Control*. 2014;21(4):266-278. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25310208>.
47. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26831502>.
48. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20583924>.
49. 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: <http://www.ncbi.nlm.nih.gov/pubmed/22403576>.
50. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26658701>.

51. 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: <http://www.ncbi.nlm.nih.gov/pubmed/14990970>.
52. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26452066>.
53. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17627810>.
54. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15660651>.
55. Morrison BJ, Labo N, Miley WJ, Whitby D. Serodiagnosis for tumor viruses. *Semin Oncol*. 2015;42(2):191-206. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25843726>.
56. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15076237>.
57. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19156206>.
58. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24692069>.
59. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17005950>.
60. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19385734>.
61. Schennach H, Schonitzer D, Wachter H, Fuchs D. Blood donations and viruses. *Lancet*. 1997;349(9061):1327-1328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9142092>.
62. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20442214>.
63. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28394855>.

64. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20564162>.
65. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17227906>.
66. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10589755>.
67. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12115328>.
68. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18317012>.
69. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18333287>.
70. Trattner A, Hodak E, David M, Sandbank M. The appearance of Kaposi sarcoma during corticosteroid therapy. *Cancer*. 1993;72(5):1779-1783. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8348508>.
71. Hosseini-Moghaddam SM, Soleimanirahbar A, Mazzulli T, Rotstein C, Husain S. Post renal transplantation Kaposi's sarcoma: a review of its epidemiology, pathogenesis, diagnosis, clinical aspects, and therapy. *Transpl Infect Dis*. 2012;14(4):338-345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22316356>.
72. Monaco AP. The role of mTOR inhibitors in the management of posttransplant malignancy. *Transplantation*. 2009;87(2):157-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19155967>.
73. Stock PG, Barin B, Murphy B, et al. Outcomes of kidney transplantation in HIV-infected recipients. *N Engl J Med*. 2010;363(21):2004-2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21083386>.
74. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9151779>.
75. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9302441>.
76. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12508160>.

77. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21450998>.
78. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12134112>.
79. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9753702>.
80. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15994147>.
81. 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: <http://www.ncbi.nlm.nih.gov/pubmed/22180164>.
82. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15800785>.
83. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27462227>.
84. Crum-Cianflone NF, Wallace MR, Looney D. Successful secondary prophylaxis for primary effusion lymphoma with human herpesvirus 8 therapy. *AIDS.* 2006;20(11):1567-1569. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16847420>.
85. Pereira R, Carvalho J, Patricio C, Farinha P. Sustained complete remission of primary effusion lymphoma with adjunctive ganciclovir treatment in an HIV-positive patient. *BMJ Case Rep.* 2014;2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25312890>.
86. Oksenhendler E, Clauvel JP, Jouveshomme S, Davi F, Mansour G. Complete remission of a primary effusion lymphoma with antiretroviral therapy. *Am J Hematol.* 1998;57(3):266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9495391>.
87. 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: <http://www.ncbi.nlm.nih.gov/pubmed/14615380>.
88. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21487108>.

89. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21555697>.
90. Marcelin AG, Aaron L, Mateus C, et al. Rituximab therapy for HIV-associated Castleman disease. *Blood*. 2003;102(8):2786-2788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12842986>.
91. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17664482>.
92. 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: <http://www.ncbi.nlm.nih.gov/pubmed/18087054>.
93. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15998837>.
94. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24438824>.
95. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20625121>.
96. From RP, Mehta MP, Pathak D. Serum potassium concentrations following succinylcholine in patients undergoing beta-adrenoceptor blocking therapy. *J Clin Anesth*. 1989;1(5):350-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2576378>.
97. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23462220>.
98. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16051964>.
99. 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: <http://www.ncbi.nlm.nih.gov/pubmed/22095568>.
100. 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: <http://www.ncbi.nlm.nih.gov/pubmed/22395672>.

101. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20572760>.
102. 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: <http://www.ncbi.nlm.nih.gov/pubmed/19801945>.
103. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26769754>.
104. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12228826>.
105. Achenbach C, Kitahata MM. Recurrence or Worsening of AIDS-defining Opportunistic Infection (OI) due to Immune Reconstitution Inflammatory Syndrome (IRIS) During Initial HAART Among a Clinic-Based Population. Presented at: 48th ICAAC/IDSA 46th Annual Meeting; 2008. Washington, DC. Available at.
106. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9149705>.
107. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10630961>.
108. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16943357>.
109. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23258835>.
110. Berger P, Dirnhofer S. Kaposi's sarcoma in pregnant women. *Nature*. 1995;377(6544):21-22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7659155>.
111. 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: <http://www.ncbi.nlm.nih.gov/pubmed/7723844>.
112. Rabkin CS, Chibwe G, Muyunda K, Musaba E. Kaposi's sarcoma in pregnant women. *Nature*. 1995;377(6544):21; author reply 22. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7659154>.
113. Schulz TF, Weiss RA. Kaposi's sarcoma. A finger on the culprit. *Nature*. 1995;373(6509):17-18. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7800029>.

114. 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: <http://www.ncbi.nlm.nih.gov/pubmed/2923454>.
115. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8669966>.
116. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10375309>.
117. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16586362>.
118. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11745472>.
119. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11267990>.
120. Gessain A, Maucelere 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: <http://www.ncbi.nlm.nih.gov/pubmed/10188717>.
121. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9660357>.
122. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9841845>.
123. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11009141>.

Human Papillomavirus Disease

Updated: August 18, 2021

Reviewed: January 11, 2023

Epidemiology

Human papillomavirus (HPV) infection is the major risk factor for development of cervical cancer,^{1,2} the fourth most common cancer in women worldwide.^{3,4} Nearly all cervical cancers test positive for HPV genetic sequences,⁵⁻⁷ most notably the E6 and E7 oncogenes,⁸⁻¹⁰ which are thought to play a major role in immortalization of cervical epithelial cells.¹¹ Cervical infection with HPV is common and occurs primarily through sexual transmission.¹²⁻¹⁶ Penetrative sexual intercourse is not strictly necessary for HPV transmission,¹⁷ but it is the primary risk factor for HPV infection, and HPV prevalence is low in young women who report only nonpenetrative sexual contact.^{17,18} The vast majority of cervical HPV infections resolve or become latent and undetectable, but in a subset of women, infection persists.^{12,19,20} Persistence of oncogenic HPV infection is a necessary step in HPV-related cervical tumorigenesis,^{1,21,22} although it appears insufficient for final cell transformation.¹¹ At least 12 HPV types are considered oncogenic, including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.²²⁻²⁴ HPV68 is considered “probably oncogenic,” and several other HPV types are considered “possibly oncogenic.” HPV16 alone, though, accounts for approximately 50% of cervical cancers in the general population and HPV18 for another 10% to 15%. The other oncogenic HPV types each individually account for fewer than 5% of tumors. HPV types 6 and 11 cause 90% of genital warts, but in general are not considered oncogenic.²²⁻²⁴

In the United States and Western Europe, women with HIV (WWH) have significantly higher rates of cervical cancer than women in the general population,²⁵⁻³¹ and recent cohort data show a direct relationship between low CD4 T lymphocyte (CD4) cell count and cervical cancer risk.³²⁻³⁴ In Africa, the data are more limited,³⁵ but a prospective registry-based study found elevated risk of cervical cancer^{36,37} as well as anal, vulvar, and penile cancer (each of which increased in incidence among people with HIV [PWH] between 2003 and 2015).³⁷ HIV infection and low CD4 cell count also have been associated consistently and strongly with HPV infection itself and with precancerous cervical lesions—including low-grade cervical intraepithelial neoplasia (CIN)—and the precursor to cervical cancer, CIN 3.³⁸⁻⁵⁰

Higher rates of HPV infection and CIN also were reported in HPV-unvaccinated adolescents with HIV, regardless of whether HIV was acquired vertically or horizontally.^{39,51,52} For example, Brogly and colleagues reported that 30% of female adolescents with perinatal HIV infection had an abnormality (e.g., atypical squamous cells of uncertain significance [ASC-US] or greater) on their first Pap test; genital warts also were common in this group, with a cumulative rate of 12% by age 19 years.^{52,53} However, few data exist regarding HPV vaccine efficacy or effectiveness in male or female adolescents or adults with HIV.⁵⁴ A recent paper shows the qHPV vaccine is effective in young men who have sex with men (MSM) with HIV to prevent anal squamous intraepithelial lesions associated with qHPV vaccine types among those naive to those types prior to vaccination.⁵⁵

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx.^{1,23,56-59} HPV16 is the type present in most HPV-positive noncervical cancers.^{1,23,56,60,61} PWH have a significantly elevated incidence of each of these HPV-

related tumors relative to the general population,^{25,62-64} and CD4 cell count has been associated with the risk of anal cancer.^{32,65} Furthermore, high-grade anal intraepithelial neoplasia (AIN), the likely anal cancer precursor lesion, is more common in adults and adolescents who are HIV seropositive than in those who are HIV seronegative,⁶⁶⁻⁶⁸ as are anal and genital warts, and in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).⁶⁹⁻⁷¹ In the general U.S. population, HPV also causes approximately 70% of oropharyngeal cancers (OPC).^{72, 73} HPV16 causes 84% of HPV-associated OPC, and the HPV types contained in the nonavalent HPV vaccine cause approximately 94%.⁷⁴ HPV-associated OPC incidence is four- to fivefold higher in males than in females,⁷⁵ and two- to threefold higher among PWH.⁷⁶⁻⁷⁹ Furthermore, PWH's high risk of HPV-associated cancers continues into older age (>50 years of age). This includes tumors of the cervix, anus, and oropharynx—an important finding given the increasing longevity of PWH.⁸⁰

During the era of combination antiretroviral therapy (cART) the incidence of HPV-associated cancers has remained elevated in PWH relative to the general population,⁶⁴ though the extent of this disparity has decreased for at least some of these tumors. A recent registry-based study, for example, reported a highly statistically significant downward trend in anal cancer incidence relative to the general population ($P = 0.0001$) (i.e., a reduction in standardized incidence ratio [SIR] from approximately SIR ~40 in 1996 to SIR ~20 in 2012).⁶⁴ A possible (nonsignificant; $P = 0.09$) decrease in cervical cancer from SIR ~5 in 1996 to SIR ~3 in 2012, as well as a nonsignificant decrease in oral cavity/pharyngeal cancer, was observed.⁸¹ Other HPV-related tumors are less common, and reliable data regarding the trends in their incidence are limited. Nonetheless, low-grade vulvar lesions and genital warts were found to decrease with cART,⁶⁹ and several studies found decreased incident detection, persistence, and progression of HPV and CIN with cART use⁸²; including one study that distinguished between adherent versus nonadherent or effective versus ineffective cART use (based on HIV RNA level).⁸³

Cervical cancer screening and treatment of precancer are, in and of themselves, a major burden confronting WWH. Positive HPV screening tests are several-fold more common in WWH than in the general population, and as many as 25% to 35% of WWH have an abnormal Pap test (ASC-US+) at each clinical visit⁸⁴; leading to frequent, often repeated colposcopy and biopsy. Furthermore, most colposcopies and biopsies find low-grade lesions rather than clinically relevant disease (e.g., precancer, cancer). Thus, methods to reduce the high burden of unnecessary colposcopy and biopsy in WWH by improving the specificity and positive predictive value of cervical cancer screening methods is of great importance, especially because generations of WWH are above the age to receive the HPV vaccine.

For anal cancer, a major unresolved question is whether or not to conduct screening. Anal cancer risk varies extensively between MSM with HIV and MSM without AIDS, as well as between MSM with HIV and WWH or men who do not have sex with men.^{85,86} For example, a recent study based on HIV/AIDS registry and cancer registry data found that the 5-year risk (cumulative incidence) of anal cancer was 0.33% and 0.52% in MSM without and with AIDS, respectively, whereas the results were 0.04% and 0.10% for men who do not have sex with men, and 0.08% and 0.20% for women. As a point of reference, colorectal and breast cancer, two cancers for which screening is conducted, the 5-year cumulative incidence is 0.27% and 0.89%.³⁰ However, anal cancer may have higher mortality. An NIH-funded randomized clinical trial of anal cancer screening, the [ANCHOR Study](#), is underway.

Anogenital warts are also an important HPV-associated disease in PWH. These lesions are very common, and more likely to be persistent in PWH than the general population. Approximately 80%

to 90% of anogenital warts are caused by non-oncogenic HPV types 6 or 11.⁸⁷ In the United States from 2003 to 2006, the incidence of anogenital warts was 4.0 to 5.2/1,000 person-years in women (ages 20–24 years) and 3.0 to 3.6/1,000 person-years in men (ages 25–29 years).⁸⁸ From the [NHANES](#) database, the estimated prevalence of anogenital warts is 2.9% of men ages 18 to 59 years and 2.2% of men reported a history of anogenital warts,⁸⁹ with several-fold greater rates in PWH.^{69,89} HPV types 6 and 11 also have been associated with conjunctival, nasal, oral, and laryngeal warts.

Data regarding outcomes following treatment of HPV-related cancers in PWH are limited and need to be interpreted accordingly. Cancer-specific survival following treatment of anal and oropharyngeal cancer was reported to be similar in PWH and the general population, whereas cervical cancer survival following treatment was reported to be worse in PWH.^{90,91} Another study found that although response to initial therapy for invasive cervical cancer (e.g., radiation treatment) was similar in PWH and other patients, HIV was associated with high risk of relapse (hazard ratio [HR] = 3.6; 1.86–6.98) and higher cervical cancer mortality.⁹² Data from the AIDS Malignancy Consortium showed that PWH on antiretroviral therapy with locally advanced cervical cancer in sub-Saharan Africa can complete routine cisplatin and radiation therapy and that one-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.⁹³

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 are also caused by HPV.⁹⁴

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.

Intraepithelial neoplasias (CIN, VIN, VAIN, and AIN) 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.

Diagnosis

Warts/Condyloma

Diagnosis of genital and oral warts is made by visual inspection and can be confirmed by biopsy, although biopsy is needed only if the diagnosis is uncertain; the lesions do not respond to standard therapy; or 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 PWH.⁹⁵

Cervical Neoplasia

The same cytology (Pap test), and colposcopic techniques with biopsy are used to detect CIN among patients who are HIV seronegative and those who are HIV seropositive (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, 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.⁹⁶

Cervical Cancer Screening Recommendations

In a recent report from the HIV/AIDS Cancer Match Study (2002–2016)—which included a population of 164,084 WWH (64% Black, 21.8% Hispanic, 12.7% White, and 1.1% other race)—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 among 40- to 44-year-olds and 35- to 39-year-olds (rate = 66.1 and 64.5 per 100,000, respectively). Zero cases of ICC occurred among <25-year-old WWH during 69,900 person-years of follow-up (SIR=0; 95% CI 0,7.1). When compared to the general population, rates of cervical cancer were elevated significantly—3 to 4 times overall (95% CI, 3.13–3.70). Because the absolute incidence of ICC is exceedingly low among WWH under 25 years, it is recommended that cervical cancer screening 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 WWH exceeds that of the general population.⁹⁷

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. **Note:** HPV testing is always for oncogenic HPV types only; there is no role in testing for non-oncogenic HPV.

Observational epidemiologic “bridging studies” in PWH 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 WWH, normal cytology with negative HPV co-testing had a strong negative predictive value, with low 3- to 5-year incidence of CIN2+ regardless of CD4 count.^{98,99} Conversely, the risk of precancer was high in WWH who tested positive for oncogenic HPV despite a normal Pap and several-fold greater still if HPV16 was specifically detected.¹⁰⁰ Additional studies showed that oncogenic HPV testing had high sensitivity and negative predictive value in the triage of borderline Pap test results (i.e., ASC-US).¹⁰¹

Possible Pap test results include the following:

- Normal (negative for intraepithelial lesion or malignancy)
- LSIL (low-grade squamous intraepithelial lesion) or CIN1 (cervical intraepithelial neoplasia grade 1)

- HSIL (high-grade squamous intraepithelial lesion) or CIN2, 3 (cervical intraepithelial neoplasia grade 2, 3)
- ASC-US (atypical squamous cells of uncertain significance)
- ASC-H (atypical squamous cells, cannot rule out a high-grade lesion)
- AGC (atypical glandular cells)

Women With HIV Aged <30 years

Screening

The Pap test is the primary mode for cervical cancer screening for WWH <30 years of age. WWH ages 21 to 29 years should have a Pap test at the time of initial diagnosis with HIV. Provided the initial Pap test for a young (or newly diagnosed) woman with HIV is normal, the next Pap test should occur in 12 months (**BII**). If the results of three consecutive Pap tests are normal, follow-up Pap tests should be every 3 years (**BII**). Co-testing (Pap test and HPV test) is not recommended for WWH <30 years of age.

Abnormal Pap Test Results

Colposcopy is recommended for HPV-positive ASC-US (**AII**). If reflex HPV testing is not performed on ASC-US results, then repeat cytology in 6 to 12 months is recommended (**AII**). For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AII**).

For LSIL or worse (including ASC-H, AGC, and HSIL), referral to colposcopy is recommended.

Rationale

Because of the relatively high HPV prevalence before age 30 years, HPV co-testing is not recommended for women in this age group.

Women With HIV Aged ≥30 years

Cervical cancer screening in WWH should continue throughout a woman's lifetime (and not, as in the general population, end at 65 years of age). Either Pap testing only, or Pap testing and HPV co-testing is acceptable for screening.

Pap Testing Only

If screening with Pap tests alone, WWH should have a Pap test at the time of HIV diagnosis (baseline), then every 12 months (**BII**). If the results of three consecutive Pap tests are normal, follow-up Pap tests should be every 3 years (**BII**).

Pap and HPV Co-Testing

If co-testing with Pap and HPV is available, then co-testing can be done at the time of diagnosis or at age 30 years. (**BII**). Women who co-test negative (i.e., a normal Pap and negative HPV test) can

have their next cervical cancer screening in 3 years.

Those with a normal Pap test but a positive HPV test should have repeat co-testing in one year (unless genotype testing for HPV16 or HPV16/18 is positive). If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

If the initial HPV results identify HPV16 or HPV16/18, referral to colposcopy is recommended. If the HPV testing is positive, but the genotype specific testing for HPV16 or HPV16/18 is negative, then repeat co-testing in one year is recommended. If either of the co-tests at one year is abnormal (i.e., abnormal cytology or positive HPV), referral to colposcopy is recommended.

Abnormal Pap Test Results

For ASC-US Pap test, if reflex HPV testing is negative, a repeat Pap test in 6 to 12 months or repeat co-testing in 12 months is recommended. For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AI**).

For ASC-US Pap test, if reflex HPV testing is positive, then referral to colposcopy is recommended. If HPV testing is not available, repeat cytology in 6 to 12 months is recommended (**AI**). For any result equal to or greater than ASC-US on repeat cytology, referral to colposcopy is recommended (**AI**).

For LSIL or worse (including ASC-H, AGC, and HSIL) referral to colposcopy is recommended (regardless of HPV result, if done).

Rationale

Current guidelines from both the American Cancer Society and the U.S. Preventive Services Task Force 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 WWH who are older than 29 years and have normal cervical cytology with concurrent negative HPV testing.

For women older than 65 years, it is recommended to continue cervical cancer screening because WWH are at higher risk for cervical cancer. However, clinicians should consider other factors, such as the life expectancy of the patient and the risk for developing cervical cancer at this age.

Preventing HPV Infection

HPV Vaccine

Three FDA-approved HPV vaccines exist: bivalent, quadrivalent, and 9-valent. Currently, only the 9-valent vaccine (HPV viral-like particles 6, 11, 16, 18, 31, 33, 45, 52, and 58) is available in the United States. This vaccine has an FDA indication for prevention of cervical, vaginal, vulvar, anal cancer, genital warts, and oropharyngeal and other head and neck cancers¹⁰² due to vaccine types based on randomized clinical trial (RCT) data; albeit, these studies were not conducted in PWH.^{103-105,106-109} Although no efficacy data exist for the 9-valent HPV vaccine in men with HIV, clinical trials established the safety of the vaccine in young men aged 16 to 26 years and showed similar antibody levels as in young women without HIV aged 16 to 26 years in whom efficacy was

established.^{110,111}

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 vaccine-type HPV infections are reduced with vaccination.^{112,113} One prospective trial of the quadrivalent HPV vaccine in PWH older than 27 years suggested efficacy for prevention of oral HPV infection.¹¹⁴

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with 9-valent HPV vaccine. The target age for vaccination is 11 to 12 years (**AIII**). Vaccination through age 26 years is recommended, but vaccine effectiveness is lower if vaccination occurs after onset of sexual activity (**BII**). The vaccine series can be started at age 9 years. Catch-up vaccination is recommended for all 13- to 26-year-olds who have not been vaccinated.¹¹⁵⁻¹¹⁷ Shared clinical decision-making regarding HPV vaccination is recommended for some adults aged 27 through 45 years who are not adequately vaccinated.

The 9-valent vaccine should be delivered through a series of three intramuscular injections over a 6-month period. The second and third doses should be given at 1 to 2 months and then 6 months after the first dose.^{115,116} Although ACIP recommends a two-dose schedule for adolescents initiating the vaccine series at ages 9 to 14 years,¹¹⁸ three doses of HPV vaccine (0, 1–2, and 6 months) are recommended for females and males with HIV or other immune suppression because their immune response to vaccination might be attenuated.

One randomized, double-blind, clinical trial evaluated the efficacy of the quadrivalent HPV vaccine in PWH older than 27 years.¹¹⁴ The trial did not show efficacy for prevention of new anal HPV infections or improvement in anal HSIL outcomes in this population with high levels of prior and current HPV infection. This trial and several other studies have established the safety and immunogenicity of HPV vaccines^{119,120} in a broad range of PWH.¹²¹ Some studies have demonstrated lower antibody levels in PWH than in those who do not have HIV; however, the clinical significance of this observation is unknown.¹²²⁻¹²⁴ Studies have shown that HPV vaccination induces an anamnestic response in children and adults with HIV.^{120,125,104} Immune responses appear stronger among those with higher CD4 counts and suppressed HIV viral loads.^{121,126}

A recent prospective observational cohort study of female youth who had received quadrivalent HPV vaccine showed unexpectedly high rates of abnormal cervical cytology occurred in 33 of 56 perinatally infected youth and only 1 of 7 of perinatally exposed uninfected youth, yielding incidence rates of 100 person-years of 15 (10.9 to 29.6) and 2.9 (0.4 to 22.3), respectively. The majority of the diagnoses were LSIL or less, and the genotypes associated with these abnormal cytology results were unknown.¹²⁷

For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give an additional full series (three doses) of vaccination with recombinant 9-valent vaccine, but no data exist to define who might benefit or how cost effective this approach might be (**CIII**). The additional five high-risk HPV types covered by the 9-valent vaccine were found in 4.2% to 18.3% of HPV-associated anogenital cancers in U.S. men and women, depending on the cancer's location.⁷⁴

HPV vaccination is recommended for girls and boys with HIV aged 13 to 26 years (**AIII**). HPV vaccination prevents initial HPV infection and is ideally administered before sexual exposure to HPV. Because some PWH have had many sex partners prior to vaccination, HPV vaccination may be less beneficial in these patients than in those with few or no lifetime sex partners. Given that HPV

vaccination is safe and immunogenic, and because of its potential benefit in preventing HPV-associated disease and cancer in this population, HPV vaccination is recommended for males and females with HIV aged 13 through 26 years (**AIII**). Current data do not support routine vaccination for those older than 26 years among PWH. Nonetheless, although most PWH ages 27 to 45 years would not benefit from the vaccination, some situations suggest the possibility of vaccine benefit (e.g., PWH with minimal HPV exposure). In these situations, shared clinical decision-making between the provider and patient is recommended. The public health benefit for HPV vaccination in this age range is minimal.

WWH who have been vaccinated also should have 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 WWH (especially those with low CD4 cell counts) than in women 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**). 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.¹⁸ Similarly, recent cross-sectional data suggested that among heterosexual men, consistent condom use was associated with 50% lower odds of HPV infection of the penis. A meta-analysis found that condom use was associated with reduced risk of genital warts and, in women, with lower rates of CIN.¹²⁸ A 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. In WWH, several studies have observed lower rates of HPV detection associated with use of condoms.

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.

Male Circumcision

Evidence is growing that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from RCTs¹²⁹⁻¹³² and observational studies. 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 who are HIV seropositive, however, are limited, and the findings to date suggest that, while protective, the effects of circumcision against HPV infection may be less in PWH than in those who are HIV seronegative. Furthermore, no clinical trials have assessed whether circumcision of men who are HIV seropositive reduces 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, in the United States.

Preventing Disease

Preventing Vaginal and Vulvar Cancer

Following hysterectomy for benign disease, routine screening for vaginal cancer is not recommended for women who are HIV seropositive (**AIII**). However, women with a history of high-grade CIN, adenocarcinoma in situ, or invasive cervical cancer are at increased risk and should be followed with an annual vaginal cuff Pap test (**BIII**). For patients not known to have had a hysterectomy for a benign indication, continue screening because for women with intact cervices, studies have shown that CIN is the most common indication for hysterectomy in WWH. Although vaginal Pap tests are often abnormal in WWH and more common than in women without HIV, VAIN 2+ and vaginal cancers are infrequent.¹³³ Another study by Smeltzer *et al* in WWH with previous hysterectomy and no previous abnormal Pap test, showed that among those with vaginal biopsies, 29% had VAIN 2 or VAIN 3. However, this study was limited because the sample size was small, and it was a retrospective study. For patients with abnormal vaginal cuff Pap test 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 parallels that of the cervix, that is, VAIN 1, VAIN 2, and VAIN 3.

No screening procedure is available for vulvar cancer. However, biopsy or referral is indicated when inspection/palpation identifies lesions suspicious for VIN or cancer.

Preventing Anal Cancer

Some cost-effectiveness evaluations indicate that in patients who are HIV seropositive, screening for lesions using anal cytology and treating anal precancerous lesions to reduce risk of anal cancer in PWH may provide clinical benefits comparable to measures to prevent other opportunistic infection. AIN lesions are similar in many ways to CIN, but differences may exist in natural history, optimal screening, and treatment approaches to prevent cancer. At this time, no national recommendations exist for routine screening for anal cancer. However, some specialists recommend anal cytologic screening or high-resolution anoscopy (HRA) for men and women who are HIV seropositive (**CIII**). An annual digital anal examination may be useful to detect masses on palpation that could be anal cancer (**BIII**). Screening for such symptoms as anorectal bleeding, anorectal pain, and palpable anorectal masses or nodules also may be useful (**CIII**). Screening for anal cancer with anal cytology should not be done without the availability of referral for HRA. If anal cytology is performed and indicates ASC-US, ASC-H, LSIL, or HSIL, then it should be followed by HRA (**BIII**). Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer (**BIII**) (see section on Treating Disease for details on treating AIN).

Preventing Oropharyngeal Cancer

Although HPV DNA detection and HPV serology 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 pre-cancer 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 PWH,⁷⁶ and oral potentially malignant disorders can be diagnosed in some cases; albeit, the effectiveness of this approach has not been tested in RCTs.¹³⁴

Treating Disease

Preferred and Alternative Approaches for Treatment, Including Duration of Therapy

Treating Genital and Oral Warts

PWH 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 they may regress without therapy, even in PWH, especially when immunity is relatively preserved. Treatments are available for genital warts, but none are effective or preferred uniformly. Lacking RCTs specific to PWH, guidelines for the treatment of STIs in PWH should be followed. More than one treatment option may be required for refractory or recurrent lesions in PWH. Histologic diagnosis should be obtained for refractory lesions to confirm the absence of high-grade disease. Intra-anal, vaginal, 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**).

No clinical trials of this latter treatment option have been conducted in PWH.

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%) each 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**).

Topical application of cidofovir has reported activity against genital warts (**CIII**), but no topical

formulation is commercially available. 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. Many treatments for anogenital warts cannot be used in the oral mucosa. Given the lack of RCTs, surgery is the most common treatment for oral warts that interfere with function or need to be removed for aesthetic reasons.

Treating CIN and Cervical Cancer

WWH and CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in WWH should be managed according to American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines.

Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN 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 women 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 ages 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; and histologic HSIL in adolescents and WWH younger than 25 years (**BIII**). If compliance is questionable, it may be preferable to follow the treatment arm of management for CIN 2; CIN 2,3; and HSIL (**BIII**).

Management of invasive cervical cancer should follow [National Comprehensive Cancer Network \(NCCN\) guidelines](#). Although complication and failure rates may be higher in WWH, standard treatment appears safe and efficacious.⁹³

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 CO₂ laser, and excisional procedures.^{136,137}

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following [NCCN guidelines](#).

Treating AIN and Anal Cancer

An NIH-funded RCT to determine if treatment of anal HSIL is effective in reducing the incidence of anal cancer, the [ANCHOR Study](#), is underway. Definitive guidelines on anal screening and treatment in PWH will likely follow from the results of this study. Until then, management options for AIN 2 and 3 include treatment (with topical or ablative therapies) or active monitoring (regularly scheduled re-assessments with HRA); management decisions are based on assessment of the size and location of the lesion(s), histologic grade, and patient preference. Topical treatment options include 5-FU, imiquimod, cidofovir, and provider-applied TCA; ablative therapies include infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfreacator.¹³⁸⁻¹⁴⁰ All treatment modalities have moderate efficacy, are well tolerated, and are associated with high rates of recurrence.^{141,142} Repeated or combinations of treatment methods are often required for long-term clearance of AIN 2 and 3.¹⁴³ No indications exist for systemic chemotherapy or radiation therapy for patients with AIN in the absence of evidence of invasive cancer.

Management of anal cancer must be individualized in consultation with a specialist, following [NCCN guidelines](#).

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. Surgery, chemotherapy, and radiation are treatment modalities used for oropharyngeal cancers.

Special Considerations With Regard to Starting Antiretroviral Therapy

Given the strong evidence that early antiretroviral therapy (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 in patients who are HIV seropositive, these individuals should be followed after treatment with frequent cytologic screening and colposcopic examination, according to published guidelines (**AII**) (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.

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 WWH 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 women who have been treated for VIN. Women 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 physician. 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 (**CIII**). 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.

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 of women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children.¹⁴⁴ No change in obstetrical management is indicated for women with genital warts unless extensive condylomata are present that might impede vaginal delivery or cause extensive bleeding (**AIII**).

Pregnant women should undergo cervical cancer screening as recommended above for nonpregnant women. 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 in pregnant women (**AIII**).

Pregnant women with ASC-US or LSIL can be managed the same as nonpregnant women, 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. Pregnant women 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 women with invasive cervical cancer. For women with CIN and without suspicion of invasive disease, re-evaluation with co-testing and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally.

At present, vaccination with commercially available HPV vaccine **is not recommended** during pregnancy (**CIII**). However, 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.¹⁴⁵ 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.¹⁴⁶ Data on the use of the 9-valent vaccine during pregnancy are more limited, but to date are also reassuring.¹⁴⁷

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.

Recommendations for Cervical Cancer Screening for Women with HIV

Women with HIV Aged <30 Years

- WWH aged 21 to 29 years should have a Pap test following initial diagnosis of HIV.
- Pap test should be done at baseline and every 12 months **(BII)**.
- If the results of three consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**.
- Co-testing (Pap test and HPV test) is not recommended for women younger than 30 years.

Women with HIV Aged ≥30 Years

Pap Testing Only

- Pap test should be done at baseline and every 12 months **(BII)**.
- If the results of three consecutive Pap tests are normal, follow-up Pap tests can be performed every 3 years **(BII)**.

Or

Pap Test and HPV Co-Testing

- Pap test and HPV co-testing should be done at baseline **(BII)**.
- If the result of the Pap test is normal and HPV co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 years **(BII)**.
- If the result of the Pap test is normal but HPV co-testing is positive:

Either

- Follow up with Pap test and perform HPV co-test in 1 year.
- If the 1-year follow-up Pap test is abnormal, or HPV co-testing is positive, referral to colposcopy is recommended.

Or

- Perform HPV genotyping.
 - If positive for HPV16 or HPV18, colposcopy is recommended.
 - If negative for HPV16 and HPV18, repeat co-test in 1 year is recommended. If the follow-up HPV test is positive or Pap test is abnormal, colposcopy is recommended.

Or

Pap Test and HPV16 or HPV16/18 Specified in Co-Testing

- Pap test and HPV16 or 16/18 co-testing should be done at baseline **(BII)**.
- If the result of the Pap test is normal, and HPV16 or 16/18 co-testing is negative, follow-up Pap test and HPV co-testing can be performed every 3 years **(BII)**.
- If the initial test or follow-up test is positive for HPV16 or 16/18, referral to colposcopy is recommended **(BII)**.

Primary HPV testing is not recommended **(CIII)**.

Recommendations for Preventing Human Papillomavirus Infections

Preventing First Episode of HPV Infection

Indications for HPV Vaccination

The target age for vaccination is 11 to 12 years **(AIII)**. Vaccination through age 26 years is recommended, but vaccine effectiveness is lower if vaccination occurs after onset of sexual activity **(BII)**.

- HPV recombinant 9-valent vaccine is not recommended for PWH ages 27 to 45 years of age or older **(AI)**. In some situations, there might be vaccine benefit (e.g., PWH with minimal HPV exposure). In these situations, shared clinical decision-making between the provider and patient is recommended. The public health benefit for HPV vaccination in this age range is minimal.

Vaccination Schedules

HPV recombinant vaccine 9-valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1 to 2, and 6 months **(BIII)**

- 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 recombinant 9-valent vaccine, but no data exist to define who might benefit or how cost effective this approach might be **(CIII)**.

Treating Condyloma Acuminata (Genital Warts)

Note: PWH may have larger or more numerous warts, may not respond as well to therapy for genital warts, and have a higher risk of recurrence after treatment than individuals who are HIV negative. More than one treatment option may be required for refractory or recurrent lesions. Intra-anal, vaginal, cervical, and refractory warts should be biopsied, treated, and managed by a specialist.

Patient-Applied Therapy

For Uncomplicated External Warts That Can Be Easily Identified and Treated by the Patient

- Imiquimod 5% cream: Apply to lesions at bedtime on three nonconsecutive nights a week, and wash the treatment area with soap and water 6 to 10 hours after application **(BII)**, repeating the cycle until lesions are no longer seen, for up to 16 weeks, *or*
- Podofilox 0.5% solution or gel: Apply 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)**, *or*
- Sinecatechins 15% ointment: Apply to area three times daily for up to 16 weeks, until warts are not visible **(BIII)**.

Provider-Applied Therapy

For Complex or Multicentric Lesions, Lesions Inaccessible to Patient-Applied Treatments, or Patient/Provider Preference

- Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen; repeat every 1 to 2 weeks for up to 4 weeks until lesions are no longer visible **(BIII)**. Some specialists allow the lesion to thaw, and then freeze a second time in each session **(BIII)**.
- TCA or BCA cauterization: 80% to 90% aqueous solution, apply to warts only and allow the area to dry until a white frost 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. Repeat treatment weekly for up to 6 weeks until lesions are no longer visible **(BIII)**.

- Surgical excision **(BIII)** or laser surgery **(CIII)** can be performed for external or anal warts.

Key: BCA = bichloroacetic acid; HPV = human papillomavirus; IM = intramuscular; PWH = people with HIV; TCA = trichloroacetic acid; WWH = women with HIV

References

1. Volume 90: Human Papillomaviruses. 2007 [Type]. Lyon, France.
2. 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>.
3. 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>.
4. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21351269>.
5. 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>.
6. 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>.
7. 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>.
8. Kraus I, Molden T, Holm R, et al. Presence of E6 and E7 mRNA from human papillomavirus types 16, 18, 31, 33, and 45 in the majority of cervical carcinomas. *J Clin Microbiol*. 2006;44(4):1310-1317. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16597856>.
9. Castle PE, Dockter J, Giachetti C, et al. A cross-sectional study of a prototype carcinogenic human papillomavirus E6/E7 messenger RNA assay for detection of cervical precancer and cancer. *Clin Cancer Res*. 2007;13(9):2599-2605. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17473189>.
10. Ratnam S, Coutlee F, Fontaine D, et al. Clinical performance of the PreTect HPV-Proofer E6/E7 mRNA assay in comparison with that of the Hybrid Capture 2 test for identification of women at risk of cervical cancer. *J Clin Microbiol*. 2010;48(8):2779-2785. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20573862>.
11. Doorbar J. Molecular biology of human papillomavirus infection and cervical cancer. *Clin Sci (Lond)*. 2006;110(5):525-541. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16597322>.
12. 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>.
13. 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>.
 14. 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>.
 15. 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>.
 16. 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>.
 17. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol*. 2003;157(3):218-226. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12543621>.
 18. 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>.
 19. Moscicki AB, Shiboski S, Broering J, et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr*. 1998;132(2):277-284. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9506641>.
 20. Evander M, Edlund K, Gustafsson A, et al. Human papillomavirus infection is transient in young women: a population-based cohort study. *J Infect Dis*. 1995;171(4):1026-1030. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7706782>.
 21. 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>.
 22. 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>.
 23. 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>.

24. 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>.
25. 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>.
26. 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>.
27. 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>.
28. 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>.
29. 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>.
30. 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>.
31. 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>.
32. Guiguet M, Boue F, Cadranet 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>.
33. Clifford GM, Franceschi S, Keiser O, et al. Immunodeficiency and the risk of cervical intraepithelial neoplasia 2/3 and cervical cancer: A nested case-control study in the Swiss HIV cohort study. *Int J Cancer*. 2016;138(7):1732-1740. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26537763>.
34. Rohner E, Butikofer L, Schmidlin K, et al. Cervical cancer risk in women living with HIV across four continents: a multicohort study. *Int J Cancer*. 2020;146(3):601-609. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31215037>.
35. Orem J, Otieno MW, Remick SC. AIDS-associated cancer in developing nations. *Curr Opin Oncol*. 2004;16(5):468-476. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15314517>.

36. Mbulaiteye SM, Katabira ET, Wabinga H, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. *Int J Cancer*. 2006;118(4):985-990. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16106415>.
37. Dhokotera T, Bohlius J, Spoerri A, et al. The burden of cancers associated with HIV in the South African public health sector, 2004-2014: a record linkage study. *Infect Agent Cancer*. 2019;14:12. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31073325>.
38. 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>.
39. 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>.
40. Schragger 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>.
41. 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>.
42. 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>.
43. 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>.
44. Massad LS, Riestler 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>.
45. 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>.
46. 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>.

47. 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>.
48. 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>.
49. 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>.
50. 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>.
51. Moscicki AB, Ellenberg JH, Farhat S, Xu J. Persistence of human papillomavirus infection in HIV-infected and -uninfected adolescent girls: risk factors and differences, by phylogenetic type. *J Infect Dis.* 2004;190(1):37-45. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15195241>.
52. Brogly SB, Watts DH, Ylitalo N, et al. Reproductive health of adolescent girls perinatally infected with HIV. *Am J Public Health.* 2007;97(6):1047-1052. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17463385>.
53. Phanuphak N, Teeraananchai S, Hansudewechakul R, et al. Incidence and persistence of high-risk anogenital human papillomavirus infection among female youth with and without perinatally acquired HIV infection: a 3-year observational cohort study. *Clin Infect Dis.* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31768522>.
54. Lacey CJ. HPV vaccination in HIV infection. *Papillomavirus Res.* 2019;8:100174. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31252073>.
55. Palefsky J, 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 HIV. *Clin Infect Dis.* 2021;ciab434. Available at: <https://pubmed.ncbi.nlm.nih.gov/33991185/>.
56. 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>.
57. 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>.
58. 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>.

59. Ye Y, Burkholder GA, Wiener HW, et al. Comorbidities associated with HPV infection among people living with HIV-1 in the southeastern U.S.: a retrospective clinical cohort study. *BMC Infect Dis*. 2020;20(1):144. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32059635>.
60. 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>.
61. 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>.
62. 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>.
63. 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>.
64. 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>.
65. 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>.
66. 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>.
67. 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>.
68. Palefsky JM, Holly EA, Efird 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>.
69. 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>.

70. 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>.
71. 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>.
72. 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>.
73. 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>.
74. Saraiya M, Unger ER, Thompson TD, et al. U.S. assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. *J Natl Cancer Inst*. 2015;107(6):dju086. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25925419>.
75. Viens LJ, Henley SJ, Watson M, et al. Human Papillomavirus-Associated Cancers—United States, 2008-2012. *MMWR Morb Mortal Wkly Rep*. 2016;65(26):661-666. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27387669>.
76. 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>.
77. 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>.
78. 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>.
79. 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>.
80. Mahale P, Engels EA, Coghill AE, Kahn AR, Shiels MS. Cancer risk in older persons living with human immunodeficiency virus infection in the United States. *Clin Infect Dis*. 2018;67(1):50-57. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29325033>.
81. 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>.
82. 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>.
 83. 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>.
 84. 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>.
 85. 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>.
 86. Clifford G, Georges D, Shiels M, et al. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. *Int J Cancer*. 2020;148(1). Available at: <https://pubmed.ncbi.nlm.nih.gov/32621759/>.
 87. 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>.
 88. 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>.
 89. 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>.
 90. 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>.
 91. Coghill AE, Pfeiffer RM, Shiels MS, Engels EA. Excess mortality among HIV-infected individuals with cancer in the United States. *Cancer Epidemiol Biomarkers Prev*. 2017;26(7):1027-1033. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28619832>.
 92. 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>.

93. 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/>.
94. 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>.
95. Workowski KA, Berman S, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1-110. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21160459>.
96. 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/>.
97. Stier EA, Engels E, Horner MJ, et al. Cervical cancer incidence stratified by age in women living with HIV compared with the general population in the United States, 2002-2016. *AIDS*. 2021. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34049357>.
98. 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>.
99. 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>.
100. 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>.
101. 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>.
102. Gardasil 9 [package insert]. Food and Drug Administration. 2020. Available at: <https://www.fda.gov/media/90064/download>.
103. 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>.
104. Group FIS. 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>.
105. 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>.
 106. 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>.
 107. 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>.
 108. 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>.
 109. 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>.
 110. Castellsague X, Giuliano AR, Goldstone S, et al. Immunogenicity and safety of the 9-valent HPV vaccine in men. *Vaccine*. 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26144901>.
 111. Kuehn B. Studies support HPV safety. *JAMA*. 2020;323(4):302. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31990322>.
 112. 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>.
 113. 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>.
 114. 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>.
 115. Centers for Disease C, Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(50):1705-1708. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22189893>.

116. 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>.
117. 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>.
118. Meites E, Kempe A, Markowitz LE. Use of a 2-dose schedule for human papillomavirus vaccination—updated recommendations of the Advisory Committee on Immunization Practices. *MMWR Morb Mortal Wkly Rep*. 2016;65(49):1405-1408. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27977643>.
119. 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>.
120. 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>.
121. 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>.
122. 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>.
123. 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>.
124. 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>.
125. 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>.
126. 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>.
127. 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/>.
 128. 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>.
 129. 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>.
 130. 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>.
 131. 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>.
 132. 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>.
 133. 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>.
 134. 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>.
 135. Stier EA, Goldstone SE, Einstein MH, et al. Safety and efficacy of topical cidofovir to treat high-grade perianal and vulvar intraepithelial neoplasia in HIV-positive men and women. *AIDS*. 2013;27(4):545-551. Available at: <https://pubmed.ncbi.nlm.nih.gov/23032420/>.
 136. 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/>.
 137. 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>.
 138. Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod,

- topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. *Lancet Oncol.* 2013;14(4):346-353. Available at: <https://pubmed.ncbi.nlm.nih.gov/23499546/>.
139. Deshmukh AA, Chiao EY, Cantor SB, et al. Management of precancerous anal intraepithelial lesions in human immunodeficiency virus-positive men who have sex with men: clinical effectiveness and cost-effectiveness. *Cancer.* 2017;123(23):4709-4719. Available at: <https://pubmed.ncbi.nlm.nih.gov/28950043/>.
 140. Goldstone SE, Lensing SY, Stier EA, et al. A randomized clinical trial of infrared coagulation ablation versus active monitoring of intra-anal high-grade dysplasia in adults with human immunodeficiency virus infection: an AIDS Malignancy Consortium trial. *Clin Infect Dis.* 2019. Available at: <https://pubmed.ncbi.nlm.nih.gov/30060087/>.
 141. Stier EA, Abbasi A, Agyemang AF, Valle Álvarez EA, Chiao EY, Deshmukh AA. Recurrence of anal high-grade squamous intraepithelial lesions among women living with HIV. *J Acquir Immune Defic Syndr.* 2020;84(1):66-69. Available at: <https://pubmed.ncbi.nlm.nih.gov/31977596/>.
 142. Burgos J, Curran A, Landolfi S, et al. Risk factors of high-grade anal intraepithelial neoplasia recurrence in HIV-infected MSM. *AIDS.* 2017;31(9):1245-1252. Available at: <https://pubmed.ncbi.nlm.nih.gov/28252530/>.
 143. Goldstone SE, Kawalek AZ, Huyett JW. Infrared coagulator: a useful tool for treating anal squamous intraepithelial lesions. *Dis Colon Rectum.* 2005;48(5):1042-1054. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15868241>.
 144. Fife KH, Katz BP, Brizendine EJ, Brown DR. Cervical human papillomavirus deoxyribonucleic acid persists throughout pregnancy and decreases in the postpartum period. *Am J Obstet Gynecol.* 1999;180(5):1110-1114. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10329863>.
 145. 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>.
 146. 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>.
 147. 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>.

Immunizations for Preventable Diseases in Adults and Adolescents **Living** with HIV

Updated: September 7, 2022

Reviewed: January 11, 2023

Overview

The Advisory Committee on Immunization Practices (ACIP) recommends immunizing people with HIV similarly to the general population with a few key exceptions:

- Many live virus vaccines are contraindicated in people with HIV.
 - For any CD4 T lymphocyte (CD4) cell count
 - Live attenuated influenza (LAIV)
 - For CD4 count <200 cells/mm³ or uncontrolled HIV
 - Measles
 - Mumps
 - Rubella
 - Varicella (VAR)
 - Live attenuated typhoid Ty21a
 - Yellow fever
- The following have specific recommendations related to HIV status:
 - COVID-19
 - Hepatitis A (HAV)
 - Hepatitis B (HBV)
 - Meningococcus serogroup A, C, W, Y (MenACWY)
 - Pneumococcal vaccine

The National Institutes of Health (NIH)/Infectious Diseases Society of America (IDSA)/Centers for Disease Control and Prevention (CDC) 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.

Specific Immunizations

COVID-19 Vaccine

Whether people with HIV are at greater risk of acquiring SARS-CoV-2 infection is currently unknown. Data are emerging on the clinical outcomes of COVID-19 in people with HIV.

Worse outcomes for patients 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.¹⁻¹⁰ 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 that included data from 24

countries.¹ In a multicenter cohort study of 286 patients with HIV and COVID-19 in the United States, lower CD4 T lymphocyte (CD4) cell counts (i.e., <200 cells/mm³) were associated with a higher risk for the composite endpoint of intensive care unit (ICU) admission, invasive mechanical ventilation, or death. This increased risk was observed even in patients who had achieved virologic suppression of HIV.²

Individuals ages 5 and older should be vaccinated for COVID-19 regardless of their CD4 count or HIV viral load.^{11,12} Those with severe immunosuppression may have a diminished immune response to the vaccine.^{12,13} Routine serologic testing following vaccination is not recommended.¹⁴

COVID-19 is a rapidly evolving situation. For current COVID-19 vaccination recommendations please visit [CDC.gov](https://www.cdc.gov).

Note: People with advanced or untreated HIV are considered moderately or severely immunocompromised. Advanced HIV is defined as people with CD4 counts <200 cells/mm³, a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV. Further information is available in the [NIH COVID-19 Treatment Guidelines](#).

Hepatitis A Vaccine

See the “Hepatitis A virus (HAV)” section in the table below for detailed guidance for immunization against HAV.

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[®] or 0 and 6–18 months for Vaqta[®]) 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) (**AIH**).
- For travelers, some clinicians recommend a four-dose accelerated regimen (days 0, 7, 21–30 days, and 12 months) of HepA-HepB (**AIH**).
- Assess antibody response 1 to 2 months after completion of the series. If negative, revaccinate when CD4 count is >200 cells/mm³ (**BIII**).
- People with HIV presenting with CD4 cell count <200 cells/mm³ with ongoing risk for HAV should be immunized and assessed for antibody response 1 to 2 months after completion of the series. For people with HIV without risk factors, waiting for CD4 >200 cells/mm³ is an option. Assess antibody response 1 to 2 months after completion of the series. If negative, revaccinate when CD4 cell counts are >200 cells/mm³ (**BIII**).

For pre-exposure prophylaxis (travel)

- For people with HIV who are non-immune and are 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, then 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 non-immune, administer HAV vaccine and IgG 0.1 mL/kg simultaneously in different anatomical sites as soon as possible, ideally within 2 weeks of exposure.

Hepatitis B Vaccine

See the “Preventing Disease” section in [Hepatitis B Virus \(HBV\) Infection](#) for detailed guidance for immunization against HBV, as well as the evidence summary.

Summary of Recommendations

For vaccination

- For people with HIV who are non-immune to HBV (surface antibody titer negative) and do not have chronic HBV infection (surface antigen negative), administer a double dose, three-dose series of recombinant hepatitis B vaccine (Engerix® 40 mcg or Recombivax® 20 mcg) (**AII**).
- A two-dose (0 and 1 month) recombinant hepatitis B vaccine that uses a toll-like receptor 9 immunostimulatory adjuvant (HepBCpG, Heplisav-B®) can also be used. Observational data in individuals with HIV suggest superior response rates. A randomized controlled trial of Heplisav-B in people with HIV is enrolling currently. If a two-dose vaccine is preferred, Heplisav-B® is an option for vaccinating people with HIV (**CIII**).
- Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series. People with anti-HBs ≥ 10 mIU/mL are vaccine responders.
- Because of waning immunity, some experts would check anti-HBs annually and would give a booster dose if levels fall below 10mIU/mL, particularly if patients have on going risk factors for acquiring HBV and are not receiving tenofovir.
- For people with HIV who do not respond to a complete HepB vaccination series—
 - Revaccinate with a second double dose, three-dose vaccine series of recombinant hepatitis B vaccine (**BIII**). Some experts consider that a double dose, four-dose vaccine series of recombinant hepatitis B vaccine (Engerix-B® 40 mcg or Recombivax® 20 mcg at 0, 1, 2, and 6 months) may produce a better immunologic response but this approach has not been demonstrated to be superior to a double-dose three-dose series; *or*
 - Two-dose series of HepBCpG (Heplisav-B®).
 - For people with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after the CD4 count is ≥ 200 cells/mm³ (**CIII**).
- For individuals with isolated hepatitis B core antibody (anti-HBc), vaccinate with one standard dose of HBV vaccine (**BII**) and check anti-HBs titers 1 to 2 months afterward (**BII**). If the anti-HBs titer is ≥ 100 IU/mL, no further vaccination is needed. If the titer is < 100 IU/mL, then complete another series of HBV vaccine (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**).

For post-exposure prophylaxis

- For exposed people who have been vaccinated previously with a complete HepB vaccine series and have documented antibody response, no additional vaccine is needed.
- For exposed people who have received a complete HepB vaccine series without documentation of antibody response, administer a single dose of HepB vaccine.
- For exposed people who have not received any HepB vaccine or have not received a complete HepB vaccine series, administer/complete HepB vaccine series and administer one dose of hepatitis B immune globulin (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).
- For exposed non-immune people with HIV on tenofovir or lamivudine, HBIG may not be necessary.

Human Papillomavirus Vaccine

See the “HPV Vaccine” section in [Human Papillomavirus \(HPV\) Disease](#) for detailed guidance for immunization against HPV, as well as the evidence summary.

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 aged 13 to 26 years who were not vaccinated previously, regardless of gender, 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** in people with HIV.
- For people with HIV aged 27 to 45 years not adequately vaccinated previously, HPV vaccine is not routinely recommended; instead, shared clinical decision-making regarding HPV vaccination is recommended.
- At present, vaccination with commercially available HPV vaccine is **not recommended** during pregnancy (**CIII**).
- 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 to define the efficacy and cost-effectiveness of this approach (**CIII**).

Influenza Vaccine

Summary of Recommendations¹⁵

- For all adults and adolescents with HIV, administer age-appropriate inactivated influenza vaccine or recombinant influenza vaccine annually (**AI**).
- For pregnant individuals with HIV, administer inactivated influenza or recombinant vaccine at any time during pregnancy (**AI**).

- The live attenuated influenza vaccine (LAIV) administered via nasal spray **is contraindicated** in people with HIV (**AIII**).
- High-dose and adjuvanted influenza vaccines are recommended for people with HIV aged 65 years or older over standard-dose unadjuvanted vaccines (**AII**).

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: hemagglutinin (HA) and neuraminidase (NA). Although vaccine-induced immunity to the surface antigens HA and NA reduces the likelihood of infection,^{16,17} the frequent emergence of antigenic variants through antigenic drift¹⁸ (i.e., point mutations and recombination events within a subtype) is the virologic basis for seasonal epidemics and necessitates revaccination each season.¹⁹

Some studies of influenza have noted higher hospitalization rates²⁰⁻²³ and increased mortality^{23,24} among people with HIV; however, these findings have not been observed in all settings.²⁵ Increased morbidity may be greatest for people with HIV not on antiretrovirals (ARV) or with advanced disease. People with HIV are at high risk of serious influenza-related complications. For more information, see the CDC's webpage on [Flu & 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.²⁶⁻²⁸ Among people with low CD4 counts or who have advanced HIV disease, IIV might not induce protective antibody titers.²⁸⁻³⁰ In one study, markers of inflammation in older people (≥ 60 years) with HIV were associated with lower post-vaccination influenza antibody titers.³¹ In people with HIV, a second dose of vaccine does not improve immune response,^{29,32} and intradermal influenza vaccine dosing did not improve the immune response compared with intramuscular dosing.³³

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,²⁰ vaccination was most effective at preventing influenza-like illness among people with >100 CD4 cells/mm³ and among those with HIV RNA $<30,000$ copies/mL. In a randomized placebo-controlled trial conducted in South Africa among 506 individuals with HIV, including 349 people on ARV treatment and 157 who were ARV treatment-naïve, efficacy of trivalent IIV for prevention of culture- or RT-PCR–confirmed influenza illness was 75 percent (95% confidence interval, 9% to 96%).³⁴

Several clinical studies also have evaluated the immunogenicity of influenza vaccine in people with HIV. In a randomized study³⁵ comparing the immunogenicity of high-dose (60 μ g of antigen per strain) versus standard-dose (15 μ g of antigen per strain) trivalent IIV among 195 adults with HIV aged ≥ 18 years (10% of whom had CD4 counts <200 cells/mm³), seroprotection rates were higher in the high-dose group for influenza A (96% versus 87%; $P = 0.029$) and influenza B (91% versus 80%; $P = 0.030$). However, in a comparative study of 41 children and young adults aged 3 to 21 years with cancer or HIV, high-dose trivalent IIV was no more immunogenic than the standard dose among the recipients with HIV.³⁶

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.¹⁵ 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.

Although booster doses can make the influenza vaccine more effective, that benefit is limited to specific groups, such as solid-organ transplant recipients.³⁷ 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.³² Based on this study, influenza booster immunizations are **not recommended** for people with HIV.

Many licensed injectable influenza vaccine options are available, with no recommendation favoring one product over another.¹⁵ Information on currently available influenza vaccines is obtainable through the CDC recommendation, “[Prevention and Control of Seasonal Influenza with Vaccines](#).” For adults aged ≥ 65 years, high-dose IIV,³⁸ adjuvanted IIV,³⁹ or recombinant influenza vaccine⁴⁰ are preferentially recommended over standard-dose unadjuvanted vaccines based on data suggesting higher efficacy in preventing invasive pneumococcal disease in this age group.⁴¹

Influenza vaccines are quadrivalent (two A components and two B components) with formulations that change from season to season. Although a quadrivalent live attenuated influenza vaccine (LAIV4) is available, it **is contraindicated** for people with HIV because of the paucity of safety data and the availability of alternative vaccines.¹⁵ Although unintentional administration of LAIV4 to adults with HIV has been well tolerated,⁴² **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

Summary of Recommendations

For vaccination

- Administer two doses of measles, mumps, and rubella vaccine (MMR) at least 1 month apart to people with a CD4 count ≥ 200 cells/mm³ and who have no evidence of immunity to measles, mumps, and rubella (evidence of immunity is defined as: patient was born before 1957, and/or had documentation of receipt of MMR, and/or has laboratory evidence of immunity or disease) **(AIII)**.
- The MMR vaccine **is contraindicated** during pregnancy.
- People of childbearing potential who get the MMR vaccine should wait 4 weeks before getting pregnant.
- For pregnant people without immunity to rubella, ***delay immunization until after pregnancy***, then administer two doses of the MMR vaccine at least 1 month apart if the CD4 count is ≥ 200 cells/mm³ **(AIII)**.
- If no serologic evidence of immunity exists after two doses of MMR vaccine, consider repeating the two-dose MMR series, especially the person if vaccinated while not virologically suppressed **(CIII)**.
- **Do not administer** MMR vaccine to people with HIV with CD4 count < 200 cells/mm³ **(AIII)**.

For post-exposure prophylaxis

- For measles exposure of non-immune individuals with CD4 count >200 cells/mm³, 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 non-immune individuals with CD4 count <200 cells/mm³ or those who are pregnant, administer IG within 6 days of exposure.

Evidence Summary

Measles is particularly virulent in the immunocompromised host, with a reported mortality rate as high as 40 percent in people with advanced HIV.⁴³ Recently, measles outbreaks have occurred across the United States. From January 1 to October 3, 2019, 1,250 individual cases of measles were confirmed in 31 states: the most cases in 25 years. Current information regarding outbreaks can be found on the CDC website: [Measles Cases and Outbreaks](#). Measles is a highly contagious and potentially life-threatening disease.

With a resurgence of measles both domestically⁴⁴ and globally,⁴⁵ people with HIV should be assessed for immunity. Acceptable evidence of immunity includes being born before 1957, documented evidence of two doses of the MMR vaccine, or presence of positive antibody titers.

Individuals who do not fulfill any criteria for immunity and have CD4 count ≥ 200 cells/mm³ should receive two doses of MMR 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.

Several studies from the 1990s found that approximately 90 percent to 95 percent of adults with HIV were immune to measles.⁴⁶⁻⁴⁸ In these studies, serostatus did not vary by CD4 count, suggesting 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 percent.⁴⁹ Similarly, people with HIV appear to retain immunity to mumps and rubella even after acquisition of HIV.⁴⁹

MMR vaccine **is contraindicated** for people with HIV with CD4 count <200 cells/mm³ because 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 low CD4 counts.^{50,51} For people with HIV with CD4 count ≥ 200 cells/mm³, the vaccine has been shown to be safe, although antibody response may be lower than for patients without HIV.^{49,52,53}

For more detailed information regarding post-exposure prophylaxis, please see [Measles \(Rubeola\)](#).

Meningococcal Vaccine

Summary of Recommendations

- Administer two doses of quadrivalent meningococcal conjugate vaccine, at least 8 weeks apart to all people with HIV age ≥ 18 years (**AII**).
- For people with HIV receiving primary vaccination, administer two doses given at least 8 weeks apart.

- For individuals with HIV who have been vaccinated previously and are age ≥ 7 years, repeat vaccination every 5 years throughout life (**BIII**).
- Serogroup B meningococcal vaccination (MenB) is not routinely indicated for adults and adolescents with HIV at this time.

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 during 1998 to 2007 identified 2,262 cases of meningococcal disease from a sample of 13 percent of the U.S. population from several states. All available formulations of meningococcal vaccine are inactivated. Three quadrivalent meningococcal conjugate (MenACWY) vaccines are currently licensed and available in the United States: (1) Meningococcal groups A, C, W, and Y polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D, Menactra[®]); (2) Meningococcal groups A, C, W, and Y oligosaccharide diphtheria CRM197 conjugate vaccine (MenACWY-CRM, Menveo[®]) and (3) Meningococcal groups A, C, W, and Y polysaccharide tetanus toxoid conjugate vaccine (MenACWY-TT, MenQuadfi[®]). These vaccines are recommended for all adolescents aged 11 to 18 years and people aged 2 to 55 years who are at increased risk for disease.

A growing body of evidence supports an increased risk of meningococcal disease in people with HIV. Studies have shown a 5- to 24-fold increased risk of meningococcal disease in people with HIV compared with people without HIV; low CD4 count and high HIV viral load are associated with increased risk.⁵⁴ The average annual incidence rate of invasive meningococcal disease (IMD) was 0.39 cases per 100,000 people. People with HIV with lower CD4 counts are at higher risk of invasive disease.⁵⁵ 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.⁵⁶

The safety and immunogenicity of MenACWY-D vaccine have been evaluated only in people with HIV aged 11 to 24 years. Patients with CD4% $\geq 15\%$ received either one or two doses (at 0 and 24 weeks) of vaccine, and those with CD4% $< 15\%$ received two doses (at 0 and 24 weeks). Among people with HIV who received one dose of vaccine, 21 percent to 63 percent developed an antibody titer of $\geq 1:128$ at 72 weeks after vaccination. Antibody responses at 72 weeks in individuals with CD4% $< 15\%$ were less robust,⁵⁷ with only 6 percent to 28 percent achieving titers $\geq 1:128$. Local site reactions—such as pain and tenderness at 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 MenACWY-CRM in people with HIV, and clinical outcome data for both vaccines in people with HIV are lacking as well.

Menactra[®], Menveo[®], and MenQuadfi[®] are recommended for all adults with HIV, regardless of age.

MenB is not routinely indicated for adults and adolescents with HIV at this time. MenB vaccine may be administered to adolescents and young adults with HIV aged 16 to 23 years (preferred range, ages 16–18 years) for short-term protection against most strains of serogroup B meningococcal disease and for patients at increased risk (e.g., those living in dormitories or barracks) and during outbreaks. Those with functional or anatomic asplenia should also be vaccinated. For more information, see the CDC's webpage on [Asplenia and Adult Vaccination](#). Two MenB vaccines are available, MenB-4C (Bexsero[®]; two-dose series given at 0 and 1 month) and MenB-FHbp (Trumenba[®]; people with HIV should receive the three-dose series given 0, 1–2, and 6 months and not the two-dose option). MenB vaccines are not interchangeable; the same product must be used for all doses in the series.

Urban outbreaks of meningococcal meningitis have been reported among men who have sex with men in the United States, in men both with and without HIV. 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 who have sex with men without HIV.⁵⁸

Pneumococcal Vaccine

See the “Preventing Disease” section in [Community-Acquired Pneumonia](#) for detailed guidance for immunization against pneumococcal disease, as well as the evidence summary.

Summary of 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 PCV15 is used, a dose of 23-valent pneumococcal polysaccharide vaccine (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 previously received only the 13-valent pneumococcal conjugate vaccine (PCV13) should receive PPSV23 at least 8 weeks later **(BIII)**.
- People with HIV who have received PCV13 and PPSV23 should receive a booster PPSV23 at least 5 years after the first dose. 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 **(BIII)**.
- 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 **(BIII)**.

Tetanus, Diphtheria, and Pertussis Vaccine

Summary of Recommendations

- Administer the combination tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) once if person with HIV had 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 individuals 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 primary vaccination series for tetanus, diphtheria, or pertussis: administer one dose Tdap followed by one dose Td or Tdap at least 4 weeks after Tdap, and another dose Td or Tdap 6 months to 12 months after the last Td or Tdap. Tdap can be substituted for any Td dose but is preferred as first dose **(AIII)**.

Evidence Summary

Antibody response to tetanus and diphtheria vaccination varies by CD4 count. For individuals with advanced HIV and low CD4 counts, immunologic response is attenuated for both tetanus and diphtheria when compared to HIV-uninfected controls.^{59,60} For people with CD4 counts >300 cells/mm³, antibody response to tetanus vaccination is similar to the general population, whereas response to diphtheria remains diminished.⁵⁹⁻⁶¹ 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 for immunization against varicella, as well as the evidence summary.

Summary of Recommendations

- People with HIV with any of the following have presumed immunity to varicella: receipt of two doses of varicella vaccine (VAR 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 non-immune with CD4 count ≥ 200 cells/mm³, administer two doses of VAR 3 months apart (**BIII**).
- VAR is **contraindicated** for people with HIV with CD4 count <200 cells/mm³ (**AIII**).

Herpes Zoster Vaccine

See “Vaccination to Prevent Re-activation Disease (Herpes Zoster)” in the [Varicella-Zoster Virus Disease](#) section for detailed guidance for immunization against zoster, as well as the evidence summary.

Summary of Recommendations

- For people with HIV ≥ 18 years, administer RZV two doses 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 ≥ 200 cells/mm³ to ensure a robust vaccine response (**CIII**).
- People with HIV ≥ 18 years should receive RZV regardless of previous history of herpes zoster or previous receipt of zoster vaccine live (no longer available).

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
COVID-19	All people regardless of CD4 count or viral load (AIII)	PWH should receive a complete COVID-19 vaccine series regardless of their CD4 count or HIV viral load (AIII) . For current COVID-19 vaccination recommendations please visit CDC.gov .	People with advanced or untreated HIV are considered moderately or severely immunocompromised. Advanced HIV is defined as people with CD4 counts <200 cells/mm ³ , a history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV.	No difference in recommendations.
Hepatitis A virus (HAV)	HAV susceptible with HIV infection (AIII)	2-dose series of either single antigen vaccine: <ul style="list-style-type: none">• Havrix®: 1.0 mL IM (0, 6–12 months) (AII) OR <ul style="list-style-type: none">• Vaqta®: 1.0 mL IM (0, 6–18 months) (AIII) Alternative for individuals susceptible to both HAV and HBV: <ul style="list-style-type: none">• Twinrix®: 1.0 mL IM<ul style="list-style-type: none">◦ 3-dose series (0, 1, 6 months) (AII)	Assess antibody response (total or IgG anti-HAV) 1–2 months 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: <ul style="list-style-type: none">• 4-dose series (0, 7, 21–30 days, 12 months) of Twinrix® (BII)	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 in people who are non-immune.		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
Hepatitis B virus (HBV)	HBV susceptible and never vaccinated (i.e., anti-HBs <10 mIU/mL)	<p>Patients may receive any of the following single-antigen vaccines:</p> <ul style="list-style-type: none"> Double dose of Engerix-B® (40 mcg) or Recombivax® (20 mcg) in a 3-dose series (0, 1, 6 months) (AII), or Heplisav®: 2-dose series (0, 1 month) 20 µg in 0.5 mL IM (CIII) <p>Alternative for individuals susceptible to both HAV and HBV:</p> <ul style="list-style-type: none"> Twinrix®: 1.0 mL IM: 3-dose series (0, 1, 6 months) (AII) 	<p>Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series.</p> <p>Vaccinate individuals with isolated anti-HBc with 1 standard dose of HepB (BII) and check anti-HBs titers 1–2 months afterward. If anti-HBs ≥100 IU/mL, no further vaccination is needed, but if the titer is <100 IU/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).</p> <p>Safety and efficacy of Heplisav® has not yet been studied in PWH. If a 2-dose vaccine is preferred, Heplisav® is an option.</p> <p>If a significant delay occurs between doses, there is no need to restart the series.</p> <p>For travelers, some clinicians recommend:</p> <ul style="list-style-type: none"> 4-dose series (0, 7, 21–30 days, 12 months) of Twinrix® (BII) <p>Some experts consider that a double dose, four-dose vaccine series of recombinant hepatitis B vaccine (Engerix-B® 40 mcg or Recombivax® 20 mcg at 0, 1, 2, and 6 months) may produce a better immunologic response but this approach has not been demonstrated to be superior to a double dose, three-dose series.</p>	ACIP does not recommend the use of double dose Engerix-B® or Recombivax® for PWH.
	Vaccine nonresponder (if anti-HBs <10 mIU/mL after 3-dose series)	<p>Revaccinate with either:</p> <ul style="list-style-type: none"> Second double dose, 3-dose series of Engerix-B® (40 mcg) or Recombivax® (20 mcg) (BIII) <p>OR</p> <ul style="list-style-type: none"> 2-dose series of Heplisav-B® (BIII) <p>Delay repeat vaccination until after the CD4 count is ≥200 cells/mm³ (CIII).</p>		
	Post-exposure prophylaxis	<p>For exposed people who have been previously vaccinated with complete series and have documented antibody response, no additional vaccine needed.</p> <p>For exposed people who have received complete series without documentation of antibody response, administer a single dose of HepB vaccine.</p> <p>For exposed people who have not received a vaccine or have not received the complete series, administer or complete the HepB vaccine series and</p>		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
		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	Recombinant 9-valent human papillomavirus vaccine (Gardasil®9): 0.5 mL IM 3-dose series (0, 1–2, 6 months) (AIII)	If a significant delay occurs between doses, there is no need to restart the series. Routine vaccination is not recommended for people ages 27–45 years (AI). Some PWH may benefit from vaccination in this age group, and shared clinical decision-making between the provider and patient is recommended in these situations.	No difference in 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).	Vaccination is not recommended during pregnancy (CIII). Delay until after pregnancy.	
Influenza	All	1 dose of age appropriate IIV or RIV annually (AI). LAIV is contraindicated (AIII).	Information on currently available influenza vaccines is available through the CDC recommendation, " Prevention and Control of Seasonal Influenza with Vaccines. " Influenza vaccines are quadrivalent, with formulations that change from season to season. Adults age ≥65 years are recommended to receive high-dose IIV (Fluzone® High-Dose) or adjuvanted IIV	No difference in recommendations.

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
			<p>(FLUAD®) over standard-dose unadjuvanted vaccine (AII).</p> <p>People age ≥ 18 years also may use RIV (Flublok® Quadrivalent).</p> <p>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).</p> <p>For pregnant individuals with HIV, administer inactivated influenza or recombinant vaccine at any time during pregnancy (AI).</p>	
Measles, mumps, and rubella (MMR)	CD4 count ≥ 200 cells/mm ³ and no evidence of immunity to measles, mumps, or rubella	<p>2-dose series of MMR vaccine at least 1 month apart (AIII)</p> <p>MMR is contraindicated if CD4 count < 200 cells/mm³.</p> <p>MMR vaccine is contraindicated during pregnancy.</p>	<p>Evidence of immunity to MMR:</p> <ul style="list-style-type: none"> • Birth date before 1957, <p>OR</p> <ul style="list-style-type: none"> • Documentation of receipt of MMR, <p>OR</p> <ul style="list-style-type: none"> • Laboratory evidence of immunity or disease for each pathogen <p>For pregnant people without immunity to rubella, after pregnancy administer 2 doses of MMR vaccine at least 1 month apart if CD4 count > 200 cells/mm³ (AIII).</p>	No difference in recommendations.
	Post-exposure prophylaxis	For measles non-immune individuals with CD4 counts > 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.		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
		For measles non-immune individuals with CD4 counts <200 cells mm^3 or those who are pregnant, administer IG.		
Meningococcus serogroup A, C, W, Y (MenACWY)	Not received any polyvalent meningococcal vaccine	Menactra® or Menveo® or MenQuadfi®: 2-dose series given at least 8 weeks apart (AII) • Revaccinate with a dose of same MenACWY vaccine every 5 years (BIII) .	MenACWY vaccine is routinely recommended. If Menactra® is used in a person (of any age) with functional or anatomic asplenia or HIV infection, it should not be administered until at least 4 weeks after completion of all PCV doses.	No difference in recommendations.
Meningococcus serogroup B	MenB is not routinely indicated for individuals with HIV, except for those at increased risk for serogroup B meningococcal disease (asplenia, complement deficiency, eculizumab use, occupational exposure).	2-dose series of Bexsero® or 3-dose series of Trumenba® Even if they are not at increased risk for serogroup B meningococcal disease, MenB may be given to adolescents and young adults ages 16–23 years (preferred age range, 16–18 years).	Two MenB vaccines are available and not interchangeable, MenB-4C (Bexsero®) and MenB-FHbp (Trumenba®).	No difference in recommendations.
Pneumococcal	No prior pneumococcal vaccine or vaccination history unknown	Administer either of the following: • PCV20 (Prevnar20®): 0.5 mL IM x 1 (AII) OR • PCV15 (Vaxneuvance®): 0.5 mL IM x 1 (AII) Followed at least 8 weeks later by: • PPSV23 (Pneumovax®): 0.5 mL IM x 1 (AII)	Administer PCV (15 or 20) to PWH, on ART with CD4 count >50 cells/ mm^3 (AII) . In those who received PCV13 when their CD4 count was <200 cells/ mm^3 , some experts may choose to defer PPSV23 until CD4 count is >200 cells/ mm^3 to optimize vaccine efficacy (CIII) . In contrast to prior recommendations, after the initial vaccine series is complete, there is no longer a recommendation for additional doses (boosters).	No difference in recommendations.

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Previously received PCV13 and PPSV23	Revaccinate the following with PPSV23 0.5 mL IM x 1 (BIII) : <ul style="list-style-type: none"> Adults aged 19–64 years if ≥ 5 years since the first PPSV23 dose If age ≥ 65 years and if ≥ 5 years since the previous PPSV23 dose at least 8 weeks after receipt of PCV13 	Patients should receive a maximum of 3 doses of PPSV23. There is no need to give additional doses of PPSV23 every 5 years.	
	Previously received only PCV13	Administer initial dose of PPSV23 0.5 mL IM x 1 (AII) . Revaccinate the following with PPSV23 0.5 mL IM x 1 (BIII) : <ul style="list-style-type: none"> Adults aged 19–64 years if ≥ 5 years since the first PPSV23 dose Adults ages ≥ 65 years if ≥ 5 years since the previous PPSV23 dose. 		
	Previously received only PPSV23	Administer either of the following: <ul style="list-style-type: none"> PCV20: 0.5 mL IM x 1 (BIII) OR <ul style="list-style-type: none"> PCV15: 0.5 mL IM x 1 (BIII) 	When PCV15 is used in those with history of PPSV23 receipt, it need not be followed by another dose of PPSV23.	
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 epidemic or endemic—can be vaccinated with IPV (CIII) .	3 doses IPV IM at 0, 1–2 months, and third dose given 6–12 months after second dose (CIII)		

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Previously vaccinated with 1–2 doses of vaccine	Give remaining doses of vaccine at recommended intervals (CIII) .		
Tetanus, diphtheria, and pertussis	Did not receive Tdap at age 11 years or older	1 dose 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.	No difference in recommendations.
	Pregnancy	Give Tdap preferably in early part of gestational weeks 27–36 (AIII) . 1 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	2-dose series of VAR 3 months apart (BIII) VAR is contraindicated if CD4 count < 200 cells/mm ³ (AIII) .	Evidence of immunity to varicella: <ul style="list-style-type: none"> • Documented receipt of 2 doses of VAR 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.
Zoster	Age ≥ 18 years, regardless of past episode of herpes zoster or receipt of attenuated ZVL (Zostavax®) and regardless of CD4 count	Give 2-dose series of RZV (Shingrix®) IM 2–6 months apart (AIII) .	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) to maximize immunologic response to the vaccine. Do not give RZV (Shingrix®) during an acute episode of herpes zoster (AIII) .	ACIP recommends RZV for adults ≥ 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	Indication	Recommendations	Additional Comments	ACIP Recommendations
Immunizations for Travel				
Cholera	Not routinely recommended for most travelers (CIII) . Age 18–64 years old with CD4 counts >200 cells/mm ³ traveling to an area where cholera is 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 individuals with HIV. No adverse effects reported with older formulation of vaccine in individuals with HIV infection without an AIDS diagnosis.	No current recommendations for individuals with HIV infection.
Typhoid	At risk of <i>Salmonella</i> serotype typhi infection (travel, intimate exposure to a chronic carrier, occupational exposure) Revaccination only if continued or renewed exposure to <i>Salmonella</i> serotype typhi is expected.	1 dose Vi capsular polysaccharide vaccine (Typhim Vi [®]) via intramuscular 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 PWH (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 (AIII) .	ACIP has no position on the use of typhoid vaccine in PWH except not to give immunocompromised people the live attenuated vaccine.
Yellow fever (YF)	Age ≤59 years and at risk for YF virus acquisition (travel to or live 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 >500 cells/mm ³ : 1 dose of YF vaccine, revaccinate in >10 years if risk remains (BIII) . Any age and asymptomatic with CD4 200–499 cells/mm ³ : YF vaccine may be considered depending on risk (BIII) . YF vaccine is contraindicated for people with CD4 counts <200 cells/mm ³ . This recommendation is based on a theoretic increased risk for encephalitis in this population (AII) .	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. If international travel requirements rather than an increased risk for acquiring YF infection are the only reason to vaccinate PWH, excuse the person from vaccination and issue a medical waiver to fulfill health regulations.	No difference in recommendations.

Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
			Closely monitor PWH who have received YF vaccine for evidence of adverse events.	

Key: ACIP = Advisory Committee on Immunization Practices; 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; FDA = U.S. Food and Drug Administration; HAV = hepatitis A virus; HBIG = hepatitis B immune globulin; HBV = hepatitis B virus; HepA = hepatitis A vaccine; HepB = hepatitis B vaccine; HPV = human papillomavirus; IG = immunoglobulin; IgG = immunoglobulin G; 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; PPSV23 = 23-valent pneumococcal polysaccharide vaccine; PWH = people with HIV; PVC13 = 13-valent pneumococcal conjugate vaccine; RIV = recombinant influenza vaccine; RZV = recombinant zoster vaccine; 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

Note: Recommendations may vary from the Advisory Committee on Immunization Practices.

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

Vaccine	All People	Where Varies by Age	Where Varies by CD4 Cell Count (cells/mm ³)	
			< 200	≥ 200
Hepatitis A	2–3 doses (varies by formulation)			
Hepatitis B	2–4 doses (varies by formulation and indication)			
Human papillomavirus (HPV)		3 doses for ages 18–26*		
Influenza	1 dose annually			
Measles, mumps, rubella (MMR)			Contraindicated	2 doses if born after 1956 with no history of vaccination or positive antibody titer
Meningococcal A,C,W,Y conjugate (MenACWY)	2 doses, booster every 5 years			
Meningococcal B (MenB)	2–3 doses (varies by formulation)			
Pneumococcal conjugate (PCV15 or PCV20)	1 dose			
Pneumococcal polysaccharide (PPSV23)	1 dose (if conjugate vaccine was PCV-15)			
COVID-19	For current COVID-19 vaccination recommendations, please visit CDC.gov .		Recommendations differ with advanced or untreated HIV infection	
Tetanus, diphtheria, pertussis (Tdap/Td)	Tdap once, then Td or Tdap booster every 10 years			
Varicella (VAR)			Contraindicated	2 doses
Zoster recombinant (RZV)		2 doses for ages 18 and older		



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

References

1. 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>.
2. 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>.
3. 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>.
4. 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>.
5. 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>.
6. Western Cape Department of Health in collaboration with the National Institute for Communicable Diseases South Africa. 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>.
7. 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>.
8. 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>.
9. Centers for Disease Control and Prevention. COVID-19 information for specific groups of people. 2022. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/index.html>
10. Singson JRC, Kirley PD, Pham H, et al. Factors associated with severe outcomes among immunocompromised adults hospitalized for COVID-19 - COVID-NET, 10 states, March 2020–February 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(27):878-884. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35797216>.

11. National Institutes of Health. Special considerations in people with HIV. 2021. Available at: <https://www.covid19treatmentguidelines.nih.gov/special-populations/hiv>.
12. Centers for Disease Control and Prevention. HIV and COVID-19 basics. 2021. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/hiv.html>.
13. World Health Organization. Coronavirus disease (COVID-19) and people living with HIV. 2021. Available at: [https://www.who.int/news-room/q-a-detail/coronavirus-disease-\(covid-19\)-covid-19-vaccines-and-people-living-with-hiv](https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-covid-19-vaccines-and-people-living-with-hiv).
14. Caliendo AM, Hanson KE. COVID-19: diagnosis. 2021. Available at: <https://www.uptodate.com/contents/covid-19-diagnosis>.
15. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices—United States, 2018–19 Influenza Season. *MMWR Recomm Rep*. 2018;67(3):1-20. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30141464>.
16. 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>.
17. 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>.
18. Cox NJ, Subbarao K. Influenza. *Lancet*. 1999;354(9186):1277-1282. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10520648>.
19. 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>.
20. 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>.
21. 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>.
22. 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>.
23. 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>.

24. 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>.
25. 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>.
26. 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>.
27. 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>.
28. 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>.
29. 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>.
30. Amoah S, Mishina M, Prapthasiri 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>.
31. 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>.
32. 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>.
33. Garg S, Thongcharoen P, Prapthasiri 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>.
34. 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>.

35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. Van Buynnder PG, Konrad S, Van Buynnder 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>.
40. 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>.
41. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US 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>.
42. Menegay JL, Xu X, Sunil TS, Okulicz JF. Live versus attenuated influenza vaccine uptake and post-vaccination influenza-like illness outcomes in HIV-infected US Air Force members. *J Clin Virol*. 2017;95:72-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28889083>.
43. 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>.
44. 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>.
45. Mahase E. Measles cases rise 300% globally in first few months of 2019. *BMJ*. 2019;365:11810. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30992273>.

46. 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>.
47. 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>.
48. 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>.
49. 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>.
50. 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>.
51. 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>.
52. 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>.
53. 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>.
54. 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>.
55. 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>.
56. Ghaswalla PK, Marshall GS, Bengtson LGS, et al. Meningococcal vaccination rates among people with a new diagnosis of HIV infection in the US. *JAMA Netw Open*. 2022;5(4):e228573. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/35486405>.
57. 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>.

58. 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>.
59. 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>.
60. 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>.
61. 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>.

Epidemiology

Leishmaniasis is caused by protozoa that survive and replicate inside vacuoles within macrophages and other mononuclear cells. The *Leishmania* genus has traditionally been differentiated into multiple species that cause cutaneous, mucosal, and/or visceral disease.^{1,2}

Leishmaniasis occurs in 98 countries or territories in the tropics, subtropics, and southern Europe, with an estimated incidence of 1.6 million new cases annually—as many as 1.2 million cases of cutaneous leishmaniasis and 0.4 million cases of visceral leishmaniasis.³ As of March 2010, HIV-leishmaniasis co-infection has been reported in 35 countries, predominantly as visceral leishmaniasis.^{3,4} The first cases of HIV-leishmaniasis co-infection were described in Spain in the late 1980s. During the 1980s and 1990s, more than 90% of co-infection cases were reported in southern Europe.^{3,5} After the introduction of combination antiretroviral therapy (ART), the incidence decreased substantially in developed countries,^{6,7} but HIV-leishmaniasis co-infection poses a growing problem in parts of Asia, Africa, and Latin America.^{3,4,8,9} In one large leishmaniasis specialty hospital in Bihar, India, the prevalence of HIV infection in patients with visceral leishmaniasis has increased from 0.88% in 2000 to 2.18% in 2006.³ A study in a treatment center in Humera in northwestern Ethiopia reported that 31% of patients with visceral leishmaniasis were co-infected with HIV.¹⁰ Most leishmanial 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.¹¹⁻¹³ After primary infection, *Leishmania* remain viable in healthy individuals for long periods, creating a population at risk of reactivation if immunosuppression occurs. In HIV-infected patients without severe immunosuppression, disease manifestations are similar to those in immunocompetent individuals. In those with advanced immunosuppression (i.e., CD4 T lymphocyte [CD4] cell count <200 cells/mm³), manifestations of leishmaniasis can be both atypical and more severe. Relapse after treatment—especially of visceral leishmaniasis—is common.^{14,15}

In endemic areas, leishmaniasis is usually spread by infected sand flies of the genera *Phlebotomus* and *Lutzomyia*.² However, in Southern Europe, HIV and *Leishmania infantum* visceral co-infections were reported in association with injection-drug use, suggesting that *Leishmania* which can be transmitted via blood transfusion, also may be acquired by needle sharing.¹⁶ *Leishmania* parasites were demonstrated in 34% to 52% of used syringes discarded by injection-drug users in Madrid, and, based on molecular characteristics, investigators have described a new, epidemiologically significant leishmaniasis transmission cycle that relies on mechanical transfer of amastigotes via contaminated syringes.^{17,18}

Clinical Manifestations

The term leishmaniasis encompasses multiple syndromes—most notably, cutaneous 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. The most common clinical presentation of leishmaniasis in HIV-infected individuals is a systemic visceral disease syndrome, but the distribution varies geographically, reflecting differences in the predominant parasite species. In Europe, visceral disease has been reported in 95% of cases (87% typical visceral, 8% atypical visceral).^{4,5} In contrast, in Brazil, mucosal, visceral, and cutaneous forms have accounted for 43%, 37%, and 20% of reported cases, respectively.¹⁹

In patients 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) (60% to 90%), hepatomegaly without splenomegaly (34% to 85%), hepatosplenomegaly (68% to 73%), lymphadenopathy (12% to 57%), and pancytopenia (50% to 80%).^{5,15} Anemia is usually marked, with <10 g hemoglobin/dL (49% to 100%); leukopenia is moderate, with <2400 leukocytes/ μ L (56% to 95%); and thrombocytopenia is usually present (52% to 93%). Splenomegaly is less pronounced in HIV-co-infected patients than in immunocompetent

patients with visceral leishmaniasis.¹⁵ In patients with more profound immunosuppression, atypical manifestations have been described, including involvement of the upper and lower gastrointestinal tract, lung, pleural and peritoneal cavities, and skin.^{4-6,15,20} Esophageal involvement can lead to dysphagia and odynophagia, and must be distinguished from other causes of esophagitis in HIV-infected patients, such as candidiasis.⁵ Non-ulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described.²¹⁻²³ 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.^{24,25}

Disfiguring mucosal lesions associated with anergy to *Leishmania* antigens have been observed in Europeans with AIDS, in contrast to mucocutaneous disease in immunocompetent patients, which is associated with strong leishmanin skin-test responses.^{20,26,27}

Diagnosis

Demonstration of *Leishmania* parasites by histopathology, cultures, and smears in tissue specimens (such as scrapings, aspirates, and biopsies) is the standard for diagnosing cutaneous leishmaniasis in HIV-co-infected patients.^{4,5}

Visceral leishmaniasis also can be diagnosed by demonstration of leishmanial parasites in blood smears (approximately 50% sensitivity in expert hands), buffy-coat smear preparations, cultures from the peripheral blood, and smears or cultures from bone marrow or splenic aspirates. PCR amplification can also be useful for detecting *Leishmania* nucleic acid in the blood or tissue of co-infected patients (>95% sensitivity).¹⁸

Serologic tests to detect *Leishmania* antibodies are highly sensitivity and can be used to diagnose visceral leishmaniasis in immunocompetent patients.²⁸ Serology should not be used as a screening test as positive serology can occur in individuals with asymptomatic infection. It should be used only as a confirmatory test in patients with a compatible clinical picture and an exposure history suggestive of visceral leishmaniasis. Serology has a low sensitivity in HIV-infected patients, especially in Europe, such that parasitological diagnosis should be sought when clinical suspicion has been raised.^{4,5,29}

The use of recombinant antigen in ELISA assays may increase sensitivity, but a proportion of co-infected patients remain seronegative.³⁰ Immunoblotting with *Leishmania infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of European patients.²⁹ Interestingly, reports suggest that the serology sensitivity may remain fairly high in HIV-co-infected patients in Ethiopia (77%-89% in HIV-visceral leishmaniasis co-infected patients, versus 87%–95% in HIV-negative patients).³¹ Leishmanial skin tests are nearly always negative in active visceral leishmaniasis, with or without HIV co-infection.²

Preventing Exposure

Prevention of exposure to leishmanial infection relies on reservoir host control in areas with zoonotic transmission and vector control activities, such as indoor residual spraying and/or use of insecticide-treated bed nets. The best way for travelers to leishmaniasis-endemic areas 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.

Measures to decrease transmission of infectious agents, including *Leishmania* parasites, in injection-drug users, such as the use of clean needles and injection works from syringe (needle) exchange programs, are appropriate.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended, and no screening or preemptive therapy is appropriate for HIV-infected patients who may have been exposed to leishmanial infection. No

vaccine against leishmaniasis is available.

Treating Disease

Visceral Leishmaniasis

For HIV-infected patients with visceral leishmaniasis, conventional and lipid formulations of amphotericin B appear to be at least as effective as pentavalent antimonials.^{4,32-35} Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than conventional amphotericin B (amphotericin B deoxycholate) or pentavalent antimony (sodium stibogluconate).³⁶⁻³⁸ The equivalent efficacy and better toxicity profile have led most clinicians to regard liposomal amphotericin B as the drug of choice for visceral leishmaniasis in HIV-co-infected patients (**AII**).^{4,39} The optimal amphotericin B dosage has not been determined.^{39,40} Regimens with efficacy include liposomal preparations of 2 to 4 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**), or 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 (**BII**).^{32,35,39,41-43} Pentavalent antimony (sodium stibogluconate), which is available in the United States through the Centers for Disease Control and Prevention (CDC), 20 mg/kg/day IV or intramuscular (IM) for 28 consecutive days, may be considered as an alternative (**BII**).

Additional treatment options for visceral leishmaniasis in HIV-co-infected patients, which are recommended primarily because of their use in non-HIV-infected patients, include oral miltefosine, which is available in the United States via www.Profounda.com, and the parenteral formulation of the aminoglycoside paromomycin, which is not available in the United States.^{40,44} In general, the target dose of miltefosine is ~2.5 mg/kg daily (maximum of 150 mg daily), and the initial treatment course is 28 days. Gastrointestinal symptoms are common but typically do not limit treatment. Data supporting the use of miltefosine in HIV-co-infected patients are relatively limited (**CIII**).^{45,46} Parenteral paromomycin has been used successfully to treat visceral leishmaniasis in HIV-negative patients, particularly in India.⁴⁰ Essentially no efficacy data are available for paromomycin in HIV-co-infected patients. A clinical trial of combination therapy (liposomal amphotericin B plus miltefosine or paromomycin; miltefosine plus paromomycin) produced promising results in non-HIV-infected patients in India whose visceral leishmaniasis was not severe.⁴⁷ Further research is needed to validate the efficacy of drug combinations, including for severe or refractory cases of visceral leishmaniasis in various geographic regions and in HIV-co-infected patients.

Cutaneous Leishmaniasis

Few systematic data are available on the efficacy of treatment for cutaneous, mucocutaneous, or diffuse cutaneous leishmaniasis in HIV-co-infected patients. On the basis of data in HIV-negative patients with cutaneous leishmaniasis and case reports in HIV-co-infected patients, HIV-infected patients should be treated with liposomal amphotericin B (**BIII**) as previously outlined,⁴⁸ or pentavalent antimony (sodium stibogluconate), depending on the form of the disease and the clinical response (**BIII**).^{2,49,50} However, pentavalent antimony can increase viral transcription and HIV replication in cultures of human peripheral blood mononuclear cells, raising concerns about its use in HIV-infected patients.⁵¹

Potential alternatives for cutaneous leishmaniasis include miltefosine, topical paromomycin, intralesional pentavalent antimony, and local heat therapy. However, no data exist for co-infected patients, and in immunocompetent patients, the effectiveness of these modalities is known to be dependent upon the infecting species of *Leishmania*.^{40,52-54}

Special Considerations with Regard to Starting ART

ART should be initiated or optimized following standard practice for HIV-infected patients (**AIII**). There are no leishmaniasis-specific data on when to start ART. Appropriate use of ART has substantially improved the survival of co-infected patients in Europe and decreased the likelihood of relapse after antileishmanial

therapy.^{7,15,55} 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**). Infusional adverse events are ameliorated by pretreatment with acetaminophen, diphenhydramine, or limited doses of corticosteroids (**BII**). Infusion of 1 L of saline one hour prior to drug infusion can 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.³⁷ Amphotericin B deoxycholate treatment is also associated with an increased risk of anemia.³³

Patients receiving pentavalent antimony (sodium stibogluconate) should be monitored closely for adverse reactions.⁴⁹ Overall, at a dose of 20 mg/kg of body weight per day, greater than 60% of patients have 1 or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase or lipase, and (in some patients) clinical pancreatitis. 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.^{33,41} Severe adverse reactions to pentavalent antimony (sodium stibogluconate), including acute pancreatitis and leukopenia, appear to be more common in co-infected patients than in those who are not infected with HIV.⁵⁶

Cases of newly symptomatic visceral and cutaneous leishmaniasis have been reported in association with immune reconstitution inflammatory syndrome (IRIS) following initiation of ART.^{57,58} Several of these cases have resembled post-kala-azar dermal leishmaniasis or disseminated cutaneous leishmaniasis.⁵⁹⁻⁶² Existing experience with IRIS-associated leishmaniasis, however, is insufficient to provide data for specific management guidelines.

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.

Immunotherapy, including interferon-gamma and recombinant human granulocyte macrophage colony stimulating factor (GM-CSF), has been used experimentally as an adjunct to antileishmanial treatment for refractory cases.^{63,64} However, a clinical trial of pentavalent antimony (sodium stibogluconate) plus interferon-gamma for visceral leishmaniasis in HIV-co-infected patients was suspended when an interim analysis indicated that there was no advantage over pentavalent antimony (sodium stibogluconate) alone.⁴¹ In addition, the use of interferon-gamma was reported to be associated with acceleration of KS in two patients with visceral leishmaniasis and HIV co-infection.²⁴

Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of antileishmanial therapy in HIV-infected patients, and frequency of relapse is inversely related to CD4 cell count. In HIV-co-infected patients with visceral leishmaniasis 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).^{5,65} Therefore, secondary prophylaxis with an effective antileishmanial drug, administered at least every 2 to 4 weeks, is recommended, particularly for patients with visceral leishmaniasis and CD4 cell counts <200 cells/ μ L (**AII**).^{5,15,34,65}

The only published, randomized trial of secondary prophylaxis compared amphotericin B lipid complex

(3 mg/kg every 21 days) in 8 patients to no prophylaxis in 9 patients; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up.³⁴ In retrospective observational studies, monthly pentavalent antimony (sodium stibogluconate) or lipid formulations of amphotericin B every 2 to 4 weeks were also associated with decreased relapse rates.^{15,65} Liposomal amphotericin B (4 mg/kg every 2–4 weeks) or amphotericin B lipid complex (3 mg/kg every 21 days) should be used for secondary prophylaxis **(AII)**. Pentavalent antimony (sodium stibogluconate), 20 mg/kg IV or IM every 4 weeks, is an alternative **(BII)**. Although pentamidine is no longer recommended to treat primary visceral leishmaniasis, a dosage of 6 mg/kg IV every 2 to 4 weeks has been suggested as another alternative for secondary prophylaxis **(CIII)**.⁶⁶ Allopurinol, used for maintenance therapy in a dose of 300 mg orally 3 times daily, is less effective than monthly pentavalent antimony and **is not recommended (BII)**.⁶⁵ 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 investigators suggest that secondary antileishmanial prophylaxis can be discontinued in patients whose CD4 count is >200 to 350 cells/mm³ in response to ART.⁶⁷ Others, however, suggest that secondary prophylaxis should be maintained indefinitely. In one study, a positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse.⁶⁸ Thus, because there is a paucity of published data or clinical trial experience, no recommendation can be made regarding discontinuation of secondary prophylaxis in HIV-*Leishmania*-co-infected persons.

Special Considerations During Pregnancy

Diagnostic considerations are the same in pregnant women as in women who are not pregnant. 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.⁶⁹ Labels for pentavalent antimony compounds (sodium stibogluconate, available in the United States through CDC, and meglumine antimoniate) state that these drugs are contraindicated for use in pregnant women, although various antimonial compounds were not teratogenic in chickens, rats, or sheep.⁷⁰⁻⁷² Good clinical and pregnancy outcomes have been reported for small series of pregnant women treated with meglumine antimoniate, amphotericin B deoxycholate, or liposomal amphotericin B.⁷³⁻⁷⁶ 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.^{77,78} Because visceral leishmaniasis is a potentially lethal disease, postponing treatment until after delivery is not an option. Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy because of concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy **(AIII)**.⁷⁴ The alternatives are amphotericin B deoxycholate **(AIII)** or pentavalent antimony (sodium stibogluconate) **(AIII)**. No data are available on the use of parenteral paromomycin in pregnancy, but concerns have been raised about fetal ototoxicity with other aminoglycosides used in pregnancy. Miltefosine is teratogenic and is contraindicated in pregnancy.⁴⁰ Perinatal transmission of *Leishmania spp.* is rare; 13 documented cases have been reported.^{77,79-81} No data are available on the risk of transmission of *Leishmania spp.* in HIV-infected pregnant women.

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

Preferred Therapy:

- Liposomal amphotericin B 2–4 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)**
- Achieve a total dose of 20–60 mg/kg **(AII)**

Alternative Therapy:

- Other amphotericin B lipid complex dosed as above, *or*
- Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams **(BII)**, *or*
- Pentavalent antimony (sodium stibogluconate) 20 mg/kg IV or IM daily for 28 days **(BII)**. (Contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov; for emergencies, call 770-488-7100.)
- Miltefosine **(CIII)** (available in the United States via www.Profounda.com)
- For patients who weigh 30–44 kg: 50 mg PO bid for 28 days
- For patients who weigh ≥45 kg: 50 mg PO tid for 28 days

Chronic Maintenance Therapy for Visceral Leishmaniasis

Indication:

- For patients with visceral leishmaniasis and CD4 count <200 cells/mm³ **(AII)**

Preferred Therapy:

- Liposomal amphotericin B 4 mg/kg every 2–4 weeks **(AII)**, *or*
- Amphotericin B Lipid Complex 3 mg/kg every 21 days **(AII)**

Alternative Therapy:

- Pentavalent antimony (sodium stibogluconate) 20 mg/kg IV or IM every 4 weeks **(BII)**

Discontinuation of Chronic Maintenance Therapy

Some investigators suggest that therapy can be discontinued after a sustained (>3 to 6 months) increase in CD4 count to >200 to 350 cells/mm³ in response to ART, but others suggest that therapy should be continued indefinitely. Therefore, no recommendation can be made regarding discontinuation of chronic maintenance therapy.

Treating Cutaneous Leishmaniasis

Preferred Therapy:

- Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BIII)**, *or*
- Pentavalent antimony (sodium stibogluconate) 20 mg/kg IV or IM daily for 28 days **(BIII)**

Alternative Therapy:

- Other options include oral miltefosine (can be obtained in the United States through a treatment IND), topical paromomycin, intralesional pentavalent antimony (sodium stibogluconate), or local heat therapy.

Chronic Maintenance Therapy for Cutaneous Leishmaniasis

- May be indicated for immunocompromised patients with multiple relapses **(CIII)**

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CDC = Centers for Disease Control and Prevention; IM = intramuscular; IND = investigational new drug; IV = intravenous

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis*. Sep 2004;27(5):305-318. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15225981>.
2. Jeronimo SMB, de Queiroz Sousa A, Pearson RD. Leishmaniasis. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical infectious diseases: principles, pathogens and practice*. Edinburgh, Scotland: Churchill Livingstone Elsevier; 2006:1095-1113.
3. World Health Organization. Leishmaniasis. Available at <http://www.who.int/leishmaniasis/burden/en/>. Accessed March

21, 2013.

4. Murray HW. Leishmaniasis in the United States: treatment in 2012. *Am J Trop Med Hyg.* Mar 2012;86(3):434-440. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22403313>.
5. Alvar J, Canavate C, Gutierrez-Solar B, et al. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev.* Apr 1997;10(2):298-319. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9105756>.
6. 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.* Oct 2000;31(4):1093-1095. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11049794>.
7. 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.* Jul 1 2002;30(3):364-366. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12131576>.
8. 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.* Jul 2006;55(Pt 7):919-922. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16772420>.
9. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging Leishmania/HIV co-infection in Africa. *Med Microbiol Immunol.* Nov 2001;190(1-2):65-67. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11770113>.
10. 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.* Jun 1 2008;46(11):1702-1709. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18419422>.
11. 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.* May-Jun 1992;86(3):249-250. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1412644>.
12. 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.* Mar-Apr 2002;96(2):129-132. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12055798>.
13. 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.* Jul 2002;83(1):13-18. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12062788>.
14. Lopez-Velez R, Perez-Molina JA, Guerrero A, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfecting with human immunodeficiency virus and Leishmania in an area of Madrid, Spain. *Am J Trop Med Hyg.* Apr 1998;58(4):436-443. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9574788>.
15. 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).* Jan 2001;80(1):54-73. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11204503>.
16. Alvar J, Jimenez M. Could infected drug-users be potential Leishmania infantum reservoirs? *AIDS.* Jun 1994;8(6):854. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8086149>.
17. 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.* Apr 2002;96 Suppl 1:S93-99. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12055859>.
18. Cruz I, Morales MA, Noguer I, Rodriguez A, Alvar J. Leishmania in discarded syringes from intravenous drug users. *Lancet.* Mar 30 2002;359(9312):1124-1125. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11943264>.
19. Rabello A, Orsini M, Disch J. Leishmania/HIV co-infection in Brazil: an appraisal. *Ann Trop Med Parasitol.* Oct 2003;97 Suppl 1:17-28. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14678630>.
20. 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.* Jun 1997;1(3):142-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11105130>.
21. 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.* Dec 2000;143(6):1316-1318. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11122042>.

22. Carnauba D, Jr., Konishi CT, Petri V, Martinez IC, Shimizu L, Pereira-Chiocola 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*. Nov 2009;13(6):e504-507. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19447660>.
23. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. *Br J Dermatol*. Feb 2009;160(2):311-318. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19187345>.
24. 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*. Dec 1994;72(12):1041-1047. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7711412>.
25. 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*. Oct 2002;41(10):670-675. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12390190>.
26. Canovas DL, Carbonell J, Torres J, Altes J, Buades J. Laryngeal leishmaniasis as initial opportunistic disease in HIV infection. *J Laryngol Otol*. Dec 1994;108(12):1089-1092. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7861090>.
27. Miralles ES, Nunez M, Hilara Y, Harto A, Moreno R, Ledo A. Mucocutaneous leishmaniasis and HIV. *Dermatology*. 1994;189(3):275-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7949483>.
28. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. *Clin Diagn Lab Immunol*. Sep 2002;9(5):951-958. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12204943>.
29. 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 coinfecting with human immunodeficiency virus type-1. *Am J Trop Med Hyg*. Jul 1998;59(1):155-162. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9684645>.
30. 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*. May 1998;177(5):1339-1344. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9593022>.
31. ter Horst R, Tefera T, Assefa G, Ebrahim AZ, Davidson RN, Ritmeijer K. Field evaluation of rK39 test and direct agglutination test for diagnosis of visceral leishmaniasis in a population with high prevalence of human immunodeficiency virus in Ethiopia. *Am J Trop Med Hyg*. Jun 2009;80(6):929-934. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19478251>.
32. Davidson RN, Di Martino L, Gradoni L, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med*. Feb 1994;87(2):75-81. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8153291>.
33. 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*. Jun 18 1999;13(9):1063-1069. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10397536>.
34. 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*. Mar 2004;53(3):540-543. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14739148>.
35. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect*. Mar 1996;32(2):133-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8708370>.
36. Lazanas MC, Tsekis GA, Papandreou S, et al. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimony compounds. *AIDS*. Jul 1993;7(7):1018-1019. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8357549>.
37. 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*. Feb 1 2004;38(3):377-383. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14727208>.
38. 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. Oct 1993;17(4):625-627. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8268341>.

39. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. *Clin Infect Dis.* Oct 1 2006;43(7):917-924. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16941377>.
40. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. *Adv Parasitol.* 2006;61:223-274. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16735166>.
41. 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.* Sep 2003;52(3):464-468. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12888588>.
42. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clin Infect Dis.* Jan 1999;28(1):42-48; discussion 49-51. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10028069>.
43. 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.* Sep 1995;21(3):711-712. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8527591>.
44. Sundar S, T. K. Jha CPT, S. K. Bhattacharya and M. Rai. Oral miltefosine for the treatment of Indian visceral leishmaniasis. *Trans R Soc Trop Med Hyg.* 2006. Available at <http://ncbi.nlm.nih.gov/pubmed/16730038>.
45. 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.* Aug 1 2006;43(3):357-364. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16804852>.
46. Sindermann H, K. R. Engel CFaWB. Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis.* 39(10): 1520-3. 2004. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15546090>.
47. Sundar S, Sinha PK, Rai M, et al. Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomised controlled trial. *Lancet.* Feb 5 2011;377(9764):477-486. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21255828>.
48. Wortmann G, Zapor M, Ressner R, et al. Liposomal amphotericin B for treatment of cutaneous leishmaniasis. *Am J Trop Med Hyg.* Nov 2010;83(5):1028-1033. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21036832>.
49. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg.* Mar 1992;46(3):296-306. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1313656>.
50. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis.* Sep 2007;7(9):581-596. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17714672>.
51. Barat C, Zhao C, Ouellette M, Tremblay MJ. HIV-1 replication is stimulated by sodium stibogluconate, the therapeutic mainstay in the treatment of leishmaniasis. *J Infect Dis.* Jan 15 2007;195(2):236-245. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17191169>.
52. 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.* Apr 2006;100(3):223-227. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16630379>.
53. 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.* Apr 15 2005;40(8):1148-1155. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15791515>.
54. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis.* May 1 2004;38(9):1266-1272. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15127339>.
55. 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.* Feb 15 2001;32(4):633-635. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11181128>.
56. 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.* Nov 1999;61(5):766-769. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10586909>.

57. 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 <http://www.ncbi.nlm.nih.gov/pubmed/15119371>.
58. Posada-Vergara MP, Lindoso JA, Tolezano JE, Pereira-Chiocola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. *J Infect Dis*. Nov 15 2005;192(10):1819-1822. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16235183>.
59. 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*. Oct 2009;81(4):559-564. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19815866>.
60. Sinha S, Fernandez G, Kapila R, Lambert WC, Schwartz RA. Diffuse cutaneous leishmaniasis associated with the immune reconstitution inflammatory syndrome. *Int J Dermatol*. Dec 2008;47(12):1263-1270. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19126013>.
61. 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*. Jan 2009;47(1):77-79. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19743785>.
62. 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*. Nov 2007;157(5):1032-1036. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17854365>.
63. Badaro R, Johnson WD, Jr. The role of interferon-gamma in the treatment of visceral and diffuse cutaneous leishmaniasis. *J Infect Dis*. Mar 1993;167 Suppl 1(Suppl 1):S13-17. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8433014>.
64. Badaro R, Nascimento C, Carvalho JS, et al. Granulocyte-macrophage colony-stimulating factor in combination with pentavalent antimony for the treatment of visceral Leishmaniasis. *Eur J Clin Microbiol Infect Dis*. 1994;13 Suppl 2:S23-28. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7875148>.
65. 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*. May 1996;100(5):496-501. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8644760>.
66. Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. *Trop Med Int Health*. Sep 2009;14(9):1064-1070. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19552658>.
67. 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*. Dec 22 2000;14(18):2946-2948. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11153679>.
68. 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*. Nov 2010;11(10):670-673. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20500233>.
69. Morgan DJ, Guimaraes LH, Machado PR, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis*. Aug 15 2007;45(4):478-482. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17638198>.
70. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. *Am J Vet Res*. Jan 1966;27(116):132-135. Available at <http://www.ncbi.nlm.nih.gov/pubmed/5913019>.
71. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. *Ann N Y Acad Sci*. Aug 8 1952;55(2):203-215. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12977037>.
72. 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 <http://www.ncbi.nlm.nih.gov/pubmed/2893463>.
73. 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 <http://www.ncbi.nlm.nih.gov/pubmed/7855563>.

74. 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.* Feb 2005;55(2):229-233. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15649998>.
75. Topno RK, Pandey K, Das VN, et al. Visceral leishmaniasis in pregnancy - the role of amphotericin B. *Ann Trop Med Parasitol.* Apr 2008;102(3):267-270. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18348781>.
76. Utili R, Rambaldi A, Tripodi MF, Andreana A. Visceral leishmaniasis during pregnancy treated with meglumine antimoniate. *Infection.* May-Jun 1995;23(3):182-183. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7499009>.
77. 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.* Dec 2009;107(3):208-210. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19766208>.
78. 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.* Oct 2006;58(4):811-815. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16916865>.
79. Boehme CC, Hain U, Novosel A, Eichenlaub S, Fleischmann E, Loscher T. Congenital visceral leishmaniasis. *Emerg Infect Dis.* Feb 2006;12(2):359-360. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17080586>.
80. Meinecke CK, Schottelius J, Oskam L, Fleischer B. Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. *Pediatrics.* Nov 1999;104(5):e65. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10545591>.
81. Zinchuk A, Nadraga A. Congenital visceral leishmaniasis in Ukraine: case report. *Ann Trop Paediatr.* 2010;30(2):161-164. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20522305>.

Malaria

Updated: March 28, 2017

Reviewed: January 11, 2023

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/mm³.³²⁻³⁴ 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/mm³ 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 macrophages³⁸ 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 persons 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, Kanya 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, 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

Updated: April 12, 2022

Reviewed: January 11, 2023

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, *P. 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 patients with HIV with diarrhea, depending on the diagnostic techniques employed and the patient population described.^{3-5,8} The incidence of microsporidiosis has declined with the widespread use of effective ART, but it continues to occur among patients with HIV who are unable to obtain ART or to remain on it.⁹ Microsporidiosis is increasingly recognized among persons without HIV, including children, travelers, organ transplant recipients, contact lens wearers, and the elderly. In patients with immune suppression, clinical signs related to microsporidiosis are most commonly observed when CD4 T lymphocyte cell (CD4) counts are <100 cells/mm³.^{3-5,8}

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} Assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

Patients with AIDS who have CD4 counts <200 cells/mm³ 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

Because chronic microsporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of ART before the patient becomes severely immunosuppressed should prevent this disease (**AII**). No specific chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treating Disease

Data suggest that treatment with ART enables a patient's own defenses to eradicate microsporidia,^{12,13} and administration of ART with immune restoration (an increase in CD4 count to >100 cells/mm³) is associated with resolution of symptoms of enteric microsporidiosis, including illness caused by *E. bienersi*.¹²⁻¹⁵ All patients therefore should be offered ART as part of the initial management of microsporidial infection (**AII**). They should be given fluid support if they have signs of diarrhea and dehydration (**AII**). Patients 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. bienersi* infection. A controlled clinical trial suggested that *E. bienersi* infection responds to oral fumagillin (60 mg/day), a water-insoluble antibiotic made by *Aspergillus fumigatus* (**BII**),^{16,17} or to its synthetic analog, TNP-470 (**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. bienersi* in the absence of ART;¹⁹ however, the effect appeared to be minimal among patients with low CD4 counts. Based on the professional experience of several experts who have treated diarrhea caused by *E. bienersi* with nitazoxanide in organ transplant patients, nitazoxanide is a reasonable alternative, if fumagillin is not available, for the treatment of diarrhea due to *E. bienersi* (**CIII**).

Albendazole, a benzimidazole that binds to β -tubulin, has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* or *V. corneae* infections. The tubulin genes of both *E. bienersi*²⁰ and *V. corneae*²¹ 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. bienersi* and *V. corneae* (AII).²²⁻²⁴

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 patients with HIV with persistent diarrhea and *E. bienersi* infection (CIII)²⁵; 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).

Ocular infections caused by microsporidia respond to treatment with topical Fumidil B (fumagillin bicyclohexylammonium) in saline (to achieve a concentration of 70 µg/mL of fumagillin) (BII).²² 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, all patients should be offered ART as part of the initial management of microsporidial infection and fluid support if they have signs of diarrhea and dehydration (AII). Data suggest that treatment with ART, which results in immune reconstitution, enables a patient'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 patient with HIV treated with ART in the setting of *E. bienersi* infection;²⁶ however, no IRIS reactions have been reported with other species of microsporidia or with other cases of *E. bienersi*. Concerns about IRIS should not alter therapy or the institution 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/mm³), treatment can probably be discontinued after ocular infection resolves (CIII), but it should be continued indefinitely if CD4 counts fall below 200 cells/mm³ of blood 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 patients who no longer have signs and symptoms of microsporidiosis and have a sustained increase in their CD4 counts to >200 cells/mm³ for 6 months after ART (**BIII**).¹³

Special Considerations During Pregnancy

Rehydration and initiation of ART should be the mainstays of initial treatment of microsporidiosis during pregnancy, as in nonpregnant people (**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.²⁷

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 risk (**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 in pregnant people (**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.²⁸ Nitazoxanide has not been associated with adverse outcomes in pregnancy and is a category B drug; 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.^{29,30} 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, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.³¹ 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**).

Recommendations for Managing Microsporidiosis
Preventing Chronic Microsporidiosis
<ul style="list-style-type: none"> Because chronic microsporidiosis occurs primarily in persons with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent the disease (AII).
Managing Microsporidiosis
<ul style="list-style-type: none"> Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm³ (AII). Severe dehydration, malnutrition, and wasting should be managed by fluid support (AII) and nutritional supplements (AIII). Anti-motility agents can be used for diarrhea control, if required (BIII). <p><i>For GI Infections Caused by Enterocytozoon bienewisi</i></p> <ul style="list-style-type: none"> 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) are two agents that are effective, but neither agent is available in the United States. Nitazoxanide can have a therapeutic effect, but this efficacy has been limited in patients with low CD4 counts (CIII). <p><i>For Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than E. bienewisi and Vittaforma corneae</i></p> <ul style="list-style-type: none"> Albendazole 400 mg PO twice daily (AII), continue until CD4 count >200 cells/mm³ for >6 months after initiation of ART (BIII) <p><i>For Disseminated Disease Caused by Trachipleistophora or Anncaliia</i></p> <ul style="list-style-type: none"> Itraconazole 400 mg PO daily plus albendazole 400 mg PO two times a day (CIII) <p><i>For Ocular Infection</i></p> <ul style="list-style-type: none"> Topical fumagillin bicyclohexylammonium (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 United States) (BII), plus albendazole 400 mg PO twice daily for management of systemic infection (BIII) For patients with CD4 count >200 cells/mm³, therapy can probably be discontinued after ocular infection resolves (CIII). For patients with CD4 count ≤200 cells/mm³, therapy should be continued until resolution of ocular symptoms and CD4 count increases to >200 cells/mm³ for ≥6 months in response to ART (BIII).

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

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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/10943515>.
4. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. *Adv Parasitol*. 1998;40:321-349. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/1370122>.
7. Weiss LM, Vossbrinck CR. Microsporidiosis: molecular and diagnostic aspects. *Adv Parasitol*. 1998;40:351-395. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9554079>.
8. Wittner M, Weiss L. *The Microsporidia and Microsporidiosis*. Washington DC: 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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/16148179>.
11. Didier ES, Weiss LM. Microsporidiosis: current status. *Curr Opin Infect Dis*. 2006;19(5):485-492. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/11103042>.

14. Contreas 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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/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.ncbi.nlm.nih.gov/pubmed/10602740>.
20. 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.ncbi.nlm.nih.gov/pubmed/17300517>.
21. 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.ncbi.nlm.nih.gov/pubmed/18056284>.
22. 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.ncbi.nlm.nih.gov/pubmed/8117342>.
23. 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.ncbi.nlm.nih.gov/pubmed/8277179>.
24. 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.ncbi.nlm.nih.gov/pubmed/9593027>.
25. 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.ncbi.nlm.nih.gov/pubmed/10023334>.
26. 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.ncbi.nlm.nih.gov/pubmed/18627278>.
 27. Ndyomugenyi 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.ncbi.nlm.nih.gov/pubmed/19052293>.
 28. Heinonen OP, Slone D, Shapiro S. *Birth Defects and Drugs in Pregnancy*. Littleton: Publishing Sciences Group; 1977.
 29. 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>.
 30. 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>.
 31. 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>.

Mpox

This section is under development.

Disseminated *Mycobacterium avium* Complex Disease

Updated: February 15, 2019

Reviewed: January 11, 2023

Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.¹⁻⁶ In the era prior to the availability of effective antiretroviral therapy (ART), *M. avium* was the etiologic agent in >95% of people living with HIV with advanced immunosuppression who acquired disseminated MAC disease.^{4,7-12} Recent studies conducted using newer bacterial typing technology suggest organisms causing bacteremia in people with HIV include a diversity of species, including the *M. avium* subspecies *hominissuis* and *M. colombiense*.¹³ An estimated 7% to 12% of adults have previously contracted MAC, although rates of disease vary in different geographic locations.^{2,4,8,11,12} Although epidemiologic associations have been identified, no environmental exposure or behavior has been consistently linked to subsequent risk of developing MAC disease.

The mode of MAC transmission is thought to be through inhalation, ingestion, or inoculation of MAC bacteria via the respiratory or gastrointestinal (GI) tract.^{1,14} 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.

MAC disease typically occurs in people with HIV with CD4 T lymphocyte (CD4) cell counts <50 cells/mm³. The incidence of disseminated MAC disease is 20% to 40% in people with HIV with advanced immunosuppression in the absence of effective ART or chemoprophylaxis.^{15,16} The overall incidence of MAC disease among people living with HIV has continued to decline 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.¹⁷⁻²⁰ In addition to CD4 count <50 cells/mm³, factors associated with increased risk for MAC disease identified in recent studies are plasma HIV RNA levels >1,000 copies/mL, ongoing viral replication despite ART, previous or concurrent OIs, and reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens, possibly reflecting defects in T-cell repertoire.¹⁸⁻²⁰

Clinical Manifestations

In people living with HIV with advanced immunosuppression who are not on ART, MAC disease often is a disseminated, multi-organ infection, although localized disease may also be seen.²¹⁻²⁵ Early symptoms may be minimal and can precede detectable mycobacteremia by several weeks. Symptoms may include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.⁸

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.^{4,5,7-12,15,16,26,27} 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.

In comparison to people with HIV who are not receiving or not responding to ART, localized manifestations of MAC disease have been reported more often in people with HIV who are receiving and have responded to ART with an increase in CD4 cell counts, suggesting improved immune function. Localized syndromes include cervical, intraabdominal or mediastinal lymphadenitis, pneumonia, pericarditis, osteomyelitis, skin or soft-tissue abscesses, bursitis, genital ulcers, or central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), as discussed below.

IRIS is recognized as a systemic inflammatory syndrome with signs and symptoms that are clinically indistinguishable from active MAC infection, although bacteremia is generally absent. Similar to tuberculosis (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.²⁸⁻³² Both variants occur primarily in those with advanced immunosuppression who begin ART and have a rapid and marked reduction in plasma HIV RNA.^{32,33} 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.

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 node, bone marrow, or other normally sterile tissue or body fluids.^{16,24,25,34,35} 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 stool or tissue biopsy material, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

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 with clarithromycin, azithromycin, rifabutin, or other drugs alone or in combination for asymptomatic colonization with MAC organisms at these sites. Therefore, routine screening of respiratory or GI specimens and pre-emptive 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

Indication for Primary Prophylaxis

Primary prophylaxis against disseminated MAC disease **is not recommended** for adults and adolescents with HIV who immediately initiate ART (**AII**). People with HIV who are not receiving ART or who remain viremic on ART but have no current options for a fully suppressive ART regimen should receive chemoprophylaxis against disseminated MAC disease if they have CD4 counts <50 cells/mm³ (**AI**).

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 observational data have demonstrated that people with HIV taking ART can discontinue primary prophylaxis with minimal risk of developing MAC disease.³⁶⁻⁴⁰

This updated recommendation is based on data from recent observational cohort studies. In an analysis of 369 people with HIV with CD4 counts <50 cells/mm³ while on ART and followed for at least six months, the overall incidence of MAC disease was 0.6 per 100 person-months. No MAC occurred among 71 persons on ART who were virologically suppressed at baseline, including 41 persons who were not receiving primary MAC prophylaxis.⁴¹ Another study enrolled 157 people with HIV who had at least one CD4 count <50 cells/mm³ and had started ART between 1998 and 2014. The study compared the incidence of disseminated MAC disease within the 12 months after the first CD4 count <50 cells/mm³ between a group of 33 participants who received primary MAC prophylaxis and a group of 122 participants who received no MAC prophylaxis.²⁰ There were no differences between the groups in the proportion of participants who achieved or the time to achieve a CD4 count >100 cells/mm³ or in the proportion of participants who achieved viral suppression within 12 months. The incidence of MAC disease was not statistically significantly different between the groups; 3.4 per 100 person-years for those on primary prophylaxis versus 0.8 per 100 person-years for those not on primary prophylaxis. 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. In a study from the OI Working Group of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), the incidence of primary MAC disease was 0.74 per 1,000 person-years (IQ range 0.68 to 0.80) among people living with HIV on ART and not receiving MAC prophylaxis.⁴² These data suggest that primary MAC prophylaxis provides no additional benefit in patients started on effective ART that results in viral suppression. Additional arguments against primary MAC prophylaxis include the potential for increased cost, adverse effects of the drugs used for prophylaxis, and, for the small number of people with HIV who might develop “unmasking MAC IRIS” after starting ART, the use of monotherapy for MAC prophylaxis may result in acquired drug resistance in those with active MAC disease.^{43,44}

Preferred and Alternative Drugs for Prophylaxis

As previously stated, primary prophylaxis for MAC is not recommended, but for those for whom prophylaxis is being considered, azithromycin⁴⁵ and clarithromycin^{5,46} are the preferred prophylactic agents (**AI**).^{1,47} 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.⁴⁵ However, based on the additional cost, increased occurrence of adverse effects, potential for drug interactions, and no greater survival benefit than with azithromycin alone, the combination regimen of azithromycin and rifabutin **is not recommended (AI)**. Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. In people with HIV who cannot tolerate azithromycin or clarithromycin, rifabutin is an alternative prophylactic agent for MAC disease (**BI**), although drug interactions may complicate use of this agent. 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. TB also should be excluded before rifabutin is used for MAC prophylaxis because treatment with rifabutin monotherapy could result in acquired resistance to *M. tuberculosis* in people with HIV who have active TB.

Treating Disease

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance **(AI)**.^{1,6,11,12,14,48-56} Clarithromycin is the preferred first agent **(AI)**; it has been studied more extensively than azithromycin in people with AIDS and appears to be associated with more rapid clearance of MAC from the blood.^{6,48,50,54,55,57} However, azithromycin can be substituted for clarithromycin when drug interactions or intolerance preclude the use of clarithromycin **(AII)**. Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all people with HIV.^{58,59}

Ethambutol is the recommended second drug for the initial treatment of MAC disease **(AI)**. Some clinicians would add rifabutin as a third drug **(CI)**. 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^{6,50} in individuals with AIDS and disseminated MAC disease. These studies were completed before the availability of effective ART. Whether similar results would be observed for people with HIV receiving effective ART has not been established. Some experts would recommend the addition of a third or fourth drug in settings in which the risk of mortality is increased and emergence of drug resistance is most likely, such as with advanced immunosuppression (CD4 count <50 cells/mm³), high mycobacterial loads (>2 log₁₀ colony-forming units/mL of blood), and/or the absence of effective ART **(CII)**. The third or fourth drug might include a fluoroquinolone such as levofloxacin or moxifloxacin **(CII)**, which have *in vitro* and animal model activity against MAC, or an injectable agent such as amikacin or streptomycin **(CII)**, although no randomized clinical trials have evaluated the added efficacy of these antibiotics in the setting of clarithromycin or azithromycin treatment or effective ART.^{58,60}

Special Considerations with Regard to Starting Antiretroviral Therapy

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 **(CII)**. The rationale for starting ART as soon as possible is to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression **(CII)**. 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 and antimycobacterial drugs **(CII)**. People with HIV will need continuous antimycobacterial treatment unless ART results in immune reconstitution.

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

A repeat blood culture for MAC should be obtained 4 weeks to 8 weeks after initiating antimycobacterial therapy only in people with HIV who do not have a clinical response to their initial treatment regimens. Improvement in fever and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 weeks 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 with clarithromycin and azithromycin include gastrointestinal upset, metallic taste, elevations in liver transaminase levels or hypersensitivity reactions. These adverse effects may be exacerbated when drug levels are increased due to drug interactions associated with rifabutin or some

antiretroviral 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)**.⁶¹ When used with clarithromycin or other drugs that inhibit cytochrome P450 (CYP450) isoenzyme 3A, rifabutin has been associated with a higher risk of adverse drug interactions.^{62,63}

Given complex drug interactions, if rifabutin is used, dose adjustment is necessary in people with HIV receiving protease inhibitors (PIs), efavirenz, rilpivirine, or doravirine; rifabutin should not be used with elvitegravir/cobicistat or bictegravir.⁶⁴⁻⁷¹ No dose adjustment for rifabutin or integrase inhibitors, other than elvitegravir/cobicistat or bictegravir, is currently recommended.^{72,73} The most updated drug-drug interaction information can be found in the [Adult and Adolescent Antiretroviral Guidelines](#). PIs can increase clarithromycin levels, but no recommendation to adjust the dose of either clarithromycin or PIs can be made based on existing data. The ability of efavirenz to induce metabolism of clarithromycin can result in reduced serum concentration of clarithromycin but increased concentration of the 14-OH active metabolite of clarithromycin. Although the clinical significance of this interaction is unknown, it could reduce the efficacy of clarithromycin for MAC prophylaxis. Azithromycin metabolism is not affected by the CYP450 system; azithromycin can be used safely in the presence of PIs, NNRTIs, or integrase inhibitors without concerns about drug interactions.

People with HIV on ART who develop moderate-to-severe symptoms typical of IRIS should receive initial treatment with non-steroidal, anti-inflammatory drugs (**CIII**). If IRIS symptoms do not improve, short-term (4 weeks–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, has been successful in reducing symptoms and morbidity (**CII**).^{29,74}

Managing Treatment Failure

MAC treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia 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. Most people with HIV who experience failure of clarithromycin or azithromycin primary prophylaxis in clinical trials had isolates susceptible to these drugs when MAC disease was detected.^{6,11,12,48,75,76}

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 are rifabutin, an injectable aminoglycoside (amikacin or streptomycin), or a fluoroquinolone (levofloxacin or moxifloxacin), although data supporting a survival or microbiologic benefit when these agents are added have not been compelling (**CII**).^{11,12,49-53,57,77-81} Data in people without HIV who are being treated for MAC indicate that an injectable aminoglycoside (amikacin or streptomycin) is a viable choice (**CIII**).⁵⁸ Continuing clarithromycin or azithromycin despite resistance is generally not recommended as there is likely to be no additional benefit and may be added toxicity. Clofazimine **should not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality (**AI**).^{49,51,79} Anecdotal evidence exists for the addition of one or more other second-line agents (e.g., ethionamide, thioacetazone [not available in the United States], cycloserine, or linezolid) to the combination of clarithromycin or azithromycin and other drugs as salvage therapy, but their role in this setting is not well defined. 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**).

Adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for its routine use.

Preventing Recurrence

People with HIV and disseminated MAC disease should continue chronic maintenance therapy (**AII**) unless ART results in immune reconstitution.^{37,38}

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/mm³ 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**).^{38,53,82-86} 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/mm³ may be indicated (**BIII**).

Special Considerations During Pregnancy

Primary prophylaxis for MAC disease in pregnant women and adolescents is **not recommended** (**AIII**). 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.^{87,88} Azithromycin did not produce defects in animal studies, but experience is limited with use in humans during the first trimester. A nested case-control study conducted within the large Quebec Pregnancy cohort found an association between azithromycin use and spontaneous miscarriage.⁸⁹ 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 azithromycins in the first trimester and major congenital malformations, include heart defects.⁹⁰⁻⁹² When primary prophylaxis is required for a pregnant woman who is not being treated with effective ART, azithromycin is the preferred agent (**BIII**). For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination (**BIII**).

Diagnostic considerations and indications for treatment of MAC disease for pregnant women are the same as for women who are not pregnant. On the basis of animal data discussed previously, azithromycin is preferred over clarithromycin as the first-line agent to use in combination with ethambutol for treatment of MAC disease (**BIII**). Use of ethambutol rather than rifabutin or other agents with the potential for drug-drug interactions should allow initiation of ART as soon as possible during pregnancy to decrease the risk of perinatal transmission of HIV. Pregnant women whose MAC disease fails to respond to a primary regimen should be managed in consultation with infectious disease and obstetrical specialists.

Recommendations for Preventing and Treating 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 Initiating Primary Prophylaxis

- Not on fully suppressive ART, *and*
- CD4 count <50 cells/mm³ after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some people with HIV) **(AI)**

Preferred Therapy

- Azithromycin 1200 mg PO once weekly **(AI)**, *or*
- Clarithromycin 500 mg PO BID **(AI)**, *or*
- Azithromycin 600 mg PO twice weekly **(BIII)**

Alternative Therapy

- Rifabutin 300 mg PO daily **(BI)** (dose adjustment may be necessary based on drug-drug interactions, please refer to [Table 4](#) for dosing recommendation when used with ARV drugs).
- **Note:** Active TB should be ruled out before starting rifabutin.

Indication for Discontinuing Primary Prophylaxis

- Initiation of effective ART **(AI)**

Indication for Restarting Primary Prophylaxis

- CD4 count <50 cells/mm³ (only if not on fully suppressive ART) **(AIII)**

Treating Disseminated MAC Disease

Preferred Therapy

- At least 2 drugs as initial therapy to prevent or delay emergence of resistance **(AI)**
 - Clarithromycin 500 mg PO twice daily **(AI)** plus ethambutol 15 mg/kg PO daily **(AI)**, *or*
 - Azithromycin 500–600 mg **(AII)** plus ethambutol 15 mg/kg PO daily **(AI)** when drug interactions or intolerance precludes the use of clarithromycin
 - **Note:** Testing of susceptibility to clarithromycin or azithromycin is recommended.

Alternative Therapy

- Some experts would recommend addition of a third or fourth drug for people with HIV with high mycobacterial loads (i.e., >2 log CFU/mL of blood), or in the absence of effective ART **(CIII)**.

The Third or Fourth Drug Options May Include:

- Rifabutin 300 mg PO daily **(CI)** (dose adjustment may be necessary based on drug-drug interactions), *or*
- A fluoroquinolone **(CIII)** (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), *or*
- An injectable aminoglycoside **(CIII)** (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily)

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Same as treatment regimens

Criteria for Discontinuing Chronic Maintenance Therapy **(AII)**

- Completed **at least** 12 months therapy, *and*
- No signs and symptoms of MAC disease, *and*
- Have sustained (>6 months) CD4 count >100 cells/mm³ in response to ART

Indication for Restarting Secondary Prophylaxis

- CD4 <100 cells/mm³ **(AIII)**

Other Considerations

- NSAIDs may be used for people with HIV who experience moderate to severe symptoms attributed to IRIS **(CIII)**.
- If IRIS symptoms persist, a short-term course (4 weeks–8 weeks) of systemic corticosteroid (equivalent to prednisone 20–40 mg) can be used **(CII)**.

Key: ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; CFU = colony-forming units; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; MAC = *Mycobacterium avium* complex; NSAIDs = non-steroidal anti-inflammatory drugs; PO = orally; TB = tuberculosis

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: <http://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: <http://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: <http://www.ncbi.nlm.nih.gov/pubmed/16675537>.
4. Inderlied PCB. Microbiology and minimum inhibitory concentration testing for *Mycobacterium avium* complex prophylaxis. *Am J Med*. 1997;102(5):2-10. Available at: <http://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 Bein Community Programs for Clinical Research on AIDS 009 Protocol Team. *J Infect Dis*. 2000;181(4):1289-1297. Available at: <http://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: <http://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: <http://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: <http://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: <http://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: <http://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: <http://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: <http://www.ncbi.nlm.nih.gov/pubmed/8204773>.
13. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28478210>.
14. Corti M, Palmero D. *Mycobacterium avium* complex infection in HIV/AIDS patients. *Expert Rev Anti Infect Ther*. 2008;6(3):351-363. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18588499>.
15. 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: <http://www.ncbi.nlm.nih.gov/pubmed/1349906>.
16. 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: <http://www.ncbi.nlm.nih.gov/pubmed/1362634>.
17. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20502317>.
18. 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>.
19. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28748197>.
20. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28592210>.
21. 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: <http://www.ncbi.nlm.nih.gov/pubmed/2772468>.

22. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8454889>.
23. 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: <http://www.ncbi.nlm.nih.gov/pubmed/7996004>.
24. 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: <http://www.ncbi.nlm.nih.gov/pubmed/2580679>.
25. 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: <http://www.ncbi.nlm.nih.gov/pubmed/6194041>.
26. Inderlied CB, Kemper CA, Bermudez LE. The *Mycobacterium avium* complex. *Clin Microbiol Rev*. 1993;6(3):266-310. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8358707>.
27. 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: <http://www.ncbi.nlm.nih.gov/pubmed/3165608>.
28. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10048898>.
29. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16231262>.
30. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9457095>.
31. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9923530>.
32. 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: <http://www.ncbi.nlm.nih.gov/pubmed/28791872>.
33. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24337386>.

34. 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: <http://www.ncbi.nlm.nih.gov/pubmed/3385000>.
35. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10395860>.
36. 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>.
37. 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 Bein Community Programs for Clinical Research on AIDS. *N Engl J Med*. 2000;342(15):1085-1092. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10766581>.
38. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11015162>.
39. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10930156>.
40. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16028167>.
41. Yangco BG, Buchacz K, Baker R, et al. Is primary *Mycobacterium avium* complex prophylaxis necessary in patients with CD4 <50 cells/ μ L who are virologically suppressed on cART? *AIDS Patient Care STDS*. 2014;28(6):280-283. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24833016>.
42. 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: <http://www.ncbi.nlm.nih.gov/pubmed/27864413>.
43. 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: <http://www.ncbi.nlm.nih.gov/pubmed/15025543>.

44. “Choosing wisely” in HIV medicine — should we stop giving MAC prophylaxis? [Type]. NEJM Journal Watch; 2016.
45. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8676932>.
46. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8663871>.
47. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23633339>.
48. 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: <http://www.ncbi.nlm.nih.gov/pubmed/7978715>.
49. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9314450>.
50. 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: <http://www.ncbi.nlm.nih.gov/pubmed/10452638>.
51. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9359722>.
52. 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 Bein Community Programs for Clinical Research on AIDS. *Clin Infect Dis*. 1999;29(1):125-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10433575>.
53. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9780266>.

54. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9827282>.
55. 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: <http://www.ncbi.nlm.nih.gov/pubmed/11073759>.
56. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23979729>.
57. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8676931>.
58. 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: <http://www.ncbi.nlm.nih.gov/pubmed/17277290>.
59. 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: <http://www.ncbi.nlm.nih.gov/pubmed/16142672>.
60. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23478956>.
61. Food and Drug Administration. Clarithromycin [package insert]. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050662s058,050698s038,050775s0261bl.pdf.
62. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8284019>.
63. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9517944>.
64. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26832753>.
65. 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>.
 66. 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: <http://www.ncbi.nlm.nih.gov/pubmed/24155058>.
 67. 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: <http://www.ncbi.nlm.nih.gov/pubmed/21348537>.
 68. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV [Type]. 2018.
 69. Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. Available at: https://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/default.htm.
 70. Rilpivirine [package insert]. Available at: https://www.janssenmd.com/pdf/edurant/edurant_pi.pdf.
 71. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) [package insert]. Available at: http://www.gilead.com/~media/files/pdfs/medicines/hiv/biktarvy/biktarvy_pi.pdf.
 72. 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>.
 73. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20852006>.
 74. 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: <http://www.ncbi.nlm.nih.gov/pubmed/7811052>.
 75. Heifets L, Lindholm LP, Libonati J. Radiometric broth macrodilution method for determination of minimal inhibitory concentrations (MIC) with *Mycobacterium avium* complex isolates: proposed guidelines. Type Presented at National Jewish Center for Immunology and Respiratory Medicine; Year.

76. Heifets L, Mor N, Vanderkolk J. *Mycobacterium avium* strains resistant to clarithromycin and azithromycin. *Antimicrob Agents Chemother*. 1993;37(11):2364-2370. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8031351>.
77. 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: <http://www.ncbi.nlm.nih.gov/pubmed/8395019>.
78. 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: <http://www.ncbi.nlm.nih.gov/pubmed/1739237>.
79. 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: <http://www.ncbi.nlm.nih.gov/pubmed/9147422>.
80. 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: <http://www.ncbi.nlm.nih.gov/pubmed/2382918>.
81. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12791475>.
82. Aberg J, Powderly W. HIV: primary and secondary prophylaxis for opportunistic infections. *BMJ Clin Evid*. 2010;2010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21418688>.
83. 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>.
84. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12416943>.
85. 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>.
86. 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: <http://www.ncbi.nlm.nih.gov/pubmed/12660918>.
87. 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>.
 88. 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>.
 89. Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ*. 2017;189(17):E625-E633. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/28461374>.
 90. 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: <http://www.ncbi.nlm.nih.gov/pubmed/26513406>.
 91. 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: <http://www.ncbi.nlm.nih.gov/pubmed/23254249>.
 92. Bahat Dinur A, Koren G, Matok I, et al. Fetal safety of macrolides. *Antimicrob Agents Chemother*. 2013;57(7):3307-3311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23650169>.

Mycobacterium tuberculosis Infection and Disease

Updated: February 17, 2022

Reviewed: January 11, 2023

Epidemiology

Tuberculosis (TB) is the leading cause of morbidity and mortality among people with HIV worldwide. In 2019, an estimated 820,000 people with HIV had TB and 208,000 deaths among people with HIV were attributed to TB.¹ Although the overall annual number of TB patients worldwide has been relatively unchanged (1.6% global average annual rate of decline), several countries in sub-Saharan Africa have seen marked reductions by 4 percent to 8 percent per year while antiretroviral therapy (ART) coverage has expanded.² People with HIV still account for a disproportionate number of TB deaths worldwide (14.7% of deaths vs. 8.2% of TB cases); however, a 69 percent reduction in deaths has occurred since 2000.¹

In the United States, TB rates are the lowest ever reported, with 8,916 people with TB reported in 2019.³ Approximately two-thirds (6,364; 71.4%) of people newly reported with TB were born outside the United States. The incidence of HIV-related TB in the United States has declined substantially, in part because of the widespread use of ART.^{4,5} Among all patients reported with TB with known HIV status in the United States in 2019, 373 persons (4.7%) were coinfecting with HIV (7.6% among TB patients aged 25–44 years).³ Four states (Florida, Georgia, Missouri, and North Dakota) and Puerto Rico have HIV coinfection rates greater than 8 percent among people with TB.

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 multiplication of tubercle bacilli. However, viable bacilli persist for years, a condition referred to as latent TB infection (LTBI). Persons 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. The annual risk of TB disease due to reactivation of LTBI for persons with untreated HIV infection has been estimated as 3 percent to 16 percent per year, which approximates the lifetime risk of TB disease for persons with LTBI who are HIV negative (approximately 5%).^{6–11} The risk of TB begins in the first year following HIV infection.¹² TB infection can occur at any CD4 T lymphocyte (CD4) cell count, although the risk increases with progressive immunodeficiency.^{12,13} Even with effective ART, the risk of TB disease among people with HIV remains greater than that among the general population. The estimated annual risk of developing TB disease among persons 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 untreated people with HIV than for those without HIV.^{14,15} Furthermore, in two studies among adults with HIV not receiving ART, persons who developed TB disease had higher viral loads¹⁶ and a greater risk of HIV disease progression¹⁶ and death¹⁷ than CD4-matched control patients without TB. In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.¹⁸

The risk of progression from LTBI to TB disease in persons with HIV is reduced both by ART and by treatment of LTBI.^{17,19–22} In combination with ART, isoniazid preventive therapy decreased the

risk of TB disease by 76 percent among people with HIV in Brazil.²³ Furthermore, isoniazid preventive therapy and ART independently and additively decreased the risk of death and severe HIV-related illness.^{19,21}

Diagnosing Latent TB Infection

All persons with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure (**AII**). The two current diagnostics available for 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. The decisions about medical and public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results.

Persons with advanced HIV infection (CD4 count <200 cells/mm³) and negative diagnostic tests for LTBI, without 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/mm³ to ensure that the initial test result was a true negative result.^{24,25} 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 persons with active TB disease (e.g., during incarceration, travel to a high-TB incidence country, homelessness, living in a congregate setting).

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 persons 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 persons who received Bacillus Calmette-Guérin (BCG) vaccination, and decreased sensitivity (false negative results) among persons with advanced immunodeficiency.²⁶ These limitations of the TST have led to broader use of IGRAs for detection of LTBI.

Older studies suggest 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 other nontuberculous mycobacteria.^{27,28} Furthermore, in a prospective study of 1,510 people with HIV in the United States, IGRAs appeared more sensitive than the TST, although both TST and IGRA (using U.S. cutoffs of 5 mm for TST and 0.35 IU/mL for QuantiFeron-TB Gold In-Tube [QFT-GIT]) may result in more LTBI overdiagnosis than underdiagnosis in a population with 5 percent or lower LTBI prevalence.²⁹

IGRAs include the T-SPOT.TB and QFT-TB Gold Plus (QFT-Plus). As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.³⁰ 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.³¹ Similar findings among health care workers led to a revised recommendation by the Centers for Disease Control and Prevention (CDC) to no longer routinely, serially test U.S. health care personnel who do not have clear risk factors for new or ongoing TB exposure.³² Similarly, annual testing for people with HIV is not recommended unless high risk exists for repeated or ongoing exposure to persons with active TB disease.

Among people with HIV, the correlation between the TST and IGRA test results is poor to moderate.^{33,34} In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease;³⁵⁻³⁷ in some studies, patients with a positive IGRA were at a higher risk of subsequently developing TB disease than those with a positive TST.^{38,39} Despite its limitations, a positive TST result strongly predicts that treatment of LTBI will decrease the risk of TB progression among people with HIV.¹⁷ Studies are underway to formally evaluate if IGRAs are similarly predictive.

In programmatic settings in the United States, TB screening has been suboptimal, with only 47 percent to 69 percent of patients completing initial screening.⁴⁰⁻⁴³ The use of an IGRA for TB screening may increase the proportion of patients who complete baseline and as-needed follow-up TB screening.

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.^{29,44} 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 its adoption 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.⁴⁵

As tests of immune reactivity against *M. tuberculosis*, the TST and IGRAs are often positive among persons with TB disease. Therefore, all persons with a positive TST or IGRA should be evaluated for the possibility of active TB disease.⁴⁴ Most, but not all, people with HIV with TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); absence of any of these symptoms had a 97 percent negative predictive value for culture-positive TB in low-resource settings, although this varied depending on pretest probability.⁴⁶ The addition of a chest radiograph improved sensitivity of this screening algorithm but decreased specificity. It is important to note that in a symptomatic patient with clinical suspicion for TB disease, a negative TST or IGRA does not rule out TB disease.

Obtaining a sputum culture 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.⁴⁴

Treating Latent TB Infection

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.⁴⁷ 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 (**AII**). 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 treatment of LTBI, and preventive therapy is

not generally recommended (**AIII**); this is in contrast to high TB endemic countries where isoniazid decreased TB risk and mortality in people with HIV, regardless of TST or IGRA result.²²

LTBI treatment and ART act independently to decrease the risk of TB disease.^{20,21,23,48,49} Therefore, use of both interventions is recommended for persons with LTBI (**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**).²¹

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 treatment of LTBI (**AI**).⁴⁷

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/mm³ and who were not yet on ART.^{50,51} 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.⁵²

Although individuals taking ART were not included in the Phase 3 trial of 3HP,⁵³ the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.^{54,55} Raltegravir concentrations were modestly increased when it was given with once-weekly rifapentine in healthy volunteers.⁵⁶ In a Phase 1/2 single-arm study of people with HIV treated with dolutegravir and 3HP, rifapentine decreased dolutegravir exposure by 26 percent; yet, trough concentrations remained above the 90 percent maximum inhibitory concentration for all but one participant, and all participants maintained an undetectable viral load throughout the study period.⁵⁷ Based on these PK data and limited outcome data, 3HP is recommended in virally suppressed persons receiving efavirenz, raltegravir, or dolutegravir (given as once daily dosing) without dose adjustment of rifapentine, isoniazid, or ART (**AI**).⁵⁸

3HR

- Daily isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25–50 mg PO daily for 3 months is also a preferred option for treatment of LTBI in people with HIV (**AI**).

In studies of HIV-negative adults and children with 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.^{59–63} 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,^{64–67} hepatotoxicity was less frequent among those receiving 3HR, but treatment-limiting adverse effects were more common.⁴⁷ When using rifampin alone for LTBI treatment, either dose adjustment or substitution of key ARVs may be needed (see [Dosing Recommendations for Anti-TB Drugs table](#) [included below]).

Alternative Drugs for Treatment of Latent TB Infection

Isoniazid

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6 to 9 months is an alternative regimen for 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.^{21,67–71} However, treatment completion rates are suboptimal, decreasing its effectiveness.⁷² Patients are more likely to complete shorter regimens.^{52,53,72–76} 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/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.⁷⁰ 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 CDC/National Tuberculosis Controllers Association (NTCA) guidelines recommend 4R as a preferred treatment for LTBI in people without HIV, given the lack of trial data in people with HIV, the 4R regimen is recommended only as an alternative to 3HP, 3HR, 6H, and 9H in people with HIV (**BI**). When using rifampin alone 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,^{77,78} some clinicians would perform a sputum culture before starting 4R for LTBI. Because limited data exist on 4R in people with HIV, concerns about using this regimen in people with low CD4 cell counts, and no data on use of 4 months of rifabutin either in people with or without HIV, rifabutin monotherapy is not recommended (**AIII**). The regimen of 2 months of rifampin plus pyrazinamide is not recommended given the risk of severe and sometimes fatal hepatotoxicity (**AII**).^{79,80, 81}

1HP

- Isoniazid 300 mg PO daily plus rifapentine PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks is an alternative therapy for treatment of LTBI in people with HIV (**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).⁷⁴ The median CD4 count of study participants was 470 cells/mm³, 50 percent of the study population was on ART (efavirenz or nevirapine-based regimens) at study entry, and 21 percent 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 percent in the 1HP arm and 90 percent 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 CDC/NTCA 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. 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 CDC/NTCA guidelines. If ART is administered together with 1HP, an efavirenz-based regimen should be used (**AI**). However, a study evaluating co-administration of 1HP with dolutegravir is in progress;^{54,82} the use of dolutegravir-based ART should await results from this trial.

Treatment of LTBI Following Exposure to Drug-Resistant TB

For persons exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities (**AIII**).⁸³

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 persons 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.⁴⁷ Persons with concomitant chronic viral hepatitis and older individuals have an increased risk of isoniazid-related hepatotoxicity, and such patients should be monitored closely when being treated for LTBI.^{84,85}

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.^{71,74} Factors that increase the risk of drug-induced clinical hepatitis include daily alcohol consumption, underlying liver disease, and concurrent treatment with other hepatotoxic drugs. 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 greater than five times the upper limit of normal without symptoms or 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 disease⁸⁶ and in consultation with an expert in treating LTBI in people with HIV.

Clinical Manifestations of TB Disease

Similar to persons without HIV infection, people with HIV with TB disease may be asymptomatic but have positive sputum cultures (subclinical TB).⁸⁷ In ambulatory people with HIV, the presence of any one of the classic symptoms of TB disease (i.e., cough, hemoptysis fever, night sweats, weight loss) has high sensitivity but low specificity for diagnosing TB as assessed in resource-limited settings.⁴⁶ The sensitivity of classic TB symptoms is lower in people with HIV on ART.⁷⁷

The presentation of TB disease is influenced by the degree of immunodeficiency.^{88,89} In patients with CD4 counts >200 cells/mm³, HIV-related TB generally resembles TB among persons without HIV. Most patients have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.⁹⁰

In patients with CD4 counts <200 cells/mm³, the chest radiographic findings of pulmonary TB are markedly different, with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon.^{88,90,91} Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures. Thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.⁹²

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. In patients who are markedly immune-suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.⁹³ Clinical manifestations of extrapulmonary TB in people with HIV are not substantially different from those described in persons without HIV. TB must be considered in disease processes involving any site in the body,⁹⁴ especially in patients with central nervous system (CNS) disease, when early TB treatment is essential to improve outcomes.⁹⁵⁻⁹⁷

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).⁴⁴ Pulmonary involvement is common at all CD4 counts.^{87,98} The initial evaluation of a patient 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 patients with advanced immunodeficiency who can have TB culture-positive sputum despite normal chest radiographs.^{99,100} Therefore, sputum smear, nucleic acid amplification (NAA) testing, and culture should be performed in people with HIV with symptoms of TB disease who have a normal chest radiograph, as well as in persons with no pulmonary symptoms but evidence of TB disease elsewhere in the body.⁴⁴

Sputum smear-negative, culture-positive TB disease is common among people with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.¹⁰¹ However, NAA tests have a higher sensitivity than smear, and the yield of sputum culture is not affected by HIV or the degree of immunodeficiency.^{44,102} Smear and culture of three sputum specimens is recommended based on a

large study in patients with HIV that showed a 10 percent incremental yield for broth culture between the second and third specimens.¹⁰³

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.¹⁰⁴ Histopathologic findings also are affected by the degree of immunodeficiency. Persons 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.⁸⁹

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if clinical evidence of involvement exists. The CDC Infectious Diseases Pathology Branch offers polymerase chain reaction (PCR) testing to aid with molecular identification of *M. tuberculosis* on both fresh and formalin-fixed tissue. Clinical providers and pathologists should first contact their state or local health department to refer specimens for evaluation. Health departments should then contact pathology@cdc.gov for consultation preapproval. The yield of mycobacterial urine and blood cultures depends on the clinical setting; among patients with advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high^{89,94} and may allow definitive diagnosis and be the only source of an isolate for drug-susceptibility testing (DST).¹⁰⁵

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 therapy and make decisions about the need for respiratory isolation.

NAA tests are more sensitive than AFB smear, being positive in 50 percent to 80 percent of smear-negative, culture-positive specimens^{106,107} and up to 90 percent when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, a NAA test be performed on at least one specimen.^{44,108} NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.⁴⁴

The Xpert MTB/RIFTM 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 patients with HIV.¹⁰⁹ 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 percent (95% confidence interval [CI], 83% to 92%) and 98 percent (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among people with HIV (pooled sensitivity of 80%; 95% CI, 67% to 88%) than among patients without HIV (pooled sensitivity of 89%; 95% CI, 81% to 94%);¹¹⁰ however, this may be, in part, attributed to a higher prevalence of smear-negative disease in people with HIV.¹¹¹ In South Africa, the sensitivity of Xpert MTB/RIF has been related to CD4 count, with higher sensitivity among patients with more advanced immunodeficiency.¹¹²

Xpert MTB/RIF sensitivity in extrapulmonary specimens is up to 95 percent in smear-positive specimens and 69 percent in smear-negative specimens.¹¹³ 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,¹¹⁴ which may provide an alternative for those people with HIV who are being evaluated for TB and unable to expectorate.

The next-generation 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. Currently, the Xpert platform is being modified to incorporate other drug-resistance targets that may assist in constructing a treatment regimen for drug-resistant TB, particularly in settings without access to conventional growth-based or sequencing-based DST (see Drug-Resistance Testing, below).¹¹⁵

Lipoarabinomannan (LAM)

LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of people with TB.¹¹⁶⁻¹¹⁹ LAM has been shown to be more sensitive and specific as an adjunct diagnostic test in people with HIV with advance immunosuppression, but LAM assays are not commercially available in the United States.

Drug-Resistance Testing

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 isoniazid and rifampin should be performed on the initial isolates from all patients suspected of having TB, because resistance to isoniazid or rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.¹²⁰

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 kanamycin, amikacin, or capreomycin) is associated with a markedly increased risk of death.¹²¹ 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*.⁴⁴

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. Molecular resistance testing should be performed, and DSTs should be repeated if sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive 1 month or

longer after culture conversion to negative. Resistance testing for second-line TB medications (fluoroquinolones, bedaquiline, linezolid, clofazimine, aminoglycosides, 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.¹⁰⁸

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,¹²² due to the slow growth of *M. tuberculosis*. During this time, patients 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.¹²¹ 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.¹²³ Commercial NAA tests—such as Xpert MTB/RIF—identify resistance mutations associated with rifampin, and commercially available line probe assays (LPAs) identify genotypic resistance for rifampin and isoniazid.^{111,124} Of note, 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 above 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 persons for drug-resistant TB (<https://www.cdc.gov/tb/topic/laboratory/default.htm>). 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 CDC's Division of TB Elimination Laboratory.

In low TB prevalence settings—such as the United States—the positive predictive value for NAA tests of rifampin resistance is low.¹²⁵ Therefore, isolates with an initial reading of rifampin resistance by commercial NAA test should undergo confirmatory testing (*rpoB* gene sequencing and phenotypic DST). 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

TB among persons 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**).

Preferred for Treatment, Including Duration of Therapy for People with HIV

Treatment of TB for people with HIV is the same as for individuals without HIV and should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide¹²⁶ (**AI**). The preferred regimens are indicated in the [table](#) at the end of this chapter. Recommended dosing for drugs is summarized in the following table.

Dosing Recommendations for Anti-TB Drugs for Treatment of Active Drug Sensitive TB

TB Drug	ARV Drugs	Daily Dose
Isoniazid	All ARVs	5 mg/kg (usual dose 300 mg)
Rifampin^{a,b} Note: DTG, RAL, and MVC doses need to be adjusted when used with rifampin.	HIV PIs, DOR, ETR, RPV, BIC, CAB, or EVG/c	Not recommended
	TAF	Use with caution ^c at dose indicated below.
	All other ARV drugs	10 mg/kg (usual dose 600 mg)
Rifabutin^a Note: DOR and RPV ^d doses need to be adjusted when used with rifabutin.	PI with COBI, TAF, RPV (IM), BIC, CAB, EVG/c-containing regimens	Not recommended
	DTG, RAL, DOR, EFV, or RPV (PO only ^d)	5 mg/kg (usual dose 300 mg)
	HIV PIs with RTV	150 mg daily ^e
	EFV	450–600 mg
Pyrazinamide	All ARVs	Weight-based dosing <ul style="list-style-type: none"> • <i>Weighing 40–55 kg:</i> 1,000 mg (18.2–25.0 mg/kg) • <i>Weighing 56–75 kg:</i> 1,500 mg (20.0–26.8 mg/kg) • <i>Weighing 76–90 kg:</i> 2,000 mg (22.2–26.3 mg/kg) • <i>Weighing >90 kg:</i> 2,000 mg^f
Ethambutol	All ARVs	Weight-based dosing <ul style="list-style-type: none"> • <i>Weighing 40–55 kg:</i> 800 mg (14.5–20.0 mg/kg) • <i>Weighing 56–75 kg:</i> 1,200 mg (16.0–21.4 mg/kg) • <i>Weighing 76–90 kg:</i> 1,600 mg (17.8–21.1 mg/kg) • <i>Weighing >90 kg:</i> 1,600 mg^f

^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 This combination has not been tested in patients to confirm pharmacokinetic and virologic efficacy among patients taking full-dose ARV and TB regimens.

^d IM long-acting RPV is not recommended with rifabutin. PO RPV can be used but the dose should be increased to 50 mg daily.

^e Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly, 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.

Key: ARV = antiretroviral; BIC = bictegravir; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; IM = intramuscular; MVC = maraviroc; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TB = tuberculosis

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.

DOT monitored by trained health care workers, who can be community-based or clinic-based, is recommended for all patients 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.¹²⁷⁻¹³⁰ 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 patients establish or re-engage with HIV care.

Drug-susceptible TB should be treated with a 2-month (8-week) intensive phase regimen 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**).¹²⁶

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.¹³¹⁻¹³⁹ Therefore, daily therapy given as DOT is recommended during both the intensive and continuation treatment phases (**AII**).^{126,137,138,140}

Although earlier recommendations¹⁴¹ for TB treatment in persons without HIV indicated that therapy should be based on the number of doses received rather than the duration of therapy, no data substantiate the minimum number of doses needed within a specified time interval in people with HIV.¹²⁶ Every effort should be made to ensure that patients receive daily therapy as previously described, allowing up to 28 weeks to complete ≥ 24 weeks (6 months) of treatment to accommodate brief interruptions of therapy for management of adverse drug reactions as described below.

The optimal duration of TB treatment for people with HIV and drug-susceptible TB disease is not known. In general, the outcomes of 6-month regimens given as DOT to people with HIV have been favorable.¹ A randomized but underpowered trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy.¹⁴²

Two trials in high-burden settings showed higher risk of recurrent TB among patients treated with 6 months of therapy than among those assigned to 9-month¹³¹ or 12-month regimens.¹⁴³ 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.

Treatment shortening for drug-susceptible TB remains a goal of current clinical trials. Three large international randomized trials of TB treatment shortening that used strategies involving substitution

of isoniazid, ethambutol, or both with a fluoroquinolone and/or rifapentine in 4-month regimens all found that the shorter regimens were inferior.¹⁴⁴⁻¹⁴⁶ In each study, the 4-month regimens were associated with higher relapse rates or unfavorable outcomes than a standard 6-month regimen. However, a recently reported trial demonstrated non-inferiority for a 4-month regimen of isoniazid, rifapentine, ethambutol, and moxifloxacin compared to a standard 6-month regimen in patients with and without HIV,¹⁴⁷ and that 4-month regimen may emerge as an acceptable alternative. Additional TB treatment shortening trials using alternative strategies in participants with HIV and TB coinfection are ongoing.

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**). Most extrapulmonary TB can be treated for 6 months, but TB meningitis should be treated for 9 to 12 months (**BII**).

Recent clinical trials have suggested the use of higher rifampin doses or addition of fluoroquinolone 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 pending results of additional studies.¹⁴⁸⁻¹⁵⁴

Adjunctive corticosteroid therapy is recommended in individuals with HIV who have TB involving the CNS (**AII**) and should include dexamethasone (0.3–0.4 mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week) for a total duration of 12 weeks.^{97,126} Adjunctive corticosteroid therapy increases survival overall for patients with TB meningitis, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV.^{97,155}

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.¹⁵⁶ A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a nonsignificant reduction in constrictive pericarditis. Notably, however, <20 percent of people with HIV in the trials analyzed were receiving ART.¹⁵⁷ No trials have been conducted comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations with Regard to Starting ART

The preponderance of data from randomized trials in people with HIV with TB disease supports the recommendation that ART should not be withheld until completion of TB treatment (**AI**).¹⁵⁸ Co-treatment of HIV and TB is complex due to adherence demands of multidrug therapy for two infections, drug–drug interactions between the rifamycins and many ARV drugs, overlapping side effect profiles of anti-TB and ARV drugs, and the risk of immune reconstitution inflammatory syndrome (IRIS), particularly with TB meningitis. However, concurrent treatment of HIV and TB for coinfecting patients in the appropriate clinical setting improved survival¹⁵⁸ (particularly for persons¹⁵⁹ with CD4 counts <50 cells/mm³); decreased the risk of additional opportunistic illnesses^{160,161}; and, despite higher rates of IRIS in those with low CD4 counts, was not associated with higher rates of ARV or anti-TB treatment limiting toxicity.¹⁶¹ Therefore, ART is recommended for all people with HIV with TB (**AI**). For ART-naïve patients, ART should be started within 2 weeks after TB

treatment initiation in those with CD4 count <50 cells/mm³ when TB meningitis is not suspected and within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts (**AI**). Rifamycin-associated drug interactions should be considered when selecting the ARV drug regimen.

The evidence supporting concurrent anti-TB therapy and ART comes primarily from four large, randomized trials. The Starting Antiretroviral Therapy at Three Points in Tuberculosis trial randomized 642 South African adults with CD4 counts <500 cells/mm³ and AFB smear-positive TB to start ART, either after the completion of the intensive phase of TB therapy or after TB treatment completion.¹⁵⁸ The study was stopped early, because integrated TB and ARV treatment decreased mortality by 56 percent compared to sequential treatment. Notably, a survival benefit was observed across the range of CD4 counts among patients enrolled, including within the stratum of baseline CD4 counts from 200 to 500/mm³.

In the Cambodian Early versus Late Introduction of Antiretrovirals trial, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 count of 25 cells/mm³ (interquartile range [IQR], 10, 56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The mortality rate was significantly lower in the early ART arm (8.28 per 100 person-years versus 13.77 per 100 person-years in the delayed ART arm; $P = 0.002$),¹⁶² and >95 percent of the study participants who survived had viral suppression. The ACTG A5221 STRIDE study and the TB-HAART trial, and additional multinational trials of early versus delayed ART in 809 and 1,538 people with HIV, respectively, demonstrated similar results; although in the TB-HAART trial, differences in mortality, adverse events, and incidence of IRIS did not reach statistical significance.

The optimal approach for initiation of ART in TB meningitis remains uncertain. A randomized trial among 253 patients with HIV-related TB meningitis conducted in Vietnam compared immediate ART (within 7 days of starting TB treatment) with delayed ART initiated 2 months after starting TB treatment.¹⁶³ Mortality was similar in both arms, and early ART was associated with more frequent and severe adverse events than delayed ART (86% vs. 75% of participants, respectively). The overall mortality rate in this study was very high (58%); most participants had advanced immunosuppression (median baseline CD4 count was 41 cells/mm³). Based upon this study, CDC/American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines recommend that patients with TB meningitis should not start ART before 8 weeks of TB treatment is completed, regardless of CD4 count,¹²⁶ but it is unclear whether the study's findings are generalizable to higher resourced settings. Many experts recommend that in people with HIV with TB meningitis, ART should be initiated within the first 2 to 8 weeks after starting anti-TB treatment, opting for the first 2 weeks in those with CD4 counts <50 cells/mm³ in settings where close monitoring of drug-related toxicities and CNS adverse events is feasible (**AIII**).

In summary, early ART initiation requires close collaboration between HIV and TB care clinics, expertise in management of ARV regimen selection, close monitoring, potential adjunctive corticosteroid therapy, and support and adherence services for patients. The prevention and management of IRIS is discussed in detail below (see TB-Associated IRIS, below).

When TB occurs in patients already on ART, treatment for TB must be started immediately (**AIII**), and ART should be modified to reduce the risk for 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

The rifamycin class of antibiotics is the key to effective and shorter-course treatment for drug-sensitive TB. However, the currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with several ARV drugs, and these interactions should be taken into consideration before initiating therapy (see [Dosing Recommendations for Anti-TB Drugs table](#), above, and the [Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines](#)). These drug–drug interactions are complex, but most result from the potent induction by the rifamycin of genes involved in the metabolism and transport of ARV agents. Although no clinical trials specifically compare rifampin- and rifabutin-containing anti-TB regimens among people with HIV with TB taking ART, in general, rifabutin is regarded as a reasonable substitute for rifampin for the treatment of TB in people with HIV who must concurrently receive antiretroviral drugs that have adverse drug interactions with rifamycins, because rifabutin is a less potent inducer of CYP3A4 than rifampin.^{164,165}

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 when used in preferred ART regimens. The newer tenofovir formulation, tenofovir alafenamide (TAF), is a substrate of drug transporters, including P-glycoprotein, and is more likely to have drug–drug interactions than TDF. A recent study conducted among healthy volunteers without HIV infection showed that concentrations of the active form of tenofovir, namely intracellular tenofovir-diphosphate, 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.¹⁶⁶ Caution is urged, however, because this combination has not been tested in patients to confirm PK and virologic efficacy among patients taking full-dose ARV and TB regimens. Neither TDF nor TAF has been fully evaluated with rifabutin, and TAF has not been evaluated with rifapentine; therefore, concurrent therapy with these drugs is not recommended (AIII).

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)—Efavirenz, Nevirapine, Etravirine, Doravirine, and Rilpivirine

One preferred 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). Efavirenz-based ART is associated with excellent TB and HIV treatment outcomes and has low rates of serious toxicity.¹⁶⁷ Recent studies in people with HIV with 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.¹⁶⁸⁻¹⁷⁰ A disadvantage of using a higher dose of efavirenz than the recommended 600 mg daily dose when co-administered with TB treatment is that slow metabolizers of efavirenz (about 20% of people of African, Thai, or Indian ancestry) who already have high efavirenz concentrations will have a further (approximately 50%) increase in efavirenz concentrations during TB treatment due to the inhibition by isoniazid of the accessory cytochrome P450 enzyme CYP2A6.¹⁷¹ Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,^{167,172} the 600 mg daily dose of efavirenz is recommended (AII).

Although still used in some international resource-limited settings, nevirapine is used rarely in high-resource settings and **is not recommended** in these settings for HIV and TB co-treatment.¹⁷³ The use of rifampin or rifapentine with doravirine, etravirine, or rilpivirine **is not recommended (AIII)** (see the [Dosing Recommendations for Anti-TB Drugs table](#), above, and the [Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines](#)).

Some experts might consider substitution of rifabutin for rifampin with appropriate dose adjustment of rifabutin or of the NNRTI (e.g., increasing doravirine dosing to 100 mg twice daily and increasing oral rilpivirine to 50 mg daily), where appropriate,^{174,175} for patients who require one of these NNRTIs;¹⁷⁶ however, IM rilpivirine is not recommended. 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

Alternatives to efavirenz-based ART for people with HIV with TB include regimens with integrase inhibitors or protease inhibitors (PIs). One alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 400 or 800 mg twice daily, with standard rifampin dosing (**BI**).¹⁷⁷ Raltegravir concentrations are decreased significantly when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.¹⁷⁸ The recommended dose of raltegravir is 800 mg twice daily if used with rifampin; this should be adjusted to standard raltegravir dosing after completion of TB treatment. 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 dose adjustment of either drug (**BII**).¹⁷⁹

Dolutegravir-based ART is also an alternative integrase inhibitor option. 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.¹⁸⁰ A Phase 2 trial in people with HIV with 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.¹⁸¹ Dolutegravir is recommended in a dose of 50 mg twice daily when used together with a rifampin-containing TB regimen (**AI**) and should be used in a standard 50 mg once-daily dose when used with rifabutin (**AII**). Bictegravir **should not be used** together with rifamycin-containing TB treatment (rifampin, rifabutin, or rifapentine) (**AI**). A recent trial conducted among healthy participants without HIV evaluated bictegravir concentrations when given twice daily together with rifampin versus once daily alone.¹⁸² Bictegravir trough concentrations, even with the dose adjustment, were reduced by 80 percent. Although studied only with rifabutin, based on similar concerns, elvitegravir/cobicistat **should not be used** together with TB treatment that contains rifamycins (**AI**).¹⁸³ When given at steady-state with oral cabotegravir, rifampin decreased cabotegravir AUC by 59% in healthy volunteers. 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 41-46%.¹⁸⁴ As a result, oral and long-acting injectable cabotegravir **should not be used** with any rifamycin (**AII**).¹⁸⁵

Protease Inhibitors with Rifampin or Rifabutin

Rifampin decreases the plasma concentrations and exposure of co-administered PIs by >75 percent.¹⁸⁶⁻¹⁸⁹ The effects of rifampin on lopinavir/ritonavir may be overcome by doubling the dose of lopinavir/ritonavir.^{188,190} High rates of hepatotoxicity were reported when dose-adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.¹⁹¹⁻¹⁹³ However, in people with HIV with TB, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampin-based TB treatment.¹⁹⁴ In a study in people with HIV with TB, the combination of double-dose lopinavir/ritonavir with rifampin resulted in acceptable safety, drug concentrations, and TB treatment response, although HIV suppression at 48 weeks was less than expected, unrelated to PK parameters.¹⁹⁴ Some experts would consider this an alternative when a PI-based ART regimen is required during TB treatment (**BI**). The strategy of increasing ritonavir dosing to 400 mg twice daily (known as “super-boosting”) may lead to higher rates of hepatotoxicity.^{190,195,196} Thus, a strategy of first increasing the dose of lopinavir/ritonavir by 50 percent, then increasing to a full double dose is recommended if this regimen is used (**BIII**). 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). A recent 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.¹⁹⁷ 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 **should not be used** together with rifampin, even with dose adjustment (**AI**).

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^{194,198} or atazanavir¹⁹⁹ and only moderately increases concentrations of ritonavir-boosted darunavir²⁰⁰ and fosamprenavir.²⁰¹ 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 to avoid dose-related toxicity, such as uveitis and neutropenia^{194,202} (**AI**).

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.^{203,204} Among people with HIV with TB, cases have been reported of acquired rifamycin resistance with 150 mg three times weekly doses of rifabutin when co-administered with a boosted PI-based ARV regimen.^{205,206} 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.¹⁹⁴ 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.

The breadth and magnitude of drug–drug interactions between the rifamycins and many ARV drugs can be daunting. Nevertheless, every effort should be made to include a rifamycin in the TB treatment regimen; the drug–drug interactions between rifamycins and ARV drugs should be managed, not avoided. Rifamycins remain the most potent drug class for TB treatment, and regimens that included only 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among patients with HIV-related TB.^{146,207} If a rifamycin cannot be used, TB treatment duration must be extended, and treatment complexity increases substantially. Thus, patients

with rifamycin-susceptible *M. tuberculosis* isolates should be treated with a regimen that does not contain a rifamycin only when the patient has had a serious adverse event that is highly likely due to a rifamycin (**AIII**).

Monitoring the Response to Therapy

Patients with pulmonary TB should have 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 by 2 months of first-line TB therapy, although sputum culture conversion to negative may take longer for patients with cavitary TB disease.²⁰⁸ Sputum cultures that do not convert to negative at or after 4 months of therapy indicate treatment failure and should prompt drug-resistance testing of any 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, 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.

Patients with suspected treatment failure should be evaluated with a medical history, physical exam, and chest radiograph to determine whether the patient has responded clinically to therapy, even though sputum culture conversion has not occurred. The initial culture results and drug-resistance tests, treatment regimen, and patient 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.^{126,209} 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 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

Many adverse drug reactions are shared between ARVs and drugs used for anti-TB therapy. Retrospective observational studies reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy,²¹⁰ but two recent randomized controlled trials of ART initiated during or after anti-TB therapy 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.^{158,161} However, 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 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.¹²⁶ Drug-induced liver injury (DILI) can be caused by isoniazid, rifamycins, pyrazinamide, many ARV drugs, and cotrimoxazole. 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) or ≥ 5 times the ULN in the absence of symptoms. An increase in ALT concentration occurs in approximately 5 percent to 30 percent of patients treated with the standard four-drug anti-TB regimen,^{86,211} but many of these patients only have transient, mild elevations of ALT.⁸⁶

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 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 should be started (e.g., ethambutol, linezolid, and moxifloxacin or levofloxacin)²¹² as a “bridging regimen” until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed (**BIII**).

After the patient’s ALT level returns to <2.5 times the ULN (or to near baseline for those with preexisting abnormalities), a 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, the patient’s ALT levels should be monitored frequently.

Rechallenge was successful in almost 90 percent of patients without HIV in one randomized controlled trial of different rechallenge regimens.²¹² 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,^{213,214} and some experts would therefore recommend rechallenge with pyrazinamide in patients 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 cotrimoxazole may be restarted.

Cutaneous adverse drug reactions may occur with all anti-TB drugs, notably rifampin and isoniazid²¹⁵; many ARV drugs, notably the NNRTIs; and cotrimoxazole. 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

cotrimoxazole 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 cotrimoxazole may be recommenced.

Managing Drug-Resistant TB

Although drug-resistant TB represents a small fraction of the TB cases in the United States, the increasing number of persons 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 first- and second-line TB medications must be used, but clinical trial data on their optimal use are limited, and most recent studies have been conducted primarily in high TB endemic resource-constrained settings.

In the United States, approximately 7 percent of patients with TB have baseline isoniazid mono-resistance.³ Growing evidence demonstrates that an increased risk of treatment failure associated with isoniazid monoresistance exists,²¹⁶ particularly in people with HIV with TB.²¹⁷ For patients with isoniazid monoresistance, it is recommended that a fluoroquinolone (levofloxacin or moxifloxacin) be substituted for isoniazid and given together with rifampin, pyrazinamide, and ethambutol for 6 months **(BII)**.^{83,218-220}

In late 2019, ATS, CDC, IDSA, and the European Respiratory Society (ERS) issued MDR TB treatment guidelines recommending a fully oral regimen for most patients with drug-resistant TB, including people with HIV.⁸³ Similar to the World Health Organization (WHO) drug-resistant TB guidelines,²²⁰ the ATS/CDC/IDSA/ERS guidelines ranked the second-line drugs and recommend an initial regimen containing bedaquiline, linezolid, levofloxacin/moxifloxacin, clofazimine, and cycloserine/terizidone. All remaining drugs were placed in a lower tier to complete the regimen only when the recommended drugs cannot be used. Notably, kanamycin and capreomycin are no longer recommended because an increased risk of treatment failure and relapse is seen with their use.²²¹ Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used.

For people with HIV with MDR TB, several important drug–drug interactions occur between bedaquiline and some ARV drugs. Specifically, efavirenz decreases bedaquiline plasma concentrations.²²² For people with HIV with MDR TB, efavirenz **should not be used** concurrently with bedaquiline **(AI)**. Lopinavir/ritonavir increases bedaquiline plasma concentrations approximately twofold when given at steady-state, but the clinical significance of this increase is not yet known.^{223,224}

Although the ATS/CDC/IDSA/ERS guidelines are largely concordant with the WHO guidelines, they recommend using a minimum of five active drugs (versus four) and a treatment duration of 15 to 24 months *after culture conversion* (compared with 18–20 months *total duration*).^{83,225} If possible, people with HIV with MDR TB should receive an all-oral regimen based on the ATS/CDC/IDSA/ERS guidelines **(AII)**. Although these current guidelines recommend a total duration of 15 to 24 months following sputum culture conversion, several clinical trials examining regimens with total durations as short as 6 to 12 months have shown TB treatment success rates comparable to or better than longer duration therapy when bedaquiline was included.²²⁵⁻²²⁸

Pretomanid, a novel oral antimycobacterial agent, was approved by the FDA in 2019 as part of a 6-month all-oral “BPaL” (bedaquiline, pretomanid, and linezolid) regimen. The study on which approval was based was a single-arm study in only 109 patients,²²⁷ of whom 51 percent were people with HIV. Although studies are underway to further evaluate this novel regimen in persons with MDR and XDR TB with and without HIV, data are insufficient to recommend the use of the BPaL regimen in individuals with or without HIV in high-resource settings like the United States, where full DST and individualized treatment options are available.

Treatment of MDR TB should involve an expert with experience in treating drug-resistant TB. If a local expert is not available through the public health department, clinicians and TB programs can contact 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’s driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.²²⁹⁻²³¹ 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.²³²

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB disease before starting ART. Typically, these patients 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,^{230,233} 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.^{230,234,235} In patients with disseminated TB, hepatic TB-IRIS is common, manifesting with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.^{231,236} A liver biopsy often reveals a granulomatous hepatitis.²³⁷ 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 recent meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18 percent in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2 percent of the cases.²³⁸ The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.²³⁹⁻²⁴⁴ The syndrome lasts for 2 to 3 months on average,^{243,245} 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.^{232,245,246} 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/mm³,^{242,247} high HIV viral load before ART^{248,249}; disseminated or extrapulmonary TB^{234,241,243,247}; 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.^{234,240,242} 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/mm³, to reduce the risk of HIV progression and death (AI).²³⁸

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).²⁵⁰

Managing Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many patients 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.²³⁴

In patients 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.²⁵¹ 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).²⁵¹ Patients on prednisone experienced more rapid symptom 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. The above study,²⁵¹ observational data,²³⁵ and clinical trials that showed reduced mortality in patients presenting with TB meningitis who were treated with corticosteroids⁹⁷ suggest that corticosteroids (either intravenous dexamethasone or oral prednisone) should be used when TB-IRIS involves the CNS (e.g., enlarging tuberculoma, new or recurrent meningeal inflammation) at the time of presentation. Rifampin increases the clearance of prednisolone (the active metabolite of prednisone),²⁵² but no such effect is seen with rifabutin; dosing of prednisone should therefore be adjusted in patients receiving rifampin or rifabutin-containing regimens (See the table below, [Recommendations for Treating *Mycobacterium tuberculosis* Infection and Disease](#)). Corticosteroids should be avoided in patients with Kaposi sarcoma because life-threatening exacerbations can occur. Case reports have been published of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.²⁵³⁻²⁵⁵

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-naïve 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.²⁵⁶ High-risk was defined as starting ART within 30 days after TB treatment initiation and a CD4 count ≤ 100 /mm³. Those with rifampin resistance,

neurological TB, Kaposi sarcoma, HBsAg positive, and poor clinical response to TB treatment before ART were excluded. The incidence of TB-IRIS was 47 percent in the placebo arm and 33 percent 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 $\leq 100/\text{mm}^3$) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (**BI**).

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in patients who have unrecognized TB (because TB is either oligo-symptomatic or it has eluded diagnosis) at the start of ART. These patients may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.²³² 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.^{232,251,257-259} Focal inflammatory manifestations—such as abscesses and lymphadenitis—also may develop.²⁶⁰ 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 no clinical trial evidence exists to support steroid use in this setting (**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.²⁶¹ 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.^{262,263} In settings with low rates of TB—such as the United States—recurrent TB due to re-infection is uncommon, even among patients with HIV.²⁶⁴

Several interventions may decrease the risk of recurrent TB among patients 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,^{265,266} suggesting that this intervention decreases the risk of re-infection. Post-treatment isoniazid **is not recommended** in low-burden settings—such as the United States—because of lack of evidence of effectiveness on reducing risk of re-infection for these settings (**AII**). 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

Pregnant people with HIV infection who do not have documentation of a prior negative TB screening test result or who are at high risk for repeated or ongoing exposure to individuals with active TB disease should be tested for TB during pregnancy (**AIII**). The frequency of anergy is not increased during pregnancy, and routine anergy testing in pregnant people with HIV is not recommended.²⁶⁷⁻²⁷⁰

Several studies have examined the performance of IGRAs for diagnosis of LTBI in pregnant women.^{271,272} In pregnant women with or without HIV, the test appears to perform well.²⁷³

A recent clinical trial of isoniazid preventive therapy (IPT) among HIV-infected women in high TB prevalence settings found increased adverse pregnancy outcomes in women treated with isoniazid during pregnancy compared to deferring this treatment until after delivery.²⁷⁴ 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. In the United States, IPT is recommended for pregnant women with HIV whose close household contacts include a person with active TB disease (**AI**). 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.^{275,276} However, the risk of progression from LTBI to active TB disease in individuals on ART is decreased significantly.²⁷⁷ Pregnant people with HIV should be receiving ART both for their own health and for prevention of perinatal transmission. For those receiving effective ART and without 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 if isoniazid is prescribed, frequent monitoring is needed.²⁷⁸ Pregnant people receiving isoniazid should receive daily pyridoxine supplementation (**AII**) because they are at risk of isoniazid-associated peripheral neuropathy.^{126,279} No data exist on alternatives to isoniazid for LTBI therapy in pregnant people with HIV. Although rifampin generally is considered safe in pregnancy, data on the use of rifapentine are extremely limited and its use in pregnant people is not recommended (**AIII**).²⁸⁰⁻²⁸²

The diagnostic evaluation for TB disease in pregnant people is the same as for nonpregnant adults. Chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure. 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 begins late in pregnancy.^{267-278,283-287} Congenital TB infection has been reported, although it appears relatively uncommon.²⁸⁸⁻²⁹²

Treatment of TB disease for pregnant people should be the same as for nonpregnant people, 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.²⁹³ 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^{294,295} have made recommendations for the routine use of pyrazinamide in pregnant individuals. Pyrazinamide has been recommended for use in pregnant people in the United States, although data characterizing its safety in this setting are limited and CDC guidance suggests that clinicians consider the use of this agent based on individual patient

considerations weighing benefit and risks.^{126,296} 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 for a pregnant person should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.

TB therapy should not be withheld because of pregnancy (**AIII**). Considering the information above, the preferred first-line treatment for drug-susceptible TB in pregnancy is isoniazid, rifampin, and ethambutol for a duration of 9 months. Experience using the majority of the second-line drugs for TB during pregnancy is limited.²⁹⁷⁻³⁰⁰ MDR TB in pregnancy should be managed in consultation with a specialist. The following concerns should be considered when selecting second-line anti-TB drugs for use in pregnant people:

- **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%; $P = 0.034$).³⁰¹ After 1 year, however, 88 percent of the children exposed to bedaquiline had gained weight and were doing well.
- **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.³⁰²⁻³⁰⁴ Case reports have documented cases of CNS defects in humans, but overall experience is limited with use during human pregnancy.³⁰⁵ 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 for pregnant people or 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.³⁰⁶⁻³⁰⁸ Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing (**CIII**).³⁰⁹
- **Para-aminosalicylic acid** is not teratogenic in rats or rabbits.²⁹⁶ 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.³¹⁰ 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 percent 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 percent 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 treatment of MDR TB (**CIII**).

Recommendations for Treating *Mycobacterium tuberculosis* Infection and Disease

Treating LTBI to Prevent TB Disease in People with HIV
<p>Indications</p> <ul style="list-style-type: none"> • Positive screening test^a for LTBI, 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, regardless of screening test result (AII) <p>Preferred Therapy</p> <ul style="list-style-type: none"> • Rifapentine (see weight-based dosing below) PO once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks (AI). Note: Rifapentine is recommended only for virally-suppressed patients receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen (AI). <ul style="list-style-type: none"> ○ Rifapentine Weekly Dose (maximum 900 mg) <ul style="list-style-type: none"> ▪ <i>Weighing 32.1–49.9 kg:</i> 750 mg ▪ <i>Weighing ≥50.0 kg:</i> 900 mg • Isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25–50 mg PO daily (AI) for 3 months. See the Dosing Recommendations for Anti-TB Drugs table for the list of ARV drugs not recommended for use with rifampin and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc). <p>Alternative Therapies</p> <ul style="list-style-type: none"> • Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6–9 months (AII) <i>or</i> • Rifampin 600 mg PO daily for 4 months (BI) See the Dosing Recommendations for Anti-TB Drugs table (above) for the list of ARV drugs not recommended for use with rifampin and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc) <i>or</i> • Isoniazid 300 mg PO daily plus rifapentine PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks (BI) Note: Rifapentine is recommended only for patients receiving an efavirenz-based ARV regimen (AI). <ul style="list-style-type: none"> ○ Rifapentine Daily Dose (maximum 600 mg) <ul style="list-style-type: none"> ▪ <i>Weighing <35 kg:</i> 300 mg ▪ <i>Weighing 35–45 kg:</i> 450 mg ▪ <i>Weighing >45 kg:</i> 600 mg <p>For persons exposed to drug-resistant TB, select drugs for prevention of TB after consultation with experts and with public health authorities (AIII).</p>
Treating Active TB Disease in People with HIV
<ul style="list-style-type: none"> • 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 Anti-TB Drugs table (above) for 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.
For Drug-Susceptible TB
<p>Intensive Phase (2 Months)</p> <ul style="list-style-type: none"> • Isoniazid plus (rifampin or rifabutin) plus pyrazinamide plus ethambutol (AI) • If drug susceptibility report shows sensitivity to isoniazid and rifampin, then ethambutol may be discontinued (AI).

<p>Continuation Phase (for Drug-Susceptible TB)</p> <ul style="list-style-type: none"> Isoniazid plus (rifampin or rifabutin) daily (AII) <p>Total Duration of Therapy</p> <ul style="list-style-type: none"> Pulmonary, drug-susceptible, uncomplicated TB: 6 months (BII) Pulmonary TB and positive culture at 2 months of TB treatment, severe cavitary disease or disseminated extrapulmonary TB: 9 months (BII) Extrapulmonary TB with CNS involvement: 9–12 months (BII) Extrapulmonary TB in other sites: 6 months (BII)
For Drug-Resistant TB
<p>Empiric Therapy for Resistance to Rifamycin Plus/Minus Resistance to Other Drugs</p> <ul style="list-style-type: none"> Isoniazid plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin) (BII) Therapy should be modified once rifampin resistance is confirmed and based on drug susceptibility results to provide ≥5 active drugs (BII). <p>Resistant to Isoniazid</p> <ul style="list-style-type: none"> (Moxifloxacin or levofloxacin) plus (rifampin or rifabutin) plus ethambutol plus pyrazinamide for 6 months (BII) <p>Resistant to Rifamycins Plus/Minus Other Antimycobacterial Agents</p> <ul style="list-style-type: none"> Therapy should be individualized based on drug susceptibility test results and clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists (AIII). <p>Duration</p> <ul style="list-style-type: none"> 12–24 months (see Management of Drug-Resistant TB section above for discussion of shorter-course therapy)
Other Considerations in TB Management
<ul style="list-style-type: none"> Adjunctive corticosteroid improves survival for patients with HIV-related TB involving the CNS (AI). 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. Despite the potential of drug–drug interactions, a rifamycin remains 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 Anti-TB Drugs table (above) 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 development of resistance in patients with HIV and is not recommended (AI). Paradoxical reaction that is not severe may be treated symptomatically (CIII). For moderately severe paradoxical reaction, use of corticosteroid may be considered. Taper over 4 weeks (or longer) based on clinical symptoms (BIII).
Examples of Prednisone Dosing Strategies for IRIS
<ul style="list-style-type: none"> In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg 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 A more gradual tapering schedule over a few months may be necessary in some patients. Preemptive prednisone regimen: 40 mg/day for 2 weeks then 20 mg/day for 2 weeks

^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: ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally

References

1. World Health Organization. Global tuberculosis report 2020. 2020. Available at: <https://www.who.int/publications/i/item/9789240013131>.
2. Dye C, Williams BG. Tuberculosis decline in populations affected by HIV: a retrospective study of 12 countries in the WHO African Region. *Bull World Health Organ*. 2019;97(6):405-414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31210678>.
3. Centers for Disease Control and Prevention. Reported Tuberculosis in the United States, 2019. 2019. Available at: <https://www.cdc.gov/tb/statistics/reports/2019/default.htm>
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. 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>.
7. 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>.
8. 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>.
9. 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>.
10. 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>.
11. 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>.
12. 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>.
13. 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>.
 14. Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR Recomm Rep*. 2000;49(RR-6):1-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10881762>.
 15. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med*. 2004;350(20):2060-2067. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15141044>.
 16. Day JH, Grant AD, Fielding KL, et al. Does tuberculosis increase HIV load? *J Infect Dis*. 2004;190(9):1677-1684. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15478075>.
 17. 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>.
 18. 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>.
 19. 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>.
 20. 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>.
 21. 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>.
 22. 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>.
 23. 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>.

24. 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>.
25. 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>.
26. 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>.
27. 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>.
28. 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>.
29. Pettit AC, Stout JE, Belknap R, et al. Optimal testing choice and diagnostic strategies for latent tuberculosis infection among U.S.-born people living with HIV. *Clin Infect Dis*. 2020:ciaa1135. Available at: <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1135/5881730>.
30. 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>.
31. 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>.
32. 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>.
33. 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>.

34. 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>.
35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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>.
40. 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>.
41. 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>.
42. 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>.
43. 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/>.
44. 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>.

45. 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>.
46. 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>.
47. 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>.
48. 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>.
49. 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>.
50. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of *M. tuberculosis* infection in HIV co-infected persons. *AIDS*. 2016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26990624>.
51. 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>.
52. 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>.
53. 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>.
54. 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>.
55. 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:

<http://www.croiconference.org/sessions/rifapentine-once-weekly-dosing-effect-efavirenz-emtricitabine-and-tenofovir-pks>.

56. 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>.
57. 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>.
58. 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>.
59. 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>.
60. 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>.
61. 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>.
62. 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>.
63. 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>.
64. 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/>.
65. 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>.

66. 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>.
67. 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>.
68. 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 Bein 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>.
69. 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>.
70. 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>.
71. 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>.
72. 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>.
73. 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 Bein 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>.
74. 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>.
75. 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>.
76. 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>.

77. 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>.
78. 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>.
79. 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>.
80. 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>.
81. 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>.
82. 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>.
83. 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>.
84. 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>.
85. 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>.
86. 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>.
87. 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>.

88. 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>.
89. 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>.
90. 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 Bein 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>.
91. 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:
92. 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>.
93. 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>.
94. 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>.
95. 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>.
96. 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>.
97. 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>.
98. 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>.

99. 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>.
100. 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>.
101. 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>.
102. 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>.
103. 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>.
104. 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>.
105. 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>.
106. 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>.
107. 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>.
108. 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>.
109. 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: http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf.
110. 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>.

111. 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>.
112. 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>.
113. 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>.
114. 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>.
115. 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>.
116. 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>.
117. 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>.
118. 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>.
119. Broger T, Moyoyeta M, Kerkhoff AD, Denking 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://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(19\)30684-X/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(19)30684-X/fulltext).
120. 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>.

121. 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>.
122. 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>.
123. 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>.
124. 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>.
125. 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>.
126. 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>.
127. 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>.
128. 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://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(18\)32993-3/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32993-3/fulltext).
129. 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>.
130. 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/publications/guidestoolkits/tbedottoolkit.htm>
131. 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>.

132. 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>.
133. 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>.
134. 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>.
135. 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>.
136. 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>.
137. 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>.
138. 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>.
139. 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>.
140. 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>.
141. 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>.
142. 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 Bein 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>.

143. 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>.
144. Merle CS, Fielding K, Sow OB, Gninafon M. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014. 2014;371:1588-1598. Available at: <https://www.nejm.org/doi/full/10.1056/nejmoa1315817>.
145. Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med*. 2014;371(17):1577-1587. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25196020>.
146. 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>.
147. 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/>.
148. 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>.
149. 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>.
150. 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>.
151. 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>.
152. 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>.
153. 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>.
154. Velasquez GE, Brooks MB, Coit JM, et al. Efficacy and safety of high-dose rifampin in pulmonary tuberculosis. a randomized controlled trial. *Am J Respir Crit Care Med*. 2018;198(5):657-666. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29954183>.

155. 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>.
156. 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>.
157. 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>.
158. 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>.
159. 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>.
160. 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>.
161. 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>.
162. 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>.
163. 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>.
164. 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>.
165. Singh R, Marshall N, Smith CJ, et al. No impact of rifamycin selection on tuberculosis treatment outcome in HIV coinfecting patients. *AIDS*. 2013;27(3):481-484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23014518>.
166. 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>.

167. 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>.
168. 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>.
169. 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>.
170. 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>.
171. McIlleron HM, Schomaker M, Ren Y, et al. Effects of rifampin-based antituberculosis therapy on plasma efavirenz concentrations in children vary by CYP2B6 genotype. *AIDS*. 2013;27(12):1933-1940. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24180002>.
172. 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>.
173. 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>.
174. 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>.
175. Janssen Therapeutics. Edurant [package insert]. 2021. Available at: <https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf>.
176. 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/>.
177. 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>.

178. 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>.
179. 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>.
180. 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>.
181. 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>.
182. 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: <http://www.croiconference.org/sessions/pharmacokinetics-bictegravir-administered-twice-daily-combination-rifampin>.
183. 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>.
184. 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>.
185. 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://www.ncbi.nlm.nih.gov/pubmed/28739783>.
186. 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/>.
187. 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/>.

188. 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>.
189. 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/>.
190. 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>.
191. Nijland HM, L'Homme R F, Rongen GA, et al. High incidence of adverse events in healthy volunteers receiving rifampicin and adjusted doses of lopinavir/ritonavir tablets. *AIDS*. 2008;22(8):931-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18453852>.
192. Haas DW, Koletar SL, Laughlin L, et al. Hepatotoxicity and gastrointestinal intolerance when healthy volunteers taking rifampin add twice-daily atazanavir and ritonavir. *J Acquir Immune Defic Syndr*. 2009;50(3):290-293. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19194314>.
193. Schmitt C, Riek M, Winters K, Schutz M, Grange S. Unexpected hepatotoxicity of rifampin and saquinavir/ritonavir in healthy male volunteers. *Arch Drug Inf*. 2009;2(1):8-16. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19381336>.
194. 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://www.ncbi.nlm.nih.gov/pubmed/34398956>.
195. Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlleron H. The safety, effectiveness and concentrations of adjusted lopinavir/ritonavir in HIV-infected adults on rifampicin-based antitubercular therapy. *PLoS One*. 2012;7(3):e32173. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22412856>.
196. Sunpath H, Winternheimer P, Cohen S, et al. Double-dose lopinavir-ritonavir in combination with rifampicin-based anti-tuberculosis treatment in South Africa. *Int J Tuberc Lung Dis*. 2014;18(6):689-693. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24903940>.
197. 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>.
198. Food and Drug Administration. Kaletra [package insert]. 2020. Available at: <https://www.rxabbvie.com/pdf/kaletratabpi.pdf>.

199. Bristol-Myers Squibb. Atazanavir [package insert]. 2018. Available at: https://packageinserts.bms.com/pi/pi_reyataz.pdf.
200. 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>.
201. 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>.
202. 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>.
203. 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>.
204. 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>.
205. 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>.
206. 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>.
207. 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>.
208. 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>.
209. 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>.

210. 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>.
211. 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>.
212. 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>.
213. 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>.
214. 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>.
215. 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>.
216. 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>.
217. 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>.
218. 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>.
219. 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>.
220. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. Available at: <https://www.who.int/publications/i/item/9789241550529>.
221. 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>.

222. 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 coinfecting with HIV and tuberculosis. *Antimicrob Agents Chemother.* 2013;57(6):2780-2787. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23571542>.
223. 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>.
224. 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>.
225. 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>.
226. 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>.
227. 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>.
228. Conradie F, Everitt D, Olugbosi M, et al. High rate of successful outcomes treating highly resistant TB in the ZeNix study of pretomanid, bedaquiline and alternative doses and durations of linezolid Type Presented at 11th IAS Conference on HIV Science; July 21, 2021, Year; Berline, Germany. Available at: https://theprogramme.ias2021.org/PAGMaterial/PPT/3261_4845/ZeNix_July_2021_IAS_Final.pdf.
229. 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>.
230. 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>.
231. 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>.
232. 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>.

233. 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>.
234. 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>.
235. 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>.
236. 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>.
237. 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>.
238. 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>.
239. 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>.
240. 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>.
241. 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>.
242. 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>.
243. 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>.

244. 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>.
245. 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>.
246. 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>.
247. 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>.
248. 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>.
249. 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>.
250. 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>.
251. 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>.
252. 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: <http://www.ncbi.nlm.nih.gov/pubmed/6403136>.
253. Brunel AS, Reynes J, Tuillon 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>.
254. 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>.
255. 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>.
256. 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>.
 257. 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>.
 258. 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>.
 259. 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>.
 260. 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>.
 261. 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>.
 262. 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>.
 263. 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>.
 264. 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>.
 265. 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>.
 266. 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>.
267. 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>.
 268. 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>.
 269. 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>.
 270. 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>.
 271. 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>.
 272. 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>.
 273. 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>.
 274. 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://www.nejm.org/doi/full/10.1056/NEJMoa1813060>.
 275. 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>.
 276. 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>.
 277. 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>.

278. Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. 2020. Available at: <https://www.cdc.gov/tb/publications/tbi/default.htm>
279. 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>.
280. 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>.
281. Food and Drug Administration. PRIFTIN (rifapentine). 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021024s009lbl.pdf.
282. 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>.
283. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *BJOG*. 2011;118(2):226-231. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21083862>.
284. 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>.
285. 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>.
286. 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>.
287. Efferen LS. Tuberculosis and pregnancy. *Curr Opin Pulm Med*. 2007;13(3):205-211. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17414128>.
288. 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>.
289. 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>.
290. 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>.
291. 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>.

292. 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>.
293. 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>.
294. Enarson D, Rieder H, Arnodottir T, Trebucq A. Management of tuberculosis: a guide for low income countries. Vol. 4th ed. Paris, France: International Union Against Tuberculosis and Lung Disease; 1996.
295. World Health Organization. Treatment of tuberculosis guidelines. 2010. Available at: https://apps.who.int/iris/bitstream/handle/10665/44165/9789241547833_eng.pdf.
296. Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberlostatic drugs. *Diss Pharm Pharmacol*. 1971;23:383-392. Available at.
297. Shin S, Guerra D, Rich M, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. *Clin Infect Dis*. 2003;36(8):996-1003. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12684912>.
298. 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>.
299. 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>.
300. Palacios E, Dallman R, Munoz M, et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. *Clin Infect Dis*. 2009;48(10):1413-1419. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19361302>.
301. 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://academic.oup.com/cid/article/72/7/1158/5788430>.
302. 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. Available at.
303. Takekoshi S. Effects of hydroxymethylpyrimidine on isoniazid- and ethionamide-induced teratosis. *Gunma J Med Sci*. 1965;14:233-244. Available at.
304. 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. Available at.

305. 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>.
306. 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>.
307. 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>.
308. 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>.
309. 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>.
310. 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>.

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 used to designate *Pneumocystis* pneumonia. 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.¹

Rodent studies and case clusters in immunosuppressed patients suggest that *Pneumocystis* spreads by the airborne route. Disease probably occurs by new acquisition of infection and by reactivation of latent infection.²⁻¹¹ Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of patients with AIDS;¹² the course of treated PCP was associated with a 20% to 40% mortality rate in individuals with profound immunosuppression. Approximately 90% of PCP cases occurred in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm³. Other factors associated with a higher risk of PCP in the pre-ART era included CD4 cell percentage <14%, previous episodes of PCP, oral thrush, recurrent bacterial pneumonia, unintentional weight loss, and higher plasma HIV RNA levels.^{13,14}

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; recent incidence among patients with AIDS in Western Europe and the United States is <1 case per 100 person-years.¹⁵⁻¹⁷ Most cases of PCP now occur in patients who are unaware of their HIV infection or are not receiving ongoing care for HIV,¹⁸ and in those with advanced immunosuppression (i.e., CD4 counts <100 cells/mm³).¹⁹

Clinical Manifestations

In patients 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 patients who do not have HIV is less common among patients with HIV.^{20,21}

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.²¹ Oral thrush is a common co infection. Fever is apparent in most cases and may be the predominant symptom in some patients. Extrapulmonary disease is rare but can occur in any organ and has been associated with use of aerosolized pentamidine prophylaxis.²²

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen [PO₂] ≥70 mm Hg or alveolar-arterial PO₂ gradient [A-a] DO₂ <35 mm Hg) to moderate ([A-a] DO₂ ≥35 to <45 mm Hg) to severe ([A-a] DO₂ ≥45 mm Hg). Oxygen desaturation with exercise is often abnormal but is non-specific.²³ Elevation of lactate dehydrogenase levels to >500 mg/dL is common but also non-specific.²⁴ The chest radiograph typically demonstrates diffuse, bilateral, symmetrical “ground-glass” interstitial infiltrates emanating from the hila in a butterfly pattern;²¹ however, in patients 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 patient with HIV infection should raise the suspicion of PCP.^{26,27} Cavitation and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancy, and their presence may indicate an alternative diagnosis or an additional pathology. In fact, approximately 13% to 18% of patients with documented PCP have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma, or bacterial pneumonia.^{28,29}

Thin-section computed tomography (CT) 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, while a normal CT has a high negative predictive value.^{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^{20,28,29,32} 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 the cystic and trophic forms of *P. jirovecii* but do not stain the cyst wall; Grocott-Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain the cyst wall. Some laboratories prefer direct immunofluorescent staining. 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. Previous 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.

Polymerase chain reaction (PCR) is an alternative method for diagnosing PCP. PCR is highly sensitive and specific for detecting *Pneumocystis*; however, PCR cannot reliably distinguish colonization from active disease, although higher organism loads as determined by quantitative PCR (Q-PCR) assays are likely to represent clinically significant disease.³³⁻³⁵ 1,3 β -D-glucan (β -glucan), which is a component of the cell wall of *Pneumocystis* cysts, is often elevated in patients with PCP. The sensitivity of the β -glucan assay for diagnosis of PCP appears to be high, thus PCP is less likely in patients 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,³⁶⁻³⁸ since many other fungal diseases, cellulose membranes used for hemodialysis, and some drugs can elevate β -glucan levels.

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 can be initiated before a definitive diagnosis is established because *P. jirovecii* persist in clinical specimens for days or weeks after effective therapy is initiated.³²

Preventing Exposure

Pneumocystis can be quantified in the air near patients with PCP,³⁹ and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients.^{5-11,40} Although these findings strongly suggest that isolating patients with known PCP from patients at high risk for PCP may be beneficial, there are insufficient data to support isolation as standard practice to prevent PCP (**III**).

Preventing Disease

Indication for Primary Prophylaxis

Adults and adolescents with HIV, including pregnant women and those on ART, with CD4 counts <200 cells/mm³ should receive chemoprophylaxis against PCP (**AI**).^{12,13,41} Persons who have a CD4 cell percentage <14% should also be considered for PCP prophylaxis (**BII**).^{12,13,41} If ART initiation must be delayed and frequent monitoring of CD4 counts (e.g., every 3 months) is impossible, some experts recommend starting PCP chemoprophylaxis at CD4 counts \geq 200 cells/mm³ to \leq 250 cells/mm³ (**BII**).¹³ Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (**AII**).⁴²

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent for PCP (**AI**).^{41,43-45} One double-strength TMP-SMX tablet daily is the preferred regimen (**AI**), but one single-strength tablet

daily⁴⁵ is also effective and may be better tolerated than the double-strength tablet (**AI**). One double-strength TMP-SMX tablet three times weekly also is effective (**BI**).⁴⁶ TMP-SMX at a dose of one double-strength tablet daily confers cross protection against toxoplasmosis⁴⁷ and many respiratory bacterial infections.^{43,48} Lower doses of TMP-SMX may also confer such protection, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable. TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in patients who have non life threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-institution of the drug should be considered after the reaction has resolved (**AII**). Therapy should be permanently discontinued (with no rechallenge) in patients 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 re-introduction of TMP-SMX if the dose is gradually increased according to published regimens (**BI**)^{49,50} or if the drug is given at a reduced dose or frequency (**CIII**). As many as 70% of patients can tolerate such re-institution of TMP-SMX therapy.⁴⁸

For patients who cannot tolerate TMP-SMX, alternative prophylactic regimens include dapsone (**BI**),⁴³ dapsone plus pyrimethamine plus leucovorin (**BI**),⁵¹⁻⁵³ aerosolized pentamidine administered with the Respirgard II nebulizer (manufactured by Marquest; Englewood, Colorado) (**BI**),⁴⁴ and atovaquone (**BI**).^{54,55} Atovaquone is as effective as aerosolized pentamidine⁵⁴ or dapsone⁵⁵ but substantially more expensive than the other regimens. For patients seropositive for *Toxoplasma gondii* who cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin (**BI**),⁵¹⁻⁵³ or atovaquone, with or without pyrimethamine, plus leucovorin (**CIII**).

The following regimens cannot be recommended as alternatives to TMP-SMX because data regarding their efficacy for PCP prophylaxis are insufficient:

- Aerosolized pentamidine administered by nebulization devices other than the Respirgard II nebulizer
- Intermittently administered parenteral pentamidine
- Oral clindamycin plus primaquine

Clinicians can consider using these agents, however, in situations in which TMP-SMX or the recommended alternative prophylactic regimens cannot be administered or are not tolerated (**CIII**).

Discontinuing Primary Prophylaxis

Primary *Pneumocystis* prophylaxis should be discontinued in adult and adolescent patients who have responded to ART with an increase in CD4 counts from <200 cells/mm³ to >200 cells/mm³ for >3 months (**AI**). In observational and randomized studies whose findings support this recommendation, most patients had CD4 counts >200 cells/mm³ for >3 months before discontinuing PCP prophylaxis.⁵⁶⁻⁶⁵ At discontinuation of prophylaxis, the median CD4 count was >300 cells/mm³, 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 months to 19 months.

Discontinuation of primary prophylaxis in patients with CD4 count increase to >200 cells/mm³ as a result of ART is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited;^{58,64} stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens. Prophylaxis should be reintroduced if the patient's CD4 count decreases to <200 cells/mm³ (**AIII**).

A combined analysis of European cohorts,^{16,66} a small randomized trial,⁶⁷ and a case series⁶⁸ found a low incidence of PCP in patients with CD4 counts between 100 cells/mm³ and 200 cells/mm³, who were receiving ART and had HIV plasma viral loads <50 to 400 copies/mL, and who had stopped or never received PCP prophylaxis, suggesting that primary and secondary PCP prophylaxis can be safely discontinued in patients with CD4 counts between 100 cells/mm³ to 200 cells/mm³ and HIV plasma RNA levels below limits of

detection of commercial assays. Data on which to base specific recommendations are inadequate, but one approach would be to stop primary prophylaxis in patients with CD4 counts of 100 cells/mm³ to 200 cells/mm³ if HIV plasma RNA levels remain below limits of detection for ≥ 3 months to 6 months (**BII**). Similar observations have been made with regard to stopping primary prophylaxis for *Toxoplasma* encephalitis.⁶⁹

Treating Disease

TMP-SMX is the treatment of choice for PCP (**AI**).^{70,71} Standard doses are summarized in the table; lower doses may also be effective, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable. 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. Adding leucovorin to prevent myelosuppression during acute treatment **is not recommended** because efficacy in preventing this toxicity is questionable and some evidence exists for a higher failure rate in preventing PCP (**AII**).⁷² Outpatient therapy with oral TMP-SMX is highly effective in patients with mild-to-moderate disease (**AI**).⁷¹

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.⁷³⁻⁷⁶ 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 PO₂ <70 mm Hg or PAO₂-PaO₂ ≥ 35 mm Hg, should receive adjunctive corticosteroids as soon as possible and certainly within 72 hours after starting specific PCP therapy (**AI**).⁷⁷⁻⁸² The benefits of starting steroids later are unclear, but most clinicians would administer them even after 72 hours for patients with moderate-to-severe disease (**BIII**). Intravenous (IV) methylprednisolone at 75% of the corresponding oral prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone and TMP (**BI**),^{71,83} which may have efficacy similar to TMP-SMX with fewer side effects, but is less convenient given the number of pills; clindamycin plus primaquine (**BI**)⁸⁴⁻⁸⁶ (clindamycin can be administered IV for more severe cases, but primaquine is only available in an oral formulation); and atovaquone suspension (**BI**),^{70,87} which is less effective than TMP-SMX for mild-to-moderate disease but has fewer side effects. Whenever possible, patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before primaquine or dapsone is administered.

Alternative therapeutic regimens for patients with moderate-to-severe disease include clindamycin-primaquine or IV pentamidine (**AI**).^{86,88,89} Some clinicians prefer clindamycin plus primaquine because this combination is more effective and less toxic than pentamidine.^{86,90-92}

Aerosolized pentamidine **should not be used** to treat PCP because it has limited efficacy and is associated with more frequent relapse (**AI**).^{88,93,94}

The recommended duration of therapy for PCP (irrespective of regimen) is 21 days (**AII**).²⁰ 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 overall the prognosis for patients with respiratory failure due to PCP is poor, over the past decades, survival for patients who require ICU care has improved as management of respiratory failure and HIV comorbidities has improved.⁹⁵⁻⁹⁸ Special attention is necessary regarding the use of ART in such critically ill patients.⁹⁹

Special Consideration with Regards to Starting ART (Including IRIS)

If not already started, ART should be initiated in patients, when possible, within 2 weeks of diagnosis of PCP (**AI**). In a randomized controlled trial of 282 patients 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 and 45 days after OI therapy initiation, respectively).¹⁰⁰ Of note, none of the participants with PCP enrolled in the study had respiratory failure requiring intubation;¹⁰⁰ initiating ART in such patients is problematic given the lack of parenteral preparations and unpredictable absorption of oral medications, as well as potential drug interactions with agents commonly used in the ICU.¹⁰¹

Paradoxical immune reconstitution inflammatory syndrome (IRIS) following an episode of PCP is rare but has been reported.^{102,103} Most cases occurred within weeks of the episode of PCP; 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 only rarely been life-threatening,¹⁰⁴ patients 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 patients 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 response to treatment 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 patients with HIV, rates of adverse reaction to TMP-SMX are high (20% to 85% of patients).^{70,71,83,85,89,105-109} 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), and hyperkalemia. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued (**AIII**). Rashes often can be “treated through” with antihistamines, nausea can be controlled with antiemetics, and fever can be managed with antipyretics.

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;^{71,83} azotemia, pancreatitis, hypoglycemia or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine;^{87-89,108} anemia, rash, fever, and diarrhea with primaquine and clindamycin;^{71,84,85} and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.^{70,107}

Managing Treatment Failure

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases after ≥ 4 days to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of patients with mild-to-moderate PCP disease. However, there are not any convincing clinical trial data on which to base recommendations for the management of PCP treatment failure due lack of drug efficacy.

Clinicians should wait ≥ 4 days 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 days 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 infections 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 the procedure was conducted before initiating therapy.

Treatment failure attributed to treatment-limiting toxicities occurs in up to one-third of patients.⁷¹ 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 or oral primaquine combined with IV clindamycin (**BII**).^{85,86,89} For mild disease, atovaquone is a reasonable alternative (**BII**). Although a meta-analysis, systematic review, and cohort study

concluded that the combination of clindamycin and primaquine might be the most effective regimen for salvage therapy,^{86,91,92} no prospective clinical trials have evaluated the optimal approach for patients who experience a therapy failure with TMP-SMX.

Preventing Recurrence

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)**.¹¹⁰ For patients who are intolerant of TMP-SMX, the alternatives are dapsone, dapsone plus pyrimethamine plus leucovorin, atovaquone, and aerosolized pentamidine.

When to Stop Secondary Prophylaxis

Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from <200 cells/mm³ to >200 cells/mm³ for >3 months as a result of ART **(AII)**. Reports from observational studies^{57,63,111,112} and from two randomized trials^{64,113} and a combined analysis of European cohorts being followed prospectively^{66,114} support this recommendation. In these studies, patients responded to ART with an increase in CD4 counts to ≥ 200 cells/mm³ for >3 months. At the time secondary PCP prophylaxis was discontinued, the median CD4 count was >300 cells/mm³ and most patients had a CD4 cell percentage $>14\%$. Most patients 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 patients with CD4 counts of 100 cells/mm³ to 200 cells/mm³ can potentially be discontinued if HIV plasma RNA levels remain below limits of detection for ≥ 3 months to 6 months **(BII)**.⁶⁶

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/mm³ **(AIII)** regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for patients with CD4 counts of 100 cells/mm³ to 200 cells/mm³ 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 patients with CD4 counts of 100 cells/mm³ to 200 cells/mm³ who have had HIV plasma RNA levels below limits of detection for ≥ 3 to 6 months **(BII)**.^{16,66}

If an episode of PCP occurs at a CD4 count >200 cells/mm³ 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 patients in whom PCP occurs at a CD4 count >200 cells/mm³ 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 During Pregnancy

PCP diagnostic considerations for pregnant women are the same as for women who are not pregnant.

Indications for PCP therapy are the same for pregnant women as for non-pregnant women. Some data suggest an increased risk of PCP-associated mortality in pregnancy, although there are no large, well-controlled studies evaluating the impact of pregnancy on PCP outcomes.¹¹⁵

The preferred initial therapy for PCP during pregnancy is TMP-SMX, although alternate therapies can be used if patients are unable to tolerate or are unresponsive to TMP-SMX **(AI)**.¹¹⁶ In case-control studies, trimethoprim has been associated with an increased risk of neural tube defects and cardiovascular, urinary tract, and multiple anomalies after first-trimester exposure.¹¹⁷⁻¹¹⁹ One small study reported an increased risk of birth defects in infants born to women receiving antiretrovirals and folate antagonists, primarily

trimethoprim; by contrast, no such increase was observed among infants exposed to either an antiretroviral or a folate antagonist alone.¹²⁰ Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, women in their first trimester with PCP still should be treated with TMP-SMX because of its considerable benefit **(AIII)**.

Although folic acid supplementation at 0.4 mg/day is routinely recommended for all pregnant women,¹²¹ 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 in women with HIV. Epidemiologic data suggest that folic acid supplementation may reduce the risk of congenital anomalies.^{118,119} 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 (odds ratio [OR] 1.24; 95% CI, 0.94–1.62).¹¹⁷ 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. On the basis of these findings, clinicians can consider giving supplemental folic acid (>0.4 mg/day routinely recommended) to women in their first trimester who are on TMP-SMX **(BIII)**. On the other hand, a randomized, controlled trial demonstrated that adding folinic acid to TMP-SMX treatment for PCP was associated with an increased risk of therapeutic failure and death.⁷² In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent folinic acid use.¹²² Therefore, if supplemental folic acid (>0.4 mg/day routinely recommended) is given, its use should be limited to the first trimester during the teratogenic window **(AIII)**. Whether a woman receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy **(BIII)**.

A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of mortality, specifically kernicterus, than infants who received oxytetracycline.¹²³ Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, although no published studies to date link late third-trimester exposure to either drug with neonatal death or kernicterus.

Adjunctive corticosteroid therapy should be used to improve the mother's treatment outcome as indicated in non-pregnant adults **(AIII)**.¹²⁴⁻¹²⁷ Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air PO₂ <70 mm Hg or PAO₂ - PaO₂ >35 mm Hg, should receive adjunctive corticosteroids as early as possible. A systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4 increased odds of delivering a baby with a cleft palate.¹²⁸ On the other hand, other large population-based studies have not found an association between maternal use of corticosteroids and congenital anomalies.^{129,130} Corticosteroid use in pregnancy may be associated with an increased risk of maternal hypertension, glucose intolerance or gestational diabetes, and infection.¹³¹ Maternal glucose levels should be monitored closely when corticosteroids are used in the third trimester because the risk of glucose intolerance is increased **(AIII)**. Moreover, women receiving 20 mg/day of prednisone (or its dosing equivalent for other exogenous corticosteroids) for >3 weeks may have hypothalamic-pituitary-adrenal (HPA) axis suppression and use of stress-dose corticosteroids during delivery should be considered **(BIII)**. HPA axis suppression is rarely seen among neonates born to women who received chronic corticosteroids during pregnancy.

Alternative therapeutic regimens for mild-to-moderate PCP disease include dapsone and TMP, primaquine plus clindamycin, atovaquone suspension, and IV pentamidine.

Dapsone appears to cross the placenta.^{132,133} For several decades, dapsone has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.^{133,134} 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.¹³⁵

Clindamycin, which appears to cross the placenta, is a Food and Drug Administration (FDA) Pregnancy Category B medication and is considered safe for use throughout pregnancy.

Primaquine generally is not used in pregnancy because of the risk of maternal hemolysis. As with dapsone, there is potential risk of hemolytic anemia in a primaquine-exposed fetus with G6PD deficiency. The degree of intravascular hemolysis appears to be associated with both dose of primaquine and severity of G6PD deficiency.¹³⁶

Data on atovaquone in human pregnancy are limited but preclinical studies have not demonstrated toxicity.¹³⁶

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.¹³⁷

All-cause pneumonia during pregnancy increases rates of preterm labor and delivery. Women at >20 weeks gestation who have with pneumonia should be closely monitored for evidence of contractions (**BIII**).

Chemoprophylaxis for PCP should be administered to pregnant women as for non-pregnant adults and adolescents (**AIII**). TMP-SMX is the recommended prophylactic agent. Given theoretical concerns about possible teratogenicity associated with first-trimester drug exposures, health care providers may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during the first-trimester (**CIII**) rather than withholding chemoprophylaxis.

Preconception Care

Clinicians who are providing pre-conception care for women with HIV receiving PCP prophylaxis can discuss with their patients the option of deferring pregnancy until PCP prophylaxis can be safely discontinued (i.e., CD4 cell count >200 cells/mm³ for 3 months) (**BIII**).

Recommendations for Preventing and Treating *Pneumocystis* Pneumonia

Preventing First Episode of PCP (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- CD4 count <200 cells/mm³ (**AI**) *or*
- CD4 percentage <14% of total lymphocyte count (**BII**) *or*
- CD4 count >200 cells/mm³, *but* <250 cells/mm³ if ART initiation must be delayed and if CD4 count monitoring (e.g., every 3 months) is not possible (**BII**).

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^a (**AI**) *or*
- TMP-SMX, 1 SS tablet PO daily^a (**AI**)

Alternative Therapy:

- TMP-SMX 1 DS tablet PO three times weekly (**BI**) *or*
- Dapsone^{b,c} 100 mg PO daily *or* dapsone 50 mg PO twice a day (**BI**) *or*
- Dapsone^b 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly (**BI**) *or*
- (Dapsone^b 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly (**BI**) *or*
- Aerosolized pentamidine^c 300 mg via Respigard II™ nebulizer every month (**BI**) *or*
- Atovaquone 1500 mg PO daily with food (**BI**) *or*
- (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily with food (**CIII**).

Indication for Discontinuing Primary Prophylaxis:

- CD4 count increased from <200 cells/mm³ to ≥200 cells/mm³ for ≥3 months in response to ART (**AI**)
- Can consider when CD4 count is 100–200 cells/mm³ and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months (**BII**)

Indication for Restarting Primary Prophylaxis:

- CD4 count <100 cells/mm³ regardless of HIV RNA (**AIII**)
- CD4 count 100–200 cells/mm³ and HIV RNA above detection limit of the assay used (**AIII**)

Treating PCP

Note: Patients who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (**BIII**).

For Moderate to Severe PCP: Total Duration of Treatment is 21 Days (**AII**)

Preferred Therapy:

- TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given every 6 or 8 hours (**AI**), may switch to PO formulations after clinical improvement (**AI**).

Alternative Therapy:

- 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**), *or*
- Primaquine^b 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**).

Note: Adjunctive corticosteroids are indicated in moderate to severe cases of PCP (see indications and dosage recommendations below).

For Mild to Moderate PCP: Total Duration of Treatment is 21 Days (**AII**)

Preferred Therapy:

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) PO (3 divided doses) (**AI**), *or*
- TMP-SMX 2 DS tablets PO three times daily (**AI**)

Alternative Therapy:

- Dapsone^b 100 mg PO daily plus TMP 15 mg/kg/day PO (3 divided doses) (**BI**) *or*
- Primaquine^b 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**)

Adjunctive Corticosteroids

For Moderate to Severe PCP Based on the Following Criteria (**AI**):

- PaO₂ <70 mmHg at room air *or*
- Alveolar-arterial DO₂ gradient ≥ 35 mmHg

Dosing Schedule:

- Prednisone doses (beginning as soon 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 given as 75% of prednisone dose.

Preventing Subsequent Episode of PCP (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**)

Alternative Therapy:

- TMP-SMX 1 DS tablet PO three times weekly (**BI**) *or*
- Dapsone^{b,c} 100 mg PO daily (**BI**) *or*
- Dapsone 50 mg PO twice daily (**BI**) *or*
- Dapsone^b 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly (**BI**) *or*
- (Dapsone^b 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly (**BI**) *or*
- Aerosolized pentamidine^c 300 mg via Respigard II™ nebulizer every month (**BI**) *or*
- Atovaquone 1500 mg PO daily with food (**BI**) *or*

- (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily with food **(CIII)**

Indications for Discontinuing Secondary Prophylaxis:

- CD4 count increased from <200 cells/mm³ to >200 cells/mm³ for >3 months as a result of ART **(BII)** or
- Can consider if CD4 count is 100–200 cells/mm³ and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months **(BII)**
- For patients in whom PCP occurs at a CD4 count >200 cells/mm³ 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 months 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/mm³ while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART **(BIII)**.

Indications for Restarting Secondary Prophylaxis:

- CD4 count <100 cells/mm³ regardless of HIV RNA **(AIII)**
- CD4 count 100–200 cells/mm³ and HIV RNA above detection limit of the assay used **(AIII)**.

Other Considerations/Comments:

- For patients 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, re-institution 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)**.
- Therapy should be permanently discontinued, with no rechallenge, in patients with suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis **(AIII)**.

^a TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; a lower dose also likely confers protection.

^b Whenever possible, patients should be tested for G6PD deficiency before administration of dapsone or primaquine. An alternative agent should be used if the patient is found to have G6PD deficiency.

^c Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in patients who are seropositive for *Toxoplasma gondii*.

Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenously; PCP = *Pneumocystis pneumonia*; PO = orally; SS = single strength; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. 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>.
2. 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>.
3. 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>.
4. 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>.
5. 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>.
6. 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>.
7. 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.

8. 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>.
9. 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>.
10. Schmoldt S, Schuegger 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>.
11. Yazaki H, Goto N, Uchida K, Kobayashi T, Gatanaga H, Oka S. Outbreak of *Pneumocystis jirovecii* pneumonia in renal transplant recipients: *P. jirovecii* is contagious to the susceptible host. *Transplantation*. 2009;88(3):380-385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19667941>.
12. 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>.
13. Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. *J Infect Dis*. 1998;178(4):1126-1132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9806044>.
14. Kaplan JE, Hanson DL, Jones JL, Dworkin MS. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. *AIDS*. 2001;15(14):1831-1836. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11579245>.
15. 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: <http://www.ncbi.nlm.nih.gov/pubmed/20502317>.
16. 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 jirovecii* 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>.
17. 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>.
18. 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>.
19. 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>.
20. 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>.
21. Selwyn PA, Pomerantz 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>.
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, et al. 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.
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. Torres J, Goldman M, Wheat LJ, et al. Diagnosis of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients with polymerase chain reaction: a blinded comparison to standard methods. *Clin Infect Dis*. 2000;30(1):141-145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10619742>.
34. Larsen HH, Masur H, Kovacs JA, et al. Development and evaluation of a quantitative, touch-down, real-time PCR assay for diagnosing *Pneumocystis carinii* pneumonia. *J Clin Microbiol*. 2002;40(2):490-494. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11825961>.
35. Larsen HH, Huang L, Kovacs JA, et al. A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of *Pneumocystis* pneumonia in HIV-infected patients. *J Infect Dis*. 2004;189(9):1679-1683. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15116305>.
36. Pisculli ML, Sax PE. Use of a serum beta-glucan assay for diagnosis of HIV-related *Pneumocystis jirovecii* 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>.
37. 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>.
38. 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>.
39. 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>.
40. Pliquet 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>.
41. 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>.
42. 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>.

43. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three anti*Pneumocystis* 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>.
44. Schneider MM, Hoepelman AI, Eeftink 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>.
45. 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>.
46. 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 Beinr 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>.
47. 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>.
48. 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>.
49. 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>.
50. 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>.
51. Podzamczar 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>.
52. 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>.
53. Girard PM, Landman R, Gaubert 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: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=8479488&query_hl=14&itool=pubmed_docsum.
54. 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>.
55. 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>.
56. 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>.
57. 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>.
58. 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>.
 59. 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>.
 60. 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>.
 61. 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>.
 62. 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>.
 63. 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>.
 64. 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>.
 65. 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>.
 66. 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.
 67. Chaiwarith R, Praparattanapan J, Nuntachit N, Kotarathitithum 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>.
 68. 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>.
 69. 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: CROI; 2016; Boston, Massachusetts. Available at: <http://www.croiconference.org/sessions/safety-stopping-primary-t-gondii-prophylaxis-suppressed-viremia-and-cd4100>.
 70. 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>.
 71. 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>.
 72. 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>.

73. 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>.
74. 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>.
75. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jirovecii* pneumonia. *Emerg Infect Dis*. 2004;10(??):1760-1765.
76. 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>.
77. 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>.
78. 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>.
79. 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>.
80. 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>.
81. 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>.
82. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for *Pneumocystis jirovecii* 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>.
83. 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>.
84. 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>.
85. 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>.
86. 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>.
87. 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>.
88. 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>.
89. 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>.
90. 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>.
 91. 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>.
 92. 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>.
 93. 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>.
 94. 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>.
 95. 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>.
 96. 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>.
 97. 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>.
 98. 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>.
 99. 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>.
 100. 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>.
 101. 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>.
 102. 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>.
 103. 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>.
 104. 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>.
 105. 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>.
 106. 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>.

107. 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>.
108. 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>.
109. 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>.
110. Masur H, Kaplan JE, Holmes KK, Service USPH, Infectious Diseases Society of A. 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>.
111. 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>.
112. 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>.
113. 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>.
114. 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>.
115. 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>.
116. Connelly RT, Lourwood DL. *Pneumocystis carinii* pneumonia prophylaxis during pregnancy. *Pharmacotherapy*. 1994;14(4):424-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7937279>.
117. 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>.
118. 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>.
119. 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>.
120. 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://www.ncbi.nlm.nih.gov/pubmed/11714944>.
121. 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>.
122. 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>.
123. 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>.

124. 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.
125. 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>.
126. 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>.
127. 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>.
128. 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>.
129. Czeizel AE, Rockenbauer M. Population-based case-control study of teratogenic potential of corticosteroids. *Teratology*. 1997;56(5):335-340. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9451758>.
130. Kallen B. Maternal drug use and infant cleft lip/palate with special reference to corticoids. *Cleft Palate Craniofac J*. 2003;40(6):624-628. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14577813.
131. 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>.
132. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. 1986;11(4):299-315. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3530584>.
133. 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>.
134. 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>.
135. 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>.
136. 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>.
137. 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>.

Progressive Multifocal Leukoencephalopathy/JC Virus Infection

Updated: October 19, 2022

Reviewed: January 11, 2023

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 asymptotically 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 natalizumab¹⁷ 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 AIDS²²⁻²⁴ 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/mm³, 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 perilesional 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 titers⁵² and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing⁵³ 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 (**AI**).

Treating Disease

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 (**AI**). 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/mm³ 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, cypheptadine, 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 PML⁸⁷ 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 inclusion 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

Diagnostic evaluation of PML should be the same in pregnant or nonpregnant individuals. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen.

Recommendations for Treating and Monitoring PML
Treatment
<p>The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART.</p> <ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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.

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 tonsillar 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 leukoencephalopathy. *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 zispradone], risperidone 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 leukoencephalopathy 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 Leukoencephalopathy 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, Korálník 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 leukoencephalopathy. *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 leukoencephalopathy 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 leukoencephalopathy? *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 (Last updated December 17, 2015; last reviewed January 11, 2023)

NOTE: Update in Progress

Epidemiology

Syphilis is associated with an increased risk of sexual acquisition and transmission of HIV.¹⁻⁵ In recent years, there has been a resurgence of the disease among men across the United States and in Western Europe (<http://www.cdc.gov/std/stats>).⁶⁻¹³ Although coexistent HIV infection (particularly in the advanced stages) may modify the diagnosis, natural history, or management of *Treponema pallidum* infection, the principles of syphilis management remain the same for persons with and without coexistent HIV infection.¹⁴⁻¹⁹

Clinical Manifestations

The effect of coexistent 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 persons with HIV and syphilis, the clinical manifestations of syphilis are similar to persons without HIV infection. There are some studies that suggest HIV infection may affect the clinical presentation of syphilis, as atypical genital lesions are more apparent, and accelerated progression of syphilis may be seen in persons with advanced immunosuppression.^{15,16,20,21} Primary or secondary syphilis also may cause a transient decrease in CD4 T lymphocyte (CD4) count and increase in HIV viral load that improves with recommended syphilis treatment regimens.^{19,22-25}

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 chancres occur and primary lesions may be absent or missed in persons with HIV infection.^{15,26} Progression to secondary syphilis typically follows 2 to 8 weeks after primary inoculation. The most common manifestations of secondary syphilis are mucocutaneous lesions that are macular, maculopapular, papulosquamous, or pustular, can involve the palms and soles, and are often accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache.^{16,17,19} Condyloma lata (moist, flat, papular lesions in warm intertriginous regions) can occur and may resemble condyloma accuminata 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.^{27,28} Manifestations of secondary syphilis involving other organs can occur (e.g., hepatitis, nephrotic syndrome, gastritis, pneumonia), however there is no evidence of increased frequency in persons with HIV infection. Constitutional symptoms, along with nonfocal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities such as lymphocytic pleocytosis with a mildly elevated CSF protein, can be seen in secondary syphilis and acute primary HIV infection.^{20,21,26,29-32} Signs and symptoms of secondary syphilis can persist from a few days to several weeks before resolving and evolving to latent stages.

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Tertiary syphilis includes cardiovascular syphilis and gummatous syphilis, a slowly progressive disease that can affect any organ system.

Neurosyphilis can occur at any stage of syphilis with different clinical presentations, including cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, acute or chronic change in mental status, and loss of vibration sense. Manifestations of neurosyphilis in persons with HIV infection are similar to those in individuals who do not have HIV infection. However, clinical manifestations of neurosyphilis, such as concomitant uveitis or meningitis, may be more common in persons with HIV infection.^{20,21,32-34} A recent clinical advisory has documented increased reports of ocular syphilis, a clinical manifestation of neurosyphilis that often occurs in during early syphilis.³⁵

Diagnosis

Darkfield microscopy and tests to detect *T. pallidum* in lesion exudates (e.g., DFA-TP) or tissue (e.g., biopsy with silver stain) are definitive for diagnosing early syphilis. 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*. A presumptive serologic diagnosis of syphilis is possible based upon non-treponemal tests (i.e., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]) and treponemal tests (i.e., fluorescent treponemal antibody absorbed [FTA-ABS], *T. pallidum* particle agglutination [TP-PA], enzyme immunoassays [EIAs], chemiluminescence immunoassays [CIA], immunoblots, and rapid treponemal assays).

Serologic diagnosis of syphilis traditionally has involved screening for non-treponemal antibodies with confirmation of reactive tests by treponemal-based assays.^{19,36} Some laboratories have initiated a testing algorithm using EIA or CIA as a screening test, followed by a reflex-quantitative, non-treponemal test if the EIA or CIA is positive. This latter strategy may identify those with previously treated syphilis infection, persons with untreated or incompletely treated syphilis, or those with a false positive result in persons with a low likelihood of infection.³⁷

In persons with a positive treponemal screening test and a negative reflex-quantitative, non-treponemal test, the laboratory should perform 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, persons with a history of previous treatment appropriate for the stage of syphilis will require no further treatment unless sexual risk history suggests likelihood of re-exposure. In this instance, a repeat non-treponemal 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 persons 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.^{19,38} Two studies demonstrated that high quantitative index values from treponemal EIA/CIA tests correlated with TP-PA positivity; however, the range of optical density values varies among different treponemal immunoassays, and the clinical significance of these findings warrant further investigation.^{39,40} If the risk of syphilis is high (e.g., high risk population or community with high prevalence), a repeat nontreponemal test in 2 to 4 weeks is recommended to evaluate for early infection. In the absence of neurologic signs or symptoms, risk of neurosyphilis is low in persons with a reactive treponemal test and a non-reactive, non-treponemal test;^{39,41} examination of CSF is not recommended.

Early-stage disease (i.e., primary, secondary, and early-latent syphilis) in persons with HIV infection is identified using the same diagnostic tests used in persons without HIV infection: darkfield microscopy of mucocutaneous lesions and standard serologic tests. Results with VDRL and RPR may be higher, lower (in rare instances), or delayed in persons with HIV infection with early-stage syphilis.⁴²⁻⁴⁶ No data indicate that treponemal tests perform differently among persons with HIV infection,⁴⁷ although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.^{45,46} Therefore, if serologic tests do not support the diagnosis of syphilis, presumptive treatment is recommended if syphilis is suspected and use of other tests should be considered (e.g., biopsy, darkfield examination, PCR of lesion material, exclusion of prozone phenomenon, repeat serology in 2–4 weeks).

By definition, persons with latent syphilis have serological evidence of syphilis (nontreponemal and treponemal testing) in the absence of clinical manifestations. Early latent syphilis is defined by evidence of infection during the preceding year by

1. A documented seroconversion or four-fold or greater increase in nontreponemal titer; or
2. Symptoms of primary or secondary syphilis; or
3. A sex partner with documented primary, secondary or early latent syphilis.¹⁹

Late latent syphilis is defined as syphilis in a person who does not have evidence of acquiring infection in the preceding year.

All persons with syphilis and signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, auditory or ophthalmic abnormalities, meningitis, stroke, altered mental status,) warrant

evaluation for neurosyphilis. An immediate ophthalmologic evaluation is recommended for persons with syphilis and ocular complaints, however a normal CSF evaluation can occur with ocular syphilis. Ocular syphilis should be managed according to the treatment recommendations for neurosyphilis, regardless of CSF results.

CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early stage syphilis⁴⁸ and in persons with HIV infection, even those with no neurologic symptoms. The clinical and prognostic significance of CSF laboratory abnormalities with early stage syphilis in persons without neurologic symptoms is unknown. Several studies have demonstrated that in persons with syphilis and HIV infection, CSF laboratory abnormalities are associated with CD4 counts ≤ 350 cells/mm³ or in combination with RPR titers $\geq 1:32$.^{31,32,49,50} However, unless neurologic signs and symptoms are present, a CSF examination has not been associated with improved clinical outcomes.

Laboratory testing is helpful in supporting the diagnosis of neurosyphilis; however, no single test can be used to diagnose neurosyphilis. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count or protein, and a CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. Cerebrospinal fluid (CSF) abnormalities are common in persons with early stage syphilis and are of unknown significance in the absence of neurologic signs or symptoms. CSF examination may indicate mononuclear pleocytosis (6–200 cells/mm³), mildly elevated protein concentration, or a reactive CSF-VDRL. Among persons with HIV infection, the CSF leukocyte count can be elevated (>5 white blood cell count [WBC]/mm³); using a higher cutoff (>20 WBC/mm³) might improve the specificity of neurosyphilis diagnosis.³¹ In persons with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood), is considered diagnostic of neurosyphilis. If the CSF-VDRL is negative, but serologic tests are reactive, CSF cell count or protein are abnormal, and clinical signs of neurologic involvement are present, treatment for neurosyphilis is recommended. If the neurologic signs and symptoms are nonspecific, additional evaluation using FTA-ABS testing on CSF can be considered. The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive; in the absence of specific neurological signs and symptoms, neurosyphilis is unlikely with a negative CSF FTA-ABS test.^{51,52} RPR tests on the CSF have been associated with a high false negative rate and are not recommended.⁵³ PCR-based diagnostic methods are not currently recommended as diagnostic tests for neurosyphilis.

Preventing Exposure and Disease

The resurgence of syphilis in men who have sex with men (MSM) with HIV infection in the United States 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 client-centered risk reduction messages and provide specific actions that can reduce the risk of acquiring sexually transmitted diseases and of transmitting HIV infection.^{19,54-58} Routine serologic screening for syphilis is recommended at least annually for all persons with HIV infection who are sexually active, with more frequent screening (i.e., every 3–6 months) for those who have multiple or anonymous partners.^{19,59-61} The occurrence of syphilis or any other sexually transmitted infection in a person with HIV infection 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 of referral for behavioral intervention.⁶² Patients undergoing screening or treatment for syphilis also should be evaluated for other sexually transmitted diseases such as chlamydia and gonorrhea at anatomic sites of exposure in men and for chlamydia, gonorrhea, and trichomonas in women.^{19,63}

Preventing Disease

Frequent serologic screening can identify persons recently infected and in some instances, before infectious lesions develop. Treatment can prevent disease progression in the individual and transmission to a partner. Studies in the pre-HIV era demonstrated that approximately one-third of the sex partners of persons who have primary syphilis will develop syphilis within 30 days of exposure, and empiric treatment of incubating

syphilis will prevent the development of disease in those who are exposed and onward syphilis transmission to their partners.⁶⁴⁻⁶⁷ Those who have had recent sexual contact with a person with syphilis in any stage should be evaluated clinically and serologically and treated presumptively with regimens outlined in current recommendations.

Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative (**AIII**). Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis more than 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. If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and stage of syphilis. Long-term sex partners of persons 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 infected persons considered at risk of infection should be notified of their exposure and the importance of evaluation.¹⁹ The following sex partners of persons 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 3 months plus the duration of symptoms for persons who receive a diagnosis of primary syphilis,
- Partners who have had sexual contact within 6 months plus duration of symptoms for those with secondary syphilis, and
- Partners who have had sexual contact within 1 year for persons with early latent syphilis.

Treating Disease

Treatment regimens for syphilis demonstrate that most persons with HIV infection respond appropriately to single dose benzathine penicillin for primary, secondary, and early latent syphilis.^{18,19,43} Closer follow-up is recommended, however, because serologic nonresponse and neurologic complications may be higher in persons with HIV infection.^{21,68,69}

Penicillin G remains the treatment of choice for syphilis. Persons with HIV infection with early-stage (e.g., primary, secondary, or early-latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million Units (U) of benzathine penicillin G (**AII**).¹⁹ The available data demonstrate that high-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.⁴³ Persons with a penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (**AIII**).

The efficacy of alternative non-penicillin regimens in persons with HIV infection 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. Several retrospective studies support use of doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis (**BII**).^{70,71} Limited clinical studies, mainly in persons without HIV infection suggest that ceftriaxone, 1 g daily either IM or intravenously (IV) for 10 to 14 days, is effective for treating early stage syphilis (**BII**), but the optimal dose and duration of therapy have not been defined.⁷² A single 2-g oral dose of azithromycin has been shown to be effective for treating early syphilis.⁷³⁻⁷⁵ However *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been reported most commonly in MSM.⁷⁶⁻⁸¹ Azithromycin treatment has not been well studied in persons with HIV infection with early stage syphilis and it should be used with caution in instances when treatment with penicillin or doxycycline is not feasible (**BII**). Azithromycin has not been studied in pregnant women. Therefore, azithromycin should not be used in MSM or in pregnant women (**AII**).

In persons with HIV infection who have late latent syphilis, treatment with 3 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 persons with HIV infection (**BIII**). Limited clinical studies and biologic and pharmacologic evidence suggest that ceftriaxone may be effective; however, the optimal dose and duration of therapy have not been determined.^{82,83} If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

Persons with HIV infection who have clinical evidence of tertiary syphilis (i.e., 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 3 weekly IM injections of 2.4 million U benzathine penicillin G (**AII**).¹⁹ However, the complexity of tertiary syphilis management, especially cardiovascular syphilis, is beyond the scope of these guidelines and health care providers are advised to consult an infectious disease specialist.

Persons with HIV infection diagnosed with neurosyphilis or ocular or otic syphilis should receive IV aqueous crystalline penicillin G, 18 to 24 million U daily, administered 3 to 4 million U IV every 4 hours or by continuous infusion for 10 to 14 days (**AII**) or procaine penicillin, 2.4 million U IM once daily plus probenecid 500 mg orally 4 times a day for 10 to 14 days (**BII**).^{19,31,32} Persons with HIV infection who are allergic to sulfa-containing medications should not be given probenecid because of potential allergic reaction (**AIII**). Although systemic steroids are used frequently as adjunctive therapy for otologic 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 U benzathine penicillin IM once per week for up to 3 weeks after completion of neurosyphilis treatment can be considered to provide a comparable duration of therapy (**CIII**).¹⁹ Desensitization to penicillin is the preferred approach to treating neurosyphilis in patients who are allergic to penicillin. However, limited data indicate that ceftriaxone (2 g daily IV for 10–14 days) may be an acceptable alternative regimen (**BII**).⁸³ Other alternative regimens for neurosyphilis have not been evaluated adequately. Syphilis treatment recommendations are also available in the 2015 Centers for Disease Control and Prevention Sexually Transmitted Disease Treatment Guidelines.¹⁹

Special Considerations with Regard to Starting Antiretroviral Therapy

There are no special considerations regarding the initiation of antiretroviral therapy (ART) in patients with syphilis. Specifically, there is currently no evidence that treatment with ART needs to be delayed until treatment for syphilis has been completed. Immune reconstitution inflammatory syndrome (IRIS) in association with syphilis and treatment with ART in persons with HIV infection is uncommon.⁸⁴

Monitoring and Adverse Events (Including IRIS)

Clinical and serologic responses (four-fold 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 seroconversion or a four-fold decline in nontreponemal titers within 12 to 24 months. Clinical and serologic responses to treatment are similar in persons with HIV infection; subtle variations can occur, however, including a slower temporal pattern of serologic response in persons with HIV infection.^{18,19,43,85} Factors associated with the serologic response to treatment in persons without HIV infection include younger age, earlier syphilis stage, and higher RPR titer.^{86,87} If clinical signs and symptoms persist, treatment failure should be considered. If clinical signs or symptoms recur or there is a sustained four-fold increase in non-treponemal titers of greater than 2 weeks, treatment failure or re-infection should be considered and managed per recommendations (see Managing Treatment Failure). The potential for re-infection should be based on the sexual history and risk assessment. Clinical trial data have demonstrated that 15% to 20% of persons (including persons with HIV infection) treated with recommended therapy for early stage syphilis will not achieve the four-fold decline in nontreponemal titer used to define treatment response at one year.^{19,43} Serum non-treponemal test titers may remain reactive at a stable level (serofast), usually $\leq 1:8$, although rarely may be higher, for prolonged periods. In addition, persons treated for early stage syphilis who have a four-fold decline in titer may not sero-revert to a negative nontreponemal test

and may remain serofast. These serofast states probably do not represent treatment failure.

Response to therapy for late latent syphilis should be monitored using non-treponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a four-fold decline in titer, if initially high ($\geq 1:32$), within 12 to 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Most persons with low titers and late latent syphilis remain serofast after treatment often without a four-fold decline in the initial titer. If clinical symptoms develop or a four-fold increase in non-treponemal titers is sustained, then treatment failure or re-infection should be considered and managed per recommendations (see Managing Treatment Failure). The potential for reinfection should be based on the sexual history and risk assessment.¹⁹

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF-VDRL may respond more slowly. If CSF pleocytosis was present initially, a CSF examination should be repeated at 6 months. Limited data suggest that changes in CSF parameters may occur more slowly in persons with HIV infection, especially with advanced immunosuppression.^{20,31} If the cell count has not decreased after 6 months or if the CSF WBC is not normal after 2 years, re-treatment should be considered. In persons on ART with neurosyphilis, declines in serum RPR titers after treatment correlate with normalization of CSF parameters.⁸⁸ Use of ART in persons with syphilis has also been associated with a reduced risk of serologic failure of syphilis treatment,²⁰ and a lower risk of developing neurosyphilis.²⁰

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache and myalgia 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 persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment.⁸⁹ Persons with syphilis should be warned about this reaction, instructed how to manage it, and informed it is not an allergic reaction to penicillin.

Managing Possible Treatment Failure or Re-infection

Re-treatment should be considered for persons with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease, or a sustained four-fold increase in serum non-treponemal titers after an initial four-fold 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. One study showed that 6% of MSM had a repeat early stage syphilis infection within 2 years of initial infection; HIV infection, Black race, and having multiple sexual partners were associated with increased risk of reinfection.¹⁰ 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. Person with HIV infection may be at increased risk of treatment failure, but the magnitude of these risks is not precisely defined and is likely low.^{19,30,69}

Persons who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur or a four-fold 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. Persons whose non-treponemal titers do not decrease four-fold with 12 to 24 months of therapy can also be managed as a possible treatment failure. Management includes a CSF examination and retreatment with benzathine penicillin G, 2.4 million U at 1-week intervals for 3 weeks (**BIII**), unless the CSF examination is consistent with CNS involvement. If titers do not respond appropriately after re-treatment, the value of repeated CSF examination or additional therapy is unclear, but it is generally not recommended. Treatment with benzathine penicillin, 2.4 million U IM without a CSF examination unless signs or symptoms of syphilis, and close clinical follow-up can be considered in persons with recurrent signs and symptoms of primary or secondary syphilis or a four-fold increase in non-treponemal titers within the past year who are at high risk of syphilis re-infection (**CIII**).

Persons 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 four-fold increase in serum non-treponemal test

titer and are low risk for infection; this can also be considered if they experience an inadequate serologic response (i.e., less than four-fold decline in an initially high $\geq 1:32$ non-treponemal test titer) within 12 to 24 months of therapy. If CSF examination is consistent with CNS involvement, re-treatment should follow the recommendations for treatment of neurosyphilis. Persons with a normal CSF examination should be treated with benzathine penicillin 2.4 million U IM weekly for 3 doses (**BIII**). As with early stage syphilis, the value of repeated CSF examination or additional therapy is unclear, but is generally not recommended. Treatment with benzathine penicillin 2.4 million U IM without a CSF examination unless signs or symptoms of neurosyphilis, and close clinical follow-up can be considered in persons with signs or symptoms of primary or secondary syphilis or a four-fold increase in non-treponemal titers within the past year who are at high risk of re-infection (**CIII**).

Re-treatment for neurosyphilis should be considered if the CSF cell count has not decreased 6 months after completion of treatment or if the CSF cell count or protein is not normal after 2 years.¹⁹

Preventing Recurrence

No recommendations indicate the need for secondary prophylaxis or prolonged chronic maintenance antimicrobial therapy for syphilis. Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.⁹⁰ Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in persons with HIV infection and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum*.^{76-78,80,81} A small pilot study has demonstrated that daily doxycycline prophylaxis was associated with a decreased incidence of syphilis among MSM with HIV infection.⁹¹

Special Considerations During Pregnancy

Pregnant women should be screened for syphilis at the first prenatal visit. In communities and populations in which the prevalence of syphilis is high and in women at high risk of infection, serologic testing should also be performed twice in the third trimester (ideally at 28–32 weeks gestation) and at delivery.¹⁹ Syphilis screening also should be offered at sites providing episodic care to pregnant women at high risk, including emergency departments, jails, and prisons.⁹² Antepartum screening with non-treponemal testing is typical but treponemal screening is being used in some settings. Pregnant women with reactive treponemal screening tests should have additional quantitative testing with non-treponemal tests because titers are essential for monitoring treatment response. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA/CIA tests should be confirmed with a quantitative, non-treponemal test (RPR or VDRL). If the non-treponemal test is negative and the prozone reaction is ruled out, then the results are discordant; a second treponemal test should be performed, preferably on the same specimen (see Diagnosis section above).⁹³

No mother or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at least once during pregnancy.⁹⁴ All women 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.⁹⁵⁻¹⁰⁰

Pregnant women with reactive syphilis serology should be considered infected 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 it $\geq 1:8$. Serofast low antibody titers after documented treatment for the stage of infection might not require additional treatment; however, rising or persistently high antibody titers may indicate reinfection or treatment failure, and treatment should be considered.¹⁹

Penicillin is recommended for the treatment of syphilis during pregnancy. Penicillin is the only known

effective antimicrobial for preventing maternal transmission to the fetus and for treatment of fetal infection; however evidence is insufficient to determine the optimal penicillin regimen.¹⁰¹ There is some evidence to suggest that additional therapy (a second dose of benzathine penicillin G, 2.4 million U IM administered 1 week after the initial dose) may be considered for pregnant women with early syphilis (primary, secondary, and early-latent syphilis) **(BII)**.^{19,102,103} Because of concerns about the efficacy of standard therapy in pregnant women who have HIV infection, a second injection in 1 week should also be considered for pregnant women with HIV infection **(BIII)**.

Since no alternatives to penicillin have been proven effective and safe for prevention of fetal infection, pregnant women who have a history of penicillin allergy should undergo desensitization and treatment with penicillin **(AIII)**.¹⁹ Erythromycin and azithromycin do not reliably cure maternal or fetal infection **(AII)**; tetracyclines should not be used during pregnancy because of concerns about hepatotoxicity and staining of fetal bones and teeth **(AII)**.^{98,104} Data are insufficient on use of ceftriaxone¹⁰⁵ for treatment of maternal infection and prevention of congenital syphilis **(BIII)**.

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if it is associated with a Jarisch-Herxheimer reaction.¹⁰⁶ Pregnant women should be advised to seek obstetric attention after treatment if they notice contractions or a decrease in fetal movement. 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 indicate a greater risk of fetal treatment failure.¹⁰⁷ 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.

At a minimum, repeat serologic titers should be performed in the third trimester and at delivery for women treated for syphilis during pregnancy, appropriate for the stage of infection. Data are insufficient on the non-treponemal serologic response to syphilis after stage-appropriate therapy in pregnant women with HIV infection. Non-treponemal titers can be assessed monthly in women at high risk of re-infection. Clinical and non-treponemal antibody titer responses should be appropriate for the stage of disease, although most women will deliver before their serologic response can be definitively assessed. Maternal treatment is likely to be inadequate if delivery occurs within 30 days of therapy, if a woman has clinical signs of infection at delivery, or if the maternal antibody titer is four-fold higher than the pre-treatment titer.¹⁹ The medical provider caring for the newborn should be informed of the mother's serologic and treatment status so that proper evaluation and treatment of the infant can be provided.

Recommendations for Treating *Treponema pallidum* Infections (Syphilis) to Prevent Disease (page 1 of 2)

Empiric treatment of incubating syphilis is recommended to prevent the development of disease in those who are sexually exposed.

Indication for Treatment:

- Persons who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis within 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AIII)**.
- Persons 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)**.

Treatment:

- Same as for early stage syphilis listed below

General Considerations for Treating Syphilis:

- The efficacy of non-penicillin alternatives has not been well evaluated in persons with HIV infection and should be undertaken only with close clinical and serologic monitoring.
- The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgias that can occur within the first 24 hours after therapy. It occurs more frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment. Patients should be warned about this reaction and informed it is not an allergic reaction to penicillin.

Treatment Recommendations Depending on Stage of Disease

Early Stage (Primary, Secondary, and Early-Latent Syphilis)

Preferred Therapy:

- Benzathine penicillin G 2.4 million U IM for 1 dose (**All**)

Alternative Therapy (For Penicillin-Allergic Patients):

- Doxycycline 100 mg PO BID for 14 days (**BII**), or
- Ceftriaxone 1 g IM or IV daily for 10–14 days (**BII**), or
- Azithromycin 2 g PO for 1 dose (**BII**)

Note: Chromosomal mutations associated with azithromycin resistance and treatment failures have been reported, most commonly in MSM. Azithromycin should be used with caution and only when treatment with penicillin, doxycycline or ceftriaxone is not feasible. Azithromycin **is not recommended** for MSM or pregnant women (**All**)

Note: Persons with penicillin allergy whose compliance or follow-up cannot be ensured and all pregnant women with penicillin allergy should be desensitized and treated with benzathine penicillin.

For pregnant women with early syphilis, a second dose of benzathine penicillin G 2.4 million units IM after one week the single dose treatment may be considered (**BII**).

Late-Latent (>1 year) or Latent of Unknown Duration

Preferred Therapy:

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses (**All**)

Alternative Therapy (For Penicillin-Allergic Patients):

- Doxycycline 100 mg PO BID for 28 days (**BIII**)

Note: Persons with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin

Late-Stage (Tertiary—Cardiovascular or Gummatous Disease)

- Perform CSF examination to rule out neurosyphilis and obtain infectious diseases consultation to guide management

Preferred Therapy:

- Benzathine penicillin G 2.4 million U IM weekly for 3 doses (**All**)

Neurosyphilis, Otic, or Ocular Disease

Preferred Therapy:

- Aqueous crystalline penicillin G, 18–24 million U per day, administered as 3–4 million U IV q4h or by continuous IV infusion for 10–14 days (**All**) +/- benzathine penicillin G 2.4 million U IM weekly for 1 to 3 doses after completion of IV therapy (**CIII**)

Alternative Therapy:

- Procaine penicillin G 2.4 million U IM daily plus probenecid 500 mg PO QID for 10–14 days (**BII**) +/- benzathine penicillin G 2.4 million U IM weekly for up to 3 doses after completion of above (**CIII**)
- Persons who are allergic to sulfa-containing medications **should not** be given probenecid, thus the procaine penicillin regimen is not recommended (**All**).

For Penicillin-Allergic Patients:

- Desensitization to penicillin is the preferred approach; if not feasible, ceftriaxone 2 g IM or IV daily for 10–14 days (**BII**)

Key to Acronyms: BID = twice a day; CSF = cerebrospinal fluid; IM = intramuscular; IV = intravenously; MSM = men who have sex with men; PO = orally; QID = four times a day; q(n)h = every “n” hours; U = Units

References

1. 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.* Feb 1999;75(1):3-17. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10448335>.
2. 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.* Oct 2001;28(10):579-597. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11689757>.
3. 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.* Mar-Apr 2014;129(2):164-169. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24587551>.
4. 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.* Oct 2014;59(7):1020-1026. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24928295>.
5. Patton ME, Su JR, Nelson R, Weinstock H, Centers for Disease C, Prevention. Primary and secondary syphilis—United States, 2005–2013. *MMWR Morb Mortal Wkly Rep.* May 9 2014;63(18):402-406. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24807239>.
6. Chesson HW, Sternberg M, Leichliter JS, Aral SO. Changes in the state-level distribution of primary and secondary syphilis in the USA, 1985–2007. *Sex Transm Infect.* Dec 2010;86 Suppl 3:iii58-62. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20929854>.
7. Torrone EA, Bertolli J, Li J, et al. Increased HIV and primary and secondary syphilis diagnoses among young men—United States, 2004–2008. *J Acquir Immune Defic Syndr.* Nov 1 2011;58(3):328-335. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21826012>.
8. Kerani RP, Handsfield HH, Stenger MS, et al. Rising rates of syphilis in the era of syphilis elimination. *Sex Transm Dis.* Mar 2007;34(3):154-161. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17179773>.
9. Buchacz K, Klausner JD, Kerndt PR, et al. HIV incidence among men diagnosed with early syphilis in Atlanta, San Francisco, and Los Angeles, 2004 to 2005. *J Acquir Immune Defic Syndr.* Feb 1 2008;47(2):234-240. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18340654>.
10. 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.* Jan 2012;102(1):e1-8. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22095364>.
11. Centers for Disease Control and Prevention. Notes from the field: repeat syphilis infection and HIV coinfection among men who have sex with men—Baltimore, Maryland, 2010–2011. *MMWR Morb Mortal Wkly Rep.* Aug 16 2013;62(32):649-650. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23945772>.
12. Centers for Disease Control and Prevention. 2012 Sexually Transmitted Disease Surveillance. 2013. Available at <http://www.cdc.gov/std/stats12/>. Accessed January 7, 2015.
13. Centers for Disease Control and Prevention. Outbreak of syphilis among men who have sex with men—Southern California, 2000. *MMWR Morb Mortal Wkly Rep.* Feb 23 2001;50(7):117-120. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11393490>.
14. 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.* Oct 2002;14(5):533-534. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12462435>.
15. 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.* Aug 2001;28(8):448-454. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11473216>.
16. 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.* Dec 1 1990;113(11):872-881. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2240901>.
17. 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.* Feb 1988;18(2 Pt 2):423-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2963840>.

18. Ghanem KG, Workowski KA. Management of adult syphilis. *Clin Infect Dis*. Dec 2011;53 Suppl 3:S110-128. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22080265>.
19. Workowski KA, Bolan GA, with the Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep*. Jun 5 2015;64(RR-03):1-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26042815>.
20. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. Jun 19 2008;22(10):1145-1151. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18525260>.
21. 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*. Jun 29 2007;56(25):625-628. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17597693>.
22. 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*. Oct 21 2004;18(15):2075-2079. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15577629>.
23. Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infect Dis*. Jul 2010;10(7):455-463. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20610327>.
24. 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*. Mar 1 2007;44(3):356-359. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17159654>.
25. 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*. Mar 2006;33(3):143-148. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16505739>.
26. 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*. Mar 2001;28(3):158-165. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11289198>.
27. Wang H, Wang X, Li S. A case of lues maligna in an AIDS patient. *Int J STD AIDS*. Aug 2012;23(8):599-600. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22930302>.
28. 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*. Aug 2009;36(8):512-514. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19455078>.
29. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis. Its occurrence after clinical and serologic cure of secondary syphilis with penicillin G. *Arch Neurol*. Feb 1986;43(2):137-138. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3947251>.
30. 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*. Jun 18 1987;316(25):1587-1589. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3587291>.
31. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. Feb 1 2004;189(3):369-376. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14745693>.
32. Marra CM, Maxwell CL, Tantalos L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? *Clin Infect Dis*. Apr 1 2004;38(7):1001-1006. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15034833>.
33. Biotti D, Bidot S, Mahy S, et al. Ocular syphilis and HIV infection. *Sex Transm Dis*. Jan 2010;37(1):41-43. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20118676>.
34. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. *Sex Transm Infect*. Feb 2011;87(1):4-8. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20798396>.
35. 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 <http://www.ncbi.nlm.nih.gov/pubmed/26469141>.
36. Wicher K, Horowitz HW, Wicher V. Laboratory methods of diagnosis of syphilis for the beginning of the third millennium. *Microbes Infect*. Oct 1999;1(12):1035-1049. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10617935>.

37. Centers for Disease C, Prevention. Discordant results from reverse sequence syphilis screening--five laboratories, United States, 2006-2010. *MMWR Morb Mortal Wkly Rep*. Feb 11 2011;60(5):133-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21307823>.
38. Centers for Disease C, Prevention. Syphilis testing algorithms using treponemal tests for initial screening--four laboratories, New York City, 2005-2006. *MMWR Morb Mortal Wkly Rep*. Aug 15 2008;57(32):872-875. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18701877>.
39. 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*. Nov 2011;204(9):1297-1304. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21930610>.
40. 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*. Jun 2011;38(6):528-532. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21233789>.
41. 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 <http://www.ncbi.nlm.nih.gov/pubmed/16874420>.
42. 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*. Jun 1992;165(6):1124-1126. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1583332>.
43. 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*. Jul 31 1997;337(5):307-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9235493>.
44. 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*. Dec 1994;19(6):1040-1044. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7888531>.
45. 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*. Oct 1987;107(4):492-495. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3307583>.
46. Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfecting with human immunodeficiency virus. *Arch Dermatol*. Apr 2005;141(4):431-433. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15837859>.
47. Augenbraun M, Rolfs R, Johnson R, Joesoef R, Pope V. Treponemal specific tests for the serodiagnosis of syphilis. Syphilis and HIV Study Group. *Sex Transm Dis*. Nov 1998;25(10):549-552. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9858352>.
48. 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*. Dec 1 1988;109(11):855-862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3056164>.
49. Libois A, De Wit S, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. *Sex Transm Dis*. Mar 2007;34(3):141-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16865051>.
50. 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.
51. Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B, Schroeter AL. Tests for treponemal antibody in CSF. *Arch Intern Med*. Feb 1978;138(2):252-255. Available at <http://www.ncbi.nlm.nih.gov/pubmed/343742>.
52. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. *Sex Transm Dis*. Apr 2012;39(4):291-297. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22421696>.
53. 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*. Jun 2012;39(6):453-457. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22592831>.
54. Rietmeijer CA. Risk reduction counselling for prevention of sexually transmitted infections: how it works and how to make it work. *Sex Transm Infect*. Feb 2007;83(1):2-9. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17283359>.
55. Force USPST. Behavioral counseling to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. Oct 7 2008;149(7):491-496, W495. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18701877>.

56. 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*. Oct 7 1998;280(13):1161-1167. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9777816>.
57. Richardson JL, Milam J, Stoyanoff S, et al. Using patient risk indicators to plan prevention strategies in the clinical care setting. *J Acquir Immune Defic Syndr*. Oct 1 2004;37 Suppl 2:S88-94. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15385904>.
58. Fisher JD, Cornman DH, Osborn CY, Amico KR, Fisher WA, Friedland GA. Clinician-initiated HIV risk reduction intervention for HIV-positive persons: Formative Research, Acceptability, and Fidelity of the Options Project. *J Acquir Immune Defic Syndr*. Oct 1 2004;37 Suppl 2:S78-87. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15385903>.
59. Branger J, van der Meer JT, van Ketel RJ, Jurriaans S, Prins JM. High incidence of asymptomatic syphilis in HIV-infected MSM justifies routine screening. *Sex Transm Dis*. Feb 2009;36(2):84-85. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18971797>.
60. Aberg JA, Gallant JE, Ghanem KG, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. Jan 2014;58(1):1-10. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24343580>.
61. Centers for Disease C, Prevention, Health R, et al. Recommendations for incorporating human immunodeficiency virus (HIV) prevention into the medical care of persons living with HIV. *Clin Infect Dis*. Jan 1 2004;38(1):104-121. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14679456>.
62. Guy R, El-Hayek C, Fairley CK, et al. Opt-out and opt-in testing increases syphilis screening of HIV-positive men who have sex with men in Australia. *PLoS One*. 2013;8(8):e71436. Available at <http://www.ncbi.nlm.nih.gov/pubmed/24009661>.
63. Centers for Disease C, Prevention. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. *MMWR Recomm Rep*. Nov 7 2008;57(RR-9):1-83; quiz CE81-84. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18987617>.
64. Moore MB, Jr., Price EV, Knox JM, Elgin LW. Epidemiologic Treatment of Contacts to Infectious Syphilis. *Public Health Rep*. Nov 1963;78:966-970. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14084872>.
65. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *JAMA*. Nov 1 1971;218(5):711-713. Available at <http://www.ncbi.nlm.nih.gov/pubmed/5171497>.
66. Schober PC, Gabriel G, White P, Felton WF, Thin RN. How infectious is syphilis? *Br J Vener Dis*. Aug 1983;59(4):217-219. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6871650>.
67. Hook EW, 3rd, Marra CM. Acquired syphilis in adults. *N Engl J Med*. Apr 16 1992;326(16):1060-1069. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1549153>.
68. 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*. Jul 1995;99(1):55-63. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7598143>.
69. Walter T, Lebouche B, Mialhes 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*. Sep 15 2006;43(6):787-790. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16912958>.
70. Ghanem KG, Erbeling EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. Mar 15 2006;42(6):e45-49. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16477545>.
71. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. *Am J Med*. Oct 2008;121(10):903-908. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18823862>.
72. Hook EW, 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. *J Infect Dis*. Oct 1988;158(4):881-884. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3171231>.
73. Kiddugavu MG, Kiwanuka N, Wawer MJ, et al. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis*. Jan 2005;32(1):1-6. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15614114>.
74. 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*. Sep 22 2005;353(12):1236-1244. Available at <http://www.ncbi.nlm.nih.gov/>

pubmed/16177249.

75. 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*. Jun 1 2010;201(11):1729-1735. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20402591>.
76. Centers for Disease C, Prevention. Azithromycin treatment failures in syphilis infections--San Francisco, California, 2002-2003. *MMWR Morb Mortal Wkly Rep*. Mar 12 2004;53(9):197-198. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15017376>.
77. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med*. Jul 8 2004;351(2):154-158. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15247355>.
78. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000-2004. *Clin Infect Dis*. Feb 1 2006;42(3):337-345. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16392078>.
79. 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*. Jun 2009;47(6):1668-1673. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19339468>.
80. 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*. Jul 2012;50(7):2299-2304. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22518868>.
81. 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*. Mar 2013;51(3):908-913. Available at <http://www.ncbi.nlm.nih.gov/pubmed/23284026>.
82. 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*. Nov 1992;93(5):481-488. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1442850>.
83. 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*. May 2004;15(5):328-332. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15117503>.
84. Bernal E, Munoz A, Ortiz Mdel M, Cano A. Syphilitic panuveitis in an HIV-infected patient after immune restoration. *Enferm Infecc Microbiol Clin*. Oct 2009;27(8):487-489. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19406524>.
85. Long CM, Klausner JD, Leon S, et al. Syphilis treatment and HIV infection in a population based study of persons at high risk for sexually transmitted disease/HIV infection in Lima, Peru. *Sex Transm Dis*. 33:151-55. 2006.
86. 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*. Dec 2011;53(11):1092-1099. Available at <http://www.ncbi.nlm.nih.gov/pubmed/21998287>.
87. 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 <http://www.ncbi.nlm.nih.gov/pubmed/24369955>.
88. 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*. Oct 1 2008;47(7):893-899. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18715154>.
89. 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*. Oct 15 2010;51(8):976-979. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20825309>.
90. Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. *Lancet*. Jan 25 2003;361(9354):313-314. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12559870>.
91. 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*. Feb 2015;42(2):98-103. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25585069>.

92. Wolff T, Shelton E, Sessions C, Miller T. Screening for syphilis infection in pregnant women: evidence for the U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* May 19 2009;150(10):710-716. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19451578>.
93. 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.* Oct 1 2015;61(7):1049-1053. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26063719>.
94. Genç M, Ledger WJ. Syphilis in pregnancy. *Sex Transm Infect.* Apr 2000;76(2):73-79. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10858706>.
95. Berman SM. Maternal syphilis: pathophysiology and treatment. *Bull World Health Organ.* Jun 2004;82(6):433-438. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15356936>.
96. 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.* Mar 26 1998;12(5):513-520. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9543450>.
97. 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.* Dec 1998;63(3):247-252. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9989893>.
98. 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.* Oct 15 2002;35(Suppl 2):S200-209. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12353207>.
99. 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.* Jun 2004;111(6):579-584. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15198786>.
100. 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.* Sep 11 2006;20(14):1869-1877. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16954728>.
101. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. *Cochrane Database Syst Rev.* 2001(3):CD001143. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11686978>.
102. 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.* Feb 1997;24(2):94-101. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9111755>.
103. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol.* Mar 2002;186(3):569-573. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11904625>.
104. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. *Am J Obstet Gynecol.* Mar 2003;188(3):714-718. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12634646>.
105. 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.* Aug 2005;32(8):495-498. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16041252>.
106. Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol.* Mar 1990;75(3 Pt 1):375-380. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2304710>.
107. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD, Jr. Fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol.* Jun 2001;97(6):947-953. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11384701>.

Epidemiology

Talaromycosis is an invasive fungal infection caused by the dimorphic fungus *Talaromyces marneffe* (formerly *Penicillium marneffe*) 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) (see the geographic distribution of talaromycosis in Figure 1).¹⁻⁴ *Talaromyces marneffe* 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 marneffe* was changed to *Talaromyces marneffe*, and the disease penicilliosis is now called talaromycosis.

HIV is a major risk factor for talaromycosis in highly-endemic regions, accounting for approximately 88% of disease.² The fungus is also a major cause of HIV-associated opportunistic infections in these regions, making up to 16% of hospital admissions due to AIDS,^{2,3,6-8} and is a leading cause of HIV-associated blood stream infection and death in Vietnam and southern China.^{6,9-11} Infection occurs predominantly in individuals who have very advanced HIV disease with a CD4 T lymphocyte (CD4) cell count of <100 cells/mm³.^{2,3,12} Talaromycosis is increasingly diagnosed in immunocompromised individuals who are returning travelers or immigrants from the endemic regions, and has been reported in Japan, Australia, Belgium, France, Germany, the Netherlands, Sweden, Switzerland, the United Kingdom, Oman in the Middle East, and the United States.^{13,14} Talaromycosis is increasingly recognized in individuals who have a primary immunodeficiency condition (e.g., idiopathic CD4 lymphopenia, anti-interferon-gamma autoantibody-associated immunodeficiency, conditions due to mutations in CYBB, CD40L, or gain-of-function mutation in STAT1/STAT3 pathways); secondary immunodeficiency conditions (e.g., autoimmune diseases in patients on corticosteroids and/or other immunosuppressive therapy, solid and hematological malignancies, solid organ transplantation, hematopoietic stem cell transplantation, and therapy with novel target therapies such as monoclonal antibodies against CD20 and kinase inhibitors).¹⁵ Talaromycosis-related mortality despite antifungal therapy in patients both with and without HIV is up to 30%.^{2,3,12,16,17}

Similar to other endemic mycoses, talaromycosis is a saprozoontic infection, meaning the transmissible source has a reservoir both in an abiotic environment and in an animal host. The wild bamboo rat in highland areas in the endemic regions is the known animal reservoir of *T. marneffe*;^{18,19} 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.^{20,21} Talaromycosis incidence increased 30% to 50% during the rainy months in southern Vietnam and northern Thailand,^{3,22} and was associated with increased humidity and not precipitation,^{23,24} suggesting that humidity facilitates an expansion of the environmental reservoir resulting in increased exposure to the fungus. Reactivation of latent infections has been demonstrated in non-autochthonous cases with a history of remote travel to the endemic countries and can occur many years after exposure.^{13,14,25} One case of presumed laboratory-acquired talaromycosis was reported in an African man with HIV while at the Pasteur Institute in Paris;²⁶ however, laboratory-acquired infection has never been reported from the endemic regions. Donor-acquired transmission has been reported in a lung-transplant recipient from Belgium.²⁷

Clinical Manifestations

Disseminated infection involving multiple organ systems is the most common manifestation of talaromycosis in patients with advanced HIV disease. The infection frequently begins as a subacute illness characterized by fever, weight loss, hepatosplenomegaly, lymphadenopathy, and respiratory and gastrointestinal abnormalities.^{3,28} These clinical features are non-specific 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 but late manifestations of talaromycosis, with central-necrotic papules appearing on the face, trunk, and extremities occurring in 40% to 70% of patients.^{1,3,29} Pulmonary involvement manifested as cough or shortness of breath occurs in 40% of patients. Gastrointestinal involvement presenting as diarrhea or abdominal pain occurs in 30% of patients. Significant hepatosplenomegaly is present in 70% of patients and together with intra-abdominal lymphadenopathy cause abdominal distention and pain.^{3,7} Meningoencephalitis is a rare manifestation, occurring in <1% of patients, and has a rapid disease course with a mortality of 80%.³⁰ Concurrent infections with other opportunistic pathogens occur in up to 60% of patients, with oropharyngeal candidiasis being the most common.²

Tuberculosis coinfection is common (occurring in up to 22% of patients in highly endemic regions) and complicates disease management because of itraconazole and rifampin drug interactions.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 aminotransferase is common, with serum aspartate aminotransferase (AST) over alanine aminotransferase (ALT) ratio of approximately 2.³

The median CD4 count in multiple cohorts is <50 cells/mm³.^{2,3}

The chest radiographical findings are broad, ranging from diffuse interstitial disease to reticulonodular infiltrates to alveola infiltrates causing respiratory failure.³¹

Diagnosis

A diagnosis of talaromycosis should be considered in all patients with HIV with CD4 count <100 cells/mm³ 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 have typical central-necrotic appearance and can be a diagnostic sign. However, skin lesions are a late manifestation of talaromycosis and are absent in up to 60% of patients.^{1,3,29} The current diagnostic methods for talaromycosis are still based on conventional microscopy, histology, and culture. Culture results usually return within 4 days to 5 days but can take up to 14 days. Diagnostic delay, particularly in patients presenting without fever or skin lesions, is associated with increased mortality.^{2,3,15,32} Antigen detection and polymerase chain reaction (PCR)-based methods are promising rapid diagnostics currently being evaluated.

Microscopy, Histology, and Culture are the Current Gold Standard Diagnostic Methods

A presumptive diagnosis of talaromycosis can be made based on the microscopic examination of Giemsa-, Wright-, or Gomori Methenamine Silver (GMS)-stained samples of skin lesion scrapings, lymph node aspirate, bone marrow aspirate, or tissue sections showing round to oval extracellular and intra-macrophage yeast-like organisms measuring 3 to 6 µm in diameter. Identification of a clear midline septum in a dividing yeast cell is what distinguishes *T. marneffei* from *Histoplasma* or *Candida* species.¹ In some patients, the fungus can be identified by microscopic examination of a Wright's-stained peripheral blood smear.³³

A definitive diagnosis of talaromycosis can be made by the histopathologic demonstration of the organism in biopsy specimens. There are three histopathological forms. The granulomatous reaction is formed by histiocytes, lymphocytes, and plasma, epithelioid, and giant cells and can be seen in reticuloendothelial organs in patients who are HIV-negative or immunocompetent. The suppurative reaction develops with the joining of multiple abscesses seen in the lung and subcutaneous tissues of immunocompetent patients. The anergic and necrotizing reaction is characterized by focal necrosis surrounded by distended histiocytes containing proliferating fungi seen in the lung, liver, and spleen of immunocompromised patients.³⁴

Most frequently a definitive diagnosis of talaromycosis is based on isolation of the organism from cultures of clinical specimens.

Compared to other endemic dimorphic fungi, *T. marneffei* grows more readily in standard BACTEC blood culture media and Sabouraud dextrose agar, but takes 5 to 14 days to grow and to demonstrate temperature dimorphism. At 25°C to 30°C, the fungus grows as a mold producing yellow-green colonies with sulcate folds and a red diffusible pigment in the media. Microscopically, filamentous hyphae with characteristic spore-bearing structures called conidiophores and conidia can be seen. At 32°C to 37°C, 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 (70%).^{3,35} Less commonly, talaromycosis has been diagnosed from sputum, pleural fluid, peritoneal fluid, cerebrospinal fluid, pericardium fluid, stool, and urine.

Molecular Diagnosis

Molecular diagnostics for talaromycosis have been based on PCR amplification and sequence identification of specific regions within the fungal ribosome's internally transcribed spacer regions, the 5.8S rRNA, and the 18S rRNA genes of *T. marneffei*.³⁶⁻³⁹ These assays have high specificity (100%), but limited sensitivity (60% to 70%). At present, none of the real-time PCR assays has been prospectively validated, standardized, or commercially developed for clinical use.

Antigen Detection

The commercial assay for the detection of *Aspergillus* galactomannan cross reacts with *T. marneffei* and has a sensitivity of 95.8% (23 of 24 patients with culture-positive talaromycosis were correctly identified) and a specificity of 90.9% (30 of 33 people without talaromycosis were correctly identified) for the detection of talaromycosis (at cutoff index = 1.0).⁴⁰ However, the galactomannan test also cross reacts with other endemic fungi such as *Histoplasma* and *Blastomyces* and has not been evaluated prospectively.

The Mp1p ELISA has been shown to be more sensitive than blood culture (in 372 culture-proven talaromycosis cases, sensitivity was 86.3% for the Mp1p ELISA and 74% for blood culture) and is highly specific (98.1% specificity in 338 healthy controls and 179 patients without HIV, but with other infections).⁴¹ This assay was used to screen a large serum bank of 8,131 patients with HIV in Guangzhou, China and showed a Mp1p antigenemia prevalence of 9.4%, with prevalence of antigenemia increased from 4.5% to 28.4% as the CD4 count decreased from 200 cells/mm³ to 50 cells/mm³, demonstrating a significant burden of disease in southern China.²⁴ In Vietnam, the Mp1p ELISA identified 4.2% antigenemia in 1,123 asymptomatic patients initiating antiretroviral therapy (ART) in 22 HIV clinics across Vietnam who had a CD4 count <100 cells/mm³. Antigenemia was found to be independently associated with 12-month mortality.⁴² These data demonstrate that the Mp1p ELISA has the potential to detect infection earlier than culture allows and can potentially be used as a screening tool for sub-clinical infection, permitting pre-emptive antifungal therapy to prevent disease development. This is an area of active research.

Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) Method

The Matrix-Assisted Laser Desorption/Ionization-Time of Flight (MALDI-TOF) method has recently been used for identification of *Talaromyces* to the species level from cultured specimens based on either an in-house database generated from institution's *T. marneffei* clinical strain collection^{43,44} or from the comprehensive National Institutes of Health MDL Mold Library.⁴⁵ The MALDI-TOF represents a rapid and reliable tool for downstream fungal identification, eliminating the need to demonstrate thermal dimorphism.

Antifungal Susceptibility Testing

The minimum inhibitory concentrations (MIC) have been consistently low for itraconazole, intermediate for amphotericin B, and high for fluconazole. Thus far, only one retrospective case series from Chiang Mai in Thailand correlated MIC data of 30 clinical isolates with patient outcomes. More recent studies reported

low MIC values for the newer generation azole drugs voriconazole (MICs 0.016 µg/mL–0.063 µg/mL) and posaconazole (MICs 0.001 µg/mL–0.002 µg/mL), and intermediate to high MIC values of 2 µg/mL to 8 µg/mL for anidulafungin,⁴⁶ the later study utilized a commercial Sensititre YeastOne™ YO10 assay.⁴⁷ These results suggest promising activity of voriconazole and posaconazole for the treatment of talaromycosis, and suggest that the echinocandins are less effective against *T. marneffeii*.

Preventing Exposure

Two case-controls studies in Thailand and Vietnam demonstrated that patients with World Health Organization (WHO) Stage 4 HIV disease or a CD4 count <100 cells/mm³ who had an occupational exposure to plants and farmed animals were at increased risk for infection.^{20,21} The risk was higher in the rainy and humid months.^{3,22}

Residency or a history of traveling to the highland regions (as short as 3 days) was a risk factor for talaromycosis in patients with advanced HIV disease in southern Vietnam.²⁰ These data suggest that patients with advanced HIV should avoid visiting the areas where talaromycosis is highly endemic, particularly highland regions during the rainy and humid months (**BIII**).

Preventing Disease

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, demonstrated that oral itraconazole 200 mg daily for primary prophylaxis significantly reduced the occurrence of invasive fungal infections (predominantly cryptococcosis and talaromycosis) in patients with HIV with a CD4 count <200 cells/mm³.⁴⁸

In a retrospective study also in Chiang Mai, fluconazole (400 mg weekly) was shown to be as effective as itraconazole (200 mg daily) for primary prophylaxis.⁴⁹ However, these studies were conducted prior to the widespread use of ART, had small sample sizes, and a mortality benefit was not observed.

Therefore, primary prophylaxis has not been widely adopted given concerns about long-term toxicity, drug-drug interactions, and costs.

Indication for Primary Prophylaxis

Primary prophylaxis is only recommended for patients with HIV with CD4 counts <100 cells/mm³ who reside in the highly-endemic regions in northern Thailand, southern China, and northern and southern Vietnam who are unable to have 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 patients who are on or about to start effective ART and is not recommended in geographic areas outside of the mentioned highly endemic regions (**AIII**).

For patients with HIV from the United States and from countries outside of the endemic region who are not on effective ART, have a CD4 count <100 cells/mm³, and must travel to the highly-endemic areas mentioned, primary prophylaxis with either itraconazole 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 patients who are ART adherent and have a sustained CD4 count ≥100 cells/mm³ for over 6 months (**BII**). In areas where viral load monitoring has replaced CD4 count monitoring, primary prophylaxis can reasonably be discontinued in patients who achieve sustained virologic suppression over 6 months (**BIII**).

Treating Disease

Disseminated talaromycosis is fatal if untreated.⁵⁰

The case fatality rates with antifungal therapy range from 10% to 30%.^{2,3,6,16}

Antifungal therapy for talaromycosis is divided into induction, consolidation, and maintenance phases. The treatment recommendations are based on several observational studies in Thailand and China⁵¹⁻⁵⁴ and the recent Itraconazole versus Amphotericin B for Penicilliosis (IVAP) randomized, controlled trial in Vietnam.⁵⁵

In an earlier non-comparative prospective study of 74 patients in Thailand, induction therapy with deoxycholate amphotericin B 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%.⁵¹

Voriconazole has been used for induction therapy in patients who could not tolerate amphotericin B and was shown to have favorable clinical and microbiological outcomes in 8 of 9 patients in Thailand⁵³ and 10 of 14 patients in China.⁵²

The IVAP trial randomized 440 patients across 5 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; hazard ratio of death in the itraconazole arm was 1.88 [95% confidence interval, 1.15—3.09, $P = 0.012$]). 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 four-fold 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/mm³ or ≥ 50 cells/mm³), ART status, or intravenous (IV) drug use.⁵⁵

The recommended induction therapy for all patients, regardless of disease severity, is amphotericin B, preferably liposomal amphotericin B 3 to 5 mg/kg body weight/day where available, or deoxycholate amphotericin B 0.7 mg/kg body weight/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**).⁵⁵ After this period, maintenance therapy (or secondary prophylaxis) with oral itraconazole 200 mg/day is recommended to prevent recurrence until the CD4 count rises above 100 cells/mm³ for ≥ 6 months (**AI**).⁵⁶

For patients unable to tolerate any form of amphotericin, induction therapy with IV voriconazole 6 mg/kg every 12 hours on day 1 (loading dose), then 4 mg/kg every 12 hours 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**).^{52,53}

Thereafter, either oral voriconazole or oral itraconazole 200 mg every 12 hours can be used for consolidation therapy for 10 weeks, followed by itraconazole 200 mg/day for secondary prophylaxis. The optimal dose of voriconazole for secondary prophylaxis beyond 12 weeks has not been studied.

Itraconazole is not recommended as an induction therapy for talaromycosis, regardless of disease severity (**AI**).⁵⁵

Special Considerations with Regard to Starting ART

No studies exist regarding the optimal time to start ART in patients with HIV who have talaromycosis. In the IVAP trial, the median time to ART initiation, which was similar in both arms, was 3 weeks (range: 1 week–5 weeks).

Paradoxical IRIS events occurred only in the itraconazole arm (in 11.4% of patients), suggesting

that ART can be safely initiated as early as 1 week after starting effective antifungal therapy with amphotericin B (**BIII**).⁵⁵

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

Adverse Event Monitoring

Patients treated with 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 (**AII**). Infusion-related adverse reactions can be ameliorated by pretreatment with acetaminophen and diphenhydramine.

Drug-Drug Interactions and Therapeutic Drug Monitoring

Itraconazole and voriconazole and antiretroviral (ARV) drugs such as protease inhibitors (PIs), some integrase strand transfer inhibitors (INSTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) can have bi-directional interactions with each other, leading to increased or decreased drug concentrations (see [Drug-Drug Interactions](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). Close monitoring is recommended when using these drugs together.

In settings where therapeutic drug monitoring (TDM) is available, serum itraconazole and voriconazole levels should be obtained in all patients to ensure adequate drug exposure (**BIII**). This is because itraconazole and voriconazole can interact with some ARV drugs, because absorption of itraconazole can be erratic, and because of the extensive interindividual variability and non-linear pharmacokinetics of voriconazole. The target serum trough concentration should be >0.5 $\mu\text{g/mL}$ for itraconazole and >1 $\mu\text{g/mL}$ for voriconazole (**BIII**). Because it is more bioavailable, itraconazole solution is preferred over the capsule formulation.

Prevention and Management of IRIS

Both unmasking and paradoxical IRIS have been described in patients with talaromycosis when ART is initiated.⁵⁷⁻⁵⁹ In the IVAP trial, 188 of 432 (44%) patients had started ART a median of 3–4 months before developing talaromycosis, indicating the role of ART in the unmasking of subclinical infection in a significant proportion of patients.⁵⁵ This finding highlights the need for a sensitive assay to screen for subclinical infection and the importance 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,⁵⁵ 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 non-steroid anti-inflammatory medicine. Corticosteroids are reserved for synovitis that interferes with daily function.⁵⁹ Although the IRIS events in the IVAP trial were not associated with increased mortality and were managed effectively with continuation of ART and antifungal therapy, they were associated with higher morbidity, including lower quality of life and increased diagnostic testing, duration of hospitalization, and cost.⁵⁵

Managing Treatment Failure and Relapse

Talaromycosis treatment failure and disease relapse were associated with ineffective induction therapy with itraconazole, highlighting the importance of amphotericin B induction therapy.⁵⁵ On the basis of

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 treatment (**BII**).

Disease relapse is associated with higher mortality⁵⁵ 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 (**AIII**).

Preventing Recurrence

When to Start Secondary Prophylaxis/Chronic Maintenance Therapy

A study showed that >50% of patients not treated with ART had disease relapse within 6 months after discontinuation of antifungal therapy. A double-blind, placebo-controlled study conducted in Chiang Mai, Thailand, demonstrated that secondary prophylaxis with oral itraconazole 200 mg daily in patients with AIDS reduced the talaromycosis relapse rate from 57% to 0% ($P < 0.001$).⁵⁶ All patients who successfully complete induction and consolidation treatment for talaromycosis should receive secondary prophylaxis (maintenance therapy) with oral itraconazole 200 mg/day until they reach criteria for stopping secondary prophylaxis (**AI**).

When to Stop Secondary Prophylaxis/Chronic Maintenance Therapy

No randomized, controlled study has demonstrated the safety of discontinuation of secondary prophylaxis for talaromycosis. However, a retrospective cohort study reported no relapse of talaromycosis after itraconazole was discontinued in patients receiving ART whose CD4 counts were >100 cells/mm³.⁶⁰

Therefore, secondary prophylaxis for talaromycosis can be discontinued in patients who are ART adherent and have CD4 counts >100 cells/mm³ for at least 6 months (**BII**).

Secondary prophylaxis can reasonably be discontinued in patients with sustained virologic suppression for ≥ 6 months (**BIII**).

Secondary prophylaxis/chronic maintenance therapy should be reintroduced if the CD4 count decreases to <100 cells/mm³ (**BIII**).

Special Considerations During Pregnancy

The diagnosis and treatment of talaromycosis during pregnancy is similar to that in non-pregnant adults, with the following considerations regarding antifungal use in pregnancy. 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. Neonates born to women on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Itraconazole at high doses has been shown to be teratogenic in animals, but because humans lack the metabolic mechanism accounting for these defects, the animal teratogenicity data are not applicable to humans. Case series in humans do not suggest an increased risk of birth defects with itraconazole, but experience is very limited.⁶¹

Voriconazole is Food and Drug Administration Category D because of teratogenicity (cleft palate and renal defects) seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended.

Substitution of amphotericin B for high-dose azoles in the first trimester is recommended (**BIII**). Women on secondary prophylaxis 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 women become pregnant while receiving itraconazole prophylaxis, the decision as to whether to continue should be individualized based on current CD4 count and viral suppression and patient preference.

Recommendations for Preventing and Treating Talaromycosis

Preventing First Episode of Talaromycosis (Primary Prophylaxis)

Indication for Primary Prophylaxis:

- Persons with a CD4 count <100 cells/mm³, who are unable to have ART, or have treatment failure without access to effective ART options and who either:
 - Reside in the highly endemic 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 endemic region and must travel to the region **(BIII)**.

Primary Prophylaxis

For Individuals Residing in Endemic Areas:

- Preferred Therapy: Itraconazole 200 mg PO once daily **(BI)**
- Alternative Therapy: Fluconazole 400 mg PO once weekly **(BII)**

For Individuals Traveling to Endemic Areas:

- Preferred Therapy: Begin itraconazole 200 mg PO once daily 3 days before travel and continue for 1 week after leaving the endemic area **(BIII)**.
- Alternative Therapy: Begin fluconazole 400 mg 3 days before travel, then continue 400 mg once weekly while in the area, and take final dose after leaving the endemic area **(BIII)**.

Indication for Discontinuing Primary Prophylaxis for Persons who Reside in Endemic Areas:

- CD4 count >100 cells/mm³ for ≥ 6 months in response to ART **(BII)**
- Viral load suppression for ≥ 6 months on ART **(BIII)**

Indication for Restarting Primary Prophylaxis:

- CD4 count decreases to <100 cells/mm³ **(BIII)** and patient still resides in or travels to high-risk areas. Primary prophylaxis for travelers may begin three days prior to travel to allow serum drug level to reach steady state and may continue for one week after travel **(BIII)**.

Treating Acute Infection in Severely Ill Patients

Preferred Therapy:

- Induction therapy with liposomal amphotericin B 3 to 5 mg/kg/day IV for 2 weeks, followed by consolidation therapy with itraconazole 200 mg PO twice daily for 10 weeks **(AI)**, followed by maintenance therapy or secondary prophylaxis with itraconazole 200 mg PO daily **(AII)**

Alternative Therapy:

- In settings where liposomal amphotericin B is not available, induction therapy with deoxycholate amphotericin B 0.7 mg/kg/day IV for 2 weeks, followed by consolidation therapy with itraconazole 200 mg PO twice daily for 10 weeks **(AI)**, followed by maintenance therapy or secondary prophylaxis with itraconazole 200 mg PO daily **(AII)**
- In settings where amphotericin B is not available, induction therapy with voriconazole 6 mg/kg IV every 12 hours for 1 day (loading dose) and then voriconazole 4 mg/kg IV every 12 hours for 2 weeks, or oral voriconazole 600 mg every 12 hours on day 1 (loading dose) and then voriconazole 400 mg PO every 12 hours for 2 weeks; followed by consolidation therapy with voriconazole 200 mg PO twice daily or itraconazole 200 mg PO twice daily for a maximum of 10 weeks **(BII)**; followed by maintenance therapy or secondary prophylaxis with itraconazole 200 mg PO daily **(AII)**
- Itraconazole is not recommended as induction therapy for talaromycosis **(AI)**.

Criteria for Discontinuing Chronic Maintenance Therapy:

- CD4 count >100 cells/mm³ for ≥ 6 months in response to ART **(BII)**
- Virologic suppression for ≥ 6 months on ART **(BIII)**

Criteria for Restarting Chronic Maintenance Therapy:

- CD4 count decreases to <100 cells/mm³ **(AIII)**

Other Considerations

- ART can be initiated as early as one week after the initiation of treatment for talaromycosis with amphotericin B induction therapy to improve outcomes **(BII)**.
- Given erratic absorption of itraconazole, extensive interindividual variability and non-linear PKs of voriconazole, and the potential for drug interactions with ARV drugs, itraconazole and voriconazole concentrations should be monitored, and serum trough concentration should be >0.5 µg/mL for itraconazole and >1 µg/mL for voriconazole **(BIII)**. Both itraconazole and voriconazole can have significant drug-drug interactions with various ARV drugs; dosage adjustment may be necessary, and TDM to guide therapy can be considered (see the [Drug-Drug Interactions](#) tables in the [Adult and Adolescent Antiretroviral Guidelines](#) for further recommendations).

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; IV = intravenous; PK = pharmacokinetic; PO = orally; TDM = therapeutic drug monitoring

Figure 1. Geographic Distribution of Talaromyces

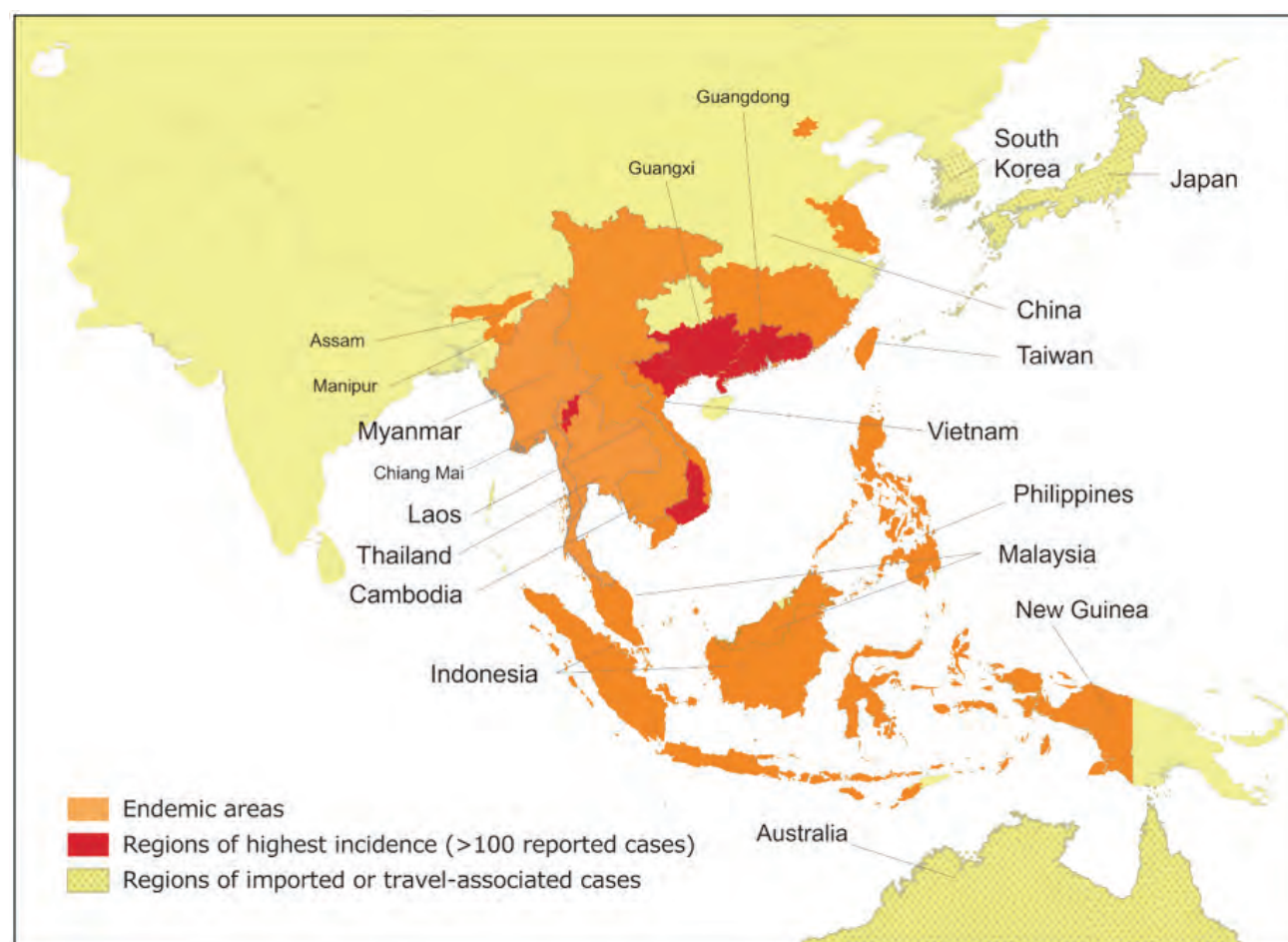


Figure courtesy of Dr. Thuy Le, Division of Infectious Diseases and International Health, Duke University School of Medicine

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, Houbbraken 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. 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>.
7. 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/22308048>.

nih.gov/pubmed/22897817.

8. 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>.
9. 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>.
10. 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>.
11. 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>.
12. 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>.
13. 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>.
14. 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>.
15. 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>.
16. 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>.
17. 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>.
18. 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>.
19. 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>.
20. 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.
21. 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>.
22. 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>.
23. Bulterys PL, Le T, Quang VM, Nelson KE, Lloyd-Smith JO. Environmental predictors and incubation period of AIDS-associated *Penicillium marneffei* infection in Ho Chi Minh City, Vietnam. *Clin Infect Dis*. 2013;56(9):1273-1279. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23386634>.
24. 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>.
25. 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>.
26. Hilmarisdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated *Penicillium marneffei* infection in a patient with AIDS. *Clin Infect Dis*. 1994;19(2):357-358. Available at: <https://www.ncbi.nlm.nih.gov/>

pubmed/7986922.

27. 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>.
28. 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>.
29. 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>.
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. Limper AH, Adenis A, Le T, Harrison TS. Fungal infections in HIV/AIDS. *Lancet Infect Dis*. 2017;17(11):e334-e343. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28774701>.
32. 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>.
33. 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>.
34. 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>.
35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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>.
40. 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>.
41. Thu NT, Chan JF, Hien HTA, et al. Clinical performance of the Mp1p immunoassay for rapid diagnosis of *Talaromyces marneffei* infection. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017; Seattle, WA.
42. Thu N, Dat V, Chan J, et al. Asymptomatic *Talaromyces marneffei* infection is associated with HIV mortality. Presented at: Asia Pacific AIDS and CoInfection Conference; 2018; Hong Kong, China.
43. 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>.
44. 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>.

45. 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>.
46. 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>.
47. 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>.
48. 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>.
49. 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>.
50. 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>.
51. 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>.
52. 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>.
53. 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>.
54. 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>.
55. 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>.
56. 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>.
57. 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>.
58. 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>.
59. 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>.
60. 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>.
61. 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>.

***Toxoplasma gondii* Encephalitis** (Last updated July 25, 2017; last reviewed January 11, 2023)

Toxoplasmic encephalitis (TE) is caused by the protozoan *Toxoplasma gondii*. Disease appears to occur almost exclusively because of reactivation of latent tissue cysts.¹⁻⁴ Primary infection occasionally is associated with acute cerebral or disseminated disease.

Epidemiology

Seroprevalence of anti-*Toxoplasma* antibody varies substantially among different geographic locales, with a prevalence of approximately 11% in the United States, versus 50% to 80% in certain European, Latin American, and African countries.⁴⁻⁶ In the era before antiretroviral therapy (ART), the 12-month incidence of TE was approximately 33% in patients with advanced immunosuppression who were seropositive for *T. gondii* and not receiving prophylaxis with drugs against the disease. A low incidence of toxoplasmosis is seen in patients who are seronegative for *T. gondii*. If patients are truly seronegative, their toxoplasmosis presumably represents one of three possible scenarios:

- 1) Primary infection,
- 2) Re-activation of latent disease in individuals who cannot produce detectable antibodies, *or*
- 3) Testing with insensitive assays.^{7,8}

Clinical disease is rare among patients with CD4 T lymphocyte (CD4) cell counts >200 cells/μL. Patients with CD4 counts <50 cells/μL are at greatest risk.^{1,3,8,9} Primary infection occurs after eating undercooked meat containing tissue cysts or ingesting oocysts that have been shed in cat feces and sporulated in the environment, a process that takes at least 24 hours. In the United States, eating raw shellfish including oysters, clams, and mussels recently was identified as a novel risk factor for acute infection.¹⁰ Up to 50% of individuals with documented primary infection do not have an identifiable risk factor.¹¹ Patients may be infected with the parasite even in the absence of conventional risk factors for infection in their epidemiological history. The organism is not transmitted through person-to-person contact.

Clinical Manifestations

Among patients with AIDS, the most common clinical presentation of *T. gondii* infection is focal encephalitis with headache, confusion, or motor weakness and fever.^{1,3,9} Patients may also present with non-focal manifestations, including only non-specific headache and psychiatric symptoms. Focal neurological abnormalities may be present on physical examination, and in the absence of treatment, disease progression results in seizures, stupor, coma, and death. Retinochoroiditis, pneumonia, and evidence of other multifocal organ system involvement can occur but are rare in patients with AIDS. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain will typically show multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema.^{1,9,12-14} Toxoplasmosis also can manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies.¹⁵ This latter presentation tends to be rapidly progressive and fatal.

Diagnosis

HIV-infected patients with TE are almost uniformly seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies.^{1,3,9,16} The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies usually are absent. 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. On imaging studies, lesions are usually ring-enhancing and have a predilection for the basal ganglia. MRI has sensitivity superior to that of CT studies

for radiological diagnosis of TE. MRI should be obtained in patients with equivocal or negative CT studies. Positron emission tomography¹³ or single-photon emission computed tomography scanning¹⁴ 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 a brain biopsy, which is most commonly performed by a stereotactic CT-guided needle biopsy. Hematoxylin and eosin stains can be used for detection of *T. gondii*, but sensitivity is significantly increased if immunoperoxidase staining is used and if experienced laboratories process the specimens.¹⁷ If safe and feasible, a lumbar puncture should be performed for *T. gondii* polymerase chain reaction (PCR), as well as for cytology, culture, cryptococcal antigen and PCR for *Mycobacterium tuberculosis*, Epstein-Barr Virus (EBV) and JC Virus (JCV), either at initial presentation or subsequently, especially in patients in whom empiric therapy fails. Detection of *T. gondii* by PCR in CSF has high specificity (96%–100%), but low sensitivity (50%), especially once specific anti-toxoplasma therapy has been started.^{18–20}

The differential diagnosis of focal neurological disease in patients with AIDS most often includes primary CNS lymphoma and progressive multifocal leucoencephalopathy (PML). In the absence of immune reconstitution inflammatory syndrome (IRIS), PML (but not lymphoma) can be distinguished on the basis of imaging studies. PML lesions typically involve white matter rather than gray matter, are non-contrast enhancing, and produce no mass effect. Less common causes of focal neurologic disease in patients with AIDS include mycobacterial infection (especially tuberculosis [TB]); fungal infection, such as cryptococcosis; Chagas disease; and pyogenic brain abscess, particularly in IV drug abusers.

Most clinicians initially rely on an empiric diagnosis, which can be established as an objective response, documented by clinical and radiographic improvement, to specific anti-*T. gondii* therapy in the absence of a likely alternative diagnosis. Brain biopsy is 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 studies are negative and/or suggest an etiology other than toxoplasmosis. In patients with contrast-enhancing mass lesions, detection of EBV and JCV by PCR in CSF is highly suggestive of CNS lymphoma^{21,22} or PML,²³ respectively.

Preventing Exposure

HIV-infected individuals should be tested for IgG antibody to *Toxoplasma* soon after they are diagnosed with HIV to detect latent infection with *T. gondii* (**BIII**). They also should be counseled regarding sources of *Toxoplasma* infection, especially if they lack IgG antibody to *Toxoplasma*.

To minimize risk of acquiring toxoplasmosis, HIV-infected individuals 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;²⁴ 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. To minimize the risk for acquiring toxoplasmosis, HIV-infected individuals 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**). Patients who are seronegative and who own cats should be advised to have someone who is HIV-negative and not pregnant change the litter box daily. If they must change the litter box themselves, they should wear gloves and wash their hands thoroughly afterwards (**BIII**). HIV-infected patients 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**). Patients do not need to be advised to part with their cats or to have their cats tested for toxoplasmosis (**AII**).

Preventing Disease

Indication for Primary Prophylaxis

Toxoplasma-seropositive patients who have CD4 counts <100 cells/μL should receive prophylaxis against TE (**AII**).^{25,26} All patients at risk for toxoplasmosis are also at risk for developing *Pneumocystis jirovecii* pneumonia

(PCP), and should be receiving PCP prophylaxis. They should be managed as follows: patients receiving trimethoprim-sulfamethoxazole (TMP-SMX) or atovaquone for PCP prophylaxis require no additional medications; patients receiving dapsone should have pyrimethamine plus leucovorin added to the regimen or be switched to TMP-SMX or atovaquone; patients receiving aerosol pentamidine should be switched if possible to a regimen which also has anti-toxoplasma activity, i.e. switching to either trimethoprim-sulfamethoxazole or atovaquone if that is feasible. For patients in whom other alternatives are not possible, pyrimethamine alone (plus leucovorin) may have some efficacy as primary prophylaxis **(CIII)**.⁸

The double-strength-tablet daily dose of TMP-SMX, which is the preferred regimen for PCP prophylaxis, is also effective against TE and is recommended **(AII)**. TMP-SMX, one double-strength tablet three times weekly, is an alternative **(BIII)**. If patients cannot tolerate TMP-SMX, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against PCP **(BI)**.²⁷⁻²⁹ Atovaquone with or without pyrimethamine/leucovorin is active against PCP and also can be considered for toxoplasmosis as well as PCP, **(CIII)**. Aerosolized pentamidine does not protect against TE and **is not recommended** for antitoxoplasma prophylaxis **(AI)**.^{25,30}

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued in adult and adolescent patients receiving ART whose CD4 counts increase to >200 cells/ μ L for more than 3 months **(AI)**. Multiple observational studies³¹⁻³³ and two randomized trials^{34,35} have reported that primary prophylaxis can be discontinued, with minimal risk for development of TE, in patients receiving ART whose CD4 counts increase from <200 cells/ μ L to >200 cells/ μ L for more than 3 months. In these studies, most patients were taking HIV protease inhibitor-containing regimens and the median CD4 count at the time prophylaxis was discontinued was >300 cells/ μ L. At the time prophylaxis was discontinued, most patients had sustained suppression of plasma HIV RNA levels below the detection limits of available assays; the median follow-up was 7 to 22 months. CD4 count increases to >200 cells/ μ L were studied because regimens used for prophylaxis of TE also provide PCP prophylaxis, and the risk of PCP in untreated patients increases once the CD4 count is <200 cells/ μ L. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/ μ L. When CD4 counts are >200 cells/ μ L for at least 3 months, 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 ART and had HIV RNA plasma viral loads <400 copies/mL, and who had stopped or never received TE prophylaxis, suggesting 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.³⁶ Similar observations have been made with regard to stopping primary or secondary prophylaxis for PCP.³⁶⁻³⁸ Data on which to base specific recommendations are inadequate, but one approach would be to stop primary prophylaxis in patients with CD4 counts of 100 to 200 cells/ mm^3 if HIV plasma RNA levels remain below limits of detection for at least 3 to 6 months **(BII)**.³⁶

Treating Disease

The initial therapy of choice for TE consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin **(AI)**.^{2,39-41} Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.⁴² Leucovorin reduces the likelihood of development of hematologic toxicities associated with pyrimethamine therapy.⁴³ Pyrimethamine plus clindamycin plus leucovorin **(AI)**^{39,40} is the preferred alternative regimen for patients with TE who cannot tolerate sulfadiazine or do not respond to first-line therapy. This combination, however, does not prevent PCP, therefore additional PCP prophylaxis must be administered when it is used **(AII)** (see discussion under [Preventing Recurrence](#)).

In a small (77 patients) randomized trial, TMP-SMX was reported to be effective and better tolerated than pyrimethamine-sulfadiazine.⁴⁴ Others have reported similar efficacy in open-label observational studies.⁴⁵

TMP-SMX has less *in vitro* activity and experience using this drug to treat toxoplasmosis in developed countries is limited. However, if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin (**BI**). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (**BI**).⁴⁶⁻⁵¹ 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 parenteral TMP-SMX (**BI**) 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, or atovaquone plus sulfadiazine, or, for patients intolerant of both pyrimethamine and sulfadiazine, atovaquone as a single agent, have also been shown to be effective in treating TE, although the relative efficacy compared with the previous regimens is unknown. (**BII**)^{52,53,54} If atovaquone is used alone, clinicians should be aware that the absorption of the drug from patient to patient is highly variable; plasma levels >18.5 µg/mL are associated with an improved response rate but atovaquone therapeutic drug monitoring is not routinely available.⁵³⁻⁵⁵

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**);^{56,57} clarithromycin plus pyrimethamine plus leucovorin (**CIII**);⁵⁸ 5-fluorouracil plus clindamycin (**CIII**);⁵⁹ dapsone plus pyrimethamine plus leucovorin;⁶⁰ and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin (**CIII**).^{61,62} Although the clarithromycin dose used in the only published study was 1g twice a day, doses >500 mg have been associated with increased mortality in HIV-infected patients treated for disseminated *Mycobacterium avium* Complex. Doses >500 mg twice a day **should not be used** (**BIII**).

Clinical response to acute therapy occurs in 90% of patients with TE within 14 days of initiation of appropriate anti-toxoplasma treatment.² The reasons why some patients fail therapy are not clearly proven; whether such failures are due to poor adherence or to other host factors or antimicrobial resistance has not been well delineated. Acute therapy for TE should be continued for at least 6 weeks, if there is clinical and radiologic improvement (**BII**).¹⁻⁴ Longer courses may be necessary 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 (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. Adjunctive corticosteroids such as dexamethasone should only be administered to 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 TB.

Anticonvulsants should be administered to patients with TE who have a history of seizures (**AII**), but **should not be administered** prophylactically to all patients (**BII**). Anticonvulsants, if indicated, should be continued at least through the period of acute therapy.

Special Considerations with Regard to Starting ART

There are no data on which to base a recommendation regarding when to start ART in a patient with TE. However, many physicians would initiate ART within 2 to 3 weeks after the diagnosis of toxoplasmosis (**CIII**), based on the significantly lower incidence of AIDS progression or death (a secondary study endpoint) seen in the ART arm of a controlled trial of 282 patients with OIs other than TB (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 ART.⁶³

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

Changes in antibody titers are not useful for monitoring responses to therapy. Patients with TE should be monitored routinely for adverse events and clinical and radiologic improvement (**AIII**). 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 4 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 anticonvulsants and antiretroviral agents should be evaluated carefully; if necessary, doses should be adjusted or alternative anticonvulsants should be used.

IRIS associated with TE has been reported but appears to be rare (~5% in one report).⁶⁴⁻⁶⁶ Most cases develop as paradoxical worsening with increase in the size and number of lesions, peri-lesional edema, and greater enhancement in T1.^{65,67,68} Given the rarity of TE-associated IRIS, recommendations for management of such events are difficult to develop.

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**)^{39,40} until immune reconstitution occurs as a consequence of ART, in which case treatment discontinuation is indicated. 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,⁶⁹ and limited clinical experience suggests that twice-daily dosing is effective.⁷⁰ Pyrimethamine 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,³⁹ a dose of 600 mg clindamycin every 8 hours is recommended (**CIII**). Because this regimen does not provide protection against PCP (**AII**), an additional agent, such as aerosol pentamidine, must be used. Atovaquone with or without pyrimethamine or sulfadiazine is also active against both TE^{54,55} and PCP⁷¹ (**BII**). 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 to reduce pill burden.⁷² For patients being treated with TMP-SMX, this drug should be continued as chronic maintenance, at a reduced dose of 1 double-strength tablet twice daily (**BII**) or once daily (**BII**). The lower dose may be associated with an increased risk of relapse, and if the once daily dosing is used, a gradual transition may be beneficial (e.g. follow acute therapy with 4-6 weeks of 1 double-strength tablet twice daily

before lowering to 1 double-strength tablet once daily (**CIII**).^{44,45,72}

Although there are no data on the long-term suppressive efficacy of the other alternative regimens noted above, clinicians might consider using these agents in unusual situations in which the recommended agents cannot be administered (**CIII**).

When to Stop Chronic Maintenance Therapy

Adult and adolescent patients receiving chronic maintenance therapy for TE are at low risk for recurrence of TE if they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increase in their CD4 counts to >200 cells/ μ L after ART that is sustained for more than 6 months.^{32,35,73,74} Discontinuing chronic maintenance therapy in such patients is a reasonable consideration, although occasional recurrences have been reported. The recommendation is based on results in a limited number of patients from observational studies and one randomized clinical trial and inference from more extensive cumulative data indicating the safety of discontinuing secondary prophylaxis for other OIs during advanced disease (**BI**). 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.

When to Restart Primary Prophylaxis or Maintenance Therapy

Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm³ (**AIII**) regardless of the HIV plasma viral load. Based on results from the COHERE study, primary prophylaxis may not need to be restarted in patients with CD4 counts of 100 to 200 cells/mm³ who have had HIV plasma RNA levels below limits of detection for at least 3 to 6 months (**BII**).^{36,37} For patients with CD4 counts of 100-200 cells/ μ L with HIV plasma viral load above detection limits of the utilized assay, PCP prophylaxis should be reintroduced, and this will provide prophylaxis for toxoplasmosis as well.

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/ μ L, and recurrent TE can be debilitating and potentially life-threatening, maintenance therapy should be reintroduced if the CD4 count decreases to <200 cells/ μ L (**AIII**) regardless of the HIV plasma viral load.⁷⁵

Special Considerations During Pregnancy

Documentation of baseline maternal *T. gondii* serologic status (IgG) should be obtained in HIV-infected women who become pregnant 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 HIV-infected women with severe immunosuppression.^{76,77} Knowing maternal toxoplasmosis sero-status 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.

Primary *T. gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, IgA, and IgE antibodies; IgG avidity; and the differential agglutination tests.^{78,79} Because serologic testing is often difficult to interpret, pregnant HIV-infected women with suspected primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine specialist who can access specialized laboratory testing (**BIII**)^{79,80} (e.g., the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory; Palo Alto, CA; <http://www.pamf.org/serology/> at 650-853-4828 and toxolab@pamf.org; and the National Collaborative Chicago-based Congenital Toxoplasmosis Study; Chicago, IL; <http://www.uchospitals.edu/specialties/infectious-diseases/toxoplasmosis/> at 773-834-4131 and rmcleod@midway.uchicago.edu).

Toxoplasmosis diagnostic considerations are the same in pregnant women as in non-pregnant women.

While maternal infection is usually asymptomatic, after a 5-23 day incubation period, non-specific symptoms may develop including fever, fatigue, headache, and myalgia. Parasitemia can seed the placenta and lead to

fetal infection. With respect to congenital toxoplasmosis, the risk of transmission is highest in the setting of an acute maternal infection as compared to reactivation. While the risk of transmission increases with advancing gestational age, the severity of fetal sequelae is more pronounced the earlier in gestation the fetus is affected.⁸¹ Detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done for HIV-infected women with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy (**AIII**).⁷⁹ Prenatal diagnosis requires an amniocentesis with PCR testing for *T. gondii* DNA in the amniotic fluid.⁸² Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in women receiving HAART.⁸³ Therefore, PCR of amniotic fluid can be considered during gestation in pregnant women on ART with serologic evidence of recently acquired infection, women suspected to have reactivated their toxoplasma latent infection during pregnancy, and those with ultrasound findings suggestive of fetal *T. gondii* infection (**BIII**).⁷⁹ Amniotic fluid testing for *T. gondii* PCR should be avoided at less than 18-week gestation in an effort to minimize false-negative results.⁸⁴ Because the risk for transmission with chronic infection that does not reactivate during gestation appears to be low, routine fetal evaluation for infection with amniocentesis is not indicated.

Pediatric-care providers should be informed about HIV-infected mothers who have suspected or confirmed *T. gondii* infection to allow evaluation of their neonates for evidence of congenital infection (**AIII**).

Indications for treatment of *T. gondii* during pregnancy should be based on confirmed or suspected infection in the mother and the risk of transmission of the parasite from mother to fetus. 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 pregnant women are universally screened and treated, infected offspring are reported to have primarily mild disease and rarely severe disease. In contrast, in countries without a universal screening program (e.g. United States), infected offspring mostly present with severe disease.⁸⁵

Pregnant HIV-infected women who have evidence of primary toxoplasmic infection, without TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists (**BIII**). Studies published since 2007 support treatment of toxoplasmosis during pregnancy in an effort to decrease vertical transmission and reduce the severity of clinical signs in the offspring.⁸⁶⁻⁸⁹ In the setting of primary infection during pregnancy, spiramycin is recommended to prevent congenital transmission. Spiramycin is not commercially available in the United States but can be obtained at no cost after consultation with PAMF-TSL, telephone number (650) 853-4828, or the US [Chicago, IL] National Collaborative Treatment Trial Study [NCCTS], telephone number (773) 834-4152 through the US Food and Drug Administration, telephone number (301) 796-1400. It is administered orally at a dosage of 1.0 g (or 3 million U) every 8 h (total dosage of 3 g or 9 million U per day). Spiramycin is not teratogenic, does not treat infection in the fetus and is primarily indicated for fetal prophylaxis. Spiramycin should be continued until delivery in women with low suspicion of fetal infection or those with documented negative results of amniotic fluid PCR and negative findings on ultrasounds at follow-up.

Pyrimethamine/sulfadiazine/leucovorin is recommended for pregnant women with a strong suspicion of fetal infection: those suspected of having acquired the infection at ≥ 18 weeks of gestation,⁹⁰ those with positive AF PCR, or those with ultrasounds suggestive of congenital toxoplasmosis. Pyrimethamine should not be used in the first trimester because of teratogenicity concerns. The combination of pyrimethamine and sulfadiazine can decrease disease severity.

Treatment of pregnant women with TE should be the same as in non-pregnant adults (**BIII**), including pyrimethamine plus sulfadiazine plus leucovorin (**AI**), and in consultation with appropriate specialists (**BIII**).^{2,39-41} Of note, this regimen is often used to treat the infected fetus.⁷⁹

Although pyrimethamine has been associated with birth defects in animals, human data have not suggested an increased risk for defects, therefore, it can be administered to pregnant women after the first trimester.^{77,91-94} Similarly, sulfadiazine appears safe in pregnancy.⁹⁵ A randomized, controlled trial published in 1956 found that premature infants receiving prophylactic penicillin/sulfisoxazole were at significantly higher risk of mortality (specifically kernicterus), compared with infants who received oxytetracycline.⁹⁶

Because of these findings, some clinicians are concerned about the risk of neonatal kernicterus in the setting of maternal use of sulfa (including sulfadiazine) near delivery, although there are no studies published to date linking late third-trimester maternal sulfa use and neonatal death or kernicterus. The infant's care provider should be notified of maternal sulfa use in late pregnancy.

The preferred alternative regimen for patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin (**AI**).^{39,40} Clindamycin is considered safe throughout pregnancy. Atovaquone may be used if indicated. While there are limited data on atovaquone safety in humans, preclinical studies have not demonstrated toxicity.⁹²

TMP-SMX can be administered for primary prophylaxis against TE as described for PCP (**AIII**). The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk of TE. Maintenance therapy should be provided, using the same indications as for non-pregnant women. As noted above, pyrimethamine and sulfadiazine are considered safe in pregnancy. Clindamycin may be substituted for sulfadiazine for sulfa-intolerant patients. Dapsone appears to cross the placenta.^{97,98} Over the past several decades, dapsone (used for primary prophylaxis) has been used safely in pregnancy to treat leprosy, malaria, and various dermatologic conditions.^{98,99} With long-term therapy, there is a risk of mild maternal hemolysis and a potential—although extremely low—risk of hemolytic anemia in exposed fetuses with G6PD deficiency.¹⁰⁰

When providing preconception care for HIV-infected women receiving TE prophylaxis, providers should discuss the option of deferring pregnancy until TE prophylaxis can be safely discontinued (**BIII**).

Recommendations for Preventing and Treating *Toxoplasma gondii* Encephalitis (page 1 of 2)

Preventing 1st Episode of *Toxoplasma gondii* Encephalitis (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis:

- *Toxoplasma* IgG positive patients with CD4 count <100 cells/mm³ (**AII**)

Note: All the recommended regimens for preventing 1st episode of toxoplasmosis are also effective in preventing PCP.

Preferred Regimen:

- TMP-SMX 1 DS PO daily (**AII**)

Alternative Regimens:

- TMP-SMX 1 DS PO three times weekly (**BIII**), *or*
- TMP-SMX 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 (**BI**), *or*
- Atovaquone^b 1500 mg PO daily (**CIII**), *or*
- (Atovaquone^b 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily (**CIII**)

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >200 cells/mm³ for >3 months in response to ART (**AI**); *or*
- Can consider if CD4 count is 100-200 cells/mm³ and HIV RNA levels remain below limits of detection for at least 3-6 months (**BII**).

Indication for Restarting Primary Prophylaxis:

- CD4 count <100 to 200 cells/mm³ (**AIII**)

Treating *Toxoplasma gondii* Encephalitis

Preferred Regimen (AI):

- Pyrimethamine 200 mg PO once, followed by dose based on body weight:

Body weight ≤ 60 kg:

- pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

Body weight >60 kg:

- pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

Note: if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (**BI**). 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**).

Alternative Regimens:

- Pyrimethamine (leucovorin)^c plus clindamycin 600 mg IV or PO q6h (**AI**); preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine; must add additional agent for PCP prophylaxis, *or*
- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID (**BI**), *or*
- Atovaquone^b 1500 mg PO BID + pyrimethamine (leucovorin)^c (**BI**), *or*
- Atovaquone^b 1500 mg PO BID + sulfadiazine (**BII**), *or*
- Atovaquone^b 1500 mg PO BID (**BII**), *or*

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 Regimen:

- Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily (**AI**)

Alternative Regimen:

- Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily (**BI**); must add additional agent to prevent PCP (**AII**), *or*
- TMP-SMX DS 1 tablet BID (**BII**), *or*
- TMP-SMX DS 1 tablet daily (**BII**), *or*
- Atovaquone^b 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, *or*
- Atovaquone^b 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) (**BII**), *or*
- Atovaquone^b 750–1500 mg PO BID (**BII**)

Discontinuing Chronic Maintenance Therapy:

- Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4 count >200 cells/mm³ for >6 months in response to ART (**BI**)

Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance

- CD4 count <200 cells/mm³ (**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**); discontinue as soon as clinically feasible.
- Anticonvulsants should be administered to patients with a history of seizures (**AIII**) and continued through at least through the period of acute treatment; anticonvulsants **should not be used** as seizure prophylaxis (**BIII**).

^a Whenever possible, patients should be tested for G6PD deficiency before administering 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 as doses listed in Preferred Regimen for Acute Infection

^d Sulfadiazine dose: Same as weight-based dose listed in Preferred Regimen for Acute Infection

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; IV = intravenous; PCP = *Pneumocystis Pneumonia*; PO = orally; q(n)h = every “n” hours; SS = single strength; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole

References

1. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet*. Apr 9 1983;1(8328):781-784. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Sep 30 1993;329(14):995-1000. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8366923>.
3. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med*. Jan 1984;100(1):36-42. Available at <http://www.ncbi.nlm.nih.gov/pubmed/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*. Apr 1993;6(4):414-418. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8455146>.
5. Mathews WC, Fullerton SC. Use of a clinical laboratory database to estimate Toxoplasma seroprevalence among human immunodeficiency virus-infected patients. Overcoming bias in secondary analysis of clinical records. *Arch Pathol Lab Med*. Aug 1994;118(8):807-810. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8060230>.
6. Jones JL, Kruszon-Moran D, Sanders-Lewis K, Wilson M. Toxoplasma gondii infection in the United States, 1999-2004, decline from the prior decade. *Am J Trop Med Hyg*. Sep 2007;77(3):405-410. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17827351>.
7. 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*. Nov 15 2001;33(10):1747-1755. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11595976>.
8. 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*. Jan 1996;173(1):91-97. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8537688>.
9. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA*. Aug 17 1984;252(7):913-917. Available at <http://www.ncbi.nlm.nih.gov/pubmed/6748191>.
10. Jones JL, Dargelas V, Roberts J, Press C, Remington JS, Montoya JG. Risk factors for Toxoplasma gondii infection in the United States. *Clin Infect Dis*. Sep 15 2009;49(6):878-884. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19663709>.
11. 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*. Feb 2005;192(2):564-571. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15696004>.
12. 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 <http://www.ncbi.nlm.nih.gov/pubmed/2325518>.
13. 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*. Oct 15 1995;123(8):594-598. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7677300>.
14. 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*. Nov 1994;15(10):1885-1894. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1251111>.

nlm.nih.gov/pubmed/7863938.

15. Gray F, Gherardi R, Wingate E, et al. Diffuse “encephalitic” cerebral toxoplasmosis in AIDS. Report of four cases. *J Neurol*. Jul 1989;236(5):273-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2760644>.
16. 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*. Nov 1996;10(13):1521-1527. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8931787>.
17. 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*. Aug 1981;12(8):690-698. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7026410>.
18. 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*. Dec 1994;8(12):1691-1694. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7888118>.
19. 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*. Jan 1997;11(1):1-17. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9110070>.
20. 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*. Jun 2010;59(Pt 6):641-647. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20150319>.
21. 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*. Mar 1997;48(3):687-694. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9065549>.
22. 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*. Feb 1999;17(2):554-560. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10080599>.
23. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. Jan 15 1999;52(2):253-260. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9932940>.
24. US Department of Health & Human Services. FoodSafety.gov: your gateway to federal food safety information. Available at <http://www.foodsafety.gov>. Accessed March 26, 2013.
25. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. Jul 15 1992;117(2):106-111. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1351371>.
26. Miro JM, Murray HW, Katlama C. Toxoplasmosis. In: Dolin R, Masur H, Saag MS, eds. *AIDS Therapy*. Third ed. New York, New York: Churchill Livingstone 2008:659-681.
27. Podzamczar 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*. May 15 1995;122(10):755-761. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7717598>.
28. 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*. Mar 1995;20(3):531-541. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7756472>.
29. 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*. May 27 1993;328(21):1514-1520. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8479488>.
30. 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*. Mar 16 1995;332(11):693-699. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7854375>.
31. 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*. Aug 2000;182(2):611-615. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10915098>.
32. 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*. Sep 10 1999;13(13):1647-1651. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10509565>.

33. 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*. Jun 24 2000;355(9222):2217-2218. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10881897>.
34. 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*. May 2000;181(5):1635-1642. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10823763>.
35. Miro JM, Lopez JC, Podzamczar 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*. Jul 1 2006;43(1):79-89. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16758422>.
36. 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. CROI; 2016; Boston, Massachusetts.
37. Opportunistic Infections Project Team of the Collaboration of Observational HIViE, Mocroft A, Reiss P, et al. Is it safe to discontinue primary *Pneumocystis jirovecii* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. Sep 1 2010;51(5):611-619. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20645862>.
38. Furrer H, Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. HIV Replication is a Major Predictor of Primary and Recurrent *Pneumocystis Pneumonia* - Implications for Prophylaxis Recommendations. 15th European AIDS Conference; October 21-24, 2015, 2015; Barcelona, Spain.
39. 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*. Feb 1996;22(2):268-275. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8838183>.
40. 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*. Jan 1 1992;116(1):33-43. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1727093>.
41. 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*. Jan 1988;84(1):94-100. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3337134>.
42. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS*. Sep 1992;6(9):1040-1041. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1388895>.
43. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for *Toxoplasma encephalitis* are associated with better outcome. *J Infect Dis*. May 1996;173(5):1294-1295. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8627092>.
44. 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*. Jun 1998;42(6):1346-1349. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9624473>.
45. 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*. Apr 2009;80(4):583-587. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19346380>.
46. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. Aug 2004;24(3):425-443, vi. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15242719>.
47. 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*. Apr 1995;20(4):849-853. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7795084>.
48. Nguyen MT, Weiss PJ, Wallace MR. Two-day oral desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients. *AIDS*. Jun 1995;9(6):573-575. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7662195>.
49. 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*. Oct 15 2001;184(8):992-997. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11574913>.
50. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol*. Dec 1998;102(6 Pt 1):1033-1036. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9847446>.
 51. 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*. Feb 2000;54(1):45-49. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10721462>.
 52. 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*. May 1 2002;34(9):1243-1250. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11941551>.
 53. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. *Lancet*. Sep 12 1992;340(8820):637-638. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1355212>.
 54. 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*. Mar 1997;24(3):422-429. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9114194>.
 55. 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*. Sep 1996;10(10):1107-1112. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8874627>.
 56. 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*. Nov 1993;12(11):853-856. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8112357>.
 57. 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*. Mar 30 2001;15(5):583-589. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11316995>.
 58. 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*. Oct 1991;35(10):2049-2052. Available at <http://www.ncbi.nlm.nih.gov/pubmed/1836943>.
 59. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS*. Jan 1993;7(1):143-144. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8442914>.
 60. 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*. Feb 1991;35(2):252-255. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2024957>.
 61. 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*. Jan 1995;39(1):276-277. Available at <http://www.ncbi.nlm.nih.gov/pubmed/7695324>.
 62. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis*. 1993;25(1):157-160. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8460343>.
 63. 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>.
 64. Pfeffer G, Prout A, Hooge J, Maguire J. Biopsy-proven immune reconstitution syndrome in a patient with AIDS and cerebral toxoplasmosis. *Neurology*. Jul 28 2009;73(4):321-322. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19636053>.
 65. Tremont-Lukats IW, Garcarena P, Juarbe R, El-Abassi RN. The immune inflammatory reconstitution syndrome and central nervous system toxoplasmosis. *Ann Intern Med*. May 5 2009;150(9):656-657. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19414855>.
 66. 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*. Jun 2011;82(6):691-693. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20660912>.

67. Cabral RF, Valle Bahia PR, Gasparetto EL, Chimelli L. Immune reconstitution inflammatory syndrome and cerebral toxoplasmosis. *AJNR Am J Neuroradiol*. Aug 2010;31(7):E65-66. Available at <http://www.ncbi.nlm.nih.gov/pubmed/20507930>.
68. van Bilsen WPH, van den Berg C, Rijnders BJA, et al. Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients. *AIDS*. Jun 19 2017;31(10):1415-1424. Available at <http://www.ncbi.nlm.nih.gov/pubmed/28375874>.
69. 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*. Feb 2004;48(2):635-637. Available at <http://www.ncbi.nlm.nih.gov/pubmed/14742225>.
70. Podzamczar 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*. Feb 2000;19(2):89-95. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10746493>.
71. 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*. Dec 24 1998;339(26):1889-1895. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9862944>.
72. 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*. Jun 18 2004;18(9):1342-1344. Available at <http://www.ncbi.nlm.nih.gov/pubmed/15362670>.
73. 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*. Mar 10 2000;14(4):383-386. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10770540>.
74. 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*. Jul 2006;12(7):666-671. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16774564>.
75. Miro JM. Stopping Secondary TE Prophylaxis in Suppressed Patients with CD4 100-200 Is Not Safe. CROI; 2017; Seattle, Washington.
76. 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*. Sep 1996;68(1-2):93-96. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8886688>.
77. 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*. Sep 15 1996;223(2):351-361. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8806570>.
78. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. Feb 15 2002;185 Suppl 1:S73-82. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11865443>.
79. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. Aug 15 2008;47(4):554-566. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18624630>.
80. 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*. Jul 1990;9(7):512-518. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2371084>.
81. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet*. May 29 1999;353(9167):1829-1833. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10359407>.
82. 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 <http://www.ncbi.nlm.nih.gov/pubmed/27055272>.
83. 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*. Feb 2009;200(2):160 e161-169. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18986640>.
84. 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*. Feb 2001;97(2):296-300. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11165598>.

85. Peyron F, McLeod R, Ajzenberg D, et al. Congenital Toxoplasmosis in France and the United States: One Parasite, Two Diverging Approaches. *PLoS Negl Trop Dis*. Feb 2017;11(2):e0005222. Available at <http://www.ncbi.nlm.nih.gov/pubmed/28207736>.
86. 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*. Oct 12 2010;7(10). Available at <http://www.ncbi.nlm.nih.gov/pubmed/20967235>.
87. Hotop A, Hlobil H, Gross U. Efficacy of rapid treatment initiation following primary *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. Jun 2012;54(11):1545-1552. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22460980>.
88. 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*. Jan 2008;27(1):27-32. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18162934>.
89. Prusa AR, Kasper DC, Pollak A, Gleiss A, Waldhoer T, Hayde M. The Austrian Toxoplasmosis Register, 1992-2008. *Clin Infect Dis*. Jan 15 2015;60(2):e4-e10. Available at <http://www.ncbi.nlm.nih.gov/pubmed/25216688>.
90. Moncada PA, Montoya JG. Toxoplasmosis in the fetus and newborn: an update on prevalence, diagnosis and treatment. *Expert Rev Anti Infect Ther*. Jul 2012;10(7):815-828. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22943404>.
91. 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 <http://www.ncbi.nlm.nih.gov/pubmed/17536875>.
92. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. Jan 2006;1(1):1-15. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18690910>.
93. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis*. Jun 1994;18(6):853-861; quiz 862. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8086543>.
94. 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*. Jul-Aug 2001;95(4):424-428. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11579889>.
95. 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 <http://www.ncbi.nlm.nih.gov/pubmed/7388849>.
96. 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*. Oct 1956;18(4):614-625. Available at <http://www.ncbi.nlm.nih.gov/pubmed/13370229>.
97. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. Jul-Aug 1986;11(4):299-315. Available at <http://www.ncbi.nlm.nih.gov/pubmed/3530584>.
98. 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>.
99. 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*. Jun 2003;8(6):488-506. Available at <http://www.ncbi.nlm.nih.gov/pubmed/12791054>.
100. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. May 1989;82(5):668. Available at <http://www.ncbi.nlm.nih.gov/pubmed/2717998>.

Varicella-Zoster Virus Diseases

Updated: September 7, 2022

Reviewed: January 11, 2023

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/mm³, 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 exclusively²⁰ in patients with AIDS with CD4 counts <100 cells/mm³. 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/mm³ 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 coinfecting 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 $\geq 15\%$)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/mm³ (**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/mm³) 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/mm³) 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 distributors (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 ART⁴³ with CD4 count ≥ 200 cells/mm³, 14 adults receiving ART with CD4 count < 200 cells/mm³, and 15 ART-naïve adults with CD4 count ≥ 500 cells/mm³. 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/mm³. 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/mm³ 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 intravitreal injection of ganciclovir as part of the initial induction therapy. Additional intravitreal 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 valacyclovir 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/mm³ 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/mm³, 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

- Vari IG 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 Vari IG 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 V V 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

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

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 intravitreal 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-naïve 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. Pastuszek 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

This table provides recommendations for the use of chemoprophylaxis to prevent the first episode of opportunistic disease. For the use of immunizations to prevent hepatitis A virus, hepatitis B virus, human papillomavirus, influenza A and B viruses, *Streptococcus pneumoniae*, and varicella-zoster virus infections, please refer to the [Immunizations for Preventable Diseases in Adults and Adolescents with HIV](#) section.

Updated: February 17, 2022

Reviewed: January 11, 2023

Opportunistic Infections	Indication	Preferred	Alternative
Coccidioidomycosis	A new positive IgM or IgG serologic test in patients who live in a disease-endemic area and with CD4 count <250 cells/ μ L (BIII)	Fluconazole 400 mg PO daily (BIII)	
<i>Histoplasma capsulatum</i> infection	CD4 count \leq 150 cells/ μ L and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) (BI)	Itraconazole 200 mg PO daily (BI)	
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and HIV-uninfected patients. 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 .	
<i>Mycobacterium avium</i> complex (MAC) disease	CD4 count <50 cells/mm ³ Not recommended for those who immediately initiate ART (AII). Recommended for those who are not on fully suppressive ART, after ruling out active disseminated MAC disease (AI).	Azithromycin 1,200 mg PO once weekly (AI), <i>or</i> Clarithromycin 500 mg PO BID (AI), <i>or</i> Azithromycin 600 mg PO twice weekly (BIII)	Rifabutin (dose adjusted based on concomitant ART) ^a (BI); rule out active TB before starting rifabutin.

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
<i>Mycobacterium tuberculosis</i> infection (TB) (i.e., treatment of latent TB infection [LTBI])	<p>Positive screening test for LTBI,^b with no evidence of active TB, and no prior treatment for active TB or LTBI (AI), <i>or</i></p> <p>Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results (AII)</p> <p>LTBI treatment and ART act independently to decrease the risk of TB disease. Thus, ART is recommended for all persons with HIV and LTBI (AI).</p>	<p>(Rifapentine [see dose below] plus INH 900 mg plus pyridoxine 50 mg) PO once weekly for 12 weeks (AII)</p> <p>Note: Rifapentine is recommended only for persons receiving EFV, RAL, or once daily DTG -based ARV regimen.</p> <p>Weight-Based Rifapentine Dose</p> <ul style="list-style-type: none"> • <i>Weighing</i> 32.1–49.9 kg: 750 mg PO once weekly • <i>Weighing</i> >50 kg: 900 mg PO once weekly <p><i>or</i></p> <p>(INH 300 mg plus rifampin 600mg plus pyridoxine 25–50 mg) PO daily for 3 months (AI)</p> <p>See the Dosing Recommendations for Anti-TB Drugs table in the Mycobacterium tuberculosis Infection and Disease section for the list of ARV drugs not recommended to be used with rifampin and those which require dosage adjustment.</p>	<p>(INH 300 mg plus pyridoxine 25–50 mg) PO daily for 9 months (AII), <i>or</i></p> <p>Rifampin 600 mg PO daily for 4 months (BI), <i>or</i></p> <p>(Rifapentine [see dose below] plus INH 300 mg plus pyridoxine 25–50 mg) PO once daily for 4 weeks (AII)</p> <p>Weight-Based Rifapentine Dose</p> <ul style="list-style-type: none"> • <i>Weighing</i> <35 kg: 300 mg PO once daily • <i>Weighing</i> 35–45 kg: 450 mg PO once daily • <i>Weighing</i> >45 kg: 600 mg PO once daily <p>See the Dosing Recommendations for Anti-TB Drugs table in the Mycobacterium tuberculosis Infection and Disease section for the list of ARV drugs not recommended to be used with rifampin and those which require dosage adjustment.</p> <p>For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities (AII).</p>
<i>Pneumocystis</i> Pneumonia (PCP)	<p>CD4 count <200 cells/mm³ (AI), <i>or</i></p> <p>CD4 <14% (BII), <i>or</i></p> <p>If ART initiation must be delayed, CD4 count ≥200 cells/mm³ but <250 cells/mm³ and if monitoring of CD4 cell count every 3 months is not possible (BII)</p> <p>Note: Patients who are receiving pyrimethamine/ sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII).</p>	<p>TMP-SMX^c 1 DS tablet PO daily (AI), <i>or</i></p> <p>TMP-SMX^c 1 SS tablet daily (AI)</p>	<ul style="list-style-type: none"> • TMP-SMX^c 1 DS PO three times weekly (BI), <i>or</i> • Dapsone^d 100 mg PO daily or 50 mg PO BID (BI), <i>or</i> • Dapsone^d 50 mg PO daily with (pyrimethamine^e 50 mg plus leucovorin 25 mg) PO weekly (BI), <i>or</i> • (Dapsone^d 200 mg plus pyrimethamine^e 75 mg plus leucovorin 25 mg) PO weekly (BI); <i>or</i> • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month (BI), <i>or</i> • Atovaquone 1,500 mg PO daily (BI), <i>or</i> • (Atovaquone 1,500 mg plus pyrimethamine^e 25 mg plus leucovorin 10 mg) PO daily (CIII)

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
Syphilis	<p>For individuals exposed to a sex partner with a diagnosis of primary, secondary, or early latent syphilis within the past 90 days (AII), <i>or</i></p> <p>For individuals exposed to a sex partner >90 days before syphilis diagnosis in the partner, if serologic test results are not available immediately and the opportunity for follow-up is uncertain (AIII)</p>	Benzathine penicillin G 2.4 million units IM for 1 dose (AII)	<p>For penicillin-allergic patients:</p> <ul style="list-style-type: none"> • Doxycycline 100 mg PO BID for 14 days (BII), <i>or</i> • Ceftriaxone 1 g IM or IV daily for 8–10 days (BII), <i>or</i> • Azithromycin 2 g PO for 1 dose (BII)—not recommended for men who have sex with men or pregnant people (AII)
Talaromycosis (Penicilliosis)	<p>Persons with HIV and CD4 cell counts <100 cells/mm³, who are unable to have ART, or have treatment failure without access to effective ART options, and—</p> <ul style="list-style-type: none"> • Who reside in the highly endemic regions* in northern Thailand, northern or southern Vietnam, or southern China (BI), <i>or</i> • Who are from countries outside of the endemic region, and must travel to the region (BIII) <p>* Particularly in highland regions during the rainy and humid months</p>	<p>For persons who reside in endemic areas, itraconazole 200 mg PO once daily (BI)</p> <p>For those traveling to the highly endemic regions, begin itraconazole 200 mg PO once daily 3 days before travel, and continue for 1 week after leaving the endemic area (BIII).</p>	<p>For persons who reside in endemic areas, fluconazole 400 mg PO once weekly (BII)</p> <p>For those traveling to the highly endemic 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 endemic area (BIII).</p>
<i>Toxoplasma gondii</i> encephalitis	<p>Toxoplasma IgG-positive patients with CD4 count <100 cells/μL (AII)</p> <p>Note: All regimens recommended for primary prophylaxis against toxoplasmosis also are effective as PCP prophylaxis.</p>	TMP-SMX ^a 1 DS PO daily (AII)	<ul style="list-style-type: none"> • TMP-SMX^c 1 DS PO three times weekly (BIII), <i>or</i> • TMP-SMX^c 1 SS PO daily (BIII), <i>or</i> • Dapsone^d 50 mg PO daily plus (pyrimethamine^e 50 mg plus leucovorin 25 mg) PO weekly (BI), <i>or</i> • (Dapsone^d 200 mg plus pyrimethamine^e 75 mg plus leucovorin 25 mg) PO weekly (BI), <i>or</i> • Atovaquone 1500 mg PO daily (CIII), <i>or</i> • (Atovaquone 1500 mg plus pyrimethamine^e 25 mg plus leucovorin 10 mg) PO daily (CIII)

^a Refer to the [Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines](#) for dosing recommendations.

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

^b Screening tests for LTBI include tuberculin skin test or interferon-gamma release assays.

^c TMP-SMX DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection.

^d Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) before administration of dapsone or primaquine. An alternative agent should be used in patients found to have G6PD deficiency.

^e 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 Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

Key: ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; 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: January 18, 2023

Reviewed: January 18, 2023

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections	Empiric therapy pending definitive diagnosis	<p>Diagnostic fecal specimens should be obtained before the 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. Reflex culture for antibiotic susceptibilities should also be done if diagnosis is made using PCR-based methods.</p> <p>Empiric antibiotic therapy may be indicated for patients with CD4 count 200–500 cells/mm³ when diarrhea is severe enough to compromise quality of life or the ability to work (CIII) and is indicated in patients with CD4 count <200 cells/mm³ or concomitant AIDS-defining illness and with clinically severe diarrhea (≥6 stools per day or bloody stool) and/or accompanying fever or chills (AIII).</p> <p>Empiric Therapy</p> <ul style="list-style-type: none"> Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 5 days (AIII) (particularly if diarrhea is not associated with international travel) <p>Therapy should be adjusted based on the results of a diagnostic work-up.</p> <p>For patients with chronic diarrhea (>14 days) without severe clinical signs, empiric antibiotics therapy is not necessary. Treatment can be withheld until a diagnosis is made.</p>	<p>Empiric Therapy</p> <p><i>In Patients with Marked Nausea, Vomiting, Diarrhea, Electrolyte Abnormalities, Acidosis, Blood Pressure Instability, and/or When Hospitalization Is Needed</i></p> <ul style="list-style-type: none"> Ceftriaxone 1 g IV every 24 hours (BIII), or Cefotaxime 1 g IV every 8 hours (BIII) 	<p>Oral or IV rehydration (if indicated) should be given to patients with diarrhea (AIII).</p> <p>Anti-motility agents should be avoided if there is concern about inflammatory diarrhea, including CDI (BIII).</p> <p>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 interactions.</p>

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
	Campylobacteriosis	<p>For Mild Disease and if CD4 Count >200 Cells/mm³</p> <ul style="list-style-type: none"> No therapy unless symptoms persist for more than several days (CIII). <p>For Mild to Moderate Disease (if Susceptible)</p> <ul style="list-style-type: none"> Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days (BIII), <i>or</i> Azithromycin 500 mg PO daily for 5 days (BIII) (Note: Not for patients with bacteremia [AIII]) <p>For <i>Campylobacter</i> Bacteremia</p> <ul style="list-style-type: none"> 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) <p>For Recurrent Infections</p> <ul style="list-style-type: none"> Duration of therapy may be extended to 2–6 weeks (BIII). 	<p>For Mild-to-Moderate Disease (if Susceptible)</p> <ul style="list-style-type: none"> Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), <i>or</i> Moxifloxacin 400 mg (PO or IV) every 24 hours (BIII) Add an aminoglycoside to fluoroquinolone in bacteremic patients (BIII). 	<p>Oral or IV rehydration if indicated (AIII)</p> <p>Anti-motility agents should be avoided (BIII).</p> <p>If no clinical response is observed after 5–7 days, consider a follow-up stool culture, alternative diagnosis, or antibiotic resistance.</p> <p>In the United States in 2018, 29% of <i>C. jejuni</i> isolates were resistant to ciprofloxacin and 2% were resistant to azithromycin; among <i>C. coli</i> isolates, 40.5% were resistant to fluoroquinolone and 13.3% were resistant to azithromycin.</p> <p>The rationale for addition of an aminoglycoside to a fluoroquinolone in bacteremic patients is to prevent emergence of quinolone resistance.</p> <p>Effective ART may reduce the frequency, severity, and recurrence of <i>Campylobacter</i> infections.</p>
	<i>Clostridium difficile</i> infection (CDI)	<p>Fidaxomicin 200 mg PO two times daily for 10 days (AI)</p> <p>Vancomycin 125 mg PO four times daily for 10 days (AI)</p> <p>For severe, life-threatening CDI, see text and references for additional information.</p>	<p>For Nonsevere CDI</p> <p><i>If Fidaxomicin or Vancomycin Access Is Limited</i></p> <ul style="list-style-type: none"> Metronidazole 500 mg (PO) three times daily for 10 days (CII) 	<p>Recurrent CDI</p> <p>Treatment is the same as in patients without HIV infection.</p> <p>Bezlotoximab (CIII) or fecal microbiota therapy may be successful and safe to treat recurrent CDI (CIII). See text and references for additional information.</p>
	Salmonellosis	<p>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 7-fold) compared to individuals without HIV (AIII).</p> <ul style="list-style-type: none"> Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours, if susceptible (AIII) 	<ul style="list-style-type: none"> Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), <i>or</i> 	<p>Oral or IV rehydration if indicated (AIII)</p> <p>Anti-motility agents should be avoided (BIII).</p>

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
		<p>Duration of Therapy <i>For Gastroenteritis Without Bacteremia</i></p> <ul style="list-style-type: none"> If CD4 count ≥ 200 cells/mm³: 7–14 days (BIII) If CD4 count < 200 cells/mm³: 2–6 weeks (BIII) <p><i>For Gastroenteritis with Bacteremia</i></p> <ul style="list-style-type: none"> If CD4 count ≥ 200/mm³: 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/mm³: 2–6 weeks (BIII) <p>Secondary Prophylaxis Should Be Considered</p> <ul style="list-style-type: none"> For patients with recurrent <i>Salmonella</i> bacteremia (BIII), or For patients with recurrent gastroenteritis (with or without bacteremia) with CD4 count < 200 cells/mm³ with severe diarrhea (BIII) 	<ul style="list-style-type: none"> Moxifloxacin 400 mg (PO or IV) every 24 hours (BIII), or TMP 160 mg-SMX 800 mg (PO or IV) every 12 hours (BIII), or Ceftriaxone 1 g IV every 24 hours (BIII), or Cefotaxime 1 g IV every 8 hours (BIII) 	<p>The role of long-term secondary prophylaxis in patients with recurrent <i>Salmonella</i> bacteremia is not well established. Must weigh benefit against risks of long-term antibiotic exposure (BIII).</p> <p>Effective ART may reduce the frequency, severity, and recurrence of salmonella infections.</p>
	Shigellosis	<ul style="list-style-type: none"> Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (if MIC < 0.12 μg/mL (AIII)) <p>Duration of Therapy</p> <ul style="list-style-type: none"> Gastroenteritis: 7–10 days (AIII) Bacteremia: ≥ 14 days (BIII) Recurrent infections: Up to 6 weeks (BIII) <p>Note: Increased resistance of <i>Shigella</i> to fluoroquinolones is occurring in the United States. Avoid fluoroquinolones if ciprofloxacin MIC is ≥ 0.12 μg/mL, even if the laboratory identifies the isolate as</p>	<ul style="list-style-type: none"> Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), or Moxifloxacin 400 mg (PO or IV) every 24 hours (BIII), or TMP 160 mg-SMX 800 mg (PO or IV) every 12 hours (BIII) (Note: <i>Shigella</i> infections acquired outside of the United States have high rates of TMP-SMX resistance), or Azithromycin 500 mg PO daily for 5 days (BIII) (Note: not 	<p>Therapy may slightly shorten duration of illness and/or prevent spread of infection (AIII).</p> <p>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/mm³ whose diarrhea resolves prior to culture confirmation of <i>Shigella</i> infection (CIII).</p> <p>Oral or IV rehydration if indicated (AIII).</p>

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
		<p>sensitive. Many <i>Shigella</i> strains resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Thus, antibiotic sensitivity testing of <i>Shigella</i> isolates from individuals with HIV should be performed routinely.</p>	<p>recommended for patients with bacteremia [AIII].)</p> <p>Note: Azithromycin-resistant <i>Shigella</i> spp. has been reported in MSM with HIV.</p>	<p>Anti-motility agents should be avoided (BIII).</p> <p>If no clinical response after 5–7 days, consider a follow-up stool culture, alternative diagnosis, or antibiotic resistance.</p> <p>Effective ART may decrease the risk of recurrence of <i>Shigella</i> infections.</p>
Bartonellosis		<p>For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis</p> <ul style="list-style-type: none"> • Doxycycline 100 mg PO or IV every 12 hours (AII), or • Erythromycin 500 mg PO or IV every 6 hours (AII) <p>CNS Infections</p> <ul style="list-style-type: none"> • (Doxycycline 100 mg +/- RIF 300 mg) PO or IV every 12 hours (AIII) <p>Confirmed <i>Bartonella</i> Endocarditis</p> <ul style="list-style-type: none"> • (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) <p>Other Severe Infections</p> <ul style="list-style-type: none"> • (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) <p>Duration of Therapy</p> <ul style="list-style-type: none"> • At least 3 months (AII) 	<p>For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis</p> <ul style="list-style-type: none"> • Azithromycin 500 mg PO daily (BIII) • Clarithromycin 500 mg PO twice a day (BIII) <p>Confirmed <i>Bartonella</i> Endocarditis, but with Renal Insufficiency</p> <ul style="list-style-type: none"> • (Doxycycline 100 mg IV plus RIF 300 mg PO or IV) every 12 hours for 2 weeks, then continue with doxycycline 100 mg IV or PI every 12 hours (BII) 	<p>When RIF is used, take into consideration the potential for significant interaction with ARV drugs and other medications (see Table 4 for dosing recommendations).</p> <p>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/mm³ (AIII).</p>
Candidiasis (Mucocutaneous)		For Oropharyngeal Candidiasis; Initial Episodes (for 7–14 Days)	For Oropharyngeal Candidiasis; Initial Episodes (for 7–14 Days)	Chronic or prolonged use of azoles may promote development of resistance.

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
	<p><i>Oral Therapy</i></p> <ul style="list-style-type: none"> Fluconazole 100 mg PO daily (AI) <p>For Esophageal Candidiasis (for 14–21 Days)</p> <ul style="list-style-type: none"> Fluconazole 100 mg (up to 400 mg) PO or IV daily (AI), <i>or</i> Itraconazole oral solution 200 mg PO daily (AI) <p>For Uncomplicated Vulvo-Vaginal Candidiasis</p> <ul style="list-style-type: none"> Oral fluconazole 150 mg for one dose (AII), <i>or</i> Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (AII) <p>For Severe or Recurrent Vulvo-Vaginal Candidiasis</p> <ul style="list-style-type: none"> Fluconazole 100–200 mg PO daily for ≥7 days (AII), <i>or</i> Topical antifungal ≥7 days (AII) 	<p><i>Oral Therapy</i></p> <ul style="list-style-type: none"> Itraconazole oral solution 200 mg PO daily (BI), <i>or</i> Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily (BI) <p><i>Topical Therapy</i></p> <ul style="list-style-type: none"> Clotrimazole troches, 10 mg PO five times daily (BI), <i>or</i> Miconazole mucoadhesive buccal 50-mg tablet; apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet) (BI), <i>or</i> Nystatin suspension 4–6 mL four times a day or one to two flavored pastilles four to five times daily (BII) Gentian violet (0.00165%) topical application twice daily (BI) <p>For Esophageal Candidiasis (for 14–21 Days)</p> <ul style="list-style-type: none"> Voriconazole 200 mg PO or IV twice a day (BI), <i>or</i> Isavuconazole 200 mg PO as a loading dose, followed by 50 mg PO daily (BI), <i>or</i> Isavuconazole 400 mg PO as a loading dose, followed by 100 mg PO daily (BI), <i>or</i> Isavuconazole 400 mg PO once weekly (BI), <i>or</i> 	<p>Higher relapse rate for esophageal candidiasis is seen with echinocandins than with fluconazole use.</p> <p>Suppressive therapy is usually not recommended (BIII) unless patients have frequent or severe recurrences.</p> <p>If Decision Is to Use Suppressive Therapy</p> <p><i>Oropharyngeal Candidiasis</i></p> <ul style="list-style-type: none"> Fluconazole 100 mg PO daily or three times weekly (BI), <i>or</i> Itraconazole oral solution 200 mg PO daily (CI) <p><i>Esophageal Candidiasis</i></p> <ul style="list-style-type: none"> Fluconazole 100–200 mg PO daily (BI); <i>or</i> Posaconazole 400 mg PO twice a day (BII) <p><i>Vulvo-Vaginal Candidiasis</i></p> <ul style="list-style-type: none"> Fluconazole 150 mg PO once weekly (CII)

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
		<ul style="list-style-type: none"> • Anidulafungin 100 mg IV one time, then 50 mg IV daily (BI), or • Caspofungin 50 mg IV daily (BI), or • Micafungin 150 mg IV daily (BI), or • Amphotericin B deoxycholate 0.6 mg/kg IV daily (BI), or • Lipid formulation of amphotericin B 3–4 mg/kg IV daily (BIII) <p>For Uncomplicated Vulvo-Vaginal Candidiasis</p> <ul style="list-style-type: none"> • Itraconazole oral solution 200 mg PO daily for 3–7 days (BII) <p>For Azole-Refractory <i>Candida glabrata</i> Vaginitis</p> <ul style="list-style-type: none"> • Boric acid vaginal suppository 600 mg once daily for 14 days 	
Chagas Disease (American Trypanosomiasis)	<p>For Acute, Early Chronic, and Reactivated Disease</p> <ul style="list-style-type: none"> • Benznidazole 5–8 mg/kg/day PO in two divided doses for 30–60 days (BIII) (not commercially available in the United States; contact the CDC Drug Service at drugservice@cdc.gov or 404-639-3670, or the CDC emergency operations center at 770-488-7100). 	<p>For Acute, Early Chronic, And Reactivated Disease</p> <ul style="list-style-type: none"> • Nifurtimox 8–10 mg/kg/day PO for 90–120 days (CIII) (not commercially available in the United States, contact the CDC Drug Service at drugservice@cdc.gov or 404-639-3670, or the CDC emergency operations center at 770-488-7100). 	<p>Treatment is effective in reducing parasitemia and preventing clinical symptoms or slowing disease progression. It is ineffective in achieving parasitological cure.</p> <p>Duration of therapy has not been studied in patients with HIV</p> <p>Initiate or optimize ART in patients undergoing treatment for Chagas disease once they are clinically stable (AIII).</p>
Coccidioidomycosis	<p>Mild to Moderate Pulmonary Infection</p> <ul style="list-style-type: none"> • Fluconazole 400 mg PO daily (AII), or 	<p>Mild to Moderate Pulmonary Infection</p> <p><i>For Patients Who Failed to Respond to Fluconazole or Itraconazole</i></p>	<p>Some patients with meningitis may develop hydrocephalus and require CSF shunting.</p> <p>Therapy should be lifelong in patients with meningeal</p>

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
	<ul style="list-style-type: none"> Itraconazole 200 mg 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, and CD4 count ≥ 250 cells/mm³, and viral suppression on ARV (AII) <p>Severe Pulmonary or Extrapulmonary Infection (except meningitis)</p> <ul style="list-style-type: none"> Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII); or Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII) Continue until clinical improvement, then switch to an azole (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/mm³ (BIII) <p>Meningeal Infections</p> <ul style="list-style-type: none"> Fluconazole 400–800 mg IV or PO daily (AII) Duration of therapy: lifelong (AII) 	<ul style="list-style-type: none"> Posaconazole delayed release tablet 300 mg PO twice a day for first day, then 300 mg PO once daily (BIII), or Voriconazole 400 mg PO twice daily for first day, then 200 mg PO twice a day (BIII) <p>Severe Pulmonary or Extrapulmonary Infection (except meningitis)</p> <ul style="list-style-type: none"> Some specialists will add a triazole (fluconazole or itraconazole, with itraconazole preferred for bone disease) 400 mg per day to amphotericin B therapy and continue triazole once amphotericin B is stopped (CIII). <p>Meningeal Infections</p> <ul style="list-style-type: none"> Itraconazole 200 mg PO two or three times daily (BII), or Voriconazole 200–400 mg PO twice a day (BIII), or Posaconazole delayed release tablet 300 mg PO twice on first day, then 300 mg PO daily (CIII), or Isavuconazole sulfate 372 mg PO every 8 hrs for 6 doses, then 372 mg daily (CIII) Intrathecal amphotericin B deoxycholate, when triazole antifungals are ineffective (AIII) 	<p>infections because relapse occurs in 80% of patients with HIV after discontinuation of triazole therapy (AII).</p> <p>See Table 4 for antifungal drug-drug interactions.</p> <p>Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bi-directional. 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.</p> <p>Intrathecal amphotericin B should only be given in consultation with a specialist and administered by an individual with experience with the technique.</p>
Community-Acquired Pneumonia (CAP)	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and	Empiric antibiotic therapy should be initiated promptly for patients	Duration

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<p>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.</p> <p>Empiric Outpatient Therapy</p> <ul style="list-style-type: none"> A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) (AII) <p><i>Preferred Beta-Lactams</i></p> <ul style="list-style-type: none"> High-dose amoxicillin or amoxicillin/clavulanate <p><i>Alternative Beta-Lactams</i></p> <ul style="list-style-type: none"> Cefpodoxime or cefuroxime, <i>or</i> Levofloxacin 750 mg PO once daily (AII), <i>or</i> moxifloxacin 400 mg PO once daily (AII), especially for patients with penicillin allergies <p>Empiric Therapy for Hospitalized Patients with Non-Severe CAP</p> <ul style="list-style-type: none"> An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) (AI) <p><i>Preferred Beta-Lactams</i></p> <ul style="list-style-type: none"> Ceftriaxone, cefotaxime, or ampicillin-sulbactam Levofloxacin 750 mg IV once daily (AI), <i>or</i> moxifloxacin, 400 mg IV once daily (AI), especially for patients with penicillin allergies. 	<p>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.</p> <p>Empiric Outpatient Therapy</p> <ul style="list-style-type: none"> A PO beta-lactam plus PO doxycycline (CIII) <p><i>Preferred Beta-Lactams</i></p> <ul style="list-style-type: none"> High-dose amoxicillin or amoxicillin/clavulanate <p><i>Alternative Beta-Lactams</i></p> <ul style="list-style-type: none"> Cefpodoxime or cefuroxime <p>Empiric Therapy for Hospitalized Patients with Non-Severe CAP</p> <ul style="list-style-type: none"> An IV beta-lactam plus doxycycline (CIII) <p>Empiric Therapy for Hospitalized Patients with Severe CAP</p> <p><i>For Penicillin-Allergic Patients</i></p> <ul style="list-style-type: none"> Aztreonam IV plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) (BIII) <p>Empiric Therapy for Patients at Risk of <i>Pseudomonas</i></p>	<p>For most patients, 5–7 days</p> <p>Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics.</p> <p>Longer duration is often required if severe CAP or bacteremia is present, and particularly if due to <i>S. pneumoniae</i> or complicated <i>S. aureus</i> pneumonia. Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated.</p> <p>Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance (up to 30%) (BIII).</p> <p>Patients receiving a macrolide for MAC prophylaxis may have bacterial resistance to macrolide due to chronic exposure.</p> <p>For patients begun on IV antibiotic therapy, switching to PO should be considered when they are clinically improved and able to tolerate oral medications.</p> <p>Antibiotic chemoprophylaxis is generally not recommended because of the potential for developing drug resistance and drug toxicities (AI).</p>

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
	<p>Empiric Therapy for Hospitalized Patients with Severe CAP</p> <ul style="list-style-type: none"> • 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) <p><i>Preferred Beta-Lactams</i></p> <ul style="list-style-type: none"> • Ceftriaxone, cefotaxime, or ampicillin-sulbactam <p>Empiric Therapy for Patients at Risk of <i>Pseudomonas</i> Pneumonia</p> <ul style="list-style-type: none"> • An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every 8–12 hours or levofloxacin 750 mg IV once daily) (AI) <p><i>Preferred Beta-Lactams</i></p> <ul style="list-style-type: none"> • Piperacillin-tazobactam, cefepime, imipenem, or meropenem <p>Empiric Therapy for Patients at Risk for Methicillin-Resistant <i>Staphylococcus aureus</i> Pneumonia</p> <ul style="list-style-type: none"> • 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). 	<p>Pneumonia</p> <ul style="list-style-type: none"> • 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) <p><i>For Penicillin-Allergic Patients</i></p> <ul style="list-style-type: none"> • Replace the beta-lactam with aztreonam (BIII). 	
Cryptococcosis	<p>Cryptococcal Meningitis</p> <p><i>Induction Therapy (2 weeks, followed by consolidation therapy)</i></p>	<p>Cryptococcal Meningitis</p> <p><i>Induction Therapy (for at least 2 weeks, followed by consolidation therapy)</i></p>	<p>Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and</p>

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
	<ul style="list-style-type: none"> Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day (AI) (Note: Flucytosine dose should be adjusted in patients with renal dysfunction.) Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day (AI) (if cost is an issue and the risk of renal dysfunction is low), <i>or</i> If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative (BIII). <p><i>Consolidation Therapy (for at least 8 weeks (AI), followed by maintenance therapy)</i></p> <ul style="list-style-type: none"> Fluconazole 800 mg PO (or IV) daily (AI) For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily (AII) If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, increase fluconazole dose to 1,200 mg and perform LP 2 weeks later (BIII); duration of consolidation therapy should be 8 weeks from the time of negative CSF culture (AI). <p><i>Maintenance Therapy</i></p> <ul style="list-style-type: none"> Fluconazole 200 mg PO daily for ≥1 year from initiation of antifungal therapy (AI) 	<ul style="list-style-type: none"> Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day (BII), <i>or</i> Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800–1,200 mg PO or IV daily (BIII), <i>or</i> Fluconazole 1,200 mg PO or IV daily plus flucytosine 25 mg/kg PO four times a day (BII), <i>or</i> Fluconazole 800 mg PO or IV daily plus flucytosine 25 mg/kg PO four times a day (BIII), <i>or</i> Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus fluconazole 800–1,200 mg PO or IV daily (BI), <i>or</i> Liposomal amphotericin B 3–4 mg/kg IV daily (BI), <i>or</i> Amphotericin B deoxycholate 0.7–1.0 mg/kg IV once daily alone (BI), <i>or</i> Liposomal amphotericin B 3–4 mg/kg IV once daily plus flucytosine 25 mg/kg PO four times a day for 1 week followed by fluconazole 1,200 mg PO once daily (BIII), <i>or</i> Fluconazole 1,200 mg PO or IV daily (CI) <p><i>Consolidation Therapy (for at least 8 weeks (AI), followed by maintenance therapy)</i></p>	<p>decreased risk for subsequent relapse.</p> <p>Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 25–100 mcg/mL) or at least twice weekly monitoring of complete blood counts for cytopenia. Dosage should be adjusted in patients with renal insufficiency (BII).</p> <p>In resource-limited settings, induction of 1 week of amphotericin B deoxycholate with flucytosine followed by high dose fluconazole is preferred (BIII).</p> <p>Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to effectively managing increased intracranial pressure.</p> <p>Corticosteroids and mannitol are ineffective in reducing ICP and are not recommended (AIII).</p> <p>Some specialists recommend a brief course of tapering dose of corticosteroid for management of severe IRIS symptoms (BIII).</p>

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
	<p>For Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease or Patients with Isolated Asymptomatic Antigenemia Without Meningitis and Serum CrAg. $\geq 1:640$ by LFA</p> <ul style="list-style-type: none"> Treatment same as for cryptococcal meningitis (BIII) <p>Non-CNS Cryptococcosis with Mild to Moderate Symptoms and Focal Pulmonary Infiltrates, or Patients with Isolated Asymptomatic Antigenemia Without Meningitis and Serum CrAg $\leq 1:320$ by LFA)</p> <ul style="list-style-type: none"> Fluconazole, 400 to 800 mg PO daily for 10 weeks, followed by 200 mg daily for a total of 6 months (BIII) 	<ul style="list-style-type: none"> If patient's CSF culture remains positive at the end of 2 weeks, but the patient is not ill enough to be hospitalized, continue flucytosine for an additional 2 weeks with fluconazole 1,200 mg daily, before starting a single-drug consolidation regimen. Itraconazole 200 mg PO twice a day for 8 weeks—less effective than fluconazole (CI) <p><i>Maintenance Therapy</i></p> <ul style="list-style-type: none"> No alternative therapy recommendation 	
Cryptosporidiosis	<ul style="list-style-type: none"> Aggressive oral and/or IV rehydration and replacement of electrolyte loss (AIII), and Symptomatic treatment of diarrhea with anti-motility agents (AIII), and Initiate ART to achieve immune restoration to CD4 count >100 cells/mm³ (AII). 	<p>No therapy has been shown to be effective without ART. Consider trial of these agents in conjunction with ART, rehydration, and symptomatic treatment:</p> <ul style="list-style-type: none"> 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) 	<p>Tincture of opium may be more effective than loperamide in management of diarrhea (CIII).</p> <p>Because diarrhea can cause lactase deficiency, patients should avoid milk products (CIII).</p>
Cytomegalovirus (CMV) Disease	<p>CMV Retinitis Induction Therapy (followed by chronic maintenance therapy)</p> <p><i>For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea)</i></p> <ul style="list-style-type: none"> Ganciclovir 5 mg/kg every 12 hours IV or valganciclovir 900 mg PO twice a day or for 14–21 days (AI) (some prefer IV ganciclovir initially and 	<p>CMV Retinitis</p> <p><i>For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea): Intravitreal therapy as listed in the Preferred section, plus one of the following:</i></p>	<p>The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and location of the lesion (AIII).</p> <p>Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<p>transition to PO valganciclovir when there is evidence of clinical response) with or without</p> <ul style="list-style-type: none"> Intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) to rapidly achieve high intraocular concentration, continue weekly until lesion inactivity is achieved (AIII); plus <p><i>For Peripheral Lesions</i></p> <ul style="list-style-type: none"> Valganciclovir 900 mg PO twice a day for 14–21 days, then 900 mg once daily (AI) <p><i>Maintenance Therapy</i></p> <ul style="list-style-type: none"> Valganciclovir 900 mg PO daily (AI) for 3–6 months until ART induced immune recovery <p>CMV Esophagitis or Colitis</p> <ul style="list-style-type: none"> Ganciclovir 5 mg/kg IV every 12 hours; may switch to valganciclovir 900 mg PO every 12 hours once the patient can tolerate oral therapy (BI) Valganciclovir 900 mg PO every 12 hours may be considered as initial therapy in mild diseases (CIII). Duration: 21–42 days or until symptoms have resolved (CII) Maintenance therapy is usually not necessary but should be considered after relapses (BII). <p>Well-Documented, Histologically Confirmed CMV Pneumonia</p> <ul style="list-style-type: none"> Experience for treating CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (doses same as for CMV retinitis) (CIII). 	<p>Alternative Systemic Induction Therapy (followed by chronic maintenance therapy)</p> <ul style="list-style-type: none"> Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours for 14–21 days (BI), or Cidofovir 5 mg/kg/week IV for 2 weeks; saline hydration before and after therapy and probenecid, 2 g PO 3 hours before dose, followed by 1 g PO 2 hours and 8 hours after the dose (total of 4 g) (CI) (Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid.) <p>Chronic Maintenance (for 3–6 months until ART-induced immune recovery)</p> <ul style="list-style-type: none"> Foscarnet 90–120 mg/kg IV once daily (AI), or Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as above (BI) <p>CMV Esophagitis or Colitis</p> <ul style="list-style-type: none"> Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours (BI) for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance, or Valganciclovir 900 mg PO every 12 hours in 	<p>include initiation or optimization of ART (BIII).</p> <p>Given the evident benefits of systemic therapy in preventing contralateral eye involvement, reduce CMV visceral disease and improve survival. Whenever feasible, treatment should include systemic therapy.</p> <p>The ganciclovir ocular implant, which is effective for treatment of CMV retinitis, is no longer available.</p> <p>Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution (AIII).</p> <p>IRU may develop in the setting of immune reconstitution.</p> <p>Treatment of IRU</p> <p>Periocular, intravitreal, or short courses of systemic steroid (BIII)</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<ul style="list-style-type: none"> The optimal duration of therapy and the role of oral valganciclovir have not been established. <p>CMV Neurological Disease</p> <p><i>Note: Treatment should be initiated promptly.</i></p> <ul style="list-style-type: none"> Ganciclovir 5 mg/kg IV every 12 hours plus (foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg IV every 8 hours) to stabilize disease and maximize response, continue until symptomatic improvement and resolution of neurologic symptoms (CIII) The optimal duration of therapy and the role of oral valganciclovir have not been established. 	<p>milder disease and if able to tolerate PO therapy (BII), or</p> <ul style="list-style-type: none"> Duration: 21–42 days or until symptoms have resolved (CII) For mild disease, if ART can be initiated without delay, consider withholding CMV therapy (CIII). 	
Hepatitis B Virus (HBV) Disease	<p>ART is recommended for all patients with HIV/HBV coinfection regardless of CD4 cell count (AIII).</p> <p>The ART regimen must include two drugs that are active against both HBV and HIV (AIII).</p> <p>If CrCl ≥ 60 mL/min:</p> <ul style="list-style-type: none"> (TDF 300 mg plus [FTC 200 mg or 3TC 300 mg]) or (TAF [10 or 25 mg]^a plus FTC 200 mg) PO once daily (AII) <p>Note: TAF 10 mg is in the STR tablets of EVG/COBI/TAF/FTC and DRV/COBI/TAF/FTC; when TAF is used with other ARVs, the dose is 25 mg.</p> <p>If CrCl 30–59 mL/min:</p> <ul style="list-style-type: none"> TAF (10 or 25 mg)^a plus FTC 200 mg PO once daily (AII) <p>If CrCl <30 mL/min, not on HD:</p> <ul style="list-style-type: none"> Renally dosed entecavir (in place of TDF or TAF), or 	<p>For Persons Not on ART</p> <ul style="list-style-type: none"> Anti-HBV therapy is indicated for those who meet criteria for treatment according to the AASLD Hepatitis B Guidance. Peginterferon alfa-2a 180 mcg SQ once weekly for 48 weeks (CIII), or Peginterferon alfa-2b 1.5 mcg/kg SQ once weekly for 48 weeks (CIII) 	<p>Directly acting HBV drugs—such as adefovir, emtricitabine, entecavir, lamivudine, telbivudine, or tenofovir—must not be given in the absence of a fully suppressive ART regimen to avoid selection of drug-resistant HIV (AII).</p> <p>Cross-resistance to emtricitabine or telbivudine should be assumed in patients with suspected or proven lamivudine resistance.</p> <p>When changing ART regimens, continue agents with anti-HBV activity (AIII).</p> <p>If anti-HBV therapy is discontinued and a flare occurs, therapy should be re-instituted because it can be potentially lifesaving (AIII).</p> <p>Because HBV reactivation can occur during treatment for HCV with direct-acting antivirals in the absence of anti-HBV therapy, all people with</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<ul style="list-style-type: none"> ART with renally dose-adjusted TDF and FTC can be used (BIII) if recovery of renal function is unlikely. <p>If on HD:</p> <ul style="list-style-type: none"> (TDF or TAF) plus (FTC or 3TC) can be used. Refer to Table 6 for dosing recommendation. <p>Duration</p> <ul style="list-style-type: none"> Continue treatment indefinitely (BIII). 		<p>HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation (AIII).</p> <p>If immunosuppressive therapy is given, HBV reactivation can occur. For people who are HBsAg-positive, treatment for HBV infection should be administered (AII).</p>
Hepatitis C Virus (HCV) Disease	<p>For Treatment-Naïve Patients Without Cirrhosis (Any Genotype or No Pre-Treatment Genotype)</p> <ul style="list-style-type: none"> Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AI), <i>or</i> Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AI) <p>Characteristics that exclude patients from receiving simplified approach to therapy are outlined in Box 1 of the Hepatitis C Virus section.</p> <p>For Treatment-Naïve Patients with Compensated Cirrhosis (Recommendations Based on Genotypes)</p> <p><i>Genotypes 1, 2, 4–6</i></p> <ul style="list-style-type: none"> Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AIII), <i>or</i> Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AI) 	<p>For Treatment-Naïve Patients with Compensated Cirrhosis (Recommendations Based on Genotypes)</p> <p><i>Genotypes 1, 2, 4–6</i></p> <ul style="list-style-type: none"> Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 12 weeks (CI) <p><i>Genotype 3</i></p> <ul style="list-style-type: none"> Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 12 weeks (CI) <i>or</i> 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) 	<p>Simplified approach to HCV treatment can be used in treatment-naïve 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.</p> <p>See Hepatitis C Virus section to review a summary of drug–drug interactions between HCV therapy and ARV drugs.</p> <p>HCV treatment should not be withheld solely due to perceived lack of adherence to ART or untreated HIV (BIII).</p> <p>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.</p> <p>Recommendations for treatment after DAA failure are not provided. The reader is referred to the corresponding</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<p><i>Genotype 3</i></p> <ul style="list-style-type: none"> Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AIII) <p>For Treatment of Acute HCV Infection</p> <ul style="list-style-type: none"> Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AII) <i>or</i> Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AII) 		<p>section in the AASLD/IDSA HCV treatment guidance.</p>
Herpes Simplex Virus (HSV) Disease	<p>Orolabial Lesions (for 5–10 Days)</p> <ul style="list-style-type: none"> Valacyclovir 1 g PO twice a day (AIII), <i>or</i> Famciclovir 500 mg PO twice a day (AIII), <i>or</i> Acyclovir 400 mg PO three times a day (AIII) <p>Initial or Recurrent Genital HSV (for 5–14 days)</p> <ul style="list-style-type: none"> Valacyclovir 1 g PO twice a day (AI), <i>or</i> Famciclovir 500 mg PO twice a day (AI), <i>or</i> Acyclovir 400 mg PO three times a day (AI) <p>Severe Mucocutaneous HSV</p> <ul style="list-style-type: none"> Initial therapy acyclovir 5 mg/kg IV every 8 hours (AIII) After lesions begin to regress, change to PO therapy as above. Continue until lesions are completely healed. <p>Chronic Suppressive Therapy <i>For Patients with Severe Recurrences of Genital Herpes</i></p>	<p>For Acyclovir-Resistant HSV</p> <p><i>Preferred Therapy</i></p> <ul style="list-style-type: none"> Foscarnet 80–120 mg/kg/day IV in two to three divided doses until clinical response (AI) <p><i>Alternative Therapy (CIII)</i></p> <ul style="list-style-type: none"> IV cidofovir (dosage as in CMV retinitis), <i>or</i> Topical trifluridine 1% three times a day, <i>or</i> Topical cidofovir 1% once daily, <i>or</i> Topical imiquimod 5% three times weekly, <i>or</i> Topical foscarnet 1% five times daily <p>Duration of Therapy</p> <ul style="list-style-type: none"> 21–28 days or longer 	<p>Patients with HSV infection can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences.</p> <p>Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet.</p> <p>An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection. For more information, see the AiCuris Pritelivir website.</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<p><i>(AI) or Patients Who Want to Minimize Frequency of Recurrences (AI)</i></p> <ul style="list-style-type: none"> Valacyclovir 500 mg PO twice a day (AI), or Famciclovir 500 mg PO twice a day (AI), or Acyclovir 400 mg PO twice a day (AI) Continue indefinitely, regardless of CD4 count. 		
Histoplasmosis	<p>Moderately Severe to Severe Disseminated Disease</p> <p><i>Induction Therapy</i></p> <ul style="list-style-type: none"> For at least 2 weeks or until clinically improved Liposomal amphotericin B 3 mg/kg IV daily (AI) <p><i>Maintenance Therapy</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) <p>Less Severe Disseminated Disease</p> <p><i>Induction and Maintenance Therapy</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) <p><i>Duration of Therapy</i></p> <ul style="list-style-type: none"> At least 12 months <p>Meningitis</p> <p><i>Induction Therapy (4–6 weeks)</i></p> <ul style="list-style-type: none"> Liposomal amphotericin B 5 mg/kg/day (AIII) <p><i>Maintenance Therapy</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg PO twice a day to three times a day for ≥12 months and until 	<p>Moderately Severe to Severe Disseminated Disease</p> <p><i>Induction Therapy (for at least 2 weeks or until clinically improved)</i></p> <ul style="list-style-type: none"> Amphotericin B lipid complex 5 mg/kg IV daily (AIII), or <p>Alternatives to Itraconazole for Maintenance Therapy or Treatment of Less Severe Disease</p> <ul style="list-style-type: none"> Posaconazole extended release 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 twice a day (BIII), or Fluconazole 800 mg PO daily (CII) <p>Meningitis (These Recommendations Are Based on Limited Clinical Data for Patients with Intolerance to Itraconazole)</p> <ul style="list-style-type: none"> Posaconazole extended release 300 mg PO twice a day for 1 day, 	<p>Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bi-directional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations.</p> <p>Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities.</p> <p>Random serum concentration of itraconazole between 1–2 mcg/mL is recommended. Frequency and severity of toxicities increase when concentration is >4 mcg/mL.</p> <p>Acute pulmonary histoplasmosis in patients with HIV with CD4 counts >300 cells/mm³ should be managed as non-immunocompromised host (AIII).</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<p>resolution of abnormal CSF findings (AII)</p> <p>Long-Term Suppression Therapy</p> <p><i>For patients with severe disseminated or CNS infection (AIII) after completion of at least 12 months of therapy and who relapse despite appropriate therapy (BIII)</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg PO daily (AIII) 	<p>then 300 mg PO once daily (BIII)</p> <ul style="list-style-type: none"> Voriconazole 400 mg PO twice a day for 1 day, then 200 mg twice a day (BIII), or Fluconazole 800 mg PO daily (CII) <p>Long-Term Suppression Therapy</p> <ul style="list-style-type: none"> Posaconazole 300 mg extended release tablet PO once daily (BIII) Voriconazole 200 mg PO twice daily (BIII) Fluconazole 400 mg PO once daily (CII) 	
<p>Human Herpesvirus-8 Diseases</p> <p><i>(Kaposi Sarcoma [KS], Primary Effusion Lymphoma [PEL], Multicentric Castleman's Disease [MCD])</i></p>	<p>Mild to Moderate KS (Localized Involvement of Skin and/or Lymph Nodes)</p> <ul style="list-style-type: none"> Initiate or optimize ART (AII). <p>Advanced KS (Visceral [AI] or Disseminated Cutaneous KS [BIII])</p> <ul style="list-style-type: none"> Chemotherapy (per oncology consult) plus ART Liposomal doxorubicin first-line chemotherapy (AI) <p>Primary Effusion Lymphoma</p> <ul style="list-style-type: none"> Chemotherapy (per oncology consult) plus ART (AIII) PO valganciclovir or IV ganciclovir can be used as adjunctive therapy (CIII) <p>MCD Therapy Options (in Consultation with Specialist, Depending on HIV/HHV-8 Status, Presence of Organ Failure, and Refractory Nature of Disease)</p> <p>ART (AIII) along with one of the following:</p>	<p>MCD</p> <ul style="list-style-type: none"> Rituximab (375 mg/m² given weekly for 4–8 weeks) may be an alternative to or used adjunctively with antiviral therapy (CII). 	<p>Corticosteroids should be avoided in patients with KS, including those with KS-IRIS (AIII).</p> <p>Corticosteroids are potentially effective as adjunctive therapy for MCD, but should be used with caution, especially in patients with concurrent KS.</p> <p>Patients who received rituximab for MCD may experience subsequent exacerbation or emergence of KS.</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<ul style="list-style-type: none"> Valganciclovir 900 mg PO twice a day for 3 weeks (CII), <i>or</i> Ganciclovir 5 mg/kg IV every 12 hours for 3 weeks (CII), <i>or</i> Valganciclovir PO or Ganciclovir IV plus zidovudine 600 mg PO every 6 hours for 7–21 days (CII) Rituximab +/- Prednisone (CII) Monoclonal antibody targeting IL-6 or IL-6 receptor (BII) <p>Concurrent KS and MCD</p> <ul style="list-style-type: none"> Rituximab plus liposomal doxorubicin (BII) 		
Human Papillomavirus (HPV) Disease	Treatment of Condyloma Acuminata (Genital Warts)		<p>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.</p> <p>Topical cidofovir has activity against genital warts, but the product is not commercially available (CIII).</p> <p>Intralesional interferon-alpha is usually not recommended because of high cost, difficult administration, and potential for systemic side effects (CIII).</p> <p>The rate of recurrence of genital warts is high despite treatment in patients with HIV.</p> <p>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.</p>
	<p>Patient-Applied Therapy for Uncomplicated External Warts That Can Be Easily Identified by Patients</p> <ul style="list-style-type: none"> Podophyllotoxin (e.g., podofilox 0.5% solution or 0.5% gel): Apply to all lesions twice a day for 3 consecutive days, followed by 4 days of no therapy, repeat weekly for up to 4 cycles, until lesions are no longer visible (BIII), <i>or</i> Imiquimod 5% cream: Apply to lesion at bedtime and remove in the morning on 3 nonconsecutive nights weekly 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), <i>or</i> 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). 	<p>Provider-Applied Therapy for Complex or Multicentric Lesions, or Lesions Inaccessible to Patient</p> <p><i>Applied Therapy</i></p> <ul style="list-style-type: none"> 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 providers allow the lesion to thaw, then freeze a second time in each session (BIII), <i>or</i> Trichloroacetic acid or bichloroacetic acid cauterization: 80%–90% aqueous solution, apply to wart only, allow to dry until a white frost develops. Repeat weekly for up to 6 weeks, until lesions are no longer visible (BIII), <i>or</i> 	

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
			<ul style="list-style-type: none"> Surgical excision (BIII) or laser surgery (CIII) to external or anal warts, <i>or</i> Podophyllin resin 10%–25% in tincture of benzoin: Apply to all lesions (up to 10 cm²), then wash off a few hours later, repeat weekly for up to 6 weeks until lesions are no longer visible (CIII). 	
Isosporiasis (Cystoisosporiasis)		<p>For Acute Infection</p> <ul style="list-style-type: none"> TMP-SMX (160 mg/800 mg) PO (or IV) four times a day for 10 days (AII), <i>or</i> TMP-SMX (160 mg/800 mg) PO (or IV) twice a day for 7–10 days (BI) Can start with twice a day dosing first and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist (BIII) IV therapy may be used for patients with potential or documented malabsorption. <p>Chronic Maintenance Therapy (Secondary Prophylaxis)</p> <ul style="list-style-type: none"> In patients with CD4 count <200/mm³, TMP-SMX (160 mg/800 mg) PO three times weekly (AI) 	<p>For Acute Infection</p> <ul style="list-style-type: none"> Pyrimethamine^b 50–75 mg PO daily plus leucovorin 10–25 mg PO daily (BIII), <i>or</i> Ciprofloxacin 500 mg PO twice a day for 7 days (CI) as a second line alternative <p>Chronic Maintenance Therapy (Secondary Prophylaxis)</p> <ul style="list-style-type: none"> TMP-SMX (160 mg/800 mg) PO daily or (320 mg/1,600 mg) three times weekly (BIII) Pyrimethamine^a 25 mg PO daily plus leucovorin 5–10 mg PO daily (BIII) Ciprofloxacin 500 mg three times weekly (CI) as a second-line alternative 	<p>Fluid and electrolyte management in patients with dehydration (AIII).</p> <p>Nutritional supplementation for malnourished patients (AIII).</p> <p>Immune reconstitution with ART may result in fewer relapses (AIII).</p>
Leishmaniasis	Visceral	<p>For Initial Infection</p> <ul style="list-style-type: none"> Liposomal amphotericin B 2–4 mg/kg IV daily (AII), <i>or</i> 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) 	<p>For Initial Infection</p> <ul style="list-style-type: none"> Other lipid formulation of amphotericin B, dose and schedule as in Preferred Therapy, <i>or</i> Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 g (BII), <i>or</i> 	<p>ART should be initiated or optimized (AIII).</p> <p>For sodium stibogluconate, contact the CDC Drug Service at 404-639-3670 or drugservice@cdc.gov.</p> <p>For miltefosine, visit https://www.impavido.com.</p>

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
		<p>Chronic Maintenance Therapy (Secondary Prophylaxis); Especially in Patients with CD4 Count <200 cells/mm³</p> <ul style="list-style-type: none"> Liposomal amphotericin B 4 mg/kg every 2–4 weeks (AII), <i>or</i> Amphotericin B lipid complex (AII) 3 mg/kg every 21 days (AII) 	<ul style="list-style-type: none"> Sodium stibogluconate (pentavalent antimony) (BII) 20 mg/kg IV or IM daily for 28 days. Miltefosine—if 30–44 kg: 50 mg two times daily; if ≥45 kg, 50 mg three times a day—for 28 days (CIII) <p>Chronic Maintenance Therapy (Secondary Prophylaxis)</p> <ul style="list-style-type: none"> Sodium stibogluconate 20 mg/kg IV or IM every 4 weeks (BII) 	
	Cutaneous	<p>For Initial Infection</p> <ul style="list-style-type: none"> Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days (BIII), <i>or</i> 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), <i>or</i> Sodium stibogluconate 20 mg/kg IV or IM daily for 3–4 weeks (BIII) <p>Chronic Maintenance Therapy</p> <p>May be indicated in immunocompromised patients with multiple relapses (CIII)</p>	<p>Possible Options</p> <ul style="list-style-type: none"> Oral miltefosine (can be obtained via a treatment IND), <i>or</i> Topical paromomycin, <i>or</i> Intralesional sodium stibogluconate, <i>or</i> Local heat therapy <p>No data exist for any of these agents in patients with HIV; choice and efficacy are dependent on species of <i>Leishmania</i>.</p>	None
Malaria		<p>Because <i>Plasmodium falciparum</i> 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 <i>P. falciparum</i> infection should be hospitalized for evaluation, initiation of treatment, and observation (AIII).</p> <p>Treatment recommendations for patients with HIV are the same as for patients without HIV (AIII).</p>	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 http://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.

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
	Choice of therapy is guided by the degree of parasitemia, the species of <i>Plasmodium</i> , 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 .		
Microsporidiosis	<p>For GI Infections Caused by <i>Enterocytozoon bienuesi</i></p> <ul style="list-style-type: none"> Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm³ (AII); <i>plus</i> Manage dehydration and diarrhea with fluid support (AII) and malnutrition and wasting with nutritional supplement (AIII). <p>For Intestinal and Disseminated (Not Ocular) Infections Caused by Microsporidia Other Than <i>E. bienuesi</i> and <i>Vittaforma corneae</i></p> <ul style="list-style-type: none"> Albendazole 400 mg PO twice daily (AII), continue until CD4 count >200 cells/mm³ for >6 months after initiation of ART (BIII) <p>For Disseminated Disease Caused by <i>Trachipleistophora</i> or <i>Anncaliia</i></p> <ul style="list-style-type: none"> Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily (CIII) <p>For Ocular Infection</p> <ul style="list-style-type: none"> Topical fumagillin bicyclohexylammonium (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 	<p>For GI Infections Caused by <i>E. bienuesi</i></p> <ul style="list-style-type: none"> 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). 	Anti-motility 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
	<p>daily, for management of systemic infection (BIII)</p> <p><i>If CD4 Count >200 Cells/mm³</i></p> <ul style="list-style-type: none"> Continue until symptoms resolved (CIII). <p><i>If CD4 Count ≤200 Cells/mm³</i></p> <ul style="list-style-type: none"> Continue until resolution of ocular symptoms and CD4 count increases to >200 cells/mm³ for >6 months in response to ART (BIII). 		
<i>Mycobacterium avium</i> Complex (MAC) Disease	<p>At Least Two Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance</p> <ul style="list-style-type: none"> Clarithromycin 500 mg PO two times daily (AI) plus ethambutol 15 mg/kg PO daily (AI), <i>or</i> If drug interaction or intolerance precludes the use of clarithromycin, azithromycin 500–600 mg plus ethambutol 15 mg/kg PO daily (AII) <p>Duration</p> <ul style="list-style-type: none"> At least 12 months of therapy; can discontinue if no signs and symptoms of MAC disease and sustained (>6 months) CD4 count >100 cells/mm³ in response to ART. 	<p>Some experts recommend addition of a third or fourth drug for patients with high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective ART (CIII).</p> <p>Third or Fourth Drug Options May Include</p> <ul style="list-style-type: none"> Rifabutin 300 mg PO daily (dose adjustment may be necessary based on drug interactions) (CI), <i>or</i> A fluoroquinolone, such as moxifloxacin 400 mg PO daily (CIII) or levofloxacin 500 mg PO daily (CIII), <i>or</i> An injectable aminoglycoside such as amikacin 10–15 mg/kg IV daily (CIII) or streptomycin 1 g IV or IM daily (CIII) 	<p>Testing of susceptibility to clarithromycin and azithromycin is recommended (BIII).</p> <p>NSAIDs can be used for moderate to severe symptoms attributed to IRIS (CIII).</p> <p>If IRIS symptoms persist, a short course (i.e., 4 weeks–8 weeks) of a systemic corticosteroid (equivalent to 20–40 mg prednisone) can be used (CII).</p>
<i>Mycobacterium tuberculosis</i> (TB) Disease	<p>After collecting a specimen for culture and molecular diagnostic tests, empiric TB treatment should be started in individuals with clinical and radiographic presentation suggestive of TB (AIII).</p> <p>Refer to the Dosing Recommendations for Anti-TB</p>	<p>Treatment for Drug-Resistant TB</p> <p><i>Empiric therapy for resistance to rifamycin +/- other drugs</i></p> <ul style="list-style-type: none"> INH plus PZA plus EMB plus (moxifloxacin or levofloxacin) plus 	<p>DOT is recommended for all patients (AII).</p> <p>All rifamycins may have significant pharmacokinetic interactions with ARV drugs; please refer to the Dosing Recommendations for Anti-TB Drugs table in the Mycobacterium tuberculosis</p>

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
	<p>Drugs Recommendations table in the Mycobacterium tuberculosis section for dosing recommendations.</p> <p>Initial Phase (8 weeks or 2 months, Given Daily by DOT) (AI)</p> <ul style="list-style-type: none"> • INH (plus pyridoxine) plus (RIF or RFB) plus PZA plus EMB (AI) • If drug susceptibility report shows sensitivity to INH and RFP, then EMB can be discontinued before the end of 2 months (AI). <p>Continuation Phase (Duration depends on site and severity of infection [as noted below].)</p> <ul style="list-style-type: none"> • INH (plus pyridoxine) plus (RIF or RFB) daily (AI) <p>Total Duration of Therapy (for Drug-Susceptible TB)</p> <ul style="list-style-type: none"> • Pulmonary, Drug-Susceptible, Uncomplicated TB • 6 months (AI) <p><i>Pulmonary TB with Positive Culture After 2 Months of TB Treatment, or Severe Cavitory or Disseminated Extrapulmonary TB</i></p> <ul style="list-style-type: none"> • 9 months (BII) <p><i>TB Meningitis</i></p> <ul style="list-style-type: none"> • 9–12 months (BII) <p><i>Extra-Pulmonary TB in Other Sites</i></p> <ul style="list-style-type: none"> • 6 months (BII) 	<p>(linezolid or amikacin) (BII)</p> <ul style="list-style-type: none"> • Therapy should be modified once rifamycin resistance is confirmed and based on drug susceptibility results to provide ≥ 5 drugs (BII). <p><i>Resistant to INH</i></p> <ul style="list-style-type: none"> • (Moxifloxacin or levofloxacin) plus (RIF or RFB) plus EMB plus P A for 6 months (BII) <p><i>Resistance to Rifamycin +/- Other Drugs</i></p> <ul style="list-style-type: none"> • 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 (AIII). 	<p>section and the Drug-Drug Interactions section in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations.</p> <p>Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART.</p> <p>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.</p> <p>Adjunctive corticosteroid is not recommended for patients with TB pericarditis.</p> <p>Paradoxical IRIS that is not severe can be treated with NSAIDs without a change in TB or HIV therapy (BIII).</p> <p>See text for prednisone dosing recommendations for preemptive treatment or management of IRIS.</p>
Pneumocystis Pneumonia (PCP)	<p>Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX (BIII).</p>	<p>For Moderate to Severe PCP</p> <ul style="list-style-type: none"> • Pentamidine 4 mg/kg IV daily infused over ≥ 60 minutes (AI); can reduce dose to 3 mg/kg 	<p>Indications for Adjunctive Corticosteroids (AI)</p> <ul style="list-style-type: none"> • PaO₂ <70 mmHg at room air, or

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
	<p>Duration of PCP treatment: 21 days (AII)</p> <p>For Moderate to Severe PCP</p> <ul style="list-style-type: none"> TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day IV given every 6 hours or every 8 hours (AI); may switch to PO formulations after clinical improvement (AI). <p>For Mild to Moderate PCP</p> <ul style="list-style-type: none"> TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day, given PO in three divided doses (AI), <i>or</i> TMP-SMX: (160 mg/800 mg or DS) two tablets PO three times daily (AI) <p>Secondary Prophylaxis, After Completion of PCP Treatment</p> <ul style="list-style-type: none"> TMP-SMX DS: One tablet PO daily (AI), <i>or</i> TMP-SMX (80 mg/400 mg or SS): One tablet PO daily (AI) 	<p>IV daily in the event of toxicities (BI), <i>or</i></p> <ul style="list-style-type: none"> 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) <p>For Mild-to-Moderate PCP</p> <ul style="list-style-type: none"> Dapsone 100 mg PO daily plus TMP 5 mg/kg PO three times a day (BI), <i>or</i> Primaquine 30 mg (base) PO daily plus (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) (BI), <i>or</i> Atovaquone 750 mg PO twice daily with food (BI) <p>Secondary Prophylaxis, After Completion of PCP Treatment</p> <ul style="list-style-type: none"> TMP-SMX DS: One tablet PO three times weekly (BI), <i>or</i> Dapsone 100 mg PO daily (BI), <i>or</i> Dapsone 50 mg PO daily with (pyrimethamine^a 50 mg plus leucovorin 25 mg) PO weekly (BI), <i>or</i> Dapsone 200 mg plus pyrimethamine^a 75 mg plus leucovorin 25 mg PO weekly (BI), <i>or</i> Aerosolized pentamidine 300 mg monthly via Respigard II™ nebulizer (BI), <i>or</i> 	<ul style="list-style-type: none"> Alveolar-arterial DO₂ gradient >35 mmHg <p>Prednisone Doses (Beginning as Early as Possible and Within 72 Hours of PCP Therapy) (AI)</p> <ul style="list-style-type: none"> Days 1–5: 40 mg PO twice daily Days 6–10: 40 mg PO daily Days 11–21: 20 mg PO daily <p>IV methylprednisolone can be administered as 75% of prednisone dose.</p> <p>Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate to severe PCP (BIII).</p> <p>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.</p> <p>Patients who are receiving pyrimethamine^a/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII).</p> <p>If TMP-SMX is discontinued because of a mild adverse reaction, re-institution should be considered after the reaction resolves (AII). The dose can be increased gradually (desensitization) (BI), reduced, or the frequency modified (CIII).</p> <p>TMP-SMX should be permanently discontinued in patients with possible or definite Stevens-Johnson</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		<ul style="list-style-type: none"> Atovaquone 1,500 mg PO daily (BI), <i>or</i> Atovaquone 1,500 mg plus pyrimethamine^a 25 mg plus leucovorin 10 mg PO daily (CIII) 	Syndrome or toxic epidermal necrosis (AII).
Progressive Multifocal Leukoencephalopathy (PML)/JC Virus Infections	<p>There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse the immunosuppression caused by HIV.</p> <p>Initiate ART immediately in ART-naïve patients (AII).</p> <p>Optimize ART to achieve viral suppression in patients who develop PML and receive ART but remain viremic (AIII).</p>	None	<p>Corticosteroids may be used for PML-IRIS (BIII). The optimal corticosteroid regimen has not been established but should be tailored to individual patients.</p> <p>ART should not be discontinued during PML-IRIS (AIII).</p>
Syphilis (<i>Treponema pallidum</i> Infection)	<p>Early-Stage (Primary, Secondary, and Early-Latent Syphilis)</p> <ul style="list-style-type: none"> Benzathine penicillin G 2.4 million units IM for one dose (AII) <p>Late-Latent Disease (>1 year or of Unknown Duration and No Signs of Neurosyphilis)</p> <ul style="list-style-type: none"> Benzathine penicillin G 2.4 million units IM weekly for three doses (AII) <p>Late-Stage (Tertiary-Cardiovascular or Gummatous Disease)</p> <ul style="list-style-type: none"> Benzathine penicillin G 2.4 million units IM weekly for three doses (AII) (Note: Rule out neurosyphilis before initiation of benzathine penicillin and obtain infectious diseases consultation to guide management.) <p>Neurosyphilis (Including Otic or Ocular Disease)</p>	<p>Early-Stage (Primary, Secondary, and Early-Latent Syphilis)</p> <p><i>For penicillin-allergic patients</i></p> <ul style="list-style-type: none"> Doxycycline 100 mg PO twice a day for 14 days (BII), <i>or</i> Ceftriaxone 1 g IM or IV daily for 10–14 days (BII), <i>or</i> Azithromycin 2 g PO for 1 dose (BII) (Note: Azithromycin is not recommended for men who have sex with men or for pregnant women [AII].) <p>Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis)</p> <p><i>For penicillin-allergic patients</i></p>	<p>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.</p> <p>Combination of procaine penicillin and probenecid is not recommended for patients who are allergic to sulfa-containing medications (AIII).</p> <p>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.</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	<ul style="list-style-type: none"> Aqueous crystalline penicillin G 18–24 million units per day (administered as 3–4 million units IV q4h or by continuous IV infusion) for 10–14 days (AII) +/- benzathine penicillin G 2.4 million units IM weekly for three doses after completion of IV therapy (CIII) 	<ul style="list-style-type: none"> Doxycycline 100 mg PO twice a day for 28 days (BIII) <p>Neurosyphilis</p> <ul style="list-style-type: none"> Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII) +/- benzathine penicillin G 2.4 million units IM weekly for three doses after completion of above (CIII), or For penicillin-allergic patients, desensitization to penicillin is the preferred approach (BIII); if not feasible, ceftriaxone, 2 g IV daily for 10–14 days (BII). 	
Talaromycosis (Penicilliosis)	<p>Induction Therapy</p> <ul style="list-style-type: none"> Liposomal amphotericin B 3–5 mg/kg/day IV (AI) <p><i>Duration</i></p> <ul style="list-style-type: none"> 2 weeks (AI), followed by consolidation therapy <p>Consolidation Therapy</p> <ul style="list-style-type: none"> Itraconazole 200 mg PO twice daily for 10 weeks (AI), followed by chronic maintenance therapy <p>Chronic Maintenance Therapy</p> <ul style="list-style-type: none"> Itraconazole 200 mg PO once daily, until CD4 count >100 cells/mm³ for ≥6 months (AII) 	<p>Induction Therapy</p> <ul style="list-style-type: none"> Amphotericin B deoxycholate 0.7 mg/kg/day IV for 2 weeks (if liposomal amphotericin B is not available) (AI) <p><i>If Amphotericin B is Not Available</i></p> <ul style="list-style-type: none"> Voriconazole 6 mg/kg IV every 12 hours for 1 day (loading dose), then 4 mg/kg IV every 12 hours (BII), or Voriconazole 600 mg PO twice daily for 1 day (loading dose), then 400 mg PO twice daily (BII) <p><i>Duration</i></p> <ul style="list-style-type: none"> 2 weeks (BII), followed by consolidation therapy with itraconazole 	<p>Itraconazole is not recommended as induction therapy for talaromycosis (AI).</p> <p>ART can be initiated as early as 1 week after initiation of treatment for talaromycosis (BIII).</p> <p>Itraconazole and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bi-directional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations.</p> <p>TDM and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities. The goals of itraconazole and voriconazole trough concentrations are</p>

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Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		<p>(preferred) or voriconazole</p> <p>Consolidation Therapy</p> <ul style="list-style-type: none"> Voriconazole 200 mg PO twice daily for 10 weeks (BII), followed by chronic maintenance therapy <p>Chronic Maintenance Therapy</p> <ul style="list-style-type: none"> Itraconazole should be used (AII). Chronic maintenance therapy with voriconazole has not been studied. 	<p>>0.5 mcg/mL and >1.0 mcg/mL, respectively.</p>
<i>Toxoplasma gondii</i> Encephalitis	<p>Treatment of Acute Infection (AI)</p> <ul style="list-style-type: none"> Pyrimethamine^a 200 mg PO one time, followed by weight-based therapy: <ul style="list-style-type: none"> If <60 kg: pyrimethamine^a 50 mg PO once daily plus sulfadiazine 1,000 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily If ≥60 kg: pyrimethamine^a 75 mg PO once daily plus sulfadiazine 1,500 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily Leucovorin dose can be increased to 50 mg daily or twice a day. <p>Duration for Acute Therapy</p> <ul style="list-style-type: none"> 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 	<p>Treatment of Acute Infection</p> <ul style="list-style-type: none"> Pyrimethamine^a (leucovorin)* plus clindamycin 600 mg IV or PO every 6 hours (AI), or TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO twice a day (BI), or Atovaquone 1,500 mg PO twice a day with food plus pyrimethamine^a (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) <p>Chronic Maintenance Therapy</p> <ul style="list-style-type: none"> Clindamycin 600 mg PO every 8 hours plus 	<p>If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine (BI).</p> <p>For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI).</p> <p>Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).</p> <p>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.</p> <p>Anticonvulsants should be administered to patients with a history of seizures (AIII) and continued through acute treatment but should not be used as seizure prophylaxis (AIII).</p>

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
	<p>initiated on chronic maintenance therapy.</p> <p>Chronic Maintenance Therapy</p> <ul style="list-style-type: none"> • Pyrimethamine^a 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) 	<p>(pyrimethamine^a 25–50 mg plus leucovorin 10–25 mg) PO daily (BI), <i>or</i></p> <ul style="list-style-type: none"> • TMP-SMX DS one tablet twice a day (BII), <i>or</i> • TMP-SMX DS one tablet once daily (BII); <i>or</i> • Atovaquone 750–1,500 mg PO twice a day plus (pyrimethamine^a 25 mg plus leucovorin 10 mg) PO daily (BII), <i>or</i> • Atovaquone 750–1,500 mg PO twice a day plus sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) (BII), <i>or</i> • Atovaquone 750–1,500 mg PO twice a day with food (BII) <p>* Pyrimethamine^a and leucovorin doses are the same as for preferred therapy.</p>	<p>If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP (AII).</p>
Varicella Zoster Virus (VZV) Disease	<p>Primary Varicella Infection (Chickenpox)</p> <p><i>Uncomplicated Cases</i></p> <ul style="list-style-type: none"> • Initiate as soon as possible after symptom onset and continue for 5–7 days: <ul style="list-style-type: none"> ○ Valacyclovir 1 g PO three times a day (AII), <i>or</i> ○ Famciclovir 500 mg PO three times a day (AII) <p><i>Severe or Complicated Cases</i></p> <ul style="list-style-type: none"> • 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). 	<p>Primary Varicella Infection (Chickenpox)</p> <p><i>Uncomplicated Cases (for 5–7 Days)</i></p> <ul style="list-style-type: none"> • Acyclovir 800 mg PO five times a day (BII) <p>Herpes Zoster (Shingles)</p> <p><i>Acute Localized Dermatomal</i></p> <ul style="list-style-type: none"> • For 7–10 days; consider longer duration if lesions are slow to resolve • Acyclovir 800 mg PO five times a day (BII) 	<p>In managing VZV of the eyes, consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended (AIII).</p> <p>Duration of therapy for VZV retinitis is not well defined and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses.</p> <p>Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) (AIII).</p> <p>In patients with herpes zoster ophthalmicus who have stromal keratitis and anterior</p>

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
	<p>Herpes Zoster (Shingles) <i>Acute Localized Dermatomal</i></p> <ul style="list-style-type: none"> 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) <p>Extensive Cutaneous Lesion or Visceral Involvement</p> <ul style="list-style-type: none"> 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). <p>ARN</p> <ul style="list-style-type: none"> 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), <i>plus</i> Intravitreal ganciclovir 2 mg/0.05 mL twice weekly for 1–2 doses (BIII) <p>PORN</p> <ul style="list-style-type: none"> Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg IV every 12 hours (AIII), <i>plus</i> ≥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). 		<p>uveitis, topical corticosteroids to reduce inflammation may be necessary. The role of ART has not been established in these cases.</p>

^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.

Table 2. Treatment of HIV-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

^b Refer to [Daraprim Direct](#) for information on accessing 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: 3TC = lamivudine; ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte cell; CDC = Centers for Disease Control and Prevention; CDI = *Clostridium difficile* infection; CFU = colony-forming unit; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; DOT = directly observed therapy; DRV = darunavir; DS = double strength; EMB = ethambutol; EVG = elvitegravir; FDC = fixed dose combination; FTC = emtricitabine; g = gram; G6PD = Glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HD = hemodialysis; ICP = intracranial pressure; IM = intramuscular; IND = investigational new drug; INH = isoniazid; IRIS = immune reconstitution inflammatory syndrome; IRU = immune reconstitution uveitis; IV = intravenous; LP = lumbar puncture; MIC = minimum inhibitory concentrations; mg = milligram; mmHg = millimeters of mercury; MSM = men who have sex with men; NSAID = non-steroidal anti-inflammatory drugs; PCR = polymerase chain reaction; PI = protease inhibitor; PO = oral; PORN = progressive outer retinal necrosis; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; SQ = subcutaneous; STR = single-tablet regimen; SVR = sustained virologic response; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TMP-SMX = trimethoprim-sulfamethoxazole; TVR = telaprevir

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents

Updated: July 1, 2021

Reviewed: January 11, 2023

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
Bacterial Enteric Infections: Salmonellosis	Not applicable	Not applicable	Resolution of <i>Salmonella</i> 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	<ul style="list-style-type: none"> Received at least 3–4 months of treatment, <i>and</i> CD4 count >200 cells/μL for ≥6 months (CIII) <p>Some specialists would only discontinue therapy if <i>Bartonella</i> titers have also decreased by four-fold (CIII).</p>	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/μL for ≥6 months (CIII)	Restart at CD4 count <250 cells/μL (BIII)	<p>Only for patients with focal coccidioidal pneumonia (AII):</p> <ul style="list-style-type: none"> Clinically responded to ≥12 months antifungal therapy, with CD4 count >250 cells/mm³, and receiving effective ART. Should continue monitoring for recurrence with serial chest radiographs and coccidioidal serology. <p>For patients with diffuse pulmonary (BIII), disseminated non-meningeal (BIII), or meningeal diseases (AII):</p> <ul style="list-style-type: none"> Suppressive therapy should be continued indefinitely, even with increase in CD4 count on ART. 	No recommendation

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents

Cryptococcal Meningitis	Not applicable	Not applicable	<p>If the following criteria are fulfilled (BII):</p> <ul style="list-style-type: none"> Completed initial (induction and consolidation) therapy, <i>and</i> Received at least 1 year of antifungal therapy, <i>and</i> Remain asymptomatic of cryptococcal infection, <i>and</i> CD4 count ≥ 100 cells/mm³ and with suppressed plasma HIV RNA in response to ART 	CD4 count < 100 cells/mm ³ (AIII)
Cytomegalovirus Retinitis	Not applicable	Not applicable	<ul style="list-style-type: none"> CMV treatment for at least 3 to 6 months; and with CD4 count > 100 cells/mm³ for > 3 to 6 months in response to ART (AII). Therapy should be discontinued only after consultation with an ophthalmologist, taking into account anatomic location of lesions, vision in the contralateral eye, and feasibility of regular ophthalmologic monitoring. Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping therapy for early detection of relapse or immune restoration uveitis, and then periodically after sustained immune reconstitution (AIII). 	CD4 count < 100 cells/mm ³ (AIII)
<i>Histoplasma capsulatum</i> Infection	On ART, with CD4 count > 150 cells/mm ³ and undetectable HIV-1 viral load for 6 months (BIII)	For patients at high risk of acquiring histoplasmosis, restart if CD4 count falls to < 150 cells/mm ³ (CIII)	<p>If the following criteria (AI) are fulfilled:</p> <ul style="list-style-type: none"> Received azole therapy for > 1 year, <i>and</i> Negative fungal blood cultures, <i>and</i> Serum or urine <i>Histoplasma</i> antigen below the level of quantification, <i>and</i> Undetectable HIV viral load, <i>and</i> CD4 count ≥ 150 cells/mm³ for ≥ 6 months in response to ART 	CD4 count < 150 cells/mm ³ (BIII)

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents

<i>Isospora belli</i> Infection	Not applicable	Not applicable	Sustained increase in CD4 count to >200 cells/mm ³ for >6 months in response to ART and without evidence of <i>I. belli</i> infection (BIII)	No recommendation
Leishmaniasis: Visceral (and possibly cutaneous leishmaniasis in immunocompromised patients with multiple relapses)	Not applicable	Not applicable	There is no consensus regarding when to stop secondary prophylaxis. Some investigators suggest that therapy can be stopped if CD4 count increases to >200 to 350 cells/mm ³ for 3 to 6 months in response to ART, but others suggest that therapy should be continued indefinitely.	No recommendation
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of non-ocular (BIII) or ocular (CIII) microsporidiosis and CD4 count >200 cells/mm ³ for >6 months in response to ART.	No recommendation
<i>Mycobacterium avium</i> Complex Disease	Initiation of effective ART (AI)	CD4 count <50 cells/mm ³ : only if not on fully suppressive ART (AIII)	If the following criteria are fulfilled (AI) : <ul style="list-style-type: none"> Completed ≥12 months of therapy, <i>and</i> No signs and symptoms of MAC disease, <i>and</i> Have sustained (>6 months) CD4 count >100 cells/mm³ in response to ART. 	CD4 count <100 cells/mm ³ (AIII)
<i>Pneumocystis</i> Pneumonia	CD4 count increased from <200 to >200 cells/mm ³ for >3 months 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 ≥3 months to 6 months (BII) .	CD4 count <100 cells/mm ³ (AIII) CD4 count 100–200 cells/mm ³ and HIV RNA above detection limit of the assay (AIII) .	CD4 count increased from <200 cells/mm ³ to >200 cells/mm ³ for >3 months in response to ART (BII) . Can consider when CD4 count is 100–200 cells/mm ³ if HIV RNA remains below limits of detection for ≥3 months–6 months (BII) . If 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 for ≥3 months to 6 months (CIII) . 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	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) .

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents

			cell count rises as a consequence of ART (BIII) .	
Talaromycosis (Penicilliosis)	CD4 count >100 cells/mm ³ for >6 months in response to ART (BII) or If achieved sustained HIV viral suppression for >6 months (BIII)	CD4 count <100 cells/mm ³ (BIII) —if patient is unable to have ART, or has treatment failure without access to effective ART options, and still resides in or travels to the endemic area	CD4 count >100 cells/mm ³ for ≥6 months in response to ART (BII) or If achieved sustained HIV viral suppression for >6 months (BIII)	CD4 count <100 cells/mm ³ (BIII)
<i>Toxoplasma gondii</i> Encephalitis	CD4 count increased to >200 cells/mm ³ for >3 months in response to ART (AI) Can consider when CD4 count 100–200 cells/mm ³ if HIV RNA remain below limits of detection for at least 3–6 months (BII)	CD4 count <100 cells/mm ³ , (AIII) CD4 count 100–200 cells/μL and with HIV RNA above detection limit of the assay (AIII) .	Successfully completed initial therapy, receiving maintenance therapy and remain free of signs and symptoms of TE, and CD4 count >200 cells/mm ³ for >6 months in response to ART (BI) .	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 Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CMV = cytomegalovirus; 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: March 8, 2023

Reviewed: March 8, 2023

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 see 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, 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. Therapeutic drug monitoring, 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

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

limited data, larger daily doses of rifampin (e.g., 1,200 mg or more) appear to produce the same maximum induction as lower doses, but the induction effect occurs more rapidly.

- *Rifabutin*: In general, rifabutin as a cytochrome P450 3A4 (CYP3A4) inducer is about 40% of the potency of rifampin, but this can vary by substrate and enzymatic reaction.
- *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.

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. Therapeutic drug monitoring (TDM), if available, may facilitate any necessary dose adjustments in these complicated patients. 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. Drug names below marked with asterisk (*) are known to have assays available in the United States and, typically, in Europe as well.

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.

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
Artemether/ Lumefantrine	Clarithromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ lumefantrine possible	Do not coadminister. 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	↓ artemether, DHA, and lumefantrine expected	Do not coadminister.
	Voriconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine 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
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	↓ atovaquone expected	Do not coadminister.
Bedaquiline*	Clarithromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ bedaquiline possible	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.
	Posaconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for 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
	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	Bedaquiline AUC ↓ 55% (with daily rifapentine)	Do not coadminister.
	Voriconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline 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).
	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 possible	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.

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	↑ 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	↓ 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.
	Fluconazole	Clarithromycin AUC ↑ 18% and C _{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	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

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
			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 AUC ↑ 57% Rifabutin AUC ↑ 76% to 99% des-Rbt 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.
	Rifampin ^a	Clarithromycin concentration ↓ 87% Rifampin AUC ↑ 60%	Do not coadminister. Use azithromycin in place of clarithromycin.
	Rifapentine ^a	↓ clarithromycin expected ↑ 14-OH and rifapentine expected	Daily Rifapentine <ul style="list-style-type: none"> Do not coadminister. Weekly Rifapentine <ul style="list-style-type: none"> 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 ↓ 7-fold to 10-fold and $t_{1/2}$ ↓ from 24 hours to 11 hours	Coadministration should be avoided, if possible. Consider alternatives for dapsone.

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	↓ 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.
	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.
	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	Use with caution. Consider azithromycin in place of

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 possible	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.
	Rifapentine ^a	↓ 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	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	↓ 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%	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
		Pibrentasvir AUC ↓ 87%	
	Rifapentine ^a	↓ 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.
	TAF	↔ TFV concentration when coadministered as EVG/c/TAF/FTC	No dose adjustment
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 TDM and adjust dose accordingly.
	Rifampin ^a	Isavuconazole AUC ↓ 97%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine ^a	Significant ↓ 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.

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
	Erythromycin	See Erythromycin.	See Erythromycin.
	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	↓ 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 Weekly Rifapentine • ↓ linezolid possible	Daily rifapentine • Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly. 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.

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	↑ 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	↓ 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.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	↑ quinine expected ↑ posaconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.
	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	Significant ↓ posaconazole expected	Do not coadminister when treating invasive fungal infections. If coadministered for treatment of non-invasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response.
	Rifapentine ^a	↓ posaconazole expected	Daily Rifapentine • 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
			<p>Weekly Rifapentine</p> <ul style="list-style-type: none"> 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	<p>↓ quinine possible</p> <p>↑ rifabutin possible</p>	<p>Monitor for quinine efficacy.</p> <p>Monitor for rifabutin toxicity.</p>
	Rifampin ^a	Quinine AUC ↓ 75% to 85%	Do not coadminister.
	Rifapentine ^a	↓ quinine expected	Do not coadminister.
	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.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.

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
	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.
	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.
	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 is available to guide therapy.
Rifampin*	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.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.

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
	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.
	TAF	TAF plus Rifampin <ul style="list-style-type: none"> • TAF AUC ↓ 56% • TFV AUC ↓ 53% • TFV-DP AUC ↓ 36% Intracellular TFV-DP concentration is 4.2-fold greater than with TDF alone.	If coadministered, monitor for HIV and HBV treatment efficacy. Note: FDA labeling recommends not to coadminister.
	TDF	TDF plus Rifampin 600 mg Daily <ul style="list-style-type: none"> • ↔ 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.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.

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
	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.
	TAF	<p>Daily Rifapentine</p> <ul style="list-style-type: none"> • ↓ TAF, TFV, TFV-DP expected <p>Weekly Rifapentine</p> <ul style="list-style-type: none"> • ↔ TAF, TFV, TFV-DP expected 	<p>Daily Rifapentine</p> <ul style="list-style-type: none"> • Do not coadminister. <p>Weekly Rifapentine</p> <ul style="list-style-type: none"> • If coadministered, monitor for HIV and HBV treatment efficacy. <p>Note: FDA labeling recommends not to coadminister.</p>
	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 ↑ 52% (when RPV/TAF/FTC given with SOF/VEL/VOX)	No dosage adjustment.
	TDF	<p>TFV AUC ↑ 35% to 40% (when given with EVG/c/FTC or RPV/FTC)</p> <p>TFV AUC ↑ 81% (when given with EFV/FTC and SOF/VEL)</p> <p>TFV AUC ↑ 39% (when given with DRV/r/FTC and SOF/VEL/VOX)</p>	<p>Monitor for TDF toxicities.</p> <p>Consider TAF in place of TDF.</p>
Tenofovir [*] Alafenamide	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Rifabutin ^a	See Rifabutin.	See Rifabutin.
	Rifampin ^a	See Rifampin.	See Rifampin.

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	See Rifapentine.	See Rifapentine.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
Tenofovir* Disoproxil Fumarate	Rifabutin ^a	See Rifabutin.	See Rifabutin.
	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.
	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 description of Rifamycin-Related Induction Interactions in the Table 4 introduction above.

* Drug names marked with asterisk (*) are known to have assays available in the United States and, typically, in Europe as well.

Key to Symbols

↑ = increase

↓ = decrease

↔ = no substantial change

Key: 14-OH = active metabolite of clarithromycin; AUC = area under the curve; C_{min} = minimum concentration; C_{ss} = concentration at steady state; des-Rbt = desacetyl rifabutin; 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 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Updated: March 8, 2023

Reviewed: March 8, 2023

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. For persons of childbearing potential, please refer to [Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy](#) for information regarding adverse effect potential of these medications during pregnancy.

Drug(s)	Adverse Reactions
Acyclovir	<ul style="list-style-type: none"> Crystalluria and nephrotoxicity secondary to obstructive urolithiasis, particularly after rapid high-dose IV infusion. Risk is increased with dehydration or pre-existing renal impairment. <ul style="list-style-type: none"> Administer IV fluid hydration to reduce the risk for nephrotoxicity. Neurotoxicity with high doses (agitation, confusion, hallucination, seizure, coma), especially in patients with renal impairment and/or older patients Thrombophlebitis at peripheral IV infusion site Nausea, vomiting, and headache
Adefovir	<ul style="list-style-type: none"> Nephrotoxicity, especially in patients with underlying renal insufficiency, predisposing comorbidities, or taking concomitant nephrotoxic drugs Nausea and asthenia
Albendazole	<ul style="list-style-type: none"> Bone marrow suppression (i.e., pancytopenia, aplastic anemia, agranulocytosis, and leukopenia) <ul style="list-style-type: none"> Patients with liver disease, including hepatic echinococcosis, appear to be at higher risk. Hepatotoxicity Reversible alopecia Nausea, vomiting, headache, and dizziness
Amikacin	<ul style="list-style-type: none"> Nephrotoxicity <ul style="list-style-type: none"> Administer IV fluid hydration to reduce the risk for nephrotoxicity. Ototoxicity, both hearing loss and vestibular toxicity, are possible. Neuromuscular blockade, especially with myasthenia or Parkinson's disease and rapid infusion of large doses
Amphotericin B Deoxycholate and Lipid Formulations	<ul style="list-style-type: none"> Nephrotoxicity (lower incidence with liposomal formulations) <ul style="list-style-type: none"> Administer IV fluid hydration to reduce the risk for nephrotoxicity. Infusion-related reactions, including fever, chills, rigors, flank or back pain, and hypotension (lower incidence with liposomal formulations) Hypokalemia, hypomagnesemia, and hypocalcemia Transaminase and bilirubin elevations

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	<ul style="list-style-type: none"> • Heart failure (rarely reported) • Anemia • Thrombophlebitis • Headache, nausea, vomiting, and diarrhea
Anidulafungin	<ul style="list-style-type: none"> • Refer to the row on Echinocandins.
Artemether/Lumefantrine	<ul style="list-style-type: none"> • QTc prolongation • Fever, chills, fatigue, arthralgia, and myalgia • Headache, dizziness, asthenia, and insomnia • Nausea, vomiting, diarrhea, abdominal pain, and anorexia • Rash and pruritus • Delayed hemolytic anemia
Artesunate	<ul style="list-style-type: none"> • Acute renal failure requiring dialysis • Hemoglobinuria and jaundice • Post-treatment hemolysis that may require transfusion • QTc prolongation and bradycardia • Hypersensitivity reactions (anaphylaxis) • Dizziness, nausea, and vomiting
Atovaquone	<ul style="list-style-type: none"> • Hepatotoxicity • Rash, nausea, vomiting, and diarrhea • Fever, headache, and insomnia
Atovaquone/Proguanil	<ul style="list-style-type: none"> • Abdominal pain, nausea, vomiting, anorexia, diarrhea, headache, asthenia, dizziness, and rash • Reversible transaminase elevations
Azithromycin	<ul style="list-style-type: none"> • Ototoxicity with prolonged use • Hepatotoxicity • Hypersensitivity reactions • QTc prolongation • Nausea, vomiting, diarrhea, and abdominal pain
Benznidazole	<ul style="list-style-type: none"> • Photosensitivity and hypersensitivity reactions (including allergic dermatitis, TEN, and DRESS) • Paresthesia and peripheral neuropathy, headache, and insomnia • Bone marrow suppression • Embryofetal toxicity • Nausea, vomiting, abdominal pain, anorexia, and weight loss

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Bedaquiline	<ul style="list-style-type: none"> • QTc prolongation • Hepatotoxicity • Nausea, vomiting, anorexia, diarrhea, elevated amylase, arthralgia, headache, and skin rash
Bezlotoxumab	<ul style="list-style-type: none"> • Exacerbation of congestive heart failure • Nausea, pyrexia, and headache
Caspofungin	<ul style="list-style-type: none"> • Refer to the row on Echinocandins.
Chloroquine and Hydroxychloroquine	<ul style="list-style-type: none"> • Auditory and visual disturbances, including blurry vision. Retinal toxicity may occur with long-term use. • QTc prolongation • Cardiomyopathy • Bone marrow suppression and hemolysis • Neuropsychiatric changes, including extrapyramidal reactions, suicidal behavior, and convulsive seizures • Neuromyopathy (may occur with long-term use) • Hypersensitivity reactions (including TEN, SJS, and EM) • Severe hypoglycemia which may require adjustment of antidiabetic medications • Photosensitivity, pruritus, skin pigmentation, and exacerbation of psoriasis • Headache, nausea, vomiting, diarrhea, anorexia, abdominal pain, and hepatitis
Cidofovir	<ul style="list-style-type: none"> • Nephrotoxicity, proteinuria, azotemia, proximal tubular dysfunction (normoglycemic glycosuria, hypophosphatemia), and metabolic acidosis (including Fanconi's syndrome) <ul style="list-style-type: none"> ◦ Administer IV fluid hydration and oral probenecid to reduce the risk for nephrotoxicity. • Neutropenia and anemia • Ocular hypotony and anterior uveitis/iritis • Possibly carcinogenic and teratogenic; may cause hypospermia • Gastrointestinal intolerance and diarrhea • Asthenia, fever, headache, and alopecia • Side effects most likely related to co-administration with probenecid are rash, nausea, vomiting, anorexia, and gout exacerbation.
Ciprofloxacin	<ul style="list-style-type: none"> • Refer to the row on Fluoroquinolones.
Clarithromycin	<ul style="list-style-type: none"> • Hepatotoxicity • Ototoxicity, including reversible hearing loss and tinnitus, with high doses or prolonged use • QTc prolongation • Increased risk of cardiac complications or death in patients with heart disease • Diarrhea

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	<ul style="list-style-type: none"> • Headache, nausea, vomiting, diarrhea, abdominal cramps, and dysgeusia
Clindamycin	<ul style="list-style-type: none"> • Diarrhea, including <i>C. difficile</i>–associated diarrhea and colitis • Metallic taste (with IV infusion), thrombophlebitis, and arrhythmia with rapid IV infusion • Hypersensitivity reactions (including SJS and TEN) • Nausea, vomiting, abdominal pain, and abnormal liver function tests
Clotrimazole (Troche)	<ul style="list-style-type: none"> • Nausea, vomiting, anorexia, and metallic taste
Cycloserine	<ul style="list-style-type: none"> • 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 patients with history of chronic alcoholism). <ul style="list-style-type: none"> ◦ Administer with pyridoxine. • Hypersensitivity reactions (including SJS), allergic dermatitis, and rash
Dapsone	<ul style="list-style-type: none"> • Methemoglobinemia, hemolytic anemia, neutropenia, and agranulocytosis <ul style="list-style-type: none"> ◦ Do not use in patients with moderate to severe G6PD deficiency. • Sulfone syndrome (fever, exfoliative dermatitis, lymphadenopathy, hepatic necrosis, and hemolysis) • Phototoxicity and severe cutaneous reactions (including SJS and TEN) • Drug-induced lupus erythematosus • Hepatotoxicity and nephrotic syndrome • Peripheral neuropathy • Nausea and anorexia
Doxycycline	<ul style="list-style-type: none"> • Pill-induced esophagitis/esophageal ulceration • Intracranial hypertension • Photosensitivity and skin hyperpigmentation • Thrombophlebitis (with IV infusion) • Nausea and vomiting
Echinocandins (Anidulafungin, Caspofungin, Micafungin)	<ul style="list-style-type: none"> • Histamine-related infusion reactions (flushing, rash, pruritus, hypotension, and dyspnea) and thrombophlebitis • Hypersensitivity reactions (including anaphylaxis and anaphylactoid reaction) • Abnormal liver enzymes and hepatotoxicity • Hypokalemia • Hemolysis (micafungin) • Embryo-fetal toxicity • Diarrhea, nausea, vomiting, fever, and headache

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Emtricitabine	<ul style="list-style-type: none"> • Headache, nausea, and diarrhea • Skin hyperpigmentation and rash (palms and soles)
Entecavir	<ul style="list-style-type: none"> • Headache, fatigue, dizziness, and nausea
Ethambutol	<ul style="list-style-type: none"> • Optic neuritis (dose- and duration-dependent) and peripheral neuropathy • Headache, nausea, vomiting, anorexia, abdominal pain, and hyperuricemia/gout flare
Ethionamide	<ul style="list-style-type: none"> • Postural hypotension, hepatotoxicity, hypothyroidism (with or without goiter), and hypoglycemia • Dizziness, drowsiness, confusion, clumsiness, visual disturbances, and depression <ul style="list-style-type: none"> ◦ Administer with pyridoxine. • Dose-dependent gastrointestinal side effects, including nausea, vomiting, anorexia, diarrhea, abdominal pain, and metallic taste • Photosensitivity and severe cutaneous reactions (including SJS, TEN, and DRESS) • Gynecomastia, acne, hair loss, and impotence
Famciclovir	<ul style="list-style-type: none"> • Nephrotoxicity (in patients with underlying renal disease) • Headache, nausea, vomiting, and diarrhea
Fidaxomicin	<ul style="list-style-type: none"> • Nausea, vomiting, and abdominal pain
Flucytosine	<ul style="list-style-type: none"> • Concentration-dependent (>100 mcg/mL) bone marrow suppression (anemia, neutropenia, agranulocytosis, and thrombocytopenia) • Hepatotoxicity • Diarrhea, nausea, vomiting, and headache • Rash, pruritus, and photosensitivity
Fluconazole	<ul style="list-style-type: none"> • Hepatotoxicity, nausea, vomiting, diarrhea, and abdominal pain • QTc prolongation • Reversible alopecia (with doses ≥ 400 mg/day for >2 months)
Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)	<ul style="list-style-type: none"> • Restlessness, insomnia, nightmares, confusion, anxiety, paranoia, tremors, seizure, 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 <i>C. difficile</i>–associated diarrhea and colitis • QTc prolongation • Photosensitivity/phototoxicity and severe cutaneous reactions (including SJS and TEN) • Transaminase elevations and interstitial nephritis • Anemia, thrombocytopenia, and leukopenia • Arthralgia and myalgia

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	<ul style="list-style-type: none"> • Peripheral neuropathy and retinal detachment • Hyper- and hypoglycemia, including hypoglycemic coma • Vasculitis and aortic dissection • Nausea, diarrhea, bloating, headache, dizziness, and malaise
Foscarnet	<ul style="list-style-type: none"> • Nephrotoxicity and electrolyte imbalances (e.g., hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, hypokalemia) <ul style="list-style-type: none"> ◦ Administer IV fluid hydration to reduce the risk for nephrotoxicity. • Paresthesia and seizure (associated with electrolyte imbalances) • Anemia • Nausea, vomiting, anorexia, and headache • Penile ulceration • Thrombophlebitis
Fumagillin (Investigational)	<p>Oral Therapy</p> <ul style="list-style-type: none"> • Neutropenia, thrombocytopenia, vertigo, nausea, vomiting, diarrhea, anorexia, and abdominal cramps <p>Ocular Therapy</p> <ul style="list-style-type: none"> • Minimal systemic effect or local effect
Ganciclovir	<ul style="list-style-type: none"> • Neutropenia, thrombocytopenia, anemia, and pancytopenia • Carcinogenic and teratogenic potential and impaired fertility • Nephrotoxicity • Neuropathy • Thrombophlebitis
Glecaprevir/Pibrentasvir	<ul style="list-style-type: none"> • Risk of hepatitis B virus reactivation • Hepatic decompensation/failure in patients with advanced liver disease • Mild headache, fatigue, nausea, and diarrhea • Altered glucose tolerance in diabetic patients
Interferon-Alfa and Peginterferon-Alfa	<ul style="list-style-type: none"> • Neuropsychiatric disorders (e.g., depression, suicidal ideation) • Neutropenia, anemia, and thrombocytopenia • Flu-like syndrome (e.g., fever, headache, fatigue, myalgia) • Hepatitis exacerbations, thyroid dysfunction, and alopecia • Nausea, anorexia, diarrhea, and weight loss • Development or exacerbation of autoimmune disorders and ocular effects (e.g., retinal hemorrhage, retinal artery or vein obstructions, and cotton wool spots)

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	<ul style="list-style-type: none"> • Ischemic and hemorrhagic cerebrovascular events, cardiovascular and pulmonary disorders, hyper- and hypoglycemia, diabetes, severe infection, and colitis • Hypersensitivity reactions
Isavuconazonium Sulfate	<ul style="list-style-type: none"> • Hepatotoxicity and cholelithiasis • Infusion-related reactions (hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia) • Hypersensitivity reactions (including SJS) • Embryo-fetal toxicity • Shortening of QT interval • Nausea, vomiting, diarrhea, headache, hypokalemia, dyspnea, and cough
Isoniazid	<ul style="list-style-type: none"> • Hepatotoxicity and asymptomatic elevation in aminotransferase enzymes • Peripheral neuropathy, paresthesia, seizures, and optic neuritis <ul style="list-style-type: none"> ◦ Administer with pyridoxine • Nausea, diarrhea, and flushing • Psychosis • Hypersensitivity reactions (including TEN and DRESS) • Arthralgia and lupus-like syndrome
Itraconazole	<ul style="list-style-type: none"> • Congestive heart failure, edema, and hypokalemia • QTc prolongation • Hepatotoxicity • Hearing loss • Neuropathy • Gynecomastia • Nausea, vomiting, diarrhea, and abdominal pain
Lamivudine	<ul style="list-style-type: none"> • Nausea and vomiting
Levofloxacin	<ul style="list-style-type: none"> • Refer to the row on Fluoroquinolones.
Linezolid	<ul style="list-style-type: none"> • Anemia, neutropenia, and thrombocytopenia (especially with treatment lasting longer than 2–4 weeks and renal insufficiency) • Peripheral neuropathy and optic neuritis with long-term therapy • Serotonin syndrome (especially in patients receiving concomitant serotonergic agents) • Seizure (in patients with a history of seizure or with risk factors for seizure) • Lactic acidosis, hypoglycemia, and hyponatremia • Nausea, vomiting, diarrhea, and headache

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Mefloquine	<ul style="list-style-type: none"> • 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
Micafungin	<ul style="list-style-type: none"> • Refer to the row on Echinocandins.
Miconazole Buccal Tablets	<ul style="list-style-type: none"> • 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 reaction (may occur in patients with known hypersensitivity reaction to milk product concentrate)
Miltefosine	<ul style="list-style-type: none"> • Nephrotoxicity and elevated transaminases and bilirubin • Retinal degeneration • Leukocytosis and thrombocytopenia • Embryo-fetal toxicity and impaired fertility, scrotal pain, and impaired ejaculation • Nausea, vomiting, diarrhea, anorexia, headache, and motion sickness • Severe cutaneous reactions (including SJS)
Moxifloxacin	<ul style="list-style-type: none"> • Refer to the row on Fluoroquinolones.
Nifurtimox	<ul style="list-style-type: none"> • Patients with a history of brain injury, seizures, psychiatric disease, and serious behavioral alterations may experience worsening of their conditions. • Vomiting, abdominal pain, headache, decreased appetite, weight loss, nausea, pyrexia, rash, polyneuropathy, insomnia, dizziness, and vertigo • Carcinogenic and teratogenic potential and impaired fertility • Hypersensitivity reactions with hypotension, angioedema, dyspnea, pruritus, rash or other severe skin reactions
Nitazoxanide	<ul style="list-style-type: none"> • Nausea, vomiting, diarrhea, abdominal pain, headache, and chromaturia
Nystatin (Oral Preparations)	<ul style="list-style-type: none"> • Unpleasant taste, nausea, vomiting, anorexia, and diarrhea
Paromomycin	<ul style="list-style-type: none"> • Nausea, vomiting, abdominal cramps, anorexia, rash, and headache • Nephrotoxicity <ul style="list-style-type: none"> ○ Inflammatory bowel disease and renal insufficiency may increase risk.
Penicillin G	<p>All Penicillin G Preparations</p> <ul style="list-style-type: none"> • 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)

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	<p>Benzathine Penicillin G and Procaine Penicillin G</p> <ul style="list-style-type: none"> • IM injection-site reactions (pain and erythema), procaine neuropsychiatric reactions (with high dose), and neurovascular damage (due to inadvertent intravascular instead of IM injection) <p>Aqueous Crystalline Penicillin G (IV)</p> <ul style="list-style-type: none"> • Thrombophlebitis • Neurotoxicity at high doses—especially in patients with renal dysfunction—and hyperkalemia or hypernatremia at high doses (depending on formulation)
Pentamidine	<ul style="list-style-type: none"> • Nephrotoxicity, infusion-related hypotension, and thrombophlebitis • QTc prolongation, arrhythmias (including Torsades de pointes), and electrolyte abnormalities • Hypoglycemia, hyperglycemia, and diabetes mellitus • Hepatotoxicity, pancreatitis, and GI intolerance • Leukopenia and thrombocytopenia • Embryotoxic • Rash <p>Aerosolized Therapy</p> <ul style="list-style-type: none"> • Bronchospasm, cough, dyspnea, tachypnea, and metallic taste
Pentavalent Antimony (Sodium Stibogluconate) (Investigational)	<ul style="list-style-type: none"> • Hepatotoxicity, transient rises in amylase and lipase, and pancreatitis • Cardiac toxicity with >20 mg/kg dose (prolonged QTc and T wave inversion) • Leukopenia, anemia, and thrombocytopenia • Arthralgia and myalgia • Nausea, vomiting, abdominal pain, and anorexia • Thrombophlebitis and rash
Posaconazole	<ul style="list-style-type: none"> • Hepatotoxicity, QTc prolongation, and hypokalemia • Pseudohyperaldosteronism • Nausea, vomiting, diarrhea, abdominal pain, and headache <p>IV Infusion</p> <ul style="list-style-type: none"> • Thrombophlebitis, SBEC accumulation, and worsening renal function with IV formulation (especially in patients with eGFR <50 mL/min per package labeling, but observational studies with IV voriconazole suggest that this may not be a concern)
Primaquine	<ul style="list-style-type: none"> • Methemoglobinemia, hemolytic anemia (use with caution in patients with mild-moderate G6PD deficiency; do not use if severe G6PD deficiency), leukopenia, and neutropenia • QTc prolongation • Abdominal cramps, nausea, vomiting, and dizziness

Table 5. Serious and/or Common Adverse Reactions Associated with Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Pyrazinamide	<ul style="list-style-type: none"> • Hepatotoxicity • Polyarthralgia and myalgia • Hyperuricemia/gout flare • Thrombocytopenia and sideroblastic anemia • Nausea, vomiting, flushing, rash, and photosensitivity
Pyrimethamine	<ul style="list-style-type: none"> • Neutropenia, thrombocytopenia, and megaloblastic anemia <ul style="list-style-type: none"> ◦ Administer with leucovorin. • Anorexia, vomiting, and rash
Quinine	<ul style="list-style-type: none"> • QTc prolongation and cardiac arrhythmias • Cinchonism (tinnitus, vertigo, and blurred vision) • Hemolytic anemia (including in patients with G6PD deficiency), thrombocytopenia, and agranulocytosis • Vision abnormalities (e.g., photophobia, altered color perception, and blindness) • Hypersensitivity reactions (including SJS and TEN) • Hypoglycemia • Headache, nausea, vomiting, and diarrhea
Rifabutin	<ul style="list-style-type: none"> • Uveitis (concentration-dependent) • Neutropenia and thrombocytopenia • Arthralgia • Hepatotoxicity • Rash and skin discoloration • Nausea, vomiting, abdominal pain, diarrhea, and anorexia • Red-orange discoloration of body fluids
Rifampin	<ul style="list-style-type: none"> • 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, and flushing, rash • Red-orange discoloration of body fluids
Rifapentine	<ul style="list-style-type: none"> • Hepatotoxicity • Anemia, neutropenia, and lymphopenia • 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
	<ul style="list-style-type: none"> • Arthralgia • Rash and pruritis • Nausea, vomiting, diarrhea, and anorexia • Red-orange discoloration of body fluids
Sofosbuvir/Velpatasvir	<ul style="list-style-type: none"> • Risk of hepatitis B virus reactivation • Headache, fatigue, and anemia (associated with ribavirin co-administration) • Altered glucose tolerance in diabetic patients
Streptomycin	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Severe cutaneous reactions (including SJS, EM, and TEN) and photosensitivity • Anemia, neutropenia, agranulocytosis, and thrombocytopenia • Crystalluria (nephrolithiasis, urolithiasis) and nephrotoxicity • Hepatotoxicity • Drug fever • Peripheral neuritis, tinnitus, vertigo, and insomnia • Nausea, vomiting, and headache
Tafenoquine	<ul style="list-style-type: none"> • Decreased hemoglobin and methemoglobinemia and hemolytic anemia <ul style="list-style-type: none"> ◦ Do not use in patients with G6PD deficiency; may cause harm to fetuses and breastfeeding infants who are G6PD deficient. • Psychiatric adverse reactions (in patients with history of psychiatric illness) • Hypersensitivity reactions (angioedema and urticaria) • Visual disturbances • Dizziness, nausea, vomiting, and headache
Tenofovir disoproxil fumarate	<ul style="list-style-type: none"> • Renal insufficiency and Fanconi syndrome (proximal renal tubulopathy with hypophosphatemia, hypouricemia, proteinuria, and normoglycemic glycosuria) • Decrease in bone mineral density • Nausea and vomiting
Tenofovir alafenamide	<ul style="list-style-type: none"> • Headache, abdominal pain, fatigue, and nausea • Lower incidence of renal or bone toxicities than with tenofovir disoproxil fumarate
Trimethoprim-Sulfamethoxazole	<ul style="list-style-type: none"> • Cutaneous reactions (in some cases 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
	<ul style="list-style-type: none"> • Hepatotoxicity • Dose-dependent increase in serum creatinine (without change in GFR), interstitial nephritis, crystalluria (in patients with inadequate hydration), and hyperkalemia (with high-dose TMP) • Hypoglycemia and hyponatremia • Drug fever • Aseptic meningitis and pancreatitis • Nausea and vomiting
Valacyclovir	<ul style="list-style-type: none"> • Neurotoxicity (e.g., agitation, confusion, hallucination, seizure, coma) with high doses, especially in patients with renal impairment • Nephrotoxicity • Nausea, vomiting, abdominal pain, and headache
Valganciclovir	<ul style="list-style-type: none"> • Bone marrow suppression • Confusion, pyrexia, and tremor • Nephrotoxicity • Carcinogenic and teratogenic potential and impaired fertility • Nausea, vomiting, and diarrhea
Voriconazole	<ul style="list-style-type: none"> • Visual disturbances (e.g., abnormal vision, color vision change, and/or photophobia) • Optic neuritis (associated with >28 days treatment) • Headache, delirium, hallucination, peripheral neuropathy, and encephalopathy (associated with trough >5.5 mcg/mL) • Hepatotoxicity • QTc prolongation • Photosensitivity and increased risk of skin cancer with long-term use • Fluorosis and periostitis with high dose and/or prolonged use • Fever, nausea, vomiting, chills, tachycardia, and peripheral edema • Embryo-fetal toxicity • SBECD accumulation with IV formulation and worsening renal function (especially in patients 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; QTc = QT corrected for heart rate; SBECD = sulfobutylether cyclodextrin; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TMP = trimethoprim

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections that Require Dosage Adjustment in Patients with Renal Insufficiency

Updated: March 8, 2023

Reviewed: March 8, 2023

Drug accumulation is the primary concern when renally cleared drugs are administered to patients with reduced renal function. However, clearance is only one of two or more pharmacokinetic parameters that affect a drug's disposition. All drugs have a volume of distribution, which can be altered. Also, oral drugs must be absorbed from the gastrointestinal tract.

Some patients with HIV or diabetes mellitus can also have reduced absorption of certain drugs. Therefore, while a drug may require a dose reduction in renal failure based on reduced clearance (i.e., increased concentrations), other factors—like an increased volume of distribution and reduced oral absorption—may also affect drug concentrations (i.e., decrease concentrations). Therapeutic drug monitoring (TDM), if available and appropriate, may facilitate any necessary dose adjustments in these complicated patients. TDM allows the clinician to make informed, individualized decisions about dose adjustments that are more precise than standardized dose adjustments based on estimated creatinine clearance. Drug names below marked with asterisk (*) are known to have assays available within the United States and typically in Europe as well.

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl [^] or eGFR [#] (mL/min)	Dose
Acyclovir*	IV Dose <i>Serious HSV</i> • 5 mg/kg IV every 8 hours <i>VZV Infections or HSV encephalitis</i> • 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	50% of dose IV every 24 hours
		HD	50% of dose every 24 hours; administer dose after HD on day of dialysis.
	PO Dose for Herpes Zoster: 800 mg PO five times per day	10–25	800 mg PO every 8 hours
		<10	800 mg PO every 12 hours
		HD	800 mg PO every 12 hours; administer dose after HD on day of dialysis
Adefovir	10 mg PO every 24 hours	30–49	10 mg PO every 48 hours
		10–29	10 mg PO every 72 hours
		HD	10 mg PO weekly; administer dose after HD

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl [^] or eGFR [#] (mL/min)	Dose
Amikacin* For mycobacterial infections	IV 15 mg/kg per day <i>or</i> 25 mg/kg three times per week	Use with caution in patients with renal insufficiency and family history of ototoxicity.	15 mg/kg two to three times per week Perform TDM to adjust dose, with target peak concentration 35–45 mcg/mL and trough concentration <4 mcg/mL. Administer dose after HD on days of dialysis.
Amphotericin B*	3–6 mg/kg IV per day (lipid formulation) <i>or</i> 0.7–1.0 mg/kg IV per day (amphotericin B deoxycholate)	N/A	No dosage adjustment necessary; consider alternative antifungals if renal insufficiency occurs during therapy despite adequate hydration.
Cidofovir	5 mg/kg IV on Day 0, repeat 5 mg/kg IV dose on Day 7, then 5 mg/kg IV every 2 weeks Give each dose with probenecid and saline hydration (see Table 2 for dosing instructions).	Pretreatment SCr >1.5 mg/dL <i>or</i> CrCl ≤55 mL/min <i>or</i> Proteinuria ≥100 mg/dL (≥2 +)	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.
		If SCr increases by 0.3–0.4 mg/dL above baseline	Decrease to 3 mg/kg IV per dose.
		If SCr increases >0.5 mg/dL above baseline <i>or</i> Proteinuria ≥3 +	Discontinue therapy.
Ciprofloxacin*	500–750 mg PO every 12 hours <i>or</i> 400 mg IV every 8–12 hours	30–50	500–750 mg PO every 12 hours <i>or</i> 400 mg IV every 12 hours
		<30	250–500 mg PO every 24 hours <i>or</i>

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl [^] or eGFR [#] (mL/min)	Dose	
			400 mg IV every 24 hours	
		HD or PD	250–500 mg PO every 24 hours <i>or</i> 200–400 mg IV every 24 hours; administer after HD or PD on days of dialysis.	
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%.	
		<30	250 mg PO twice daily <i>or</i> 500 mg PO once daily If used with an HIV PI or COBI, reduce dose by 75% (or consider using azithromycin as alternative).	
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 (not on HD) 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 patients with ESRD who are not on dialysis.	
Emtricitabine [*] (FTC)	One 200-mg capsule PO once daily <i>or</i> 240-mg solution PO once daily	CrCl [^] or eGFR [#] (mL/min)	Oral Capsules	Oral Solution
		30–49	200 mg every 48 hours	120 mg every 24 hours
		15–29	200 mg every 72 hours	80 mg every 24 hours
		<15 and not on HD	200 mg every 96 hours	60 mg every 24 hours
		HD ^a (administer dose after HD on days of dialysis)	200 mg every 24 hours	240 mg every 24 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl [†] or eGFR [#] (mL/min)	Dose	
Emtricitabine/ Tenofovir[®] Alafenamide (FTC/TAF) (FDC Trade Name: Descovy) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing FTC/TAF.	One tablet (FTC 200 mg/TAF 25 mg) PO once daily	<30 and not on HD	Coformulated tablet is not recommended.	
		HD	One tablet daily	
Emtricitabine/ Tenofovir[®] Disoproxil Fumarate (FTC/TDF) (FDC Trade Name: Truvada) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing FTC/TDF.	One (FTC 200 mg/TDF 300 mg) tablet PO daily	30–49	One tablet PO every 48 hours (monitor for worsening renal function or consider switching to TAF)	
		<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 Patients with 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	<ul style="list-style-type: none"> 0.25 mg PO every 24 hours, <i>or</i> 0.5 mg PO every 48 hours 	<ul style="list-style-type: none"> 0.5 mg PO every 24 hours, <i>or</i> 1 mg PO every 48 hours
		10 to <30	<ul style="list-style-type: none"> 0.15 mg PO every 24 hours, <i>or</i> 0.5 mg PO every 72 hours 	<ul style="list-style-type: none"> 0.3 mg PO every 24 hours, <i>or</i> 1 mg PO every 72 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl [^] or eGFR [#] (mL/min)	Dose	
		<10 or HD or CAPD (administer after HD on days of dialysis)	<ul style="list-style-type: none"> • 0.05 mg PO every 24 hours, <i>or</i> • 0.5 mg PO once every 7 days 	<ul style="list-style-type: none"> • 0.1 mg PO every 24 hours, <i>or</i> • 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 Dosing Recommendations table in the Mycobacterium tuberculosis section for additional MTB dosing recommendations.)	<30 or HD	Usual dose PO three times weekly (in patients on HD, give dose after dialysis).	
		PD	Do not use in patients on PD. Consider alternative MAI or MTB treatment (e.g., moxifloxacin). Perform TDM to guide optimal dosing.	
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 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 for patients to guide optimal dosing (target peak serum concentration 2 hours after dose: 25–100 mcg/mL). If	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 on days of dialysis	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl ^a or eGFR [#] (mL/min)	Dose
	TDM is not possible, monitor CBC twice weekly.		
Foscarnet	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.
Ganciclovir^a	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; administer dose after HD on days of dialysis.
	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; administer dose after HD on days of dialysis.
Lamivudine^b (3TC)	300 mg PO every 24 hours	15–29	150 mg PO once, then 100 mg PO every 24 hours
		5–14	150 mg PO once, then 50 mg PO every 24 hours
		<5 or HD	50 mg PO once, then 25 mg PO every 24 hours; administer dose after HD on days of dialysis.
Lamivudine/ Tenofovir Disoproxil Fumarate (3TC/TDF) (FDC Trade Names: Cimduo or Temixys)	One (3TC 300 mg/TDF 300 mg) tablet PO every 24 hours	<50	Coformulated tablet is not recommended .

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl [^] or eGFR [#] (mL/min)	Dose	
Note: Please refer to product information for dosing recommendations for other ARV FDC products containing 3TC/TDF.				
Levofloxacin [*]	500 mg (low dose) or 750–1,000 mg (high dose) IV or PO daily	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 CAPD or HD (administer dose after HD on days of dialysis)	500 mg once, then 250 mg every 48 hours, IV or PO Dose can be adjusted based on serum concentrations.	750 mg once, then 500 mg every 48 hours, IV or PO
Para-aminosalicylic acid [*]	8–12 g/day PO in two to three divided doses	<30 or HD	4 g PO twice daily; administer after HD on days of dialysis.	
Paromomycin	500 mg PO every 6 hours	<10	Minimal systemic absorption. No dosage adjustment necessary but monitor for worsening renal function and ototoxicity in patients with ESRD.	
Peginterferon Alfa-2a	180 mcg SQ once weekly	<30	135 mcg SQ once weekly	
		HD	135 mcg SQ once weekly May reduce to 90 mcg once weekly if severe adverse effects or laboratory abnormalities occur.	
Penicillin G (Potassium or Sodium)	Neurosyphilis, Ocular Syphilis, or Ootosyphilis <ul style="list-style-type: none"> 3–4 million units IV every 4 hours, <i>or</i> 18–24 million units IV daily as continuous infusion 	10–50	2–3 million units every 4 hours <i>or</i> 12–18 million units as continuous infusion	
		<10	2 million units every 4–6 hours, <i>or</i> 8–12 million units as continuous infusion	
		HD or CAPD	2 million units every 4–6 hours, <i>or</i> 8 million units as continuous infusion	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl [^] or eGFR [#] (mL/min)	Dose
Pentamidine	4 mg/kg IV every 24 hours May reduce dose to 3 mg/kg IV daily in the event of toxicities	<10	4 mg/kg IV every 48 hours
Posaconazole [*]	IV: 300 mg twice daily on Day 1; then 300 mg once daily Delayed-Release Tablet: 300 mg PO once daily Oral Suspension: 400 mg PO twice daily	<50	No dosage adjustment of oral dose in patients with renal insufficiency. Higher variability in serum concentrations observed in patients with CrCl <20 mL/min. Perform posaconazole TDM (target trough concentration at least >1.25 mcg/mL for treatment). IV posaconazole is not recommended by the manufacturer because of potential toxicity due to accumulation of SBCD (vehicle of IV product). However, an observational study did not find worsening in renal function in patients with CrCl <50 mL/min given SBCD. Switch patients with CrCl <50 mL/min to oral posaconazole when feasible.
Pyrazinamide [*]	See the Mycobacterium tuberculosis section for weight-based dosing guidelines.	<30 or HD	25–35 mg/kg/dose three times per week; administer dose after HD on dialysis days
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	If toxicity is suspected, consider 50% of dose once daily and perform rifabutin TDM.
Sofosbuvir [*]	400 mg PO daily	<30	Not recommended. Up to 20-fold higher sofosbuvir metabolite observed in patients with this level of renal impairment.
Streptomycin	15 mg/kg IM or IV every 24 hours	Use with caution in patients with renal insufficiency.	15 mg/kg two to three times weekly. Administer dose after dialysis on day of dialysis.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl [^] or eGFR [#] (mL/min)	Dose
	<i>or</i> 25 mg/kg IM or IV three times per week		TDM is no longer available. Consider an alternative aminoglycoside, as clinically appropriate.
Sulfadiazine	1,000–1,500 mg PO every 6 hours (1,500 mg every 6 hours for patients >60 kg)	≤ 50	No data. Use alternative anti-toxoplasma therapy.
Tenofovir [*] Alafenamide (TAF) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing FTC/TAF.	25 mg PO daily	<15	Not recommended
		<15 on HD	No dosage adjustment required. Administer dose after HD on days of dialysis.
Tenofovir [*] Disoproxil Fumarate (TDF) Note: Please refer to product labels for dosing recommendations for other 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 and not on dialysis	Not recommended
		HD	300 mg PO once weekly; administer dose after dialysis
Trimethoprim [*] / Sulfamethoxazole (TMP-SMX)	For PCP Treatment <ul style="list-style-type: none"> 5 mg/kg (of TMP component) IV every 6–8 hours, <i>or</i> 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/day (TMP) IV, or two TMP-SMX DS tablets PO; administer dose after HD on dialysis day. Consider TDM to optimize therapy (target TMP concentrations: 5–8 mcg/mL)
	For PCP Prophylaxis	15–30	Reduce dose by 50% (e.g., 1 SS tablet PO daily)

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl [^] or eGFR [#] (mL/min)	Dose	
	<ul style="list-style-type: none"> One TMP-SMX DS tablet PO daily; One TMP-SMX DS tablet PO three times per week; <i>or</i> One TMP-SMX SS tablet PO daily 	<15	Reduce dose by 50% or use alternative agent	
	For Toxoplasmosis Encephalitis (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	5 mg/kg (TMP component) IV or PO every 24 hours or use alternative agent	
	For TE Chronic Maintenance Therapy <ul style="list-style-type: none"> One TMP-SMX DS tablet twice daily, <i>or</i> One TMP-SMX DS tablet daily 	15–30	Reduce dose by 50%.	
		<15	Reduce dose by 50% or use alternative agent.	
	For Toxoplasmosis Primary Prophylaxis: One TMP-SMX DS tablet PO daily	15–30	Reduce dose by 50%.	
		<15	Reduce dose by 50% or use alternative agent.	
	Valacyclovir[*]	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	500 mg PO every 24 hours
			HD	500 mg PO every 24 hours; administer dose after HD on days of dialysis
Valganciclovir	Induction Therapy: 900 mg PO twice daily	CrCl [^] or eGFR [#] (mL/min)	Induction	Maintenance
		40–59	450 mg PO twice daily	450 mg PO daily
	Maintenance Therapy: 900 mg PO once 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 Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl ^a or eGFR [#] (mL/min)	Dose	
		<10 and not on dialysis	Not recommended	Not recommended
		HD Note: Clinical efficacy of these doses has not been established; consider IV ganciclovir.	200 mg (oral powder formulation) PO three times per week after HD	100 mg (oral powder formulation) PO three times per week after HD
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	IV voriconazole is not recommended by the manufacturer because of potential toxicity due to accumulation of SBCD (vehicle of IV product). An observational study did not find worsening in renal function in patients with CrCl <50 mL/min. Switch patients with CrCl <50 mL/min to oral voriconazole when feasible. No need for dosage adjustment when the oral dose is used. Perform TDM to adjust dose.	

* Drug names marked with asterisk (*) are known to have assays available within the United States and typically in Europe as well.

^a The prescribing information for emtricitabine (Emtriva) recommends a dose of 200 mg every 96 hours for patients with CrCl <15 mL/min or on hemodialysis. However, the prescribing information for several 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 patients (on days of hemodialysis, give after completion of dialysis). The recommendation in this table incorporates the dosing guidance from the FDC products.

^b The prescribing information for lamivudine (Epivir) recommends dosage adjustment from 300 mg once daily to 150 mg once daily for patients with CrCl 30–49 mL/min. However, the prescribing information for several FDC products that contain lamivudine (including Epzicom, Dovato, and Triumeq) recommends no dose adjustment for CrCl 30–49 mL/min. The recommendation in this table incorporates the dosing guidance from the FDC products.

^a Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in years}) \times \text{weight in kg}}{72 \times \text{serum creatinine}}$	Female: $\frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine}}$

[#]When estimating kidney function to facilitate drug dosing in patients with renal insufficiency, please refer to the drug's prescribing information and to National Institute of Diabetes and Digestive and Kidney Diseases' ["Determining Drug Dosing in Adults with Chronic Kidney Disease"](#) for a discussion on using CrCl based on the Cockcroft-Gault equation versus eGFR.

Key: 3TC = lamivudine; ARV = antiretroviral; CAPD = continuous ambulatory peritoneal dialysis; CBC = complete blood count; CMV = cytomegalovirus; COBI = cobicistat; CrCl = creatinine clearance; DS = double strength; eGFR = estimated glomerular

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

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*; N/A = not applicable; OI = opportunistic infection; PCP = *Pneumocystis pneumonia*; PD = peritoneal dialysis; PI = protease inhibitor; PO = orally; SCr = serum creatinine; SQ = subcutaneous; SBCD = sulfobutylether cyclodextrin; SS = single strength; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TMP-SMX = trimethoprim-sulfamethoxazole; VZV = varicella zoster virus

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Updated: February 11, 2020

Reviewed: January 11, 2023

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Acyclovir	B	No teratogenicity in mice, rats, rabbits at human levels. Extensive experience in human pregnancy (>700 first-trimester exposures reported to registry); well-tolerated.	Treatment of frequent or severe symptomatic herpes outbreaks or varicella
Adefovir	C	No increase in malformations at 23 times (rats) and 40 times (rabbits) human dose. Limited experience with use human in pregnancy.	Not recommended because of limited data in pregnancy. Report exposures during pregnancy to the Antiretroviral Pregnancy Registry .
Albendazole	C	Embryotoxic and teratogenic (skeletal malformations) in rats and rabbits, but not in mice or cows. Limited experience in human pregnancy.	Not recommended , especially in first trimester. Primary therapy for microsporidiosis in pregnancy should be ART.
Amikacin	C	Not teratogenic in mice, rats, rabbits. Theoretical risk of ototoxicity in fetus; reported with streptomycin but not amikacin.	Drug-resistant TB, severe MAC infections
Amoxicillin, Amoxicillin/Clavulanate, and Ampicillin/Sulbactam	B	Not teratogenic in animals. Extensive experience in human pregnancy does not suggest an increase in AEs.	Susceptible bacterial infections
Amphotericin B	B	Not teratogenic in animals or in human experience. Preferred over azole antifungals in first trimester if similar efficacy expected.	Documented invasive fungal disease
Antimonials, Pentavalent (Stibogluconate, Meglumine)	Not FDA approved	Antimony not teratogenic in rats, chicks, sheep. Three cases reported of use in human pregnancy in second trimester with good outcome. Labeled as contraindicated in pregnancy.	Use for therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine.
Artesunate, Artemether, and Artemether/Lumefantrine	C	Embryotoxicity, cardiovascular and skeletal anomalies in rats and rabbits. Embryotoxic in monkeys. Human experience, primarily in the second and third trimesters, has not identified increased AEs.	Recommended by WHO as first-line therapy in second/third trimester for <i>P. falciparum</i> and severe malaria. Pending more data, use for malaria in first trimester only if other drugs are not available or have failed . Report cases of exposure to a WHO Anti-Malarial Pregnancy Exposure Registry when available.
Atovaquone	C	Not teratogenic in rats or rabbits, limited human experience	Alternate agent for PCP, <i>Toxoplasma gondii</i> , malaria infections

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Azithromycin	B	Not teratogenic in animals. Moderate experience with use in human pregnancy does not suggest AEs.	Preferred agent for MAC prophylaxis or treatment (with ethambutol), <i>Chlamydia trachomatis</i> infection in pregnancy
Aztreonam	B	Not teratogenic in rats, rabbits. Limited human experience, but other beta-lactam antibiotics have not been associated with adverse pregnancy outcomes.	Susceptible bacterial infections
Bedaquiline	B	Not teratogenic in rats, rabbits. No experience in human pregnancy.	Multidrug resistant TB when effective treatment regimen cannot otherwise be provided
Benznidazole	Not FDA approved	No animal studies. Increase in chromosomal aberrations in children with treatment; uncertain significance. No human pregnancy data.	Not indicated for chronic <i>T. cruzi</i> in pregnancy. Seek expert consultation if acute or symptomatic infection in pregnancy requiring treatment.
Boceprevir	B	Not teratogenic in rats, rabbits. No human pregnancy data.	Treatment of HCV currently generally not indicated in pregnancy
Capreomycin	C	Increase in skeletal variants in rats. Limited experience in human pregnancy; theoretical risk of fetal ototoxicity.	Drug-resistant TB
Caspofungin	C	Embryotoxic, skeletal defects in rats, rabbits. No experience with human use.	Invasive <i>Candida</i> or <i>Aspergillus</i> infections refractory to amphotericin and azoles
Cephalosporins	B	Not teratogenic in animals. Extensive experience in human pregnancy has not suggested increase in adverse outcomes.	Bacterial infections; alternate treatment for MAC
Chloroquine	C	Associated with anophthalmia, micro-ophthalmia at fetotoxic doses in animals. Not associated with increased risk in human pregnancy at doses used for malaria.	Drug of choice for malaria prophylaxis and treatment of sensitive species in pregnancy
Cidofovir	C	Embryotoxic and teratogenic (meningocoele, skeletal abnormalities) in rats and rabbits. No experience in human pregnancy.	Not recommended
Ciprofloxacin and Other Quinolones	C	Arthropathy in immature animals; not embryotoxic or teratogenic in mice, rats, rabbits, or monkeys. More than 1,100 cases of quinolone use in human pregnancy have not been associated with arthropathy or birth defects.	Severe MAC infections; multidrug resistant TB, anthrax, bacterial infections
Clarithromycin	C	Cardiovascular defects noted in one strain of rats and cleft palate in mice at high doses, not teratogenic in rabbits or monkeys. Two human studies, each with >100 first-trimester exposures, did not show increase in defects but one study found an increase in spontaneous abortion.	Treatment or secondary MAC prophylaxis, if other choices exhausted

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Clindamycin	B	No concerns specific to pregnancy in animal or human studies.	Treatment of anaerobic bacterial infections and used with quinine for chloroquine-resistant malaria; alternate agent for secondary prophylaxis of <i>Toxoplasma</i>
Clofazimine	C	Not teratogenic in mice, rats, or rabbits. Limited experience reported (19 cases); no anomalies noted but red-brown skin discoloration reported in several infants exposed throughout pregnancy.	No indications
Clotrimazole Troches	C	Not teratogenic in animals at exposures expected from treatment of oral or vaginal <i>Candida</i> . No increase in adverse pregnancy outcomes with vaginal use.	Oral or vaginal <i>Candida</i> infections and prophylaxis
Cycloserine	C	Not teratogenic in rats. No data available from human studies.	Drug-resistant TB
Dapsone	C	No animal data. Limited human experience does not suggest teratogenicity; might displace bound bilirubin in the neonate, increasing the risk of kernicterus. Case reports of hemolytic anemia in fetus/infant with maternal treatment.	Alternative for primary or secondary PCP prophylaxis
Dasabuvir/ Ombitasvir/ Paritaprevir/ Ritonavir	Not assigned	No AEs in mice, rats, rabbits during pregnancy or lactation. No data in human pregnancy or breastfeeding.	Therapy in pregnancy is not recommended because ribavirin, which is recommended for concomitant use with this drug, is contraindicated in pregnancy.
Diphenoxylate	C	Limited animal and human data do not indicate teratogenicity.	Symptomatic treatment of diarrhea
Doxycycline and Other Tetracyclines	D	Risk of hepatic toxicity increased with tetracyclines in pregnancy; staining of fetal bones and teeth contraindicates use in pregnancy.	No indications
Elbasvir/ Grazoprevir	Not assigned	No AEs in rats, rabbits during pregnancy or lactation. No data in human pregnancy or breastfeeding.	May be considered for use in patients who do not need ribavirin if benefits felt to outweigh unknown risks. However, this drug is not recommended for patients who need ribavirin based on HCV subtype or resistance because ribavirin is contraindicated in pregnancy.
Emtricitabine	B	No concerns in pregnancy from limited animal and human data.	As part of fully suppressive combination ARV regimen for treatment of HIV, HBV. Report exposures during pregnancy to the Antiretroviral Pregnancy Registry .

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Entecavir	C	Animal data do not suggest teratogenicity at human doses; however, limited experience in human pregnancy.	Not recommended because of limited data in pregnancy. Use as part of fully suppressive ARV regimen with ARV agents active against both HIV and HBV. Report exposures during pregnancy to the Antiretroviral Pregnancy Registry .
Erythromycin	B	Hepatotoxicity with erythromycin estolate in pregnancy; other forms acceptable. No evidence of teratogenicity.	Bacterial and chlamydial infections
Ethambutol	B	Teratogenic, at high doses, in mice, rats, rabbits. No evidence of teratogenicity in 320 cases of human use for treatment of TB.	Active TB and MAC treatment; avoid in first trimester if possible
Ethionamide	C	Increased rate of defects (omphalocele, exencephaly, cleft palate) in rats, mice, and rabbits with high doses; not seen with usual human doses. Limited human data; case reports of CNS defects.	Active TB; avoid in first trimester if possible
Famciclovir	B	No evidence of teratogenicity in rats or rabbits, limited human experience.	Recurrent genital herpes and primary varicella infection. Report exposures during pregnancy to the Famvir Pregnancy Registry (1-888-669-6682).
Fluconazole	C	Abnormal ossification, structural defects in rats, mice at high doses. Case reports of rare pattern of craniofacial, skeletal and other abnormalities in five infants born to four women with prolonged exposure during pregnancy; no increase in defects seen in several series after single dose treatment.	Single dose may be used for treatment of vaginal <i>Candida</i> though topical therapy preferred. Not recommended for prophylaxis during early pregnancy. Can be used for invasive fungal infections after first trimester; amphotericin B preferred in first trimester if similar efficacy expected.
Flucytosine	C	Facial clefts and skeletal defects in rats; cleft palate in mice, no defects in rabbits. No reports of use in first trimester of human pregnancy; may be metabolized to 5-fluorouracil, which is teratogenic in animals and possibly in humans.	Use after first trimester if indicated for life-threatening fungal infections.
Foscarnet	C	Skeletal variants in rats, rabbits and hypoplastic dental enamel in rats. Single case report of use in human pregnancy in third trimester.	Alternate agent for treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection.
Fumagillin	Not FDA approved	Caused complete litter destruction or growth retardation in rats, depending on when administered. No data in human pregnancy.	Topical solution can be used for ocular microsporidial infections.

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Ganciclovir and Valganciclovir	C	Embryotoxic in rabbits and mice; teratogenic in rabbits (cleft palate, anophthalmia, aplastic kidney and pancreas, hydrocephalus). Case reports of safe use in human pregnancy after transplants, treatment of fetal CMV.	Treatment or secondary prophylaxis of life-threatening or sight-threatening CMV infection. Preferred agent for therapy in children.
Glecaprevir/ Pibrentasvir	Not assigned	No AEs of glecaprevir in rats or of pibrentasvir in mice, rabbits during pregnancy and lactation. No data in human pregnancy or breastfeeding.	Use may be considered for hepatitis C if benefits outweigh unknown risks.
Imipenem and Meropenem	C/B	Not teratogenic in animals; limited human experience.	Serious bacterial infections
Imiquimod	B	Not teratogenic in rats and rabbits; eight case reports of human use, only two in first trimester.	Because of limited experience, other treatment modalities such as cryotherapy or trichloroacetic acid recommended for wart treatment during pregnancy.
Influenza Vaccine	C	Not teratogenic. Live vaccines, including intranasal influenza vaccine, are contraindicated in pregnancy.	All pregnant women should receive injectable influenza vaccine because of the increased risk of complications of influenza during pregnancy. Ideally, HIV-infected women should be on ART before vaccination to limit potential increases in HIV RNA levels with immunization.
Interferons Alfa, Beta, and Gamma	C	Abortifacient at high doses in monkeys, mice; not teratogenic in monkeys, mice, rats, or rabbits. Approximately 30 cases of use of interferon-alfa in pregnancy reported; 14 in first trimester without increase in anomalies; possible increased risk of intrauterine growth retardation.	Not indicated. Treatment of HCV currently generally not recommended in pregnancy.
Isavuconazole	C	Increased perinatal mortality in rats at exposures below human exposure levels. Dose-related skeletal defects in rats at exposures below human exposure levels. No data in human pregnancy or breastfeeding.	Use alternate antifungals, especially in first trimester.
Isoniazid	C	Not teratogenic in animals. Possible increased risk of hepatotoxicity during pregnancy; prophylactic pyridoxine 50 mg/day should be given to prevent maternal and fetal neurotoxicity.	Active TB; prophylaxis for exposure or skin test conversion
Itraconazole	C	Teratogenic in rats and mice at high doses. Case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy; no increase in defect rate noted among >300 infants born after first-trimester itraconazole exposure.	Only for documented systemic fungal disease, not prophylaxis. Consider using amphotericin B in first trimester if similar efficacy expected.
Kanamycin	D	Associated with club feet in mice, inner ear changes in multiple species. Hearing loss in 2.3% of 391 children after long-term <i>in utero</i> therapy.	Drug-resistant TB

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Ketoconazole	C	Teratogenic in rats, increased fetal death in mice, rabbits. Inhibits androgen and corticosteroid synthesis; may impact fetal male genital development; case reports of craniofacial, skeletal abnormalities in humans with prolonged fluconazole exposure during pregnancy.	None
Lamivudine	C	Not teratogenic in animals. No evidence of teratogenicity with >3,700 first-trimester exposures reported to the Antiretroviral Pregnancy Registry .	HIV and HBV therapy, only as part of a fully suppressive combination ARV regimen. Report exposures to the Antiretroviral Pregnancy Registry .
Ledipasvir/Sofosbuvir	B	No evidence of teratogenicity in rats or rabbits. No experience in human pregnancy.	Treatment of HCV generally not indicated in pregnancy.
Leucovorin (Folinic Acid)	C	Prevents birth defects of valproic acid, methotrexate, phenytoin, aminopterin in animal models. No evidence of harm in human pregnancies.	Use with pyrimethamine when use of pyrimethamine cannot be avoided.
Linezolid	C	Not teratogenic in animals. Decreased fetal weight and neonatal survival at expected human exposures, possibly related to maternal toxicity. Limited human experience.	Serious bacterial infections
Loperamide	B	Not teratogenic in animals. No increase in birth defects among infants born to 89 women with first-trimester exposure in one study; another study suggests a possible increased risk of hypospadias with first-trimester exposure, but confirmation required.	Symptomatic treatment of diarrhea after the first trimester
Mefloquine	C	Animal data and human data do not suggest an increased risk of birth defects, but miscarriage and stillbirth may be increased.	Second-line therapy of chloroquine-resistant malaria in pregnancy, if quinine/clindamycin not available or not tolerated. Weekly as prophylaxis in areas with chloroquine-resistant malaria.
Meglumine	Not FDA approved	See Antimonials, pentavalent	Therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine
Metronidazole	B	Multiple studies do not indicate teratogenicity. Studies on several hundred women with first-trimester exposure found no increase in birth defects.	Anaerobic bacterial infections, bacterial vaginosis, trichomoniasis, giardiasis, amebiasis
Micafungin	C	Teratogenic in rabbits; no human experience.	Not recommended
Miltefosine	Not FDA approved	Embryotoxic in rats, rabbits; teratogenic in rats. No experience with human use.	Not recommended
Nifurtimox	Not FDA approved	Not teratogenic in mice and rats. Increased chromosomal aberrations in children receiving treatment; uncertain significance. No experience in human pregnancy.	Not indicated in chronic infection; seek expert consultation if acute infection or symptomatic reactivation of <i>T. cruzi</i> in pregnancy.

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Nitazoxanide	B	Not teratogenic in animals; no human data.	Severely symptomatic cryptosporidiosis after the first trimester
Ombitasvir/ Paritaprevir/ Ritonavir	Not assigned	No AEs in mice, rats, rabbits during pregnancy or lactation. No data in human pregnancy or breastfeeding.	Ribavirin, recommended to be used with this drug, is contraindicated in pregnancy so therapy in pregnancy is not recommended .
Para-Aminosalicylic Acid (PAS)	C	Occipital bone defects in one study in rats; not teratogenic in rabbits. Possible increase in limb, ear anomalies in one study with 143 first-trimester exposures; no specific pattern of defects noted, several studies did not find increased risk.	Drug-resistant TB
Paromomycin	C	Not teratogenic in mice and rabbits. Limited human experience, but poor oral absorption makes toxicity, teratogenicity unlikely.	Amebic intestinal infections, possibly cryptosporidiosis
Penicillin	B	Not teratogenic in multiple animal species. Vast experience with use in human pregnancy does not suggest teratogenicity, other adverse outcomes.	Syphilis, other susceptible bacterial infections
Pentamidine	C	Embryocidal but not teratogenic in rats, rabbits with systemic use. Limited experience with systemic use in human pregnancy.	Alternate therapy for PCP and leishmaniasis
Piperacillin-Tazobactam	B	Not teratogenic in limited animal studies. Limited experience in pregnancy but penicillins generally considered safe.	Bacterial infections
Pneumococcal Vaccine	C	No studies in animal pregnancy. Polysaccharide vaccines generally considered safe in pregnancy. Well-tolerated in third-trimester studies.	Initial or booster dose for prevention of invasive pneumococcal infections. Pregnant women with HIV should be on ART before vaccination to limit potential increases in HIV RNA levels with immunization.
Podophyllin and Podofilox	C	Increased embryonic and fetal deaths in rats, mice but not teratogenic. Case reports of maternal, fetal deaths after use of podophyllin resin in pregnancy; no clear increase in birth defects with first-trimester exposure.	Because alternative treatments for genital warts in pregnancy are available, use is not recommended ; however, inadvertent use in early pregnancy is not indication for abortion.
Posaconazole	C	Embryotoxic in rabbits; teratogenic in rats at similar to human exposures. No experience in human pregnancy.	Not recommended

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Prednisone	B	Dose-dependent increased risk of cleft palate in mice, rabbits, hamsters; dose-dependent increase in genital anomalies in mice. Human data inconsistent regarding increased risk of cleft palate. Risk of growth retardation, low birth weight may be increased with chronic use; monitor for hyperglycemia with use in third trimester.	Adjunctive therapy for severe PCP; multiple other non-HIV-related indications
Primaquine	C	No animal data. Limited experience with use in human pregnancy; theoretical risk for hemolytic anemia if fetus has G6PD deficiency.	Alternate therapy for PCP, chloroquine-resistant malaria
Proguanil	C	Not teratogenic in animals. Widely used in malaria-endemic areas with no clear increase in adverse outcomes.	Alternate therapy and prophylaxis of <i>P. falciparum</i> malaria
Pyrazinamide	C	Not teratogenic in rats, mice. Limited experience with use in human pregnancy.	Active TB
Pyrimethamine	C	Teratogenic in mice, rats, hamsters (cleft palate, neural tube defects, and limb anomalies). Limited human data have not suggested an increased risk of birth defects; because folate antagonist, use with leucovorin.	Treatment and secondary prophylaxis of toxoplasmic encephalitis; alternate treatment of PCP
Quinidine Gluconate	C	Generally considered safe in pregnancy; high doses associated with preterm labor. One case of fetal VIII-nerve damage reported.	Alternate treatment of malaria, control of fetal arrhythmias
Quinine Sulfate	C	High doses, often taken as an abortifacient, have been associated with birth defects, especially deafness, in humans and animals. Therapeutic doses have not been associated with an increased risk of defects in humans or animals. Monitor for hypoglycemia.	Treatment of chloroquine-resistant malaria
Ribavirin	X	Dose-dependent risk of multiple defects (craniofacial, central nervous system, skeletal, anophthalmia) in rats, mice, hamsters starting at below human doses. Reports of treatment during second half of pregnancy in nine women without incident; first 49 cases in registry did not suggest increased risk, but limited data.	Contraindicated in early pregnancy; no clear indications in pregnancy.
Rifabutin	B	Not teratogenic in rats and rabbits; no specific concerns for human pregnancy.	Treatment or prophylaxis of MAC, active TB
Rifampin	C	Teratogenic at high doses in mice (cleft palate) and rats (spina bifida) but not in rabbits. No clear teratogenicity in humans.	Active TB
Rifapentine	C	Embryofetal toxicity with increased rate of malformations and fetal loss noted in rats and rabbits. Limited experience in human pregnancy and lactation.	Use alternate drugs in pregnancy if possible.

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Simeprevir	C	Decreased fetal weights and increased skeletal variants in mice at 4 times human exposure. Increased deaths and decreased fetal and neonatal growth and developmental delay after <i>in utero</i> exposure in rats. No experience in human pregnancy.	Treatment of HCV currently generally not recommended in pregnancy.
Sinecatechin Ointment	C	No evidence of teratogenicity in rats and rabbits after oral or intravaginal dosing. No experience in human pregnancy.	Not recommended based on lack of data.
Sofosbuvir	B	No evidence of teratogenicity in rats or rabbits. No experience in human pregnancy.	Treatment of HCV generally not indicated in pregnancy. Regimens including ribavirin and interferon are contraindicated in pregnancy.
Sofosbuvir/Velpatasvir	Not assigned	No AEs in mice, rats, rabbits during pregnancy or lactation. No data in human pregnancy or breastfeeding.	Could be used if benefits felt to outweigh unknown risks in patients not needing ribavirin. Ribavirin is contraindicated in pregnancy, so not recommended for patients needing ribavirin based on subtype or resistance.
Sofosbuvir/Velpatasvir +/- Voxilaprevir	Not assigned	No AEs in mice, rats, rabbits during pregnancy or lactation. No data in human pregnancy or breastfeeding.	Could be used if benefits felt to outweigh unknown risks.
Streptomycin	D	No teratogenicity in mice, rats, guinea pigs. Possible increased risk of deafness and VIII-nerve damage; no evidence of other defects.	Alternate therapy for active TB
Sulfadiazine	B	Sulfonamides teratogenic in some animal studies. No clear teratogenicity in humans; potential for increased jaundice, kernicterus if used near delivery.	Secondary prophylaxis of toxoplasmic encephalitis
Telaprevir	B	Not teratogenic in mice, rats. No human pregnancy data.	Treatment of HCV currently generally not indicated in pregnancy.
Telbivudine	B	Not teratogenic in rats, rabbits. Limited experience in human pregnancy.	Not recommended because of limited data in pregnancy. Use as part of fully suppressive ARV regimen with ARV agents active against both HIV and HBV. Report exposures during pregnancy to the Antiretroviral Pregnancy Registry .

Table 7. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy

Drug	FDA Category ^a	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Tenofovir	B	No evidence of birth defects in rats, rabbits, or monkeys at high doses; chronic administration in immature animals of multiple species at 6–50 times human doses has led to dose-specific bone changes ranging from decreased mineral density to severe osteomalacia and fractures. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown. No evidence of increased birth defects in nearly 2,000 first-trimester exposures in women.	Component of fully suppressive ARV regimen in pregnant women. Report exposures during pregnancy to the Antiretroviral Pregnancy Registry .
Trichloroacetic Acid and Bichloroacetic Acid	Not rated	No studies. Used topically so no systemic absorption expected.	Topical therapy of non-cervical genital warts
Trifluridine	C	Not teratogenic in rats, rabbits. Minimal systemic absorption expected with topical ocular use.	Topical agent for treatment of ocular herpes infections
Trimethoprim-Sulfamethoxazole	C	Teratogenic in rats and mice. Possible increase in congenital cardiac defects, facial clefts, neural tube and urinary defects with first-trimester use. Unclear if higher levels of folate supplementation lower risk. Theoretical risk of elevated bilirubin in the neonate if used near delivery.	Therapy of PCP during pregnancy. Primary and secondary PCP prophylaxis in the second/third trimester; consider aerosolized pentamidine in first trimester. Recommend fetal ultrasound at 18–20 weeks after first-trimester exposure.
Valacyclovir	B	Not teratogenic in mice, rats, and rabbits. Experience with valacyclovir in pregnancy limited; prodrug of acyclovir, which is considered safe for use in pregnancy.	Treatment of HSV and varicella infections in pregnancy
Vancomycin	C	Not teratogenic in rats, rabbits. Limited human experience.	Serious bacterial infections
Voriconazole	D	Embryotoxic in rats, rabbits. Teratogenic in rats (cleft palate, hydronephrosis, and ossification defects). No experience with human use.	Not recommended

^a FDA has discontinued the assignment of drugs to pregnancy-risk letter categories in favor of a narrative approach. This table includes both previously assigned risk categories for older drugs and key findings based on FDA narratives for unassigned newer drugs.

Key: AE = adverse effect; ART = antiretroviral therapy; ARV = antiretroviral; CMV = cytomegalovirus; CNS = central nervous system; FDA = Food and Drug Administration; G6PD = glucose-6-phosphate dehydrogenase; HBV = hepatitis B virus; HCV = hepatitis C virus; HSV = herpes simplex virus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis pneumonia*; TB = tuberculosis; VIII nerve = vestibulocochlear nerve; WHO = World Health Organization

Appendix A. List of Abbreviations (Last updated May 7, 2013; last reviewed January 11, 2023)

Acronym/Abbreviation	Definition
ABGs	arterial blood gasses
ACTG	AIDS Clinical Trials Group
AFB	acid-fast 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	<i>Clostridium difficile</i> -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
DAA	direct acting antiviral agents
DOT	directly observed therapy
DS	double strength
EDTA	ethylenediaminetetraacetic acid
EIA	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	<i>Mycobacterium avium</i> complex
MAI	<i>Mycobacterium avium intracellulare</i>
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	<i>Mycobacterium tuberculosis</i>
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	<i>Pneumocystis pneumonia</i>
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	<i>Toxoplasma</i> encephalitis

TEN	toxic epidermal necrolysis
TID	three times daily
TIW	three times weekly
TP-PA	<i>T. pallidum</i> 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
Gary Holland	<i>David Geffen School of Medicine at the University of California, Los Angeles</i>	None	N/A
Christine Johnston	<i>University of Washington School of Medicine</i>	Gilead Sciences AbbVie	Consultant
Warren Phipps*	<i>University of Washington School of Medicine</i>	None	N/A
Ramya Ramaswami	<i>National Institutes of Health</i>	Celgene/BMS EMD Serono Janssen CTI BioPharma Merck	Research Support (paid to institution)
Shannon Ross	<i>The University of Alabama at Birmingham Marnix E. Heersink School of Medicine</i>	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Herpes (HSV/VZV)

Member	Institution	Financial Disclosure	
		Company	Relationship
Christine Durand	<i>Johns Hopkins University School of Medicine</i>	AbbVie Gilead Sciences GlaxoSmithKline	Research Support (paid to institution)
		Gilead Sciences	Grant Review Committee, Honorarium
John Gnann	<i>Medical University of South Carolina</i>	GlaxoSmithKline	Consultant
		BioCryst	Data Safety Monitoring Board
Gary Holland	<i>David Geffen School of Medicine at the University of California, Los Angeles</i>	None	N/A
Christine Johnston	<i>University of Washington School of Medicine</i>	Gilead Sciences AbbVie	Consultant
Shannon Ross	<i>The University of Alabama at Birmingham Marnix E. Heersink School of Medicine</i>	None	N/A
Nicholas Van Wagoner*	<i>The University of Alabama at Birmingham Marnix E. Heersink School of Medicine</i>	None	N/A

* Section Group Lead

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Human Papillomavirus

Member	Institution	Financial Disclosure	
		Company	Relationship
Darron Brown	<i>Indiana University School of Medicine</i>	Pfizer Johnson & Johnson Novavax Lilly	Equity Interest
		PDS Biotechnology	Scientific Advisory Board
		Merck	Research Support (paid to institution)
Susan Cu-Uvin*	<i>Brown University, Warren Alpert Medical School</i>	United Nations Population Fund	Research Support (paid to institution)
Mark Einstein	<i>Rutgers New Jersey Medical School</i>	AstraZeneca Inovio Iovance Johnson & Johnson Pfizer VBL Therapeutics	Research Support (paid to institution)
		Becton Dickinson, and Company Douglas Inovio Merck Papivax PDS Biotechnology	Consulting Fee (paid to institution)
Lauri Markowitz	<i>Centers for Disease Control and Prevention</i>	None	N/A
L. Stewart Massad	<i>Washington University School of Medicine in St. Louis</i>	None	N/A
Anna-Barbara Moscicki	<i>David Geffen School of Medicine at the University of California, Los Angeles</i>	Merck	Scientific Advisory Board
Joel Palefsky	<i>University of California, San Francisco School of Medicine</i>	Merck	Research Support (paid to institution)

Member	Institution	Financial Disclosure	
		Company	Relationship
Elizabeth Stier	<i>Boston University Medical Center</i>	None	N/A
Howard Strickler	<i>Albert Einstein College of Medicine</i>	Arbor Vista MTM Laboratories/ Ventura-Roche BD Diagnostics	Research Support (paid to institution)
John Weiser	<i>Centers for Disease Control and Prevention</i>	None	N/A
Timothy Wilkin	<i>New York-Presbyterian/Weill Cornell Medicine</i>	Merck	Scientific Advisory Board
		Merck ViiV Healthcare	Research Support (paid to institution)

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Immunizations

Member	Institution	Financial Disclosure	
		Company	Relationship
Shireesha Dhanireddy	<i>University of Washington School of Medicine</i>	None	N/A
Ellen Eaton	<i>The University of Alabama at Birmingham Marnix E. Heersink School of Medicine</i>	DKBmed, Clinical Care Options; IAS–USA	Consultant
		Gilead Research Scholars Program in HIV	Research Support (paid to institution)
Robyn Neblett Fanfair	<i>Centers for Disease Control and Prevention</i>	None	N/A
Philip Peters	<i>Centers for Disease Control and Prevention</i>	None	N/A
Daniel Solomon*	<i>Harvard Medical School</i>	None	N/A

* Section Group Lead

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Invasive Mycoses

Member	Institution	Financial Disclosure	
		Company	Relationship
John Baddley	<i>University of Maryland School of Medicine</i>	Synexis	Research Support (paid to institution)
David Boulware	<i>University of Minnesota Medical School</i>	Appili Therapeutics Matinas BioPharma	Research Support (paid to institution)
Marisa Miceli	<i>University of Michigan Medical School</i>	SCYNEXIS F2G Mayne Pharma	Research Support (paid to institution)
		SCYNEXIS	Data Safety Monitoring Board
		Astellas Pharma	Consulting
John Perfect*	<i>Duke University School of Medicine</i>	Pfizer	Scientific Advisory Board
George R. Thompson	<i>University of California, Davis Medical Center</i>	Amplify Pharmaceuticals Astellas Pharm Cidara Therapeutics F2G Mayne Pharma	Scientific Advisory Board

* Section Group Lead

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Mycobacterium avium Complex

Member	Institution	Financial Disclosure	
		Company	Relationship
Jacqueline Achkar	<i>Albert Einstein College of Medicine</i>	None	N/A
Constance Benson*	<i>University of California, San Diego School of Medicine</i>	Gilead Sciences	Research Support (paid to institution)
Maura Manion	<i>National Institutes of Health</i>	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Mycobacterium tuberculosis

Member	Institution	Financial Disclosure	
		Company	Relationship
James Brust*	<i>Albert Einstein College of Medicine</i>	None	N/A
Kelly Dooley	<i>Johns Hopkins University School of Medicine</i>	None	N/A
Neela Goswami	<i>Centers for Disease Control and Prevention</i>	None	N/A
Scott Heysell	<i>University of Virginia School of Medicine</i>	None	N/A
Jyoti Mathad	<i>New York-Presbyterian/Weill Cornell Medicine</i>	None	N/A
Graeme Meintjes	<i>University of Cape Town, South Africa, Faculty of Health Sciences</i>	None	N/A
Sarita Shah	<i>Centers for Disease Control and Prevention</i>	None	N/A
Timothy Sterling	<i>Vanderbilt University Medical Center</i>	None	N/A

* Section Group Lead

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Appendix B. Panel Roster and Financial Disclosures

Pharmacology

Member	Institution	Financial Disclosure	
		Company	Relationship
Jomy George	<i>National Institutes of Health</i>	None	N/A
Emily Heil	<i>University of Maryland School of Pharmacy</i>	Lexi-Comp	Consultant
Rupali Jain	<i>University of Washington School of Pharmacy</i>	Wolters Kluwer	Consultant
Safia Kuriakose*	<i>National Institutes of Health</i>	None	N/A
Alice Pau	<i>National Institutes of Health</i>	None	N/A
Charles Peloquin	<i>University of Florida College of Pharmacy and Emerging Pathogens Institute</i>	None	N/A
Anthony Podany	<i>University of Nebraska Medical Center</i>	None	N/A

* Section Group Lead

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Progressive Multifocal Leukoencephalopathy

Member	Institution	Financial Disclosure	
		Company	Relationship
Shruti Agnihotri	<i>The University of Alabama at Birmingham Marnix E. Heersink School of Medicine</i>	Moderna Pfizer Gilead Sciences Johnson & Johnson	Equity Interest
Paola Cinque	<i>San Raffaele Scientific Institute, Milan, Italy</i>	Janssen	Consultant
		Cellevolve	Scientific Advisory Board
		Gilead Sciences ViiV Healthcare	Research Support (paid to institution)
David Clifford*	<i>Washington University School of Medicine in St. Louis</i>	Roche Takeda Seattle Genetics Arena Pharmaceuticals	Scientific Advisory Board
		Wave Life Sciences Excision BioTherapeutics, Inc. Sanofi Genzyme Atara Biotherapeutics, Inc.	Data Safety Monitoring Board
Irene Cortese	<i>National Institutes of Health</i>	Nouscom AG Keires AG PDC*line Pharma Life Sciences Partners CV	Equity Interest
Christina Marra	<i>University of Washington School of Medicine</i>	None	N/A
Jose M. Miro	<i>Hospital Clinic–IDIBAPS, University of Barcelona, Spain</i>	None	N/A

* Section Group Lead

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Pneumocystis Pneumonia

Member	Institution	Financial Disclosure	
		Company	Relationship
Kristina Crothers	<i>University of Washington School of Medicine</i>	None	N/A
Hansjakob Furrer	<i>Universitatsspital Bern, University of Bern, Switzerland</i>	Gilead Sciences ViiV Healthcare	Research Support (paid to institution)
Jannik Helweg-Larsen	<i>Rigshospitalet, Copenhagen University, Denmark</i>	None	N/A
Aley Kalapila	<i>Emory University School of Medicine</i>	None	N/A
Joseph Kovacs*	<i>National Institutes of Health</i>	Matinas BioPharma Merck	Research Support (paid to institution)
Alison Morris	<i>University of Pittsburgh Medical School</i>	None	N/A
Sean Wasserman	<i>University of Cape Town, South Africa, Faculty of Health Sciences</i>	None	N/A

* Section Group Lead

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Pregnancy

Member	Institution	Financial Disclosure	
		Company	Relationship
Jean Anderson	<i>Johns Hopkins University School of Medicine</i>	DKBmed	Research Support (paid to institution)
Katherine Bunge	<i>UPMC Magee-Womens Hospital</i>	None	N/A
Nahida Chakhtoura*	<i>National Institutes of Health</i>	None	N/A
Oluwatosin Goje	<i>Cleveland Clinic, Lerner College of Medicine</i>	SCYNEXIS OrganiCare, LLC	Consultant
		SCYNEXIS	Scientific Advisory Board
		SCYNEXIS	Research Support (paid to institution)
Brenna Hughes	<i>Duke University School of Medicine</i>	Merck	Scientific Advisory Board
Sylvia LaCourse	<i>University of Washington School of Medicine and School of Public Health</i>	Merck	Research Support (paid to institution)
Gweneth Lazenby	<i>Medical University of South Carolina</i>	None	N/A
Rodney Wright	<i>Albert Einstein College of Medicine</i>	None	N/A

* Section Group Lead

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Syphilis

Member	Institution	Financial Disclosure	
		Company	Relationship
Laura Bachmann	<i>Centers for Disease Control and Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention; Division of STD Prevention</i>	None	N/A
Khalil Ghanem	<i>Johns Hopkins University School of Medicine</i>	None	N/A
Lisa Hollier	<i>Baylor College of Medicine</i>	None	N/A
Edward W. Hook	<i>The University of Alabama at Birmingham Marnix E. Heersink School of Medicine</i>	Visby Medical	Scientific Advisory Board
Arlene Sena	<i>The University of North Carolina at Chapel Hill School of Medicine</i>	None	N/A
Brad Stoner	<i>Queen's University School of Medicine, Kingston (Ontario), Canada</i>	None	N/A
Kimberly Workowski*	<i>Emory University School of Medicine</i>	None	N/A

* Section Group Lead

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Toxoplasma gondii

Member	Institution	Financial Disclosure	
		Company	Relationship
Sarita Boyd	<i>U.S. Food and Drug Administration</i>	None	N/A
Joseph Kovacs*	<i>National Institutes of Health</i>	Matinas BioPharma Merck	Research Support (paid to institution)
Janaki Kuruppu	<i>National Institutes of Health</i>	None	N/A
Leon Lai	<i>MedStar Washington Hospital Center</i>	None	N/A
Jose M. Miro	<i>Hospital Clinic–IDIBAPS, University of Barcelona, Spain</i>	None	N/A
Daniel Podzamczar	<i>Fight AIDS and Infectious Diseases Foundation, Hospital Germans Trias i Pujol, Badalona, Spain</i>	Janssen Gilead Sciences ViiV Healthcare	Consultant
		Gilead Sciences MSD	Research Support (paid to institution)
Bryan R. Smith	<i>National Institutes of Health</i>	None	N/A

* Section Group Lead

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