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

Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

How to Cite the Adult and Adolescent Opportunistic Infection Guidelines:

Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Available at https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Adult_OI.pdf. Accessed (insert date)[include page numbers, table number, etc. if applicable]

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

Updates to 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 that can be updated easily as relevant changes in prevention and treatment recommendations occur.

The editors and subject-matter experts are committed to timely changes in this document because so many health care providers, patients, and policy experts rely on this source for vital clinical information.

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 6 months are as follows:

What's New

November 18, 2021

Key updates to the guidelines include the following:

Appendix B: Panel Roster and Financial Disclosures

- Updated member conflict of interest information for 2021-2022
- Updated roster to include 22 new members, 6 new Section Group Leads and 1 new Leadership member.

Immunizations

- The immunization section has been updated to reflect the recommendation that all people with HIV should receive the COVID-19 vaccine regardless of their CD4 T lymphocyte count or HIV viral load.
- People with advanced or untreated HIV who received a 2-dose series with one of the mRNA COVID-19 vaccines should receive a third dose of that vaccine at least 28 days after the second dose.
- The zoster vaccine is now recommended for people with HIV age 18 years old and older in alignment with Advisory Committee on Immunization Practices (ACIP) recommendations.

August 18, 2021

Human Papillomavirus Disease. Key updates to the guidelines include the following:

- New recommendation for cervical cancer screening to start at age 21 based on the HIV/AIDS Cancer Match Study with no reported cases of cervical cancer below the age of 25.

July 21, 2021

Varicella-Zoster Virus. Key updates to the guidelines include the following:

- Updated to reflect that 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.

July 1, 2021

Cytomegalovirus. Key updates to the guidelines include the following:

- Updated to improve readability and to update references.
- The toxicities of alternative antiviral medications used to treat cytomegalovirus are highlighted.
- The document was updated for person-first language.

Cryptococcosis. Key updates to the guidelines include the following:

- Recommended an increase in the dose of fluconazole from 400 mg to 800 mg daily for consolidation therapy. For clinically stable patients who have been started on ART and whose CSF culture results return with no growth, the dose can be decreased to 400 mg daily.
- Included results of a trial in a resource-limited setting that used only one week of amphotericin B induction therapy but did NOT recommend this approach for high-resource settings.
- Clarified that the treatment of non-CNS extrapulmonary cryptococcosis and diffuse pulmonary disease should be the same as that for meningitis and that treatment of mild-moderate focal pulmonary infection should be with fluconazole, 400-800 mg daily.
- Clarified treatment for patients who have been found to have asymptomatic antigenemia.
- Revised the Pregnancy text for consistency with other sections of the guidelines.
- Revised the table of recommendations to clarify recommended treatment of the various forms of cryptococcosis in persons with HIV.

June 11, 2021

Coccidioidomycosis. Key updates to the guidelines include the following:

- Revised the section on serology for the diagnosis of coccidioidomycosis.
- Added polymerase chain reaction (PCR) as a commercially available diagnostic test.
- Revised the section on patients who are asymptomatic and have a positive serological test.

Bartonellosis. Key updates to the guidelines include the following:

- Updated the section on diagnostics, including the role of PCR-based testing.
- Updated the section on treatment for endocarditis.

Immunizations for Preventable Diseases in Adults and Adolescents Living with HIV. Key updates to the guidelines include the following:

- Revised the figure summarizing immunizations in people with HIV.
- Added a table comparing ACIP recommendations with Panel recommendations.
- Added narrative sections with evidence summaries.
- Updated the recommendation for zoster vaccines.

Table of Contents

Introduction (Last updated May 29, 2018; last reviewed October 13, 2021)

Opportunistic infections (OIs) were the first clinical manifestations that alerted clinicians to the occurrence of the acquired immunodeficiency syndrome (AIDS). *Pneumocystis* pneumonia (PCP), toxoplasma encephalitis, cytomegalovirus (CMV) 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.[1,2] Until effective antiretroviral therapy (ART) was developed, patients generally survived only 1 to 2 years after the initial manifestation of AIDS.[3]

HIV-related OIs have been defined as infections that are more frequent or more severe because of HIV-mediated immunosuppression.[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 persons 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 had the most profound influence on reducing OI-related morbidity and mortality in persons with HIV.[7-11]

Despite the availability of multiple safe, effective, and simple ART regimens, and a corresponding steady decline in the incidence of OIs,[11] the Centers for Disease Control and Prevention (CDC) estimates that more than 40% of Americans with HIV are not effectively virally suppressed.[12-17] As a result, OIs continue to cause preventable morbidity and mortality in the United States.[18]

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 2015, 15% of the people with HIV in the United States were unaware of their infections.[19] Among those with diagnosed HIV, more than 50% had had HIV for more than 3 years[20] and approximately 20% had a CD4 T lymphocyte (CD4) cell count <200 cells/mm^3 (or <14%) at the time of diagnosis.[20,21]
- *Not all persons with diagnosed HIV receive timely continuous HIV care or are prescribed ART.* CDC estimates that in 2015, 16% of persons with newly diagnosed HIV had not been linked to care within 3 months and among persons living with HIV only 57% were adequately engaged in continuous care.[21]
- *Not all persons treated for HIV achieve durable viral suppression.* CDC estimates that in 2014, only 49% of diagnosed patients were effectively linked to care and had durable viral suppression.[22] Causes for the suboptimal response to treatment include poor adherence, unfavorable pharmacokinetics, or unexplained biologic factors.[23,24]

Thus, some persons 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.

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 persons with HIV regardless of CD4 count. The likelihood of each of these OIs occurring does vary inversely with the CD4 count, however.[23-31]

When certain OIs occur— most notably tuberculosis and syphilis—they can increase plasma viral load,[32-37] which both accelerates HIV progression and increases the risk of HIV transmission.

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.[38] 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 *Mycobacterium avium* complex disease in 1993.[39] 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 NIH, the CDC, and the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA) now jointly co-sponsor these guidelines,[4,40-42] which have been published in peer-reviewed journals and/or the MMWR in 1997, 1999, and 2002.[41-53] 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 2017, there were almost 423,075 page views of the online version of the guidelines, and almost 4,000 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 at https://clinicalinfo.hiv.gov.

These guidelines are intended for clinicians, other health care providers, patients with HIV, and policy makers 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.

Guidelines Development Process

These guidelines were prepared by the OI Working Group under the auspices of the Office of AIDS Research Advisory Council (OARAC), an authorized Federal Advisory Committee to the U.S. Department of Health and Human Services established in 1994. 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 of subject group leads at ID Week each year to review progress and set an agenda for the coming year. Final guidelines revisions posted on the AIDS*info* website may include additional changes made by the co-editors under the advisement of Office of AIDS Research Advisory Committee (OARAC).

The names and affiliations of all contributors as well as their financial disclosures are provided in Panel Roster and Financial Disclosures (Appendix C).

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 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 healthcare 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 3-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 C.
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 C. 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 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 Office of AIDS Research Advisory Council (OARAC).
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, OAR, subject matter experts at CDC and HIVMA/IDSA before final approval and publication.
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, CDC, and IDSA before being endorsed as official recommendations.
Other guidelines	These guidelines focus on prevention and treatment of HIV-related OIs for adults and adolescents. A separate guideline outlines similar recommendations for children who have HIV infection. These guidelines are available on the Clinical Info website (https://Clinicalinfo.nih.gov).

Guidelines Development Process, continued	
Topic	**Comment**
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 Clinical Info website (https://Clinicalinfo.nih.gov) pending update of the guidelines with the appropriate changes.
Public comments	A 2-week public comment period follows release of a guidelines update on the Clinical Info website. Comments received are reviewed by the appropriate work group(s) and the co-editors determine whether revisions to the guidelines are indicated. The public may also submit comments to the Panel at any time at contactus@HIVinfo.nih.gov.

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 persons with HIV, but there are data derived from studies in persons 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 eight summary tables at the end of the document (Tables 1–8), a figure of the latest Advisory Committee of Immunization Practices immunization recommendations adapted to adults and adolescents with HIV, and an appendix that summarizes recommendations pertinent to preventing exposure to opportunistic pathogens, including preventing exposure to sexually transmitted diseases (STDs) (Appendix A).

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Bacterial Enteric Infections (Last updated August 10, 2017; last reviewed October 13, 2021)

NOTE: Update in Progress

Epidemiology

Rates of Gram-negative bacterial enteric infections are at least 10-fold higher among HIV-infected adults than in the general population, but these rates decline when patients are treated with antiretroviral therapy (ART).[1-7] The risk of bacterial diarrhea varies according to CD4 T lymphocyte (CD4) count and is greatest in individuals with clinical AIDS or <200 CD4 cells/mm^3.[5] The bacteria most frequently isolated by culture from HIV-infected adults 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 poorly understood because diagnosis remains a research-only test. *Clostridium difficile*-associated infection (CDI) is common in HIV-infected patients; recent data[9] suggest that low CD4 count (<50 cells/mm^3) is an independent disease risk factor in addition to the 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 should also consider CDI in the evaluation of outpatient diarrheal illnesses in HIV-infected individuals. Data on *Helicobacter pylori* infection in HIV infection are limited and do not suggest excess risk in HIV-infected individuals. 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 enteric infections in HIV-infected patients 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] (see Appendix for further details). HIV-associated alterations in mucosal immunity or intestinal integrity and treatment with acid-suppressive agents may increase risk of enteric bacterial infections.

Clinical Manifestations

The three major clinical syndromes of infection with Gram-negative enteric bacteria among HIV-infected patients are:

- Self-limited gastroenteritis;
- More 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 is often defined as ≥6 loose stools (loose stool is defined as defecated material that takes the shape of a container) per day with or without other signs of disease such as fecal blood, orthostatic hypotension, or fever. In HIV-infected patients, 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 HIV-infected patients.[17-19]

Diagnosis

Assessment of patients with diarrhea should include a complete exposure history (see below); 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 volume and nutritional status.

The diagnosis of Gram-negative bacterial enteric infection is established through cultures of stool and blood. Stool cultures are required to obtain antibiotic sensitivity testing for isolated enteric pathogens. Thus, stool cultures are preferred over or in addition to molecular diagnostics in HIV-infected patients given increasing resistance detected in enteric bacterial infections. Because incidence of bacteremia associated with *Salmonella* gastroenteritis is high in HIV-infected individuals, particularly those with advanced disease, blood cultures should be obtained from any patient with diarrhea and fever. For shigellosis, blood cultures may be helpful but are less likely to be positive than in salmonellosis.

Other infections for which HIV-infected patients are at risk, albeit at a lower rate, are non-*jejuni* non-coli *Campylobacter* species, such as *Campylobacter fetus*, *Campylobacter upsaliensis*, and *Campylobacter lari*, and the enterohepatic *Helicobacter* spp. (*Helicobacter cineadi* and *Helicobacter fennelliae*), which were originally described as *Campylobacter* spp. Blood culture systems will typically 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.

A stool sample for *C. difficile* toxin or polymerase chain reaction (PCR) assay should be routinely performed for patients with diarrhea who have recently received or are currently receiving antibiotics (including antimicrobial prophylaxis) or cancer chemotherapy, those who have been hospitalized in the past 4 to 6 weeks (or are currently hospitalized), those who reside in a long-term care facility, those with CD4 counts <200 cells/mm^3, those taking acid-suppressive medications, and those with moderate-to-severe community-acquired diarrhea.[20] The most commonly used toxin tests are enzyme immunoassays that suffer from low sensitivity. PCR assays or glutamate dehydrogenase antigen enzyme immunoassays (which must be combined with a second confirmatory test for stool toxin) are recommended for testing.[21] However, only diarrheal stool samples should be tested for *C. difficile* to limit detection of asymptomatic colonization. Regardless of the test used, the diagnosis of CDI can only be made through careful selection of the correct population for testing and a correlation of clinical and laboratory findings.

Endoscopy should generally be reserved for patients in whom stool culture, microscopy, *C. difficile* toxin 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 disease (STD). Some sexually transmitted rectal infections (e.g., proctitis due to lymphogranuloma venereum or *Neisseria gonorrhoeae*) can produce symptoms similar to those seen with colitis due to *Salmonella*, *Shigella*, and *Campylobacter* spp. If stool cultures fail to yield enteric bacterial pathogens in patients with symptoms of proctitis or colitis, diagnostic evaluation for STDs with anoscopy, culture, and biopsy should be considered.

Preventing Exposure

Multiple epidemiologic exposures can place patients at risk of enteric illnesses. The most common are ingestion of contaminated food or water and fecal-oral exposures (detailed prevention recommendations related to food and water exposures, pet exposures, and travel-related exposures can be found in the Appendix). Providing advice and education about such exposures is the responsibility of the health care provider. A patient's clinical condition and CD4 count can help the provider determine what prevention recommendations are most appropriate. Patients with CD4 counts <200 cells/mm^3 or a history of AIDS-defining illness[22] are at the greatest risk of enteric illnesses;[5] however, excess risk of undetermined magnitude or duration may persist in those with lesser degrees of immune impairment, including individuals treated with ART.

Patients should be advised to regularly wash their hands with soap and water or alcohol-based cleansers to reduce the risk of enteric infection **(AIII)**. With regard to preventing enteric infection, soap and water are preferred over alcohol-based cleansers, which do not kill *C. difficile* spores and are only partially active against norovirus and *Cryptosporidium* **(AIII)**. HIV-infected patients should be advised to wash their hands after potential contact with human feces (e.g., as through defecation, cleaning feces from infants, or 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)**. HIV-infected patients 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)**.

Preventing Disease

Antimicrobial prophylaxis to prevent bacterial enteric illness **is usually not recommended**, including for travelers **(AIII)**. Prophylactic antimicrobial treatment can elicit adverse reactions, promote the emergence of resistant organisms, and increase risk of CDI. In rare cases, however, antimicrobial prophylaxis with fluoroquinolones or rifaximin can be considered, such as for immunosuppressed travelers, depending on their level of immunosuppression, the region of travel, and the trip's duration **(CIII)**. For pregnant women and patients already taking trimethoprim-sulfamethoxazole (TMP-SMX) (such as for *Pneumocystis jirovecii* pneumonia prophylaxis), TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to fluoroquinolones or rifaximin **(BIII)**. Risk of toxicity should be considered before prophylaxis with TMP-SMX is initiated solely because of travel.

Treating Disease

Empiric Therapy

In most situations, treatment of diarrheal disease in HIV-infected patients 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 also are likely to be useful **(BIII)**. The effectiveness and safety of probiotics or antimotility agents have not been adequately studied in HIV-infected patients with diarrheal illnesses.[23] Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI **(BIII)**.

After obtaining stool samples for diagnostic evaluation, initiation and duration of empiric antimicrobial therapy depend upon 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. No further work-up may be necessary and no treatment other than oral rehydration may be required, for example, in patients with CD4 counts >500 cells/mm^3 who have had 1 to 2 days of loose stools without fever or blood. However, a short course of antibiotics may be indicated in HIV-infected patients with CD4 counts of 200 to 500 cells/mm^3 who have diarrhea severe enough to compromise quality of life or ability to work. Patients with advanced HIV disease (i.e., CD4 counts <200 cells/mm^3 or concomitant AIDS-defining illness) and clinically severe diarrhea (i.e., ≥6 liquid stools per day or bloody stools or a lower number of liquid stools per day but accompanied by fever or chills concerning for invasive bacterial disease) should undergo diagnostic evaluation to determine the etiology of the diarrheal illness and receive antimicrobial treatment. Empiric therapy with ciprofloxacin is reasonable **(AIII)**. IV ceftriaxone or IV cefotaxime are reasonable alternatives **(BIII)**. Therapy should be adjusted subsequently based on the results of the diagnostic work-up. Diarrhea that is persistent (i.e., lasting >14 days) in the absence of other clinical signs of severity, such as bloody stool or dehydration, should be evaluated and directed therapy should be started once a diagnosis is confirmed.

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 *Campylobacter jejuni* in Southeast Asia is common.[24] Clinicians should consider the possibility of a resistant infection when prescribing empiric therapy for HIV-infected travelers 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.[25-29]

Pathogen-Specific Therapy

Salmonella spp.

Immunocompetent hosts who are not HIV-infected often do not require treatment for *Salmonella* gastroenteritis, as the condition is usually self-limited and treatment may prolong the carrier state. In contrast, all HIV-infected patients with salmonellosis should be treated **(AIII)**, although no clinical trials have compared antimicrobial therapy with placebo. Notably, HIV infection increases the risk of *Salmonella* bacteremia 20- to 100-fold and mortality as much as 7-fold compared with that in patients who are not HIV-infected.[1,30]

The initial treatment of choice for *Salmonella* infection is a fluoroquinolone **(AIII)**. Ciprofloxacin is the preferred agent **(AIII)**.[31] Other fluoroquinolones, such as levofloxacin and moxifloxacin, would likely be effective in treating salmonellosis in HIV-infected patients 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/mm^3 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/mm^3), 2 to 6 weeks of antibiotics is often recommended **(CIII)**.[32] Some patients with *Salmonella* bacteremia may remain febrile for 5 to 7 days despite effective therapy.

HIV-infected patients with *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 might also be considered for patients with recurrent gastroenteritis (with or without bacteremia) and in those with CD4 counts <200 cell/mm^3 with severe diarrhea **(BIII)**. The value of this secondary prophylaxis has not been established and must be weighed against the risks of long-term antibiotic exposure. Recurrent *Salmonella* bacteremia constitutes an AIDS-defining illness[33] and suppression of HIV replication with ART appears to decrease the risk of recurrent illnesses.[34] In patients whose *Salmonella* infection is resolved and who have responded to ART with sustained viral suppression and CD4 counts >200 cells/mm^3, secondary prophylaxis for salmonellosis can probably be stopped **(CII)**.[7] Clinicians also should be aware that recurrence may represent development of antimicrobial resistance during therapy.

Shigella spp.

Therapy for *Shigella* infections is recommended both to shorten the duration of illness and to possibly prevent spread of the infection to others **(AIII)**.[31] The recommended treatment for shigellosis is with a fluoroquinolone, preferably ciprofloxacin, for 7 to 10 days **(AIII)**. Although current CLSI criteria categorizes *Shigella* isolates with MIC 0.12-1 ug/ml as susceptible, these isolates may harbor plasmid-mediated resistance genes. Until the clinical significance of these findings can be determined, fluoroquinolones should only be used to treat isolates with MIC <0.12 ug/ml.[35] Ciprofloxacin-resistant *S. sonnei* and *S. flexneri* have been reported in the United States and are associated with international travel, homelessness, and being a man who has sex with men (MSM); ciprofloxacin-resistant shigellosis among MSM appears to be acquired predominantly within the United States, rather than during travel.[29] Depending on antibiotic susceptibilities, alternative agents might include TMP-SMX (7–10 days) or azithromycin (5 days) **(BIII)**. Azithromycin has not been evaluated in HIV-infected patients with shigellosis, and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[36] Recently, azithromycin-resistant *Shigella* spp in HIV-infected MSM have been reported.[37-39] 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/mm^3, 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 HIV-infected patients is poorly defined. Culture and testing for the antibiotic susceptibility of *Campylobacter* isolates is recommended **(BIII)**. Rates of resistance to antimicrobial agents differs by *Campylobacter* species. In the United States in 2013, 22% of *C. jejuni* isolates were resistant to fluoroquinolone and 2% were resistant to azithromycin; among *C. coli* isolates, 35% of isolates were resistant to fluoroquinolones and 17% were resistant to azithromycin.[40] For patients with mild disease and CD4 counts >200 cells/mm^3, some clinicians opt to withhold therapy unless symptoms persist for more than several days **(CIII)**. For mild-to-moderate Campylobacteriosis, initiating therapy with a fluoroquinolone such as ciprofloxacin for 7 to 10 days (if the organism is sensitive) or azithromycin for 5 days is a reasonable approach **(BIII)**. Azithromycin has not been evaluated in HIV-infected patients with Campylobacteriosis and the therapy suggested is extrapolated from limited data in immunocompetent hosts.[41] Patients with *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 HIV-infected patients **(BIII)**. However, recurrent infections can occur, particularly in patients with CD4 counts <200 cells/mm^3. In recurrent disease, extending the length of antimicrobial therapy for 2 to 6 weeks is reasonable **(BIII)**. As with *Salmonella* infections, suppression of HIV replication with ART is expected to decrease the risk of recurrent *Campylobacter* spp. infections.

Clostridium difficile

Available data suggest that HIV-infected patients respond to treatment of CDI similarly to HIV-uninfected patients. Guidelines and subsequent updates to guide the treatment of CDI have been published[42-45] and can be consulted for further information. Multivariate analysis of 2 recent identical, multicenter (91 sites in United States, Canada; 109 sites in Europe), randomized, double-blind studies involving 537 non-HIV-infected patients with CDI (278 and 259 treated with metronidazole and vancomycin, respectively) found vancomycin to be superior to metronidazole for clinical success [OR 1.575 (1.035, 2.396), $P = 0.034$]. Stratification by CDI disease severity found 4.0% (mild), 8.3% (moderate), and 12.2% (severe) improved clinical success rates with vancomycin therapy compared to metronidazole therapy.[46] Given this trial and earlier data,[47] vancomycin **(AI)** is recommended for treatment of HIV-infected persons with CDI with the possible exception of mild CDI where treatment with metronidazole **(CII)** may yield clinical success. Treatment of recurrent CDI in HIV-infected patients is the same as in patients who are not HIV-infected. Limited case reports suggest that fecal microbiota therapy (aka fecal transplant) may be successful and safe to treat recurrent CDI in HIV-infected patients **(CIII)**.[48] The impact of ART on recurrence of CDI is unknown.

Special Considerations with Regard to Starting ART

ART initiation should follow standard guidelines. 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; in other words, the presence of an enteric infection should not delay ART initiation **(BIII)**.

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. A follow-up stool culture to demonstrate clearance of the organism is not required if clinical symptoms and diarrhea resolve. Follow-up stool culture may be required when public health considerations and state law dictate the need to ensure micro¬biologic cure, such as in health care or food service workers.

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

Managing Treatment Failure

Follow-up stool culture should be considered for patients who fail to respond clinically 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, in all cases, the possibility of *C. difficile* or the development of antimicrobial resistance.

Observational studies suggest that plasma drug concentrations (e.g., of ciprofloxacin) in HIV-infected patients may be decreased as a result of diarrhea or malabsorption.[49,50] Coadministration of quinolones with magnesium- or aluminum-containing antacids or with calcium, zinc, or iron should be avoided because these interfere with drug 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)**.

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 women is the same as in women who are not pregnant. Bacterial enteric infections in pregnant women should be managed the same as in women who are not pregnant, with several considerations. Based on the 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)**.[51] Arthropathy has been noted in the offspring of animals treated with quinolones during pregnancy. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[52-54] Thus, quinolones can be used in pregnancy for bacterial enteric infections in HIV-infected pregnant women 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)**.[55,56,57] However, a recent review of potential risks related to TMP-SMX use cites the low quality of current data and supports use of TMP-SMX in HIV-infected pregnant women as clinically indicated.[58] 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. Since rifaximin is not systemically absorbed, it can be used in pregnancy as in non-pregnant individuals. Limited data are available on the risks of vancomycin use during pregnancy, however minimal absorption is expected with oral therapy. With intravenous use, vancomycin readily crosses the placenta.[59] A study of 10 infants evaluated after second or third trimester in utero exposure from maternal intravenous vancomycin therapy for serious staphylococcal infections found no hearing loss or renal toxicity attributed to vancomycin.[60] A recent review of metronidazole use in pregnancy for treatment of trichomoniasis or bacterial vaginosis found no increase in risk of birth defects.[61] Studies on use for CDI in pregnancy were not found.

Recommendations for Preventing and Treating Bacterial Enteric Infections (page 1 of 3)

Preventing Bacterial Enteric Illness

- Antimicrobial prophylaxis to prevent bacterial enteric illness usually **is not 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 fluoroquinolones or rifaximin can be considered **(CIII)**.
- For pregnant women and patients already on trimethoprim-sulfamethoxazole (TMP-SMX) for prophylaxis against *Pneumocystis* pneumonia TMP-SMX may offer limited protection against travelers' diarrhea as an alternative to fluoroquinolone or rifaximin **(BIII)**.

General Considerations when Managing Patients with Bacterial Enteric Infections

- Oral or IV rehydration therapy (if indicated) should be given to patients with diarrhea **(AIII)**.
- Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including *Clostridium difficile* infection (CDI) **(BIII)**.
- Diagnostic fecal specimens should be obtained prior to initiation of empiric antimicrobial therapy.
- If stool sample is obtained, antibiotic susceptibilities should be performed to confirm and inform antibiotic choice given increased reports of antibiotic resistance.
- Risk of a bacterial enteric infection increases as CD4 count declines, with the greatest risk in patients with CD4 counts <200 cells/ mm^3. Risk of bacteremia also increases with decreasing CD4 count. If no clinical response after 3 to 4 days, 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)

For patients with advanced HIV (CD4 count <200 cells/mm^3 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) q12h **(AIII)**

Alternative Therapy:

- Ceftriaxone IV 1 g q24h **(BIII)**, *or*
- Cefotaxime IV 1g q8h **(BIII)**

Note: 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 HIV-infected travelers while traveling or upon return to the United States, particularly among travelers to South and Southeast Asia.

Treating Salmonellosis

All HIV-infected patients with salmonellosis should receive antibiotic treatment due to the increased risk of bacteremia (by 20–100-fold) and mortality (by as much as 7-fold) compared with HIV-negative individuals **(AIII)**.

Preferred Therapy for Salmonella Gastroenteritis With or Without Bacteremia:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)**

Alternative Therapy:

- Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or*
- Moxifloxacin 400 mg (PO or IV) q24h **(BIII)**

If susceptible, alternatives to fluoroquinolone may include 1 of the following:

- Trimethoprim 160 mg/sulfamethoxazole 800 mg (PO or IV) q12h **(BIII)**, *or*
- Ceftriaxone IV 1g q24h **(BIII)**, *or*
- Cefotaxime IV 1g q8h **(BIII)**

Treating Salmonellosis, *continued*

Duration of Therapy for Gastroenteritis Without Bacteremia

- If CD4 count >200 cells/mm^3: 7–14 days **(BIII)**
- If CD4 count <200 cells/mm^3 particularly if primary illness was severe: 2–6 weeks **(BIII)**

Duration of Therapy for Gastroenteritis With Bacteremia

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

Secondary Prophylaxis

The role of long-term, secondary prophylaxis for patients with recurrent bacteremia or gastroenteritis is not well established. Clinicians must weigh the benefit against the risks of long-term antibiotic exposure **(BIII)**. Antibiotic choices for secondary prophylaxis are the same as for primary treatment and are dependent on the sensitivity of the *Salmonella* isolate.

Suppression of HIV replication 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:

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

When to Stop Secondary Prophylaxis:

- After resolution of *Salmonella* infection and response to ART with sustained viral suppression and CD4 count >200 cells/mm^3 **(CII)**

Treating Shigellosis

Therapy is indicated to shorten the duration of illness and to possibly prevent spread to others **(AIII)**. However, given increasing antimicrobial resistance and limited data demonstrating that antibiotic therapy limits transmission, antibiotic treatment may be withheld in HIV-infected patients with CD4 >500 cells/mm^3 whose diarrhea resolves prior to culture confirmation of *Shigella* infection **(CIII)**.

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h if MIC<0.12 ug/ml (see **Note**) **(AIII)**

Alternative Therapy (Depending on Susceptibility Results):

- Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or*
- Moxifloxacin (PO or IV) 400 mg q24h **(BIII)** *or*
- Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV q12h **(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 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 HIV-infected individuals should be performed routinely.

Treating Campylobacteriosis

- Optimal treatment is poorly defined.
- There is an increasing rate of fluoroquinolone resistance in the United States (22% resistance in 2013 among *C. jejuni* isolates).
- Antimicrobial therapy should be modified based on susceptibility reports.

Mild Disease if CD4 Count >500 cells/mm^3:

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

Treating Campylobacteriosis, *continued*

Mild to Moderate Disease

Preferred Therapy:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)**—if susceptible, *or*
- Azithromycin 500 mg PO daily for 5 days **(BIII)** (**Not recommended** for bacteremia **[AIII]**)

Alternative Therapy (Depending on Susceptibility Results):

- Levofloxacin 750 mg PO or IV q24h **(BIII)**, *or*
- Moxifloxacin 400 mg PO or IV q24h **(BIII)**

Bacteremia:

- Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)** plus an aminoglycoside **(BIII)** in bacteremic patients to limit the emergence of antibiotic resistance

Duration of Therapy:

- Gastroenteritis: 7–10 days **(BIII)** [5 days if azithromycin is used]
- Bacteremia: ≥14 days **(BIII)**
- Recurrent bacteremic disease: 2–6 weeks **(BIII)**

Chronic Maintenance or Suppressive Therapy:

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

Treating *Clostridium difficile* Infection (CDI)

Preferred Therapy:

- Vancomycin 125 mg (PO) 4 times per day for 10–14 days **(AI)**
- For severe, life-threatening CDI, see text and references for additional information.

Alternative Therapy for Mild CDI:

- For mild, outpatient disease: metronidazole 500 mg (PO) 3 times per day for 10-14 days **(CII)**

Recurrent CDI:

- Treatment is the same as in patients without HIV infection. Fecal microbiota therapy (FMT) may be successful and safe to treat recurrent CDI in HIV-infected patients **(CIII)**. See text and references for additional information.

Key to Acronyms: CD4 = CD4 T lymphocyte cell; IV = intravenously; PO = orally; q(n)h = every "n" hours.

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Bartonellosis (Last updated June 11, 2021; last reviewed October 13, 2021)

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 resolution[8] or recrudescence. Because of interlaboratory variability, longitudinal testing should be conducted at the same laboratory, to enable direct comparison of titers over time.

Because of their fastidious nature, *Bartonella* organisms can be isolated only with difficulty from blood (drawn into ethylenediaminetetraacetic acid [EDTA] tubes, centrifuged, and then plated directly onto 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/mm^3), are at high risk of severe disease when infected by *B. quintana* and *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 age 1 year 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 reports[12] 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-naive patients, ART generally can be initiated at the same time as *Bartonella*-directed treatment; however, patients with *Bartonella* CNS or ophthalmic lesions probably should be treated with doxycycline and a rifamycin class antibiotic for 2 to 4 weeks before instituting ART **(CIII)**.

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/mm^3 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 ceftizoxime[15] 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

<u>*Preferred Therapy*</u>

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 q12h + 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)**

<u>*Alternative Therapy for Bartonella Infections (Not for Endocarditis or CNS Infections)*</u>*:*

- 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/mm^3 **(AIII)**

Indications for Discontinuing Long-Term Suppressive Therapy ***(CIII)****:*

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

Other Considerations

- Rifamycin class antibiotics are potent hepatic enzyme inducers and may lead to significant interaction with many drugs, including ARV agents (see Table 3 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

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Candidiasis (Mucocutaneous) (Last updated May 26, 2020; last reviewed October 13, 2021)

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/mm^3, 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 **(BII)**.[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 suspension[19] 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 Antiretroviral Therapy

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/mm^3 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 trial[14] in patients with HIV infection with CD4 counts <150 cells/mm^3 documented significantly fewer episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (three times a week) than with episodic fluconazole treatment for recurrences. This clinical trial also demonstrated no difference in the risk of developing clinically significant fluconazole resistance between the two 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 (**BII**I) 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/mm^3 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 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 (page 1 of 2)

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/mm^3 **(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)**

Recommendations for Treating Mucosal Candidiasis (page 2 of 2)

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 5 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

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Chagas Disease (Last updated August 8, 2018; last reviewed October 13, 2021)

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 Romaña's sign—unilateral painless swelling of the upper and lower eyelids—which usually lasts several weeks. The other symptoms of acute infection are usually limited to a non-specific febrile illness. In a small proportion of patients, however, acute, life-threatening myocarditis or meningoencephalitis may occur.[2,4] At the end of the acute phase, typically 60 to 90 days after infection, parasitemia falls below levels detectable by microscopy, and in the absence of effective 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/mm^3, 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 benzdidazole 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

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Coccidioidomycosis (Last updated July 14, 2021; last reviewed October 13, 2021)

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/mm^3, 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.[7] In patients with HIV, lack of viral suppression and CD4 count <250 cells/mm^3 are associated with increased severity of the presentation of coccidioidomycosis.[6]

Focal pneumonia is most common in patients with CD4 counts ≥250 cells/mm^3. 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.[6, 7] However, coccidioidomycosis may present with hilar or 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.[8] 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/mm^3 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/mm^3.[9]

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 *Coccididoides* spp. may be present, and in the laboratory, the culture plate lid should be kept secured with tape.[10] 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.[13] 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.[14]

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[11] serum,[12] 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.[13]

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.[14]

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

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 **<u>it is not recommended</u> (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/mm^3 and who previously tested negative for *Coccidioides*, a new positive serology test suggests possible active disease[9] 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/mm^3 **(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

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)**.[15, 16] Itraconazole is preferred for those who have bone or joint disease **(AI)**.[17] 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 >1mcg/mL and preferably >2mcg/mL.

Data to support clinical efficacy for treatment with posaconazole[18, 19] 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)**,[19] 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.[20] 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%).[21]

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)**.[16] 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 reports[22] 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)**.[16]

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)**,[15, 23] but itraconazole 400 to 600 mg daily also has been successfully used **(BII)**.[24] Therapy with voriconazole **(BIII)**,[25-27] posaconazole **(CIII)**,[19, 28] and isavuconazole **(CIII)** has been described in individual cases and has been successful.[29] 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.[30-32] In general, delaying initiation of ART while treating coccidioidomycosis **<u>is not recommended</u> (AIII)**. Conversely, a recent case series[34] and a single case report[35] suggested that, in highly immunosuppressed patients (i.e., CD4 counts <100 cells/mm^3) 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.[33] Close monitoring for clinical worsening, particularly if meningitis is present, is essential when treating highly immunosuppressed persons 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 ARV guidelines). Posaconazole and isavuconazole have fewer known drug interactions with antiretrovirals than voriconazole. In certain situations, surgical intervention may be indicated.[15]

Therapy after Immune Reconstitution

Patients with peripheral blood CD4 lymphocyte counts ≥250/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[35] Moreover, a prospective study has demonstrated that of 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/mm^3, coccidioidomycosis should be managed no differently than it is in patients in the general population **(AII)**.

For patients with focal pulmonary disease who meet the above criteria, treatment with triazole antifungal agent should continue for a minimum of <u>3</u> 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 <250/mm^3, antifungal therapy at full dose should continue **(BIII)**.

Preventioning of Relapse

Relapse of coccidioidomycosis occurs in 25% to 33% of individuals without HIV who have diffuse pulmonary coccidioidomycosis or nonmeningeal disseminated coccidioidomycosis[39,40] and may occur in persons with HIV who have CD4 counts ≥250 cells/mm^3 and are virologically suppressed on antiretrovirals.[34, 1] 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 ≥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)[35, 5] and a more recent large population-based case-control study[46] 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.[47] 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.[48] 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.[49] 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.[50,5] However, in general, all azole antifungals **shoud 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)**.[15]

Recommendations for Preventing and Treating Coccidiodomycosis (page 1 of 2)

Preventing Coccidioidomycosis

Primary antifungal prophylaxis for individuals with negative serologic tests for *Coccidiodies* **is not recommended (AIII) except** for the following indications:

Indication for Primary Prophylaxis:

- New positive IgM and/or IgG test for *Coccidioides*; and
- No sign of active coccidioidomycosis; and
- CD4 count <250 cells/mm³

Preferred Therapy:

- Fluconazole 400 mg PO once daily **(AIII)**

Discontinuation of Primary Prophylaxis:

- CD4 count ≥250 cells/mm³ with virologic suppression on ART **(BIII)**
- Close clinical follow-up is recommended **(BIII)**

Treating Mild to Moderate Pulmonary Infections

Indications for Treatment:

- Patients who have clinically mild infection, such as focal pneumonia;
- Patients with positive coccidioidal serologies but with mild or without clinical illness.

Preferred Therapy:

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

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

- Voriconazole loading dose of 400 mg 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)**

Treating Severe Pulmonary or Extrapulmonary Infection (except meningitis):

Preferred Therapy:

- 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)**.

Alternative Therapy:

- Some specialists recommend combining amphotericin B with a triazole (fluconazole or itraconazole 400mg daily) and continue the triazole once amphotericin B is stopped **(CIII)**.

Treatment For Meningeal Infections (Consultation With A Specialist Is Advised)

Preferred Therapy:

- Fluconazole 400–800 mg IV or PO once daily **(AII)**

Alternative Therapy:

- Itraconazole 200 mg PO two to three-times daily **(BII)**, *or*
- Voriconazole 200–400 mg PO twice daily **(BIII)**, *or*
- Posaconazole (delayed-release tablet) 300 mg PO 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.

Treatment in Pregnancy

- 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*
- Lipid formulation amphotericin B 3–5 mg/kg IV daily **(AIII)**

Discontinuing of Therapy

Focal Coccidioidal Pneumonia, Therapy Can Be Stopped If ***(AII)****:*

- Clinically responded to ≥3 months of antifungal therapy *and*
- CD4 count ≥250 cells/mm^3, *and*
- Virologic suppression on ARVs, *and*
- Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

- Relapse can occur in 25% to 33% of patients without HIV, and can occur in patients with HIV who have CD4 count >250 cells/mm^3.
- 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)**.

Coccidioidal Meningitis:

- Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong **(AII).**

Other Considerations:

- 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 ARV Guidelines DDI tables list these interactions and recommend dosage adjustments where feasible.

Key: Adult and Adolescent ARV Guidelines = *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV*; ARVs = antiretrovirals; CD4 = CD4 T lymphocyte cell; CSF = cerebrospinal fluid; DDI = drug-drug interaction; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; PO = orally

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Community-Acquired Pneumonia (Last updated October 10, 2019; last reviewed October 13, 2021)

Epidemiology

Bacterial respiratory diseases, including sinusitis, bronchitis, otitis, and pneumonia, are among the most common infectious complications in patients 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 patients with HIV.

In general, although data are limited, hospital-acquired pneumonia and ventilator-associated pneumonia do not differ in terms of microbiology, clinical course, treatment, or prevention in persons with HIV as compared to persons without HIV with similar HIV-unrelated comorbidities. Therefore, they will not be addressed in these guidelines.

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.[8]

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

Additional risk factors that contribute to the continued risk for bacterial pneumonia in individuals with HIV include tobacco, alcohol, and/or injection drug use; and chronic viral hepatitis.[3,10,15,16] Chronic obstructive pulmonary disease (COPD), malignancy, renal insufficiency, and congestive heart failure are emerging as risk factors for pneumonia, particularly in the population of older adults with HIV.[17] Risk for CAP can also increase with obesity,[4] an emerging health problem in people living with HIV.

Microbiology

In individuals with HIV, *Streptococcus pneumoniae* (*S. pneumoniae*) and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia, the same as in individuals without HIV.[18-24] *Staphylococcus aureus* (*S. aureus*) and *S. pneumoniae* are among the most common etiologies of pneumonia in association with influenza infection.[25,26] Atypical bacterial pathogens such as *Legionella pneumophila, Mycoplasma pneumoniae,* and *Chlamydophila* species have been reported as infrequent causes of CAP in individuals with HIV.[21,27] However, when more extensive testing such as serology to detect IgM antibodies and/or positive polymerase chain reaction (PCR) of respiratory secretions was performed, additional infections due to *Mycoplasma* and *Chlamydia* were detected.[28] Respiratory viruses are also a common cause of CAP. Although virally-induced CAP is less studied in individuals with HIV, data from a Centers for Disease Control and Prevention (CDC) study of the epidemiology of CAP in adult patients in five hospitals in Nashville and Chicago showed that respiratory viruses were detected in nearly a quarter of the adults with CAP (23% had one or more respiratory viruses and 3% had both respiratory viruses and bacteria).[29]

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.[22,30] Many of these patients often had poorly controlled HIV or the presence of other concomitant risk factors that contributed to the risk for *P. aeruginosa* or *S. aureus*. Patients with advanced HIV disease (CD4 count ≤50 cells/mm^3) or underlying neutropenia, as well as pre-existing lung disease such as bronchiectasis or severe COPD have an increased risk of infection with *P. aeruginosa*. Other risk factors for infection include the use of corticosteroids, severe malnutrition, hospitalization within the past 90 days, residence in a health care facility or nursing home, and chronic hemodialysis.[31]

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 health care contact.[32] Community outbreaks of methicillin-resistant *S. aureus* (MRSA) infection have also been seen among men who have sex with men.[33] 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.[31] 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.[34,35]

Clinical Manifestations

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.[36] Patients with pneumonia caused by bacteria such as *S. pneumoniae* or *Haemophilus* species characteristically have acute onset (3–5 days) of symptoms, including fevers, chills, rigors, chest pain or pleurisy, cough productive of purulent sputum, and dyspnea.[37] 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*.

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*.[38] In data from 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.[39] Similarly, in a study from Kenya, the rate of pneumococcal bacteremia was significantly higher in individuals with HIV infection (rate ratio of HIV-positive versus HIV-negative adults, 19.7, 95% CI, 12.4–31.1).[40] 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.[41-45] Risk factors associated with bacteremia include lack of ART, low CD4 count (particularly <100 cells/mm^3), as well as alcohol abuse, current smoking, and comorbidities, particularly liver disease.[42]

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. The use of severity scoring systems for pneumonia and their application to patients with HIV are discussed in the Treating Disease section.

Although some studies suggest that bacterial pneumonia is associated with increased mortality in individuals with HIV,[22,46,47] others do not.[36,48-50] Independent predictors of increased mortality in a prospective, multicenter study of individuals with HIV with community-acquired bacterial pneumonia were CD4 count <100 cells/mm^3, radiographic progression of disease, and presence of shock.[51] In that study, multilobar infiltrates, cavitary infiltrates, and pleural effusion on baseline imaging were all independent predictors of radiographic progression of disease. However, in patients on ART with controlled HIV viremia, and high CD4 counts (>350 cells/mm^3), the clinical courses and outcomes of pneumonia appear to be similar to those in patients without HIV.[36]

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.[52] Pneumonia has also been associated with impaired lung function and risk of subsequent lung cancer in individuals with HIV.[53-55]

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. 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. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (i.e., respiratory isolation 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). 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 persons 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.[56] 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 Community-Acquired Pneumonia

Guidelines for microbiologic testing for diagnosis of CAP in individuals without HIV generally also apply to persons with HIV.[57]

- In patients with HIV with CAP who are well enough to be treated as outpatients, routine diagnostic tests to identify a bacterial etiologic diagnosis are optional, especially if the microbiologic studies cannot be performed promptly.
- In patients with HIV hospitalized for CAP, a Gram stain of expectorated sputum and two blood cultures are recommended, particularly in those with severe pneumonia, in those who are not on ART; or in those who are known to have a CD4 count <350 cells/mm^3 (and especially if <100 cells/mm^3) prior to hospitalization. Specimens should ideally be obtained before initiation of antibiotics, or within 12 hours to 18 hours of such initiation.
- Urinary antigen tests for *L. pneumophila* and *S. pneumoniae* are recommended in hospitalized patients, particularly those with severe CAP. In addition, lower respiratory tract secretions should be cultured for *Legionella* on selective media or undergo *Legionella* nucleic acid amplification testing in adults with severe CAP. *Legionella* testing should also be done in patients 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.[58]

Gram stain and culture of sputum is recommended in all hospitalized patients meeting the criteria stated above and is optional in individuals with HIV and 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 12–18 hours after) initiation of antibiotics, and quality performance measures for collection, transport, and processing of samples can be met. Sputum cultures in patients with HIV have been shown to identify a bacterial etiology in up to 30% to 40% of good quality specimens[47,59] although yield is less in other studies.[14,28] 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 individuals 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*,[60,61] 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

Vaccination against *S. pneumoniae* and influenza, use of ART, and lifestyle modifications are all important measures in preventing bacterial pneumonia. Multiple observational studies have reported benefits of pneumococcal polysaccharide vaccine (PPV) in persons with HIV.[16,62-68] Several studies also have documented an association between vaccination and a reduced risk of pneumococcal bacteremia.[42,67] One randomized placebo-controlled trial of PPV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia.[69] Follow-up of this cohort confirmed the increase in pneumonia in vaccinated participants, but notably also showed a decrease in all-cause mortality.[70] However, subsequent observational studies have demonstrated that PPV vaccination provides people with HIV moderate protection against pneumococcal disease.[71]

The 13-valent pneumococcal conjugate vaccine (PCV13) is recommended by the Advisory Committee on Immunization Practices for use in adults with immunocompromising conditions, including HIV infection.[39] A randomized, double-blind, placebo-controlled trial of 7-valent PCV among adults with HIV in Malawi demonstrated 74% efficacy against vaccine-type invasive pneumococcal disease, with clear evidence of efficacy in those with CD4 counts <200 cells/mm^3.[72]

Adults and adolescents with HIV who have never received any pneumococcal vaccine should receive a single dose of PCV13 regardless of CD4 count **(AI)**.[39] Patients with CD4 counts >200 cells/mm^3 should receive a dose of 23-valent PPV (PPV23) at least 8 weeks later **(AI)**.[62-68,73,74] While individuals with HIV with CD4 counts <200 cells/mm^3 can also be offered PPV23 at least 8 weeks after receiving PCV13 **(CIII)** (e.g., when there are concerns with retention in care), PPV23 should preferably be deferred until after an individual's CD4 count increases to >200 cells/mm^3 while on ART **(BIII)**. Clinical evidence supporting use of PPV23 in persons with CD4 counts <200 cells/mm^3 appears strongest in patients who also have HIV RNA <100,000 copies/mL;[73,74] evidence also suggests benefit for those who start ART before receiving PPV vaccination.[67,75]

The duration of the protective effect of PPV23 is unknown; a single revaccination with PPV is recommended if ≥5 years have elapsed since the first dose of PPV23 was given **(BII)**.[66] A final dose of PPV23 is recommended after age 65 years, and should be given ≥5 years after any doses that were given before age 65 years **(BII)**. Typically, no more than three doses of PPV23 are given in a lifetime.

PCV13 should also be given to patients with HIV who have already received PPV23 **(AII)**.[76] However, in such cases, adult patients should wait ≥1 year after their most recent dose of PPV23 before receiving a single dose of PCV13 **(BIII)**;[39] adolescents aged <19 years should wait ≥8 weeks **(BIII)**. Subsequent doses of PPV23 should be given according to the schedule outlined above (i.e., ≥5 years between doses of PPV23 with no more than 3 lifetime doses).

Inactivated or recombinant influenza vaccine should be administered annually during influenza season to all individuals with HIV **(AII)**.[77] This recommendation is pertinent to prevention of bacterial pneumonia, which can occur as a complication of influenza. Influenza and pneumococcal vaccines can be administered during the same visit. Use of live attenuated influenza vaccine is contraindicated and **is not recommended** in individuals with HIV **(AIII)**.

Use of high-dose inactivated influenza vaccine is associated with decreased incidence of influenza and greater antibody response in adults without HIV aged ≥65 years.[78] One study found greater immunogenicity in individuals with HIV aged ≥18 years who were given high-dose influenza vaccine compared with standard-dose inactivated vaccine.[79] While providers can also give the high-dose influenza vaccine to their patients with HIV aged ≥65 years **(CIII)**, there are no data on the efficacy of high-dose influenza vaccine in individuals with HIV. Currently, the high-dose vaccine is trivalent rather than quadrivalent, offering protection against one rather than two Influenza B viruses and two Influenza A viruses.

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)**[75] unless a patient also has anatomic or functional asplenia.

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.[47] In many studies, daily administration of TMP-SMX for PCP prophylaxis reduced the frequency of bacterial respiratory infections.[9,80,81] This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of TMP-SMX (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, in the United States, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(AIII)**. Similarly, clarithromycin or azithromycin should not be prescribed solely for preventing bacterial respiratory infection **(AIII)**.

A decreased absolute neutrophil count (e.g., <500 cells/mm^3) is associated with an increased risk of bacterial infections, including pneumonia, although this risk has been demonstrated primarily in persons with malignant neoplasms. To reduce the risk of such bacterial infections, clinicians should take steps to reverse neutropenia, such as by stopping myelosuppressive drugs **(CIII)**. Studies of granulocyte-colony stimulating factor in persons with HIV have failed to document benefit.[82,83]

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes, using injection drugs, and consuming alcohol.[9,68,84-86] 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.[57] 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 (e.g., housing, comorbid diseases), 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 Infectious Diseases Society of America [IDSA]/American Thoracic Society [ATS] [ATS/IDSA] severity criteria[57] or CURB-65 Score for Pneumonia Severity) to guide decisions regarding inpatient or outpatient treatment location for persons 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.[51,87,88] One study suggested that the site of care decision be dictated by considering the PSI score and CD4 count together.[87] Mortality was increased in patients with higher PSI risk class; however, even in those without an increased mortality risk by PSI, a CD4 count <200 cells/mm^3 was associated with an increased risk of death.[87] This led to the suggestion to hospitalize CAP patients with CD4 counts <200 cells/mm^3 and to use the PSI to help guide decision-making in those with higher CD4 counts.[89] However, other studies have found the PSI was predictive of outcomes independent of CD4 count.[90] Furthermore, CD4 count or HIV RNA level are not clearly associated with short-term outcomes of CAP.[91] 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.[92]

Therefore, in general, validated clinical prediction scores for prognosis can be used in patients with HIV in conjunction with clinical judgement to guide treatment location for CAP. Low risk patients for whom there are no other concerns regarding adherence or complicating factors can be treated as outpatients. Patients with severe CAP, including those presenting with shock or respiratory failure, usually require a higher level of care, typically ICU admission. Additionally, severe CAP criteria can include PSI risk class of III or IV or CURB-65 scores ≥3. Patients with ≥3 of the ATS/IDSA minor severity criteria for CAP[57] 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 those for persons without HIV.

Outpatient Community-Acquired Pneumonia Treatment

Individuals with HIV who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide **(AI)**, or an oral 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 oral respiratory fluoroquinolones are moxifloxacin or levofloxacin. An oral 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 macrolide-resistant rates up to 30%,[93] prompting concerns for possible treatment failure. In this regard, local drug resistance patterns, if available, can help inform treatment decisions. Second, 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 Community-Acquired Pneumonia Inpatient Treatment

Individuals with HIV who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide **(AI)** or an IV 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.[94,95] In one study, beta-lactam monotherapy was not found to be non-inferior to beta-lactam/macrolide combination therapy. Notably, in the monotherapy arm, patients who had more severe CAP, as indicated by a PSI ≥IV, or who had atypical pathogens were less likely to reach clinical stability. There were also more 30-day readmissions among the patients on monotherapy.[94] 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.[95] 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 persons 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.[96] 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 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 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)**.[97] In patients who are allergic to penicillin, an IV 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 Community-Acquired Pneumonia 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.[98] Patients with severe pneumonia should be treated with an IV beta-lactam plus either IV azithromycin **(AI)** or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) **(AI)**. Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. In patients who are allergic to penicillin, aztreonam plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(BIII)**.

Most 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 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.

The addition of corticosteroids for treating CAP has not been studied in individuals with HIV. Data from studies in persons without HIV with CAP suggest that corticosteroids may decrease a composite outcome of mortality, time to clinical stability, and length of hospital stay,[99] except in influenza pneumonia, where corticosteroids increase mortality.[100] The optimal regimen including dose, duration, and formulation of corticosteroid, and the patient population with bacterial non-influenza related CAP most likely to benefit from the additional use of corticosteroids remain uncertain. Selecting patients without HIV 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.[101] Overall, the use of corticosteroids in patients with HIV with severe CAP is not routinely recommended **(CIII)** given the lack of data specifically in populations with HIV. If providers administer corticosteroids to patients with HIV 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, following Surviving Sepsis Guidelines[102] and administering hydrocortisone 200 mg IV daily for 3 to 7 days (or tapering once vasopressors are no longer needed) is reasonable **(CIII)**.

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)**.[58]

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 persons without HIV infection.[103] While ceftaroline has activity against MRSA, and data suggest it can be effective for MRSA pneumonia, it has been FDA approved for treatment of community-acquired bacterial pneumonia based on two studies that did not include any MRSA isolates.[104] 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. Suggested criteria for clinical stability include oral temperature <37.8°C, heart rate <100 beats/minute, respiratory rate <24 breaths/minute, systolic blood pressure ≥90 mm Hg, and room air oxygen saturation >90% or partial pressure of oxygen in arterial blood >60 mm Hg **(BII)**.[57] 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.[36,50] A clinical response (i.e., reduction in fever and improvement in respiratory symptoms, physical findings, and laboratory studies) typically is observed within 48 to 72 hours after initiation of appropriate antimicrobial therapy. A review of patients with CAP found that advanced HIV infection and CD4 count <100 cells/mm^3 were predictors for longer time to clinical stability (i.e., >7 days) and that patients who received ART tended to become clinically stable sooner and had better outcomes.[89,92] 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:

- Patients with recurrent pneumonia have not been included in the study population;
- IRIS among participants with bacterial pneumonia has not been specified, *or*
- This complication has truly not been observed.[2,105]

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, and/or noninfectious causes of pulmonary dysfunction (pulmonary embolus, COPD).

Preventing Recurrence

Patients with HIV should receive pneumococcal **(AI)** and influenza vaccines **(AII)** 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%,[106] 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 ≥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.[107,108] 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.[109,110] When indicated, quinolones can be used in pregnancy for serious respiratory infections only when a safer alternative is not available **(CIII)**.[111]

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.[112] 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.[113] A study of neonates after *in utero* exposure did not find evidence of renal or ototoxicity.[114] 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.[113] 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)**, using PPV23 for adults who have the above indications for PPV23. Although the vaccine's safety during the first trimester has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. No data are available to guide recommendations on the use of PCV13 during pregnancy but trial results are expected soon (NCT02717494).

Inactivated influenza vaccine is recommended for all pregnant women during influenza season **(AIII)**. Live attenuated influenza vaccine should not be used in persons 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 (page 1 of 3)

Preventing *Streptococcus pneumoniae* Infections

Indications for Pneumococcal Vaccination:

- All persons with HIV regardless of CD4 count **(AI)**

Vaccination Recommendations

For Individuals Who Have Not Received Any Pneumococcal Vaccination

Preferred Vaccination:

- One dose of PCV13 **(AI)**, followed by:
- CD4 count ≥200 cells/mm³: Administer PPV23 ≥8 weeks later **(AI)**; *or*
- CD4 count <200 cells/mm³: PPV23 can be offered ≥8 weeks after receipt of PCV13 **(CIII)** or can await until CD4 count increases to >200 cells/mm³ on ART **(BIII)**.

For Individuals Who Have Previously Received PPV23:

- One dose of PCV13 should be given to patients who have already received PPV23 **(AII)**.
- Adults (aged ≥19 years) should wait ≥1 year and adolescents (aged <19 years) should wait ≥8 weeks after their most recent dose of PPV23 before receiving a single dose of PCV13 **(BIII)**.

Re-Vaccination of PPV23:

- A dose of PPV23 is recommended for individuals aged 19 through 64 years if ≥5 years have elapsed since their first dose of PPV **(BII)**.
- A final dose of PPV23 is recommended for individuals aged ≥65 years, after ≥5 years have elapsed since their previous PPV23 dose **(BII)**.
- Typically, no more than 3 doses of PPV23 are given in a lifetime.

Vaccine Dosing:

- PCV13: 0.5 mL IM
- PPV23: 0.5 mL IM

Preventing Influenza and Bacterial Pneumonia as a Complication of Influenza

Indication for Influenza Vaccination:

- All persons with HIV infection during influenza season **(AII)**

Vaccination:

- Inactivated, standard dose or recombinant influenza vaccine per recommendation of the season **(AII)**; *or*
- High-dose inactivated influenza vaccine may be given to individuals aged ≥65 years **(CIII)**.

Note: Live attenuated influenza vaccine is **contraindicated** in persons 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 (e.g., PCP, TB), which may alter the empiric therapy.

Empiric Outpatient Therapy (Oral)

Preferred Therapy:

- An oral beta-lactam plus 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

Recommendations for Preventing and Treating Community-Acquired Pneumonia (page 2 of 3)

Treating Community-Acquired Bacterial Pneumonia, continued

Alternative Therapy:

- A beta-lactam plus doxycycline **(BIII)**

Empiric Therapy for Hospitalized Patients with Non-Severe CAP

Preferred Therapy:

- An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) **(AI)**

Preferred Beta-Lactams:

- Ceftriaxone, cefotaxime, or ampicillin-sulbactam, *or*
- An IV respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] **(AI)**, especially for patients with penicillin allergies.

Alternative Therapy:

- An IV beta-lactam plus 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 plus IV azithromycin **(AI)**, *or*
- An IV beta-lactam plus an IV respiratory fluoroquinolone (levofloxacin or moxifloxacin)[a] **(AI)**

Preferred Beta-Lactams:

- Ceftriaxone, cefotaxime, or ampicillin-sulbactam

Alternative Therapy:

For Penicillin-Allergic Patients:

- Aztreonam (IV) plus an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin)[a] **(BIII)**

Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia

Preferred Therapy:

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

For Penicillin-Allergic Patients:

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

Empiric Therapy for Patients at Risk of 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)**.

Recommendations for Preventing and Treating Community-Acquired Pneumonia (page 3 of 3)

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 when 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 (e.g., levofloxacin, 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 four-drug TB regimen.

Key: ART = antiretroviral therapy; CAP = community-acquired pneumonia; CD4 = CD4 T lymphocyte cell; IM = intramuscular; IV = intravenous; MAC = *Mycobacterium avium* complex; MRSA = methicillin-resistant *Staphylococcus aureus*; PCP = *Pneumocystis* pneumonia; PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; PO = orally; PPV23 = 23-Valent Pneumococcal Polysaccharide Vaccine; TB = tuberculosis

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Cryptococcosis (Last updated July 1, 2021; last reviewed October 13, 2021)

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 HIV[4] are observed in those who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3. The incidence of the disease has declined substantially among people treated 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 H_2O 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 ≥1:160, disseminated disease becomes increasingly more likely, and when CrAg LFA titers are ≥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/mm^3, the prevalence of cryptococcal antigenemia—a harbinger of disease—was 2.9%, and for those with CD4 counts ≤50 cells/ mm^3, the prevalence was 4.3%.[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/mm^3 and particularly in those with CD4 counts ≤50 cells/mm^3 (**AII**). A positive test generally should prompt CSF evaluation for CNS infection (**BIII**), particularly when the serum LFA titer is ≥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[20,21] who have CD4 counts <100 cells/mm^3.[19, 20] 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.[21] 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 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., ≤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 ≥1:640 (or ≥1:160 by EIA or latex agglutination), even in the absence of meningitis, the risk for mortality and/or progression to meningitis increases with fluconazole monotherapy alone, and 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 ≥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 H_2O 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 lumber 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 H_2O.[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 H_2O **(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 H_2O, **(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 **<u>are not recommended</u>** **(AIII)**. Acetazolamide **<u>should not be used</u>** 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 **<u>should not be used</u>** 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.[55] 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.[56, 57] Patients with HIV who have cryptococcal IRIS are more likely to be ART naive and have less CSF inflammation on initial presentation.[58] 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)**.[55, 59] 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,[58, 60] 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;[61] 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.[62] 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.[63] Therefore, susceptibility testing is not recommended routinely for initial management of cryptococcosis. However, if treatment failure or relapse occurs, *Cryptococcus* isolates should undergo antifungal susceptibility testing. Robust clinical data are lacking, but strains of *Cryptococcus* with fluconazole minimum inhibitory concentrations (MIC) ≥16 µg/mL are considered not fully susceptible.[64, 65]

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[21, 66, 67] and should be considered when initial treatment with other regimens fails **(AII)**.

In the setting of treatment failure or relapse, verifying CSF culture sterility at the completion of re-induction therapy is critical **(AIII)**. After CSF sterility is achieved, outpatient consolidation therapy should consist of fluconazole at a higher dose of 1,200 mg per day and optimization of ART. For *Cryptococcus* with decreased azole-susceptibility (i.e., ≥16 µg/mL MIC for fluconazole) some experts would recommend adjunctive weekly amphotericin B administration during consolidation therapy **(BIII)**.[65] 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 µg/mL, and only 30% when the MIC was 16 µg/mL.[65] For patients in whom susceptibility studies have been performed and the fluconazole MIC is ≥8 µg/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.[68]

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/mm^3, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[69] 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/mm^3 with a sustained undetectable HIV RNA level for 3 months on potent ART.[70] 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/mm^3 with undetectable viral loads on ART **(BII)**.[71] Maintenance therapy should be reinitiated if the CD4 count decreases to <100 cells/mm^3 **(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.[72]

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.[73] 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.[74] One registry-based cohort study included in the systematic review[75] and a more recent large population-based case-control study[76] 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.[77] 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.[78] 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.[72] 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%.[72] Stillbirths and miscarriages were common during the initial maternal hospitalization with only 33% (4 live births out of 12 pregnancies) fetal survival.[72] 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.[72]

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.[79, 80] 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 (Page 1 of 2)

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 7).

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 fluco-nazole 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 1,200 mg and perform LP 2 weeks later (BIII); duration of consolidation therapy should be 8 weeks from the time of negative CSF culture (AI).

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/mm^3 (AIII)

Treating Non-CNS Extrapulmonary, Diffuse Pulmonary Disease, or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA Titer >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 <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)**

Recommendations for Treating Cryptococcosis (page 2 of 2)

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 <u>are not recommended</u> (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 5 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

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Cryptosporidiosis (Last updated July 16, 2019; last reviewed October 13, 2021)

Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect 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/mm^3—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 patients with AIDS in developing countries, with up to 74% of diarrheal stools from patients with AIDS demonstrating the organism.[4] In developed countries with low rates of environmental contamination and widespread availability of potent antiretroviral therapy, the incidence of cryptosporidiosis has decreased. In the United States, the incidence of cryptosporidiosis in patients 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 have 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, cholera-like diarrhea.[6] More severe symptoms tend to occur in immune-suppressed patients, whereas transient diarrhea alone is typical in patients 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 patients 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 has traditionally been 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. 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 are plagued by false-positive results.[11] 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

Individuals 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] Patients 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)**.

Individuals with HIV—particularly those with CD4 counts <200 cells/mm^3—should avoid direct contact with diarrhea or stool from pets **(BIII)**. They should wear gloves when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII)**. Individuals 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.

Individuals 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, salt-water beaches, some swimming pools, recreational water parks, and ornamental water fountains may be contaminated with human or animal waste that contains *Cryptosporidium*. 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 persons with HIV boil water or avoid drinking tap water in non-outbreak settings. However, individuals 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.

Patients 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 patients with HIV, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII)**.

Individuals with HIV who travel to developing 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)**.

Individuals 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 patients with advanced immunodeficiency, initiation of ART before the patient becomes severely immunosuppressed should prevent this disease **(AII)**. Rifabutin and possibly clarithromycin taken for *Mycobacterium avium complex* prophylaxis have been found to protect against cryptosporidiosis.[14,15] 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.[16] 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/mm^3 usually leads to resolution of clinical cryptosporidiosis[17-20] and is the mainstay of treatment. Patients 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 anti-motility 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)**.[21] Because diarrhea can cause lactase deficiency, patients 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 choledocoduodenoscopy for diagnosis. They may also benefit from sphincterotomy, stenting, or both.[7,22]

Several agents, including nitazoxanide, paromomycin, and spiramycin, have been investigated in small, randomized controlled clinical trials of adults with HIV. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[23]

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 Food and Drug Administration for treatment of cryptosporidiosis in children 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.[24,25] In one study, adults with HIV with cryptosporidiosis with CD4 counts >50 cells/mm^3 were treated with nitazoxanide 500 mg to 1,000 mg twice daily for 14 days; the nitazoxanide treatment group had substantially higher rates of parasitological cure and resolution of diarrhea than the placebo group.[26] Efficacy of nitazoxanide for the treatment of cryptosporidial diarrhea in children with HIV was not confirmed, however, in two randomized trials in children.[27,28] Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts < 50 cells/mm^3, reported that a majority of patients experienced some degree of clinical response (reduction in frequency of total stool and of liquid stools), usually within the first week of treatment.[29] Adverse events associated with nitazoxanide are limited and 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, despite the paucity of evidence that such antiparasitic therapy is beneficial **(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%.[22] Two randomized trials comparing paromomycin with placebo demonstrated limited effectiveness of the drug among patients with AIDS and cryptosporidiosis.[23,30,31] One case series suggested a better response rate in patients receiving paromomycin along with ART.[32] 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 vitro* and in animal models, PIs can inhibit *Cryptosporidium*, but there is no clinical evidence that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[33,34]

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 3 cases of extra-intestinal cryptosporidiosis.[35]

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 anti-parasitic 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.[36,37]

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 women **(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 women 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 women 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.[38] Therefore, loperamide should be avoided in the first trimester, unless benefits are felt to outweigh potential risks **(CIII)**. Loperamide is the preferred anti-motility 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)**.[38]

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 anti-motility agent **(AIII)**; tincture of opium may be more effective than loperamide **(CIII)**, *and* • Initiation or optimization of ART for immune restoration to CD4 count >100 cells/mm^3 **(AII)** Consider: • Nitazoxanide 500 mg to 1,000 mg PO twice daily with food for 14 days **(CIII)** plus optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or* • Paromomycin 500 mg PO four times a day for 14 days–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

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Cystoisosporiasis (Formerly Isosporiasis) (Last updated September 10, 2015; last reviewed October 13, 2021)

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 arthritis[16] 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/mm^3.[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 isoporiasis-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/mm^3 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/mm^3 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/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

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Cytomegalovirus Disease (Last updated July 1, 2021; last reviewed October 13, 2021)

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/mm^3 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 ≥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/mm^3) relapse of the retinitis occurs at a rate of 0.03/person-year and has been documented[6] at CD4 counts as high as 1,250 cells/mm^3. 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/mm^3, 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 midepigastric 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/μL 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/mm^3 (**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/mm^3 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 **<u>is not recommended</u>** 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/mm^3) 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/mm^3, 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/mm^3 **(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 intravitreous 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 intravitreous injections is based on pharmacokinetic considerations, but the clinical benefit of such supplementation has not been confirmed in clinical trials. Although intravitreous 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 intravitreous 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. Intravitreous 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/mm^3 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, intravitreous, 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 cidofovir[57] 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 intravitreous 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 intravitreously, 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 maintenance 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/mm^3 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/mm^3). 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/mm^3 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/mm^3 **(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 intravitreous 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/mm^3, 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 birth[90] 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
- Intravitreous 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

- Intravitreous 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/kL, a calculated creatinine clearance ≤5 mL/min or a urine protein ≥100 mg/kL (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

- Periocular 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, <u>and</u> lesions are inactive, <u>and</u> 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).

Managing CMV Esophagitis or Colitis
• Doses are the same as for CMV retinitis. *Preferred Therapy* • Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can absorb and tolerate PO therapy (BI). *Alternative Therapy* • 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; *or* • Oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption (BIII); *or* *Duration of Anti-CMV Therapy* • 21–42 days or until signs and symptoms have resolved (CII). Note: Maintenance therapy is usually not necessary, but should be considered after relapses (BII).
Managing Well-Documented CMV Pneumonitis
• 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.
Managing CMV Neurological Disease
• Doses are the same as for CMV retinitis. • Treatment should be initiated promptly. • 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

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Hepatitis B Virus Infection (Last updated November 13, 2018; last reviewed October 13, 2021)

NOTE: Update in Progress

Epidemiology

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

In countries with a low prevalence of endemic chronic HBV infection, the virus is transmitted primarily through sexual contact and injection drug use, whereas perinatal and early childhood exposures are responsible for most HBV transmission in higher prevalence regions.[9] Although the general modes of transmission are similar to those for HIV, HBV is transmitted more efficiently than HIV.[1,2] The risk of progression to chronic HBV infection varies with age and is 90% among those infected before 1 year of age, 25 to 50% among those infected at 1 to 5 years of age, and <5% among those infected as adults.[9,10] Persons with HIV infection are at increased risk for developing chronic HBV infection.[11] Genotypes of HBV (A–J) have been identified, and their geographic distributions differ.[12] Genotype A is most common among patients in North America and Western Europe and genotypes B and C among patients from Asia.[13]

Clinical Manifestations

Acute HBV infection is asymptomatic in approximately 70% of patients, and <1% of patients develop fulminant hepatic failure.[3,14] 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 patients with chronic HBV infection are asymptomatic or have nonspecific symptoms, such as fatigue. Between 15% to 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.[15]

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 patients with HIV infection for chronic HBV.[9,16,17] Initial testing should include serologic testing for surface antigen (HBsAg), hepatitis B core antibody (anti-HBc total), and hepatitis B 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 2 occasions at least 6 months apart.[9] Patients with chronic HBV infection should be further tested 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.[3] Patients 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.[3,18] With cccDNA in hepatocyte nuclei, a patient with severe immune suppression, such as seen with rituximab therapy or after stem cell transplant, may become serum HBsAg-positive again with HBV viremia.[19,20]

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 patients with HIV infection.[21-25] Incidence of HBV viremia in patients with HIV infection and isolated anti-HBc ranges from 1% to 36%.[21,23,26-28] The clinical significance of isolated anti-HBc is unknown[21,25,28-30] but in individuals with HIV infection, it may indicate chronic or, more likely, resolved HBV infection.[24,31,32] In a low-prevalence country such as the United States, isolated anti-HBc may also represent a false-positive result.[24,31,33,34] Patients with HIV infection have a higher frequency of isolated anti-HBc, particularly those with underlying HCV coinfection.[24,35,36]

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

Compared with individuals with HBV monoinfection, those with HIV/HBV coinfection have higher levels of HBV viremia and lower likelihood of resolved infection following acute HBV infection.[37] In individuals 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,[38-40] and improved survival.[41-44] In comparison, persons with HIV/HBV coinfection are usually more likely to have detectable HBeAg,[37,45] lower rates of seroconversion to anti- HBe, and increased risk of HCC and liver-related mortality and morbidity.[46,47]

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 immune tolerant phase (normal ALT [upper limits of normal 19-25 U/L for women and 29-44 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).[15] Duration of disease phases is different in those who acquire infection as neonates and young children than in those who acquire infection as adults. The immune tolerant phase occurs primarily after perinatal infection. Clinicians should be knowledgeable about these phases in patients with HBV monoinfection to determine who needs treatment and who should be monitored (see AASLD guidelines 2018 https://aasldpubs.onlinelibrary.wiley.com/doi/10.1002/hep.29800). In HIV/HBV coinfection, monitoring and treatment are also focused on the simultaneous treatment of both viruses.

Persons with anti-HBe seroconversion and HBeAg loss usually transition into the inactive hepatitis B phase.[15] 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.[48] However, such spontaneous HBeAg conversion rates appear to be lower in patients with HIV/HBV coinfection than in patients with HBV monoinfection. The inactive chronic HBV state is characterized by a negative HBeAg, normal ALT levels, and an HBV DNA level <2,000 IU/mL.[48] Patients in the inactive state remain at risk of reactivation of HBV and development of HCC, but the risk is lower than for individuals with active HBV replication. In any patient, the re-emergence of abnormal liver enzyme tests may reflect HBeAg-negative chronic HBV disease, a result of mutations in the basal core and precore promoter regions.[15] Although levels of HBV DNA are usually lower, patients who are HBeAg-negative experience an unrelenting but fluctuating course of disease progression, with fluctuating HBV DNA levels.[17] Patients 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.[17]

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, patients should have a complete blood count, ALT, aspartate aminotransferase (AST), albumin, total bilirubin, alkaline phosphatase, international normalized ratio (INR), HBeAg/anti-HBe, HBV DNA, anti-HAV to determine need for vaccination, abdominal ultrasound, and liver fibrosis assessment at initial visit, and be monitored every 6 to 12 months.[3] Patients with chronic HBV infection are at increased risk of HCC; therefore, HCC surveillance every 6 months is required for patients who are cirrhotic, and for individuals 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.[49] Patients with HIV/HBV coinfection are at increased risk of HCC,[50] and some experts screen patients with HIV/HBV coinfection over 40 years of age for HCC. Assessment of the patient's liver fibrosis stage is important. There is increasing evidence that noninvasive methods (i.e., elastography and serum markers) to evaluate liver fibrosis can be used to determine fibrosis in HBV infection.[51] The decision to perform a liver biopsy should be individualized and is rarely necessary.[3]

Preventing Exposure

HBV is primarily transmitted through percutaneous or mucosal exposure to infectious blood or body fluids. Therefore, patients with HIV infection should be counseled about transmission risks for HBV 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 patients with HBV infection should be tested, and all susceptible contacts should receive HBV vaccines regardless of whether they have HIV infection **(AII)**. Hepatitis B vaccination is the most effective way to prevent HBV infection and its consequences. All patients with HIV infection who are susceptible to HBV infection should receive hepatitis B vaccination with one of the available vaccines (see below) **(AII)** or with the combined hepatitis A and hepatitis B vaccine **(AII)**.

All patients with HIV infection should be screened for hepatitis B, and screening should include HBsAg, anti-HBs, and anti-HBc.[9,16,17] 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,[52] and no further vaccinations are required.[53] The interpretation is less clear in individuals 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.[54] Most patients with HIV infection with isolated anti-HBc are HBV DNA-negative and not immune to HBV infection;[36] therefore, routinely checking HBV DNA is not recommended. However, such patients should be vaccinated with one standard dose of HBV vaccine and anti-HBs titers should be checked 1 to 2 months after vaccination. 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 HBV vaccine should be completed followed by anti-HBs testing **(BII)**.[55] The cut-off of 100 mIU/mL is used in this situation because one study demonstrated that 100% of patients with isolated anti-HBc who achieved a titer of 100 mIU/mL after a booster dose maintained an anti-HBs response for >18 months as compared to only 23% of those who achieved a titer of 10 to 100 mIU/mL.[55]

Available adult single-antigen hepatitis B 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 (TLR) 9 agonist (Heplisav-B). The magnitude and duration of immunogenicity to hepatitis B vaccination with the recombinant vaccines in adults with HIV infection is significantly lower than in healthy adults who are HIV seronegative.[53,56-58] Factors associated with poor response to vaccine include low CD4 cell counts,[56,59-64] presence of detectable HIV RNA,[60,64,65] coinfection with HCV, occult HBV infection, and the general health status of the host.[23,36,66-70] Based on these data, early vaccination is recommended in patients with HIV infection before CD4 cell counts decline to <350 cells/mm^3 **(AII)**. However, in patients who present to care with a lower CD4 cell count, vaccination should not be deferred until CD4 counts increase to >350 cells/mm^3 because some patients with HIV infection with CD4 counts <200 cells/mm^3 do respond to vaccination **(AII)**. Among persons with HIV infection who did not respond (anti-HBs titers <10 mIU/mL) to a primary 3-dose vaccine series with a recombinant vaccine, 25% to 50% responded to an additional vaccine dose, and 44% to 100% responded to a 3-dose revaccination series.[71-74] As a result, persons with HIV infection who do not respond to a complete hepatitis B vaccination series with one of the recombinant vaccines should receive a 3-dose revaccination series **(BIII)**,[53] although some specialists might delay revaccination until antiretroviral therapy (ART) results in a sustained increase in CD4 cell count **(CIII)**. Two randomised controlled trials have shown that using 4 doses of double-dose of the recombinant vaccine produces higher anti-HBs titers than 3 doses of standard-dose vaccine,[75,76] and one study also showed a higher overall response rate.[76] Some specialists consider that this approach—4 vaccinations—improves immunologic response in individuals with HIV infection either as an initial vaccination schedule or in patients who are non-responders **(BI)**. However, whether a schedule of 4 double-dose vaccines is superior to 4 single-dose or 3 double-dose vaccines is still unclear. Another study suggested that patients with HIV infection with CD4 counts >350 cells/mm^3 had improved responses when vaccinated with a double-dose recombinant vaccine on a 0-, 1-, and 6-month schedule.[59] Although other approaches have been investigated to improve responses, such as the use of combined hepatitis A and B vaccine[77,78] data are insufficient to support a broad recommendation for these approaches at this time.

In four randomized-controlled trials, Heplisav-B was superior to 3 doses of Engerix-B in HIV-negative individuals.[79-81] In the largest trial, the protection rate was 95% for Heplisav-B and 81% for Engerix-B.[81] There was an increase in the number of cardiovascular events in the Heplisav-B group that was not statistically significant. The safety and efficacy of Heplisav-B in individuals with HIV infection has not been studied. If a two-dose vaccine is preferred, Heplisav-B is an option **(CIII)**. If Hepislav-B is used, the vaccine should not be interchanged with either of the other recombinant vaccines for the second dose. If the previously administered vaccine is unknown, then the Advisory Committee on Immunization Practices provides recommendations, which state that the two-dose vaccine series only applies when both doses are Hepsliav-B. In other situations, three total doses of vaccine should be given.

Preventing Other Liver Diseases

HAV vaccination is recommended for all patients who are HAV antibody-negative and have chronic liver disease[3]; for patients who are injection and non-injection drug users; and for men who have sex with men **(AIII)**. Responses to the HAV vaccine are reduced in patients with HIV infection with CD4 counts <200 cells/mm^3.[82,83] Antibody response should be assessed 1 month after vaccination is complete. If HAV antibody immunoglobulin (HAV Ab IgG) is negative, patients should be revaccinated when the CD4 cell count is >200 cells/mm^3 **(BIII)**.

Patients with chronic HBV disease 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. Patients with HIV/HBV coinfection should receive tenofovir disoproxil fumareate (TDF)- or tenofovir alafenamide (TAF)-based ART.

Special Considerations with Regard to Starting ART

Preferred Regimen

The Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV recommend the fixed-dose coformulations of TDF or TAF/emtricitabine or abacavir/lamivudine as nucleoside reverse transcriptase inhibitor (NRTI) regimen backbones for ART-naive patients regardless of CD4 cell count.[84] Because both tenofovir and emtricitabine have anti-HBV activity, the tenofovir combinations are also the treatment of choice for patients with HIV/HBV coinfection **(AIII)** **regardless of CD4 count (AI) and HBV DNA level** **(AIII)**. (See HBV/HIV Coinfection in the Adult and Adolescents Guidelnes.) TDF and TAF are both active against wild-type and lamivudine-resistant HBV strains. Studies in patients with HIV/HBV coinfection (most of them carrying lamivudine-resistant HBV) have shown, on average, 4 $\log_{10}$ declines in HBV DNA levels.[85-90] TDF and TAF have a high genetic barrier for development of resistance mutations **(AI)**.[3,91]

The decision to use TAF/emtricitabine versus TDF/emtricitabine should be based upon creatinine clearance (CrCl) and an assessment of risk for nephrotoxicity and for acceleration of bone loss. In patients with CrCl ≥60 mL/min, either TAF/emtricitabine or TDF/emtricitabine can be considered. In patients with a CrCl 30 to 59 mL/min, a TAF/emtricitabine regimen is preferred. Currently approved TAF/emtricitabine-containing regimens for the treatment of HIV infection are not recommended for use in patients with CrCl <30 mL/min, so for these patients renally dosed entecavir with a fully suppressive ART is recommended **(BIII)**. Renally-dosed TDF can also be used if recovery of renal function is unlikely **(BIII)**. If renally-dosed TDF is used, then the CrCl needs to be monitored carefully. In patients with HIV/HBV coinfection, switching from a primarily TDF-based ART regimen to single tablet TAF/emtricitabine/elvitegravir/cobicistat maintained or achieved HBV suppression, with improved estimated glomerular filtration rate (eGFR) and bone turnover markers.[92] In patients with HBV monoinfection, TAF 25 mg was non-inferior to TDF 300 mg based on the percentage of patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy (94% for TAF vs. 93% for TDF; $P = 0.47$). Patients on TAF also experienced significantly smaller mean percentage decreases from baseline in hip and spine bone mineral density at 48 weeks than patients receiving TDF ($P < 0.0001$). Furthermore, the median change in eGFR from baseline to 48 weeks also favored TAF ($P = 0.004$).[93,94]

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

Patients receiving ART should continue HBV therapy indefinitely **(CIII)** because relapses after response occur, particularly in those with lower CD4 cell counts.[3] Additionally, discontinuation of nucleos(t)ide analogue therapy is associated with a HBV flare in approximately 30% of cases,[95,96] with loss of the benefit accrued from previous anti-HBV treatment and possible decompensation of liver disease.[56,97-99] 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)**.

Alternative Treatment of HBV in Patients with HIV Infection Who Are Not Receiving ART

HBV and HIV co-treatment is essential and recommended.[84] There are few options that can be used for treatment of HBV alone in the patient with HIV/HBV coinfection. Directly acting HBV drugs must not be given in the absence of a fully suppressive ART regimen **(AII)**. Only pegylated interferon-alfa-2a monotherapy may be considered for patients with HIV/HBV coinfection who are not receiving ART and who meet criteria for HBV therapy as described in the AASLD 2018 guidelines **(CIII)**.[100]

Some patients with HIV/HBV coinfection also have chronic HCV infection. There is scant information on the treatment of HBV/HCV/HIV coinfection. Because patients with HBV, HCV, and HIV appear to have accelerated progression of liver fibrosis, higher risk of HCC, and increased mortality,[101-103] 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 Infection) **(CIII)**. As HBV reactivation can occur during treatment for HCV with directly active agents (DAAs) in the absence of HBV-active drugs, all patients with HIV/HBV coinfection who will be treated for HCV should be on HBV-active ART at the time of HCV treatment initiation **(AIII)**.[104-107]

Regimens that are Not Recommended

Tenofovir (TDF and TAF), entecavir, lamivudine, emtricitabine, and telbivudine **should not be used alone** in the absence of a fully suppressive ART regimen because of the development of HIV-resistance mutations **(AI)**.[108,109] Other HBV treatment regimens include adefovir in combination with lamivudine or emtricitabine or telbivudine in addition to a fully suppressive ART regimen;[90,110,111] however, data on these regimens in persons with HIV/HBV coinfection are limited. In addition, compared to TDF or TAF or entecavir, these regimens are associated with higher incidence of toxicity, including renal disease with adefovir and myopathy and neuropathy with telbivudine, as well as higher rates of HBV treatment failure. Therefore, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) does not recommend these drugs/regimens for patients with HIV/HBV coinfection **(AI)**.

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

To prevent emergence of drug-resistant variants and evaluate response for patients 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 follows:

- Primary non-response is an HBV DNA <1 log10 decline at 12 weeks.[112]
- A complete virologic response is an undetectable HBV DNA by real-time polymerase chain reaction at 24 to 48 weeks.[112]
- A partial virologic response is ≥1 $\log_{10}$ decline but still detectable HBV DNA at 24 weeks.[112]
- A maintained virologic response is a response that continues while on therapy, and a sustained virologic response is one that is still present 6 months after stopping therapy.[112]

For patients 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 patients per year).[3]

Adverse Events

Renal toxicity with TDF, including increased serum creatinine or renal tubular dysfunction, has been observed; both are more frequent in patients with HIV infection who have underlying renal insufficiency, are older, or have been treated with TDF for prolonged periods.[113] These biochemical changes are usually reversible when TDF is discontinued or changed to TAF.[114]

Electrolytes and serum creatinine levels should be evaluated at baseline and every 3 to 6 months, and 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 in patients 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.[114] All nucleos(t)ides must be dose adjusted for renal dysfunction (see package insert) and TAF is not recommended in patients with CrCl <30 mL/min **(AI)**.

Entecavir-associated lactic acidosis is uncommon but has been reported in patients with HBV monoinfection with advanced cirrhosis.[115]

Major toxicities of IFN-alfa (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,"[116] which constitutes IRIS in persons with HIV/HBV coinfection. IRIS may manifest when serum aminotransferase levels dramatically increase as CD4 cell 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.[117,118] 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)**.[114]

Flares are worse in patients with more severe liver disease, especially in those with cirrhosis.[119] Distinguishing between drug-induced liver injury or other causes of hepatitis (acute hepatitis with A, C, D, or E virus, Epstein-Barr virus, herpes simplex virus, cytomegalovirus) and IRIS may be difficult. ART-associated hepatotoxicity may be dose-dependent or idiosyncratic. In individuals with HIV, the risk of ART-associated hepatotoxicity has been consistently associated 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.[120-123] However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, most (80% to 90%) patients with HIV/HBV coinfection do not have ART-associated hepatotoxicity,[124] 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.[125,126] Therefore, discontinuing ART usually is not necessary in the presence of hepatotoxicity unless patients have symptoms of 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)**.[127]

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 levels, and CD4 cell 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 (hepatitis A, C, D, and E), and nonalcoholic fatty liver disease.

Managing Treatment Failure

HBV treatment failure on nucleos(t)ide analogues is defined as primary nonresponse (HBV DNA <1 $\log_{10}$ decline) after 12 weeks of therapy in patients who consistently adhere to HBV therapy or as an increase in HBV DNA levels >1 $\log_{10}$ above nadir. In either situation, treatment failure is generally due either to drug-resistant HBV if the patient is on lamivudine/emtricitabine 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, lamivudine/emtricitabine); 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 patients with unclear prior drug history, assessing different adefovir-resistance pathways, and predicting the level of resistance to entecavir.[128] However, TDF has not been associated with clinical resistance, although slow response has been noted as discussed above. Addition of entecavir has led to suppression of HBV DNA in patients whose response to TDF is slow.[129]

Lamivudine (or emtricitabine) monotherapy for HBV leads to emergence of drug-resistant HBV, which increases with time on treatment; therefore, **should not be used** as the sole anti-HBV drug in an ART regimen **(AII)**. The rate of development of lamivudine-resistance is approximately 20% per year in patients with HIV/HBV coinfection treated with lamivudine alone.[130] If lamivudine resistance is suspected or documented, TDF or TAF should be added to the ART regimen **(BIII)**.[131-133] Because patients with lamivudine-resistant HBV will have cross-resistance to the other L-nucleosides (telbivudine, emtricitabine), and partial resistance to entecavir, those agents **should not be used** in patients found to have lamivudine-resistant HBV **(AI)**.[134] All nucleoside analogs must be dose adjusted for renal insufficiency per package insert guidelines and Table 8.

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

Patients whose HBV 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 lamivudine- or emtricitabine-experienced patients, then entecavir may be an active alternative, especially if higher doses of entecavir can be used **(CIII)**.

However, documented *in vivo* resistance to tenofovir has not yet been reported. Declines in HBV DNA levels can be slow, especially when pretherapy HBV DNA levels are very high. HBV DNA levels usually drop quickly in patients 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.[129] Nonetheless, patients 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 (TDF or TAF) with emtricitabine 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

Patients with HIV/HBV coinfection who have end-stage liver disease should be managed as an HBV monoinfected patient with end-stage liver disease including referral to a hepatologist **(CI)**. In patients with HIV/HBV coinfection in end-stage liver disease, interferon-alfa is **contraindicated** **(AI)**, but nucleoside analogs are safe and efficacious **(AI)**.[130,135,136] All patients with ascites should undergo paracentesis to exclude spontaneous bacterial peritonitis (SBP).[137,138] 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 patients 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 double-strength tablet/day) **(AI)**.[139]

Esophagogastroduodenoscopy (EGD or upper endoscopy) should be performed on all patients with cirrhosis at the time of diagnosis and then every 1 to 2 years to identify substantial gastroesophageal varices (see AASLD guidelines). Patients with varices require non-selective 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]

Patients with HBV-related cirrhosis are at increased risk of HCC140 and should have imaging studied performed every 6 to 12 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,[141] but more frequent surveillance in HIV/HBV coinfection has not been studied, and so cannot be recommended given insufficient evidence. Patients 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 in patients on suppressive ART.[142] 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 patients should continue HBV therapy (with the exception of pegylated IFN) indefinitely **(CIII)** because relapses after response occur, particularly in those with lower CD4 cell 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.[97-99]

Special Considerations During Immunosuppressive Therapy

As patients with HIV infection live longer, treatment of individuals with HIV infection with immunosuppressive therapy, both in the context of malignancy and rheumatologic/autoimmune diseases is becoming common. HBV reactivation in HIV-negative patients with HBsAg-positive/anti-HBc positive disease receiving immunomodulatory therapy is well described.[143,144] Even in patients with HBsAg-negative/anti-HBc positive disease, HBV reactivation occurs in occurs in 8% to 18% and 1.7% of patients receiving anti-cancer[145] and rheumatologic disease drugs,[146] respectively.

If not already performed, individuals with HIV infection undergoing immunosuppressive therapy should have HBsAg, anti-HBc and anti-HBs testing. Individuals who are HBsAg positive should receive treatment as detailed in ***Special Considerations with Regard to Starting ART***. The optimal approach for those patients with HBsAg-negative/anti-HBc positive disease is unknown. However, since tenofovir/emtricitabine 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 in patients with HBsAg-negative/anti-HBc positive disease **(BIII)**. If tenofovir/emtricitabine cannot be used as part of their HIV regimen, these patients could either receive entecavir for anti-HBV prophylaxis or 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)**.[147] There are no studies on the appropriate length of therapy but the Panel agrees with the AASLD 2018 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)**.[100]

Special Considerations During Pregnancy

Pregnant women with HIV infection should be screened for HBsAg, and co-infection with HBV may be first diagnosed at this time. **(AI)**.[148] Those who are both HBsAg and anti-HBs-negative should be offered vaccination against HBV. 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.[149-152] See HIV/Hepatitis B Virus Coinfection in the Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States.

ART including drugs active against both HIV and HBV is recommended for all individuals with HIV/HBV coinfection, including pregnant women **(AIII)**. TDF given in combination with 3TC or FTC is the preferred dual-NRTI backbone for pregnant women with chronic HBV infection **(AIII)**.[153] There are no data on use of TAF in pregnancy, therefore it is not recommended.[154] Once HBV therapy with nucleos(t)ide analogs and ART is initiated in patients with HIV/HBV coinfection, treatment should be continued indefinitely.

Cases of adverse events during pregnancy to any of the ARV or 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 lamivudine have been reported to the Antiretroviral Pregnancy Registry, with no indication of an increased risk of birth defects after exposure (http://www.apregistry.com/forms/interim_report.pdf). Lamivudine has been well tolerated by pregnant women and is a recommended NRTI for use in pregnancy **(AII)**.[153] Similarly, no increase in birth defects has been noted in 2,785 cases of first-trimester exposure to emtricitabine. Emtricitabine is a recommended NRTI and is commonly used in pregnancy **(BII)**.[155] 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. In a large HIV prevention of mother-to-child transmission (PMTCT) trial examining different antenatal ART regimens, TDF/emtricitabine + lopinavir/ritonavir was associated with a higher infant mortality rate at 14 days than zidovudine/lamivudine + lopinavir/ritonavir, 4.4% vs. 0.06% respectively. The mechanisms for this finding are unclear.[156] Other studies of tenofovir use in pregnancy have not suggested increased risk of adverse pregnancy outcomes.[157]

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. 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 (package insert). Data on use of entecavir and adefovir in human pregnancy are not available. Telbivudine given to women who were HBV-seropositive, HIV-seronegative during the second and third trimester was well-tolerated with no birth defects observed.[158]

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 women because of their direct antigrowth and antiproliferative effects **(AII)**.[159]

Infants born to women who are HBsAg-positive should receive hepatitis B immune globulin and hepatitis B vaccine within 12 hours of delivery **(AI)**. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively **(AI)**. For infants who weigh <2000g at birth, the birth dose should not be counted toward the 3 dose series.

Recommendations for Preventing and Treating Hepatitis B Virus (HBV) Infection (page 1 of 2)

Preventing HBV Infection

Indications for HBV Vaccination:

- Patients without chronic HBV infection and without immunity to HBV (anti-HBs <10 mIU/mL) **(AII)**
- Patients with isolated anti-HBc **(BII)**. Recommend one standard dose of HBV 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 HBV vaccine should be completed followed by anti-HBs testing **(BII)**.
- Early vaccination is recommended before CD4 count falls below 350 cells/mm^3 **(AII)**, as low CD4 count at time of vaccination has been associated with poor response to the vaccine.
- However, in a patient with low baseline CD4 cell count, vaccination should not be deferred until CD4 reaches >350 cells/mm^3, as some patients with CD4 <200 cells/mm^3 do respond to vaccination **(AII)**.

Vaccination Schedule:

- HBV vaccine IM (Engerix-B® 20 mcg/mL or Recombivax HB® 10 mcg/mL) at 0, 1, and 6 months **(AII)**; *or*
- HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL) at 0, 1, 2, and 6 months **(BI)**; *or*
- Combined HAV and HBV vaccine (Twinrix®) 1 mL IM as a 3-dose series (at 0, 1, and 6 months) or as a 4-dose series (at days 0, 7, 21 to 30, and 12 months) **(AII)**; *or*
- Vaccine conjugated to CpG (Heplisav-B®) IM at 0 and 1 months **(CIII)** – a 2-dose series can only be used when both doses given are Heplisav-B®.
- Anti-HBs should be obtained 1 to 2 months after completion of the vaccine series. Patients with anti-HBs <10 mIU/mL will be considered as vaccine non-responders **(BIII)**.

For Vaccine Non-Responders:

- Revaccinate with a second vaccine series **(BIII)**.
- For patients with low CD4 count at the time of first vaccination series, some experts might delay revaccination until after a sustained increase in CD4 count with ART **(CIII)**.

Alternative Vaccine Dose and Duration for Vaccine Non-Responders:

- Double dose, 4-dose series - HBV vaccine IM (Engerix-B® 40 mcg/mL or Recombivax HB® 20 mcg/mL at 0, 1, 2, and 6 months **(BI)**.

Treating HBV Infection

Indication for Therapy:

- All patients with HIV/HBV coinfection, regardless of CD4 count and HBV DNA level **(AII)**. Therapy should be selected to treat both HIV and HBV infections **(AIII)**.

Preferred Therapy (CrCl ≥60 mL/min):

- The ART regimen must include 2 drugs active against HBV, preferably with [TDF 300 mg + (FTC 200 mg or 3TC 300 mg)] or [TAF (10 or 25 mg)[a] + FTC 200 mg] PO once daily **(AIII)**.

Preferred Therapy (CrCl 30–59 mL/min)

- The ART regimen must include 2 drugs active against HBV, preferably with TAF (10 or 25 mg)[a] + FTC 200 mg PO once daily **(AIII)**.

Recommendations for Preventing and Treating Hepatitis B Virus (HBV) Infection (page 2 of 2)

Preferred Therapy (CrCl <30 mL/min)

- A fully suppressive ART regimen without tenofovir should be used, with the addition of renally dosed entecavir to the regimen *or*
- ART with renally dose-adjusted TDF and FTC can be used **(BIII)** **when recovery of renal function is unlikely** (see Table 7 for dosing recommendation for TDF and FTC or 3TC for patients with renal impairment). Guidance for TAF use in persons with CrCl <30 is not yet established.

Duration of Therapy:

- Patients on treatment for HBV and HIV should receive therapy indefinitely **(CIII)**.

Alternative Therapy

If the Patient Refuses ART:

- Anti-HBV therapy is indicated for all those who meet criteria for treatment according to the AASLD 2018 guidelines.
- 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)**
- Directly acting HBV drugs (such as 3TC, FTC, TAF, TDV, 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:

- Hepatitis A vaccination is recommended for all HAV antibody-negative patients who have chronic liver disease, are men who have sex with men, or who are injection drug users **(AIII)**.
- Antibody responses to HAV should be assessed 1 month after completion of vaccination series. If HAV Ab IgG is negative, patients should be revaccinated when the CD4 count is >200 cells/mm^3 **(BIII)**.
- As patients 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.
- As HBV reactivation can occur during treatment for HCV with directly active agents (DAAs) in the absence of HBV-active drugs, all patients with HIV/HBV coinfection who will be treated for HCV 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 **(BIII)**.
- 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 re-instituted, as it can be potentially lifesaving **(AIII)**.
- If immunosuppressive therapy is given, HBV reactivation can occur. For patients who are HBsAg positive, treatment for HBV should be administered **(AII)**. Patients 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 ARVs, the dose is 25mg.

Key to Acronyms: 3TC = lamivudine; ab = antibody; anti-HBs = hepatitis B surface antibody; ALT = alanine transferase; ART = antiretroviral therapy; CD4= CD4 T lymphocyte cell; FTC = emtricitabine; HAV = hepatitis A virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; IFN = interferon; IgG = immunoglobulin; IM = intramuscular; PO = orally; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate

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Hepatitis C Virus Infection (Last updated October 28, 2014; last reviewed October 13, 2021)

NOTE: Update in Progress

Epidemiology

Hepatitis C virus (HCV) is a single-stranded RNA virus; the estimated worldwide prevalence of HCV infection is 2% to 3%, which translates to an estimated 170 million infected individuals of whom approximately 3.2 million live in the United States.[1] Seven distinct HCV genotypes have been described.[2] Genotype 1 infection accounts for approximately 75% of infections in the United States and approximately 90% of infections among blacks.[3,4] Both HIV and HCV can be transmitted by percutaneous exposure to blood or blood products, through sexual intercourse, and from a mother to her infant; however, the relative efficiency of transmission by these routes varies substantially. Approximately, 20% to 30% of HIV-infected patients in the United States are coinfected with HCV.[5,6]

HCV is approximately 10 times more infectious than HIV through percutaneous blood exposures and has been shown to survive for weeks in syringes.[7-9] 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 as a result of improper reuse of parenteral medications and equipment.[10-12] Other factors that have been associated with HCV infection include accidental occupation-related needlestick injuries, intranasal cocaine use, chronic hemodialysis, and tattoo placement.

Heterosexual transmission of HCV is uncommon but more likely in those whose partners are coinfected with HIV and HCV.[13,14] Existing data also suggest that sexual contact is a relatively inefficient mode of transmission between HIV seronegative men who have sex with men (MSM).[15] However, in HIV-infected MSM, multiple outbreaks of acute HCV infection demonstrate that sexual transmission is an important mode of acquisition in this population.[16] Risk factors include unprotected receptive anal intercourse, use of sex toys, non-injection recreational drug use, and concurrent sexually transmitted diseases (STDs).[15,17-19,20,21] Temporally, the increase in the incidence of sexual transmission of HCV among HIV-infected MSMs coincides with an increase in high-risk sexual behaviors following the introduction of antiretroviral therapy (ART).[22,23]

Mother-to-child transmission of HCV infection occurs in approximately 1% to 3% of infants born to HCV-seropositive mothers without and 4% to 7% of infants born to HCV-seropositive mothers with detectable plasma HCV RNA levels.[24-27] Incidence of mother-to-child HCV transmission is increased when mothers are HIV-coinfected, reaching rates of 10% to 20%.[28,29]

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 since HCV treatment during the early phases of infection is more efficacious than treatment during the chronic phase.[30,31]

Cirrhosis develops in approximately 20% of patients with chronic HCV infection within 20 years after infection, although the risk for an individual is highly variable.[32,33] Risk factors for development of significant liver disease include older age at the time of infection, male sex, obesity, and concomitant alcohol use.[33,34] 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 (CD4 T-lymphocyte [CD4] count <200 cells/mm^3).[35,36] Further, coinfected patients with cirrhosis progress more rapidly to life-limiting outcomes such as end-stage liver disease and hepatocellular carcinoma (HCC) than do those who are HCV-monoinfected.[37,38] Because of its high prevalence and accelerated progression, HCV disease is a leading non-AIDS cause of death in HIV-infected individuals.[39-41] In addition to liver disease, HCV may be associated with symptomatic vasculitis due to cryoglobulinemia (largely affecting the skin), renal disease (membranoproliferative glomerulonephritis), and porphyria cutanea tarda.

Diagnosis

On entry into HIV care, all HIV-infected patients should undergo routine HCV screening. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.[42] For at risk HCV-seronegative individuals, HCV antibody testing is recommended annually or as indicated by risk exposure.

False-negative anti-HCV antibody results are possible but are uncommon (<1%) in HIV-infected patients with advanced immunosuppression.[43,44] 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 12 weeks. Serum ALT levels are frequently elevated early in the course of acute 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.[45]

Individuals who test positive for HCV antibody should undergo confirmatory testing by using a sensitive quantitative assay to measure plasma HCV RNA level. Importantly, plasma HCV RNA viral load does not correlate with HCV disease severity, and therefore, should not be monitored serially in patients not taking HCV treatment. Plasma HCV RNA levels do provide important prognostic information about the likelihood of response to HCV treatment.

Preventing Exposure

The primary route of HCV transmission is drug injection via a syringe or other injection paraphernalia (i.e., “cookers,” filters, or water) previously used by an infected person. HCV-seronegative injection drug users should be encouraged to stop using injection drugs by entering a substance abuse treatment program or, if they are unwilling or unable to stop, to reduce the risk of transmission by never sharing needles or injection equipment.[46-48] HCV also can be transmitted sexually, especially between HIV-infected MSM. HCV-seronegative patients must be counseled regarding the risk of sexual acquisition. The effectiveness of male condoms in reducing HCV transmission is unknown, nonetheless, barrier precautions are strongly recommended to reduce the risk of STDs, including HCV **(BIII)**.[49]

Preventing Disease

There is no vaccine or recommended post-exposure prophylaxis to prevent HCV infection. Following acute HCV infection, chronic infection may be prevented within the first 6 to 12 months after infection through antiviral treatment; relatively high rates of viral clearance have been observed with HCV treatment during the acute phase of infection.[50,51] However, patients also have the potential for spontaneous clearance after acute infection; as such, some experts recommend observation of acutely infected patients—particularly those whose infection (e.g., those with C/C IL28B genotype) is more likely to resolve—for approximately 3 to 6 months before initiating HCV treatment.[52] In the setting of evolving data, recommendations for management of acute HCV infection in HIV-infected patients are expected to change rapidly. Clinicians should refer to the most recent HCV treatment guidelines (http://www.hcvguidelines.org) for the most up-to-date guidance.

HCV-infected individuals should be counseled about methods to prevent liver damage by avoiding any alcohol consumption (as alcohol accelerates progression of liver disease), limiting ingestion of potentially hepatotoxic medications (e.g., acetaminophen should be limited to <2 g/day), and avoiding iron supplementation in the absence of documented iron deficiency.[53] HCV-infected patients should be tested for previous or concurrent hepatitis B virus (HBV) infection because co-infection with HBV is associated with increased morbidity. Those without evidence of immunity to HBV should be vaccinated (see Hepatitis B Virus Infection section). Likewise, because acute hepatitis A virus (HAV) infection is more likely to be fulminant in HCV-infected individuals, these patients should be screened for immunity (HAV IgG or antibody total) and those susceptible should be vaccinated **(BIII)**.

Coinfected patients 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;[54] some experts recommend performing ultrasonography at 6- to 12-month intervals, although the optimal screening strategy is unknown. Because of its relatively poor specificity and sensitivity, alfa-fetoprotein should not be the sole screening method. HIV infection is not an absolute contraindication to liver transplantation; accordingly, coinfected patients with decompensated liver disease and/or early HCC may be considered for transplantation at specialized transplant centers.

Although earlier studies focused on the potential for antiretroviral (ARV)-associated liver injury with certain agents, more recent studies have found that effective HIV treatment is associated with reduced risk of liver disease progression. Coinfected patients should be treated with ART in accordance with the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* developed by the Department of Health and Human Services Panel.[55] Dose adjustment of certain ARV agents may be needed in patients with decompensated cirrhosis.

Treating Disease

In general, the goals of therapy, treatment regimen, and monitoring parameters for HIV/HCV coinfected patients are similar to those recommended for HCV monoinfected patients. The field of HCV drug development is evolving rapidly. The armamenarium of approved drugs is likely to expand considerably in the next few years. Clinicians should refer to the most recent HCV treatment guidelines (http://www.hcvguidelines.org) for the most up-to-date recommendations.

Special Considerations During Pregnancy

Pregnant HIV-infected women should be tested for HCV infection to allow appropriate management for the mothers during pregnancy and after delivery, and also for their infants.[56] HCV treatment with PegIFN and ribavirin is **contraindicated** during pregnancy **(AII)**. IFNs are abortifacient at high doses in monkeys and **should not be used** in pregnant women because of their direct antigrowth and antiproliferative effects.[57] 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.[58] Pregnancies that occur in women taking ribavirin or those in women whose male partner is taking the drug should be reported to the Ribavirin Pregnancy Registry (800-593-2214 or http://www.ribavirinpregnancyregistry.com). Telaprevir, boceprevir, and sofosbuvir are Pregnancy Category B and simeprevir is Pregnancy Category C; however, these agents are often used in combination with PegIFN/ribavirin, which are **not recommended** in pregnancy. The FDA category assignment for these novel drugs, though, is based on safety in animal studies as there are no human data available.

Evaluation of HCV-infected pregnant women, including liver biopsy, can be delayed until >3 months after delivery to allow potential pregnancy-related changes in disease activity to resolve. HAV and HBV vaccines can be administered during pregnancy and women who have not previously been vaccinated should receive them. Several studies have reported that perinatal transmission of HCV occurs more frequently in women with HIV/HCV-coinfection than in those with HCV monoinfection. However, 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 HIV-uninfected and HIV-infected women, have found that elective cesarean delivery does not reduce the risk of perinatal HCV transmission.[26,59-61] Moreover, there is an increased risk of maternal morbidity associated with cesarean compared with vaginal delivery, particularly in the setting of maternal HIV infection.[62-65] Thus, while elective cesarean delivery in HIV/HCV-coinfected women can be considered based on HIV-related indications, data are insufficient to support its routine use for prevention of HCV transmission.

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Herpes Simplex Virus Disease (Last updated May 26, 2020; last reviewed October 13, 2021)

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 coinfected patients, HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions.[6]

Clinical Manifestations

Orolabial herpes (commonly known as cold sores or fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations of oral HSV-1 include a sensory prodrome in the affected area, rapidly followed by lesions on lips and oral mucosa that evolve in stages from papule to vesicle, ulcer, and crust. The course of illness in untreated 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/mm^3 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/mm^3 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 coinfected 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 testing in clinical trials for treatment of acyclovir-resistant herpes in immunocompromised persons (*ClinicalTrials.gov* Identifier: 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/mm^3 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/mm^3 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 women[54] 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/mm^3 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

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Histoplasmosis (Last updated September 13, 2019; last reviewed October 13, 2021)

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/mm^3 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/mm^3, 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 histoplasmosis[7] 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 µm 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/mm^3 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/mm^3 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/mm^3 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/mm^3 **(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/mm^3 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 conditions[18-21] 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 ug/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 ug/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 ug/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 reportedly 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 5 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/mm^3; 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/mm^3 **(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 (page 1 of 3)

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

Indications for Initiating Primary Prophylaxis:

- CD4 count <150 cells/mm^3 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/mm^3, *and*
- Undetectable HIV-1 viral load for 6 months

Indication for Restarting Primary Prophylaxis:

- CD4 count <150 cells/mm^3 **(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

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 2 of 3)

Treating Less Severe Disseminated Disease, continued

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/mm^3 for ≥6 months in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 count <150 cells/mm^3 **(BII)**

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 3 of 3)

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/mm^3 should be managed the same as in immunocompetent patients **(AIII)**.
- All triazole antifungals have the potential to interact with certain ART agents and other anti-infective agents. These interactions are complex and can be bidirectional. 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

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Human Herpesvirus-8 Disease (Last updated May 29, 2018; last reviewed October 13, 2021)

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 individuals 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/mm^3), 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 patients[31] 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 count[62] 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 $\log_{10}$ 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 **(AI)**
- 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 = intraveneously; 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.

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Human Papillomavirus Disease

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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 use[82]; 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 visit[84]; 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 WWH.[90,91] Another study found that although response to initial therapy for invasive cervical cancer (e.g., radiation treatment) was similar in WWH 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 WWH 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 **(AII)**.

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 **(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 (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 cancers[102] 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 RCTs[129-132] 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 cidofovir[135] therapy). Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO_2 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/hyfrecator.[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

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Leishmaniasis (Last updated February 6, 2017; last reviewed October 13, 2021)

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/mm^3), 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/µL (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* antbodies 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/µL **(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 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/mm^3 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/mm^3 **(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/mm^3 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

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Malaria (Last updated March 28, 2017; last reviewed October 13, 2021)

NOTE: Update in Progress

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).[5] Although *P. vivax* infections are more common and occur in a far wider geographic distribution,[6] *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections. *P. vivax*, however, should not be discounted as a risk for travelers in many parts of the world.

Malaria and HIV both cause substantial morbidity and mortality, particularly in sub-Saharan Africa. Given this substantial overlap, even modest interactions between them have public health importance.[7,8] Malaria influences the natural history of HIV infection, and HIV infection alters the natural history and severity of malaria.[9]

Many foreign-born individuals develop malaria in the United States because of distant exposure before their arrival, or as a result of more recent travel for business or family reasons. Similarly, U.S.-born individuals can develop malaria during travel to endemic areas.[10-13] Failure to take appropriate chemoprophylaxis is a common problem for both groups of individuals.[14,15] People who formerly lived in malarious areas may believe that they are immune, and therefore do not need to take prophylaxis.[16] Such patients are at high risk of infection, however, because they likely have lost partial immunity within 6 months after leaving endemic regions.

Consideration of malaria in returning travelers who are febrile is important: Of the nearly 50 million individuals who travel to developing countries each year, between 5% and 11% develop a fever during or after travel.[17-20] Malaria is a surprisingly common cause of these fevers.[21]

Clinical Manifestations

The clinical syndromes caused by *Plasmodium* species depend on prior exposure.[22] While many native U.S. travelers have no prior immunity, clinical manifestations in those who have resided in malarious areas depend on whether they lived in an area with stable endemic malaria transmission (year round) or unstable (seasonal, infrequent or very low) transmission.[23]

In stable endemic areas, children younger than age 5 years may experience chronic infections with recurrent parasitemia, resulting in severe anemia and death. Children who survive these infections usually acquire partial immunity by age 5 years, and if they remain in the area where malaria is endemic, they maintain this immunity into adulthood. In stable endemic areas, adults usually experience asymptomatic or milder infections as a result of this acquired immune response. However, as noted previously, patients who leave endemic areas and subsequently return may be at high risk of disease because they likely have lost partial immunity 6 months after leaving endemic regions.

In unstable transmission areas, protective immunity is not acquired. For populations in these areas, the overwhelming clinical manifestation is acute febrile disease that can be complicated by cerebral malaria, affecting persons of all ages.

When pregnant women in areas of unstable transmission develop acute malaria, the consequences may include spontaneous abortion and stillbirth. In more stable transmission areas, pregnant women, particularly primigravidas, may lose some acquired immunity. Although infections may continue to be asymptomatic, infected pregnant women may acquire placental malaria that contributes to intrauterine growth retardation, low birth weight, and increased infant mortality.

Patients with malaria can exhibit various symptoms and a broad spectrum of severity, depending upon factors such as the infecting species and level of acquired immunity in the host. HIV-immunosuppressed patients in endemic areas may lose acquired malarial immunity, and HIV-immunosuppressed adults with little or no previous malaria exposure (such as travelers) appear to be at increased risk of severe outcomes.[24]

The incubation period for *P. falciparum* is from a week to several months, but most often less than 60 days. Patients can present much later (>1 year), but this pattern is more common with other species, especially *P. vivax*. In non-immune patients, typical symptoms of malaria include fever, chills, myalgias and arthralgias, headache, diarrhea, vomiting, and other non-specific signs. Splenomegaly, anemia, thrombocytopenia, pulmonary or renal dysfunction, and neurologic findings also may be present. Classically, paroxysmal fevers occur every 48 hours for *P. falciparum*, *P. vivax*, and *P. ovale* malaria; those with *P. malariae* occur every 72 hours. This classic presentation is highly variable, however, and may not be present. *P. knowlesi*, known to cause human infection in Southeast Asia in travelers to jungle/forested areas, is clinically indistinguishable from other species of malaria, and the overwhelming majority of patients present with uncomplicated disease (~90%).[25]

Uncomplicated malaria infection can progress to severe disease or death within hours. Malaria with central nervous system symptoms can be particularly ominous. Cerebral malaria refers to unarousable coma not attributable to any other cause in patients infected with *P. falciparum*; in Africa, case fatality rates with cerebral malaria approach 40%.[26-28] The risk of severe and complicated illness is increased in patients with high levels of parasitemia and without partial immunity. Metabolic acidosis is an important manifestation of severe malaria and an indicator of poor prognosis.[29] Other acute complications include renal failure, hypoglycemia, disseminated intravascular coagulation, shock, and acute pulmonary edema.[30] *P. falciparum* is the species most commonly responsible for severe disease and death, although the other species can cause severe disease and death as well.[25,31]

Effect of HIV on Parasitemia and Clinical Severity

HIV infection impairs acquired immunity to malaria that is present in older children and adults in stable endemic areas. Large cohort studies have demonstrated the increased frequency (with rates one- to two-fold higher) of both parasitemia and clinical malaria in HIV-infected adults, with increasing risk and higher-density parasitemia associated with more advanced immunosuppression, particularly among those with CD4 T-lymphocyte (CD4) cell counts <350 cells/mm^3.[32-34] Increased rates of malaria among individuals with HIV do not appear to be as great as the rates observed with classic opportunistic infections such as tuberculosis and *Pneumocystis jirovecii* pneumonia.[35]

In a prospective cohort study in an area with unstable malaria transmission, HIV-infected non-immune adults were found to be at increased risk of severe malaria, and the risk was associated with a low CD4 cell count.[36] Non-immune HIV-infected patients were substantially more likely to have severe clinical malaria than were non-immune patients without HIV. In KwaZulu Natal, an area of unstable malaria transmission, HIV-infected adults hospitalized for malaria were substantially more likely to die or require an intensive care unit admission than those who were not HIV-infected.[37] In contrast, HIV infection did not confer an increased risk of poor outcomes among partially immune adults in areas with more stable transmission.[32] In a cross-sectional study of travelers returning to France from malaria-endemic areas between 2000 and 2003, HIV-infected individuals with CD4 counts <350 cells/mm^3 were at significantly higher risk of developing severe malaria, compared with those who were HIV-negative.[34]

Effects of Malaria on Mother-to-Child HIV Transmission

Placental malaria also has been associated with increased expression of CCR5 receptors in placental 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 antiretroviral therapy (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 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 5).[46] Providers are also encouraged to check for drug-drug interactions by using an interactive web-based resource from the University of Liverpool at http://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-boosed 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

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
  - o The CDC malaria website: https://www.cdc.gov/malaria
  - o 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 to Acronyms: CDC = the Centers for Disease Control and Prevention; TMP-SMX = Trimethoprim-sulfamethoxazole

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Microsporidiosis (Last updated June 14, 2019; last reviewed October 13, 2021)

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 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/mm^3.[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/mm^3 should avoid untreated water sources **(AIII)**. Additional recommendations include general 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/mm^3) is associated with resolution of symptoms of enteric microsporidiosis, including illness caused by *E. bieneusi*.[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. bieneusi* infection. A controlled clinical trial suggested that *E. bieneusi* infection may respond 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. However, fumagillin is available from Sanofi in France as FLISINT® 20 mg, capsules and has been obtained for patients in the United States (see Sanofi's Compassionate Use/Managed Access Program website). One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART;[19] however, the effect appeared to be minimal among patients with low CD4 cell counts. Based on personal experience of several experts who have treated diarrhea caused by *E. bieneusi* with nitazoxanide in organ transplant patients, nitazoxanide is a reasonable alternative, if fumagillin is not available, for the treatment of diarrhea due to *E. bieneusi* **(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. bieneusi*[20] and *V corneae*[21] have amino acid residues associated with albendazole resistance. Albendazole is only recommended for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* 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. bieneusi* 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 should be treated with topical Fumidil B (fumagillin bicylohexylammonium) 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 as 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 on 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. bieneusi* infection;[26] however, no IRIS reactions have been reported with other species of microsporidia or with other cases of *E. bieneusi*. Concerns about IRIS should not alter therapy or the 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/mm^3), treatment can probably be discontinued after ocular infection resolves **(CIII)**, but it should be continued indefinitely if CD4 counts fall below 200 cells/mm^3 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/mm^3 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 women **(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 are felt to 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 women **(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 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)**.

Recommendations for Managing Microsporidiosis

Preventing Chronic Microsporidiosis:

- 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:

- Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 **(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)**.

For GI Infections Caused by Enterocytozoon bieneusi

- The best treatment option is ART and fluid support **(AII)**.
- No specific therapeutic agent is available for this infection.
- Fumagillin 60 mg PO daily **(BII)** and TNP-470 **(BIII)** 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 cell counts **(CIII)**.

For Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than E. bieneusi and Vittaforma corneae:

- Albendazole 400 mg PO twice daily **(AII)**, continue until CD4 count >200 cells/mm^3 for >6 months after initiation of ART **(BIII)**

For Disseminated Disease Caused by Trachipleistophora or Anncaliia:

- Itraconazole 400 mg PO daily plus albendazole 400 mg PO two times a day **(CIII)**

For Ocular Infection:

- Topical fumagillin bicylohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops four times daily (investigational use only in United States) **(BII)**, plus albendazole 400 mg PO twice daily for management of systemic infection **(BIII)**
- For patients with CD4 count >200 cells/mm^3, therapy can probably be discontinued after ocular infection resolves **(CIII)**.
- For patients with CD4 count ≤200 cells/mm^3, therapy should be continued until resolution of ocular symptoms and CD4 count increases to >200 cells/mm^3 for ≥6 months in response to ART **(BIII)**.

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

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Mycobacterium avium Complex Disease (Last updated February 15, 2019; last reviewed October 13, 2021)

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/mm^3. 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/mm^3, 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/mm^3 **(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/mm^3 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/mm^3 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/mm^3 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/mm^3 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, azithromycin[45] 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/mm^3), high mycobacterial loads (>2 $\log_{10}$ colony-forming units/mL of blood), and/or the absence of effective ART **(CIII)**. The third or fourth drug might include a fluoroquinolone such as levofloxacin or moxifloxacin **(CIII)**, which have *in vitro* and animal model activity against MAC, or an injectable agent such as amikacin or streptomycin **(CIII)**, 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 **(CIII)**. 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 **(CIII)**. 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 **(CIII)**. 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 34, 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/mm^3 for ≥6 months after initiation of ART. In this setting, it is reasonable to discontinue maintenance therapy based on data from studies in people with HIV and inferences from more extensive study data that indicate the safety of discontinuing secondary prophylaxis for other OIs **(AI)**.[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/mm^3 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 **<u>is not recommended</u>** for adults and adolescents who immediately initiate ART **(AII)**. <u>Indications for Initiating Primary Prophylaxis</u>: • 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)** <u>Preferred Therapy</u>: • Azithromycin 1200 mg PO once weekly **(AI)**, *or* • Clarithromycin 500 mg PO BID **(AI)**, *or* • Azithromycin 600 mg PO twice weekly **(BIII)** <u>Alternative Therapy</u>: • Rifabutin 300 mg PO daily **(BI)** (dose adjustment may be necessary based on drug-drug interactions, please refer to <u>Table 5</u> for dosing recommendation when used with ARV drugs). • **Note:** Active TB should be ruled out before starting rifabutin. <u>Indication for Discontinuing Primary Prophylaxis</u>: • Initiation of effective ART **(AI)** <u>Indication for Restarting Primary Prophylaxis</u>: • CD4 count <50 cells/mm³ (only if not on fully suppressive ART) **(AIII)**

Treating Disseminated MAC Disease
 	
<u>Preferred Therapy</u>:
• 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.
 	
<u>Alternative Therapy</u>:
• 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)
 	
<u>Chronic Maintenance Therapy (Secondary Prophylaxis)</u>:
• Same as treatment regimens
 	
*Criteria for Discontinuing Chronic Maintenance Therapy **(AII)**:*
• Completed **<u>at least</u>** 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 to Acronyms: 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

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Mycobacterium tuberculosis Infection and Disease (Last updated September 27, 2019; last reviewed October 13, 2021)

Epidemiology

Despite being preventable and curable, tuberculosis (TB) is the leading cause of death from infectious disease globally, with 10.4 million people developing TB and 1.7 million people dying from TB in 2016.[1] TB is the leading cause of morbidity and mortality among people living with HIV worldwide, with 1 million persons with HIV reported to have TB and 374,000 deaths due to TB among PLHIV in 2016.

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% to 16% per year, which approximates the lifetime risk of TB disease for persons with LTBI who are HIV negative (approximately 5%).[2] The risk of TB begins in the first year following HIV infection.[3] TB infection can occur at any CD4 T lymphocyte (CD4) cell count, though the risk increases with progressive immunodeficiency.[3,4]

The advent of potent antiretroviral therapy (ART) resulted in a decrease in the incidence of TB disease among persons with HIV infection, and this effect has been documented in settings with low case rates of TB among PLHIV, such as the United States,[5] and in settings with very high case rates.[6-9] However, even with the beneficial effects of ART, the risk of TB disease among persons with HIV infection remains greater than that of the general population.[10]

Rates of TB in the United States are declining, with 2.8 new cases of TB disease per 100,000 population (a total of 9,105 cases) reported in 2017, a 2.3% decline in TB incidence from 2016.[11] This was the lowest number of annual cases reported on record although regional differences in incidence are noted, and TB outbreaks in U.S. communities continue to occur. The prevalence of LTBI in the general population of the United States is 4.7%,[12] which has remained unchanged since the last survey in 1999–2000. The incidence of HIV-related TB has declined more rapidly than the rate of active TB disease in the general population,[13] in part due to the widespread use of ART. Among all cases of TB reported in the United States in 2017, there were 439 persons coinfected with HIV (5.5% of TB cases that had HIV test result information).[11] Like TB disease in the general U.S. population, HIV-related TB is increasingly a disease of persons born outside of the United States.[13]

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States and globally. Unlike most opportunistic infections (OIs), TB is transmissible from persons to person, particularly to persons with HIV infection. Therefore, clinicians providing care for persons with HIV must remain vigilant in efforts to prevent TB, knowledgeable about the clinical presentation of HIV-related TB, and cognizant of the complexities of the co-treatment of HIV and TB.

Preventing Exposure

In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.[12] Therefore, persons with HIV infection who live or work internationally in settings with a high prevalence of TB should be counseled about the risk of TB acquisition and the advisability of getting tested for LTBI upon returning to the United States.

Preventing Disease: Diagnosing and Treating Latent TB Infection

The estimated annual risk for active 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 persons with HIV than for those without HIV.[14,15] Furthermore, in two studies among adults with HIV, persons who developed TB had higher viral loads[16] and a greater risk of HIV disease progression[16] and death[17] than CD4-matched control patients without TB. The risk of progression from LTBI to TB disease in persons with HIV is reduced both by ART and by treatment of LTBI.[18] In combination with ART, treatment of LTBI decreases the risk of TB disease by 76% among persons with HIV infection.[19] Isoniazid preventive therapy and ART independently and additively decrease the risk of death and severe HIV-related illness.[9,18] In a study that compared isoniazid preventive therapy to placebo among persons receiving ART, isoniazid further reduced the risk of TB by 37%.[8] In a cluster randomized trial in Brazil, a country with medium TB burden, the rate of TB was lower in the isoniazid group than in the group that did not receive isoniazid at ≤7 years of follow-up, suggesting a durable effect of 6-month isoniazid in reducing the risk of TB disease in persons with HIV with a positive TST.[20] Therefore, prevention of TB disease by screening for and treating LTBI, along with ART initiation, are key components of HIV care.

Diagnosing Latent TB Infection

All persons with HIV should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII)**. The two current methods available for detection of *M. tuberculosis* infection in the United States, IGRA and TST, help differentiate infected from uninfected people. However, diagnostic accuracy of TST and IGRA are limited; a negative test does not exclude the diagnosis of LTBI or TB disease, and a positive test does not in 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. Decisions should not be based on IGRA or TST results alone.

Among persons with HIV, some studies found that the benefit of isoniazid preventive therapy (IPT) was seen primarily in persons with a positive TST.[21,22] However, in one study in South Africa, a setting with a high TB burden, IPT decreased the TB risk among all persons with HIV regardless of TST or IGRA result.[8] Another recent study from West Africa found improved survival with IPT regardless of TST or IGRA status.[18] Persons with negative diagnostic tests for LTBI, advanced HIV infection (CD4 count <200 cells/mm^3), and without indications for initiating empiric LTBI treatment (i.e., no recent exposure to a culture-confirmed TB case) should be re-tested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3 to ensure that the initial test result was a true negative result.[23,24] Annual testing for LTBI using TST is recommended for persons with HIV who are at high risk for repeated or ongoing exposure to persons with active TB disease **(AIII)**.

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48 to 72 hours in persons with HIV) in persons with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among persons 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.[25] These limitations of the TST have led to broader use of IGRAs for detection of LTBI.

Current evidence suggests that IGRAs have higher specificity than the TST, (92% to 97% vs. 56% to 95%, respectively), better correlation with surrogate measures of exposure to *M. tuberculosis*,[26] and less cross-reactivity with BCG vaccination and nontuberculous mycobacteria.[27,28] Two IGRAs are Food and Drug Administration (FDA)-approved and available in the United States. As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.[29] In addition, the reproducibility of positive results of IGRAs has been limited among health care workers, one of the few groups that routinely undergo repeated IGRA testing in the United States.[30] Poor reproducibility might also affect those with HIV. Among 46 persons with HIV who had initial positive tests with the IGRA QuantiFERON-TB Gold In-

Tube assay, 33 (72%) had negative repeat tests, particularly those with responses at the lower range of the manufacturer's suggested range of positive results.[31]

Among persons with HIV, the correlation between the TST and IGRA test results is poor to moderate.[32,33] In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease;[34-36] in some studies, patients with a positive IGRA were at a higher risk of subsequently developing TB disease than were those with a positive TST.[37,38] Despite its limitations, a positive TST result remains strongly predictive of decreased risk of TB progression in response to IPT among persons with HIV infection.[17] Studies are underway to formally evaluate if IGRAs are similarly predictive.

In programmatic settings in the United States, TB screening based on the TST has been suboptimal, with only 47% to 65% of patients completing screening.[39-41] The use of an IGRA for TB screening may increase the proportion of patients who complete TB screening.

There have been no published definitive comparisons of the TST and IGRAs for screening persons with HIV in low-burden settings such as the United States. Both the TST and the approved IGRAs are appropriate for TB screening among persons with HIV in the United States.[42] Some experts have suggested using both the TST and an IGRA in a stepwise 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.[42]

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. Most, but not all, persons with HIV with TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); absence of any of these symptoms has a 97% negative predictive value for culture-positive TB, though this varies depending on pre-test probability.[43] The addition of a chest radiograph improved sensitivity of this screening algorithm, but decreased specificity. Obtaining a sputum culture is the gold standard for diagnosing pulmonary TB disease but is not high yield in screening asymptomatic persons with HIV, particularly in the United States where the prevalence of TB is very low. 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.

Treating Latent TB Infection

Once TB disease is excluded and in the absence of other medical contraindications, persons with HIV and a positive TB screening test should receive LTBI treatment **(AI)**, unless there is documentation of prior treatment for active TB or LTBI. Additionally, persons with HIV who are in close contact with anyone with infectious TB should receive LTBI treatment, regardless of their TB screening test results **(AI)**. Persons with HIV in the United States who have a negative TST or IGRA and no recent contact with a person with infectious TB will likely not benefit from treatment of LTBI and preventive therapy is not generally recommended **(AI)**.[21,44-46] In the international setting, two recent studies from high-burden areas of South Africa showed isoniazid decreased TB risk[8] and mortality[18] regardless of TST or IGRA result.

Preferred and Alternative Drugs for Treating Latent TB Infection, Including Duration of Therapy

Isoniazid prophylaxis for 9 months remains a preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity **(AI)**. Although peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or various antiretroviral (ARV) drugs, the risk of hepatitis—the most important of these adverse effects—is not significantly increased when isoniazid is combined with efavirenz- or nevirapine-based regimens.[8] Isoniazid prophylaxis should be supplemented with pyridoxine at a dose of 25 to 50 mg/day to prevent peripheral neuropathy **(AIII)**. A significant disadvantage of the 9-month regimen is that the majority of patients do not complete all 9 months of therapy.[47] Patients are more likely to complete shorter regimens.[47-50] Additional regimens for chemoprophylaxis are shown in Table 1.[51] 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 LTBI treatment with isoniazid, including in persons with HIV whose CD4 counts were generally >350 cells/mm^3 and who were not yet on ART.[52,53] A recent study demonstrated that 3HP treatment completion rates with self-administered therapy were inferior to those with directly-observed therapy, but non-inferior among study participants enrolled in the United States—and generally high overall.[54] Although individuals taking ART were not included in the Phase 3 trial of once-weekly rifapentine and isoniazid, the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.[55] In a PK study of 12 adults with HIV without TB receiving once-weekly rifapentine 900 mg with efavirenz, rifapentine had minimal effect on efavirenz exposure.[56] Raltegravir concentrations were modestly increased, not decreased, when it was given with once-weekly rifapentine.[57] Thus, despite the lack of clinical trial outcome data, once-weekly rifapentine/isoniazid without dose adjustment based on available PK data is recommended when used in persons receiving efavirenz or raltegravir[58] **(AII)**. Increased clinical monitoring is not routinely recommended, but should be based on clinical judgment.

A large trial comparing 4 months of daily rifampin (4R) to 9 months of daily isoniazid (9H) was recently published.[59] The study enrolled >6,000 participants who were predominantly HIV negative, and although rates of incident active TB were low in both arms, the 4R regimen was non-inferior to 9H for the primary efficacy outcome. Importantly, 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). Only 255 participants were HIV positive, however, which limits the generalizability of the findings to this population. Given the lack of trial data in PLWH, the 4R regimen is recommended only as an alternative to 9H and 3HP in persons with HIV who cannot receive isoniazid **(BI)**. Furthermore, given the theoretical risks of rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in patients with HIV on ART,[60] clinicians may consider performing a sputum culture or chest radiograph before starting 4R for LTBI. When using rifampin for preventive therapy, either dose adjustment or substitution of key ART drugs may be needed. Regarding rifabutin monotherapy for the treatment of LTBI there are no data demonstrating its efficacy in people with or without HIV infection. The regimen of two months rifampin plus pyrazinamide is not recommended given the risk of severe and sometimes fatal hepatotoxicity **(AII)**.[61,62]

The BRIEF-TB study (ACTG 5279) evaluated 1 month of daily rifapentine plus isoniazid (1HP) versus 9 months of daily isoniazid (9H) in PLWH residing in mostly high TB burden settings (TB incidence >60 per 100,000 population).[63] The median CD4 count of study participants was 470 cells/mm^3, 50% of the study population was on ART (efavirenz or nevirapine-based regimens) at study entry, and 21% of the study population was TST-positive. The study endpoint was the combination of confirmed or probable TB, death due to TB, and death due to unknown cause. The event rate was 0.65 per 100 person-years in the 1HP arm and 0.67 per 100 person-years in the 9H arm; non-inferiority of the 1HP arm was established. Treatment completion rates (by self-report) were 97% in the 1HP arm and 90% in the 9H arm. These results suggest that 1HP might be an alternative regimen for treatment of LTBI in certain situations, but the regimen has not been fully evaluated in low TB prevalence settings (only 10% of the study population was from the United States). Of note, only 23% of the participants had a positive test for LTBI; 10% of the participants at international sites did not have a TST due to manufacturer shortages, and IGRAs were only performed for U.S. participants. Furthermore, 13% had baseline CD4 counts <250 cells/mm^3, and 50% were not on ART at entry (although ART was started after enrollment). While the population enrolled was at high risk for LTBI in the setting of HIV and high endemic exposure, the number of persons at risk of progression to TB disease due to documented LTBI was low.

LTBI treatment and ART act independently to decrease the risk of TB disease.[8,19,64,65] Therefore, use of both interventions is recommended for persons with LTBI **(AI)**. For persons exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities **(AII)**.

Monitoring for Adverse Events Related to Treating Latent TB Infection

Individuals receiving self-administered daily chemoprophylaxis should be seen by the prescribing clinician monthly to assess adherence and evaluate for possible drug toxicity; generally, a clinician should not prescribe >1 month's supply of drugs. Although persons with HIV may not have a higher risk of hepatitis from isoniazid than persons without HIV, it is recommended that they have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin levels measured before starting LTBI treatment and repeated if abnormal.[14] Persons with concomitant chronic viral hepatitis have an increased risk of isoniazid-related hepatotoxicity, and such patients should be monitored closely when treated for LTBI.[66,67] With isoniazid, liver enzymes typically increase in the first 3 months of treatment but then, through the process of hepatic adaptation, return to normal despite continued therapy. If the serum aminotransferase level increases 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 upper limit of normal among patients with baseline abnormal transaminases), chemoprophylaxis should be stopped. Factors that increase the risk of clinical hepatitis include daily alcohol consumption, underlying liver disease, and concurrent treatment with other hepatotoxic drugs. At each visit, patients should be asked about 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, and arthralgia) and told to immediately stop medications and return to the clinic for an assessment should any of these occur.

The ultimate decision regarding resumption of therapy with the same or different agents for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease[68] and in consultation with an expert in treating LTBI in persons with HIV infection.

Clinical Manifestations of TB Disease

Sputum culture-positive TB disease can be subclinical and patients with HIV/TB may remain asymptomatic.[69] In ambulatory PLWH, the presence of any one of the classic symptoms of TB disease (cough, fever, night sweats, and weight loss) has high sensitivity but low specificity for diagnosing TB,[43] but, the sensitivity of classic TB symptoms is lower in PLWH on ART.[60] A clinical prediction model developed and validated in ambulatory patients with at least one classic TB symptom showed that a score consisting of ART status, CD4 count, body mass index, and presence of more than one TB symptom improved the specificity of diagnosing TB while retaining reasonable sensitivity.[70]

In patients who are markedly immune suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.[71] World Health Organization (WHO) algorithms for diagnosing TB distinguish between ambulatory patients and those who are seriously ill, defined by the presence of one or more danger signs (respiratory rate >30/min, heart rate >120/min, temperature >39°C, and inability to walk unaided). A study of inpatients with WHO danger signs and cough of any duration reported that the classic TB symptoms of fever, weight loss, and night sweats were not predictive of TB.[72] Rather, the following variables predicted TB: cough ≥14 days, inability to walk unaided, temperature >39°C, chest radiograph assessment, low hemoglobin, and elevated white blood cell count.

The presentation of active TB disease is influenced by the degree of immunodeficiency.[73,74] In patients with CD4 counts >200 cells/mm^3, 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.[75]

In patients with CD4 counts <200 cells/mm^3, the chest radiographic findings of pulmonary TB are markedly different with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon.[73,75,76] Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures. Adjunct thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.[77]

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. Clinical manifestations of extrapulmonary TB in persons 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,[78] especially processes related to central nervous system (CNS) or meningeal symptoms when early TB treatment is essential to improve outcomes.[79-81]

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 is directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid). The initial evaluation of a patient suspected of having HIV-related TB should always include a chest radiograph or other chest imaging, even in the absence of pulmonary symptoms or signs; pulmonary involvement is common at all CD4 counts.[69,82] 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.[83,84] Therefore, sputum smear and culture should be performed in symptomatic patients being evaluated for possible 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.

Sputum smear-negative TB is common among persons with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.[85] However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. When a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high.[86,87] Smear and culture of three sputum specimens is recommended based on a large study in patients with HIV that showed a 10% incremental yield for broth culture between the second and third specimens.[88]

Extrapulmonary and disseminated TB are more common in persons with HIV, particularly with advanced immunosuppression.[89,90] Nodal 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.[91] 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.[74]

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if there is clinical evidence of involvement. The yield of acid-fast bacilli (AFB) smear, culture, and nucleic acid amplification (NAA) testing is generally lower from extrapulmonary specimens than from sputum, but nonetheless these tests can be an important diagnostic tool when *M. tuberculosis* is isolated. 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[74,78] and may allow definitive diagnosis and be a source of an isolate for drug-susceptibility testing.

Nucleic-Acid Amplification Testing: Standard mycobacterial cultures for TB may take weeks to months to grow, but rapid diagnosis is essential in patients with HIV given the risk of rapid clinical progression of TB among patients with advanced immunodeficiency. NAA tests provide rapid diagnosis of TB (some assays also provide rapid detection of drug resistance—see below). NAA tests have at least two uses among patients with suspected HIV-related TB. First, NAA assays, if positive, are highly predictive of TB disease when performed on AFB smear-positive specimens. Nontuberculous mycobacterial infections are relatively common among patients with advanced immunodeficiency, and NAA tests can be used to direct therapy and make decisions about the need for respiratory isolation of patients with a smear-positive specimen. Second, NAA tests are more sensitive than AFB smear, being positive in 50% to 80% of smear-negative, culture-positive specimens[92,93] and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patents with suspected pulmonary TB, a NAA test be performed on at least one specimen.[94] NAA tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations in the *rpoB* gene associated with rifampin resistance. It has been widely implemented in resource-limited settings with high TB prevalence and as a frontline TB diagnostic test in patients with HIV.[95] Xpert MTB/RIF was licensed in the United States in 2013 for detection of *M. tuberculosis* and reporting of rifampin resistance directly from sputum samples[96] and in 2015, as an aid in decisions regarding respiratory isolation.[97] This assay combines simple processing requirements in the laboratory and rapid turnaround (results within 2 hours). In a recent meta-analysis, the overall sensitivity and specificity of the Xpert MTB/RIF assay were 88% (95% confidence interval [CI], 83% to 92%) and 98% (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among patients 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%);[98] however, this may be in part attributed to a higher prevalence of smear negative disease in individuals with HIV.[99] In some studies, the sensitivity of Xpert MTB/RIF has been related to CD4 count, with higher sensitivity among patients with more advanced immunodeficiency.[100]

In extrapulmonary specimens, a 2014 meta-analysis reported Xpert MTB/RIF sensitivity of up to 95% in smear positive specimens and 69% in smear negative specimens.[101] Median sensitivity varied by specimen type, with higher yield from lymph nodes (96%), CSF (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%).

In 2017, a newer version of the Xpert MTB/RIF assay was developed (MTB/RIF Ultra) to improve the sensitivity of the existing test platform. With several technical modifications, the newer cartridge has a limit of detection of 16 colony forming units (cfu) (compared to 113 cfu for the original Xpert MTB/RIF) and improved detection of rifampin resistance.[102] A large, multinational study tested clinical specimens using both the old and newer cartridges in parallel, as well as solid and liquid agar culture. The study found that Xpert MTB/RIF Ultra was superior to the older version of the assay (Xpert MTB/RIF), particularly in patients with smear-negative disease (sensitivities of 63% and 46%, respectively).[103] In a separate prospective study of people with HIV with suspected TB meningitis, Xpert MTB/RIF Ultra testing of CSF was also found to have improved sensitivity of 95% versus 45% for Xpert MTB/RIF, and yield was increased with larger volumes of CSF.[104] On the basis of these findings, as well as a mathematical model, WHO has endorsed replacing the older cartridges with the new version worldwide, noting that the change will benefit most in those with smear-negative disease, such as people with HIV, children, and individuals with extrapulmonary TB such as TB meningitis.[105] The Xpert MTB/RIF Ultra is currently not FDA approved or available in the United States.

Lipoarabinomannan (LAM): LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of patients with TB. LAM can be detected using an enzyme-linked immunosorbent assay (ELISA) or a lateral flow point of care test. The diagnostic utility of LAM is limited by a low sensitivity, but it has the advantage of being available as a true point of care test that can be performed on urine. LAM has demonstrated the best performance in patients with HIV with low CD4 counts (<100 cells/mm^3) with a sensitivity of 37% to 56% and specificity of up to 95%.[106-108] In addition, LAM has higher sensitivity in patients with worse prognoses.[109] Combining LAM with other diagnostic strategies, such as Xpert MTB/RIF testing of sputum or urine, may improve the diagnostic utility of LAM and identify those at greatest risk of TB-related mortality.[110-112]

Immune-Based Tests: Immunological tests for TB infection, the TST and IGRA, may be helpful in unusual circumstances in which it is difficult to obtain definitive culture evidence for active TB disease; evidence of prior TB infection increases the likelihood that a clinical illness may be TB disease. However, these tests are not diagnostic of active TB disease, and a negative TST or IGRA should never be interpreted as ruling out TB disease because TB may cause anergy and these tests may be negative in 11% to 30% of patients with active TB.[42]

Drug Resistance Testing: The presence of drug resistance should be considered in any patient with:

- Known exposure to a person with drug-resistant TB
- Residence in a setting with high rates of primary drug-resistant TB (e.g., a country or area with high rates of drug resistance in patients with newly diagnosed TB)
- Persistently positive smear or culture results at or after 4 months of treatment
- Previous TB treatment, particularly if it was not directly observed or was interrupted for any reason.

These patients should be prioritized for rapid molecular testing. Conventional drug-susceptibility testing (DST) should be performed on the initial isolates from all patients suspected of having TB, as resistance to isoniazid and/or rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[113] 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.[114] Thus, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on conventional DST results, is critical to the successful treatment of TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.

For all patients with TB disease, drug-susceptibility testing to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. 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, aminoglycosides, capreomycin, ethionamide, and others) should be performed only in reference laboratories with substantial experience in these techniques and should be limited to specimens with resistance to first-line TB medications.

Conventional Growth-Based Drug-Susceptibility Testing: Conventional DST is widely used and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turn-around time of conventional broth or agar-based culture followed by DST may be as long as 6 weeks,[115] 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 for ongoing transmission, further clinical deterioration, and death, particularly in individuals with HIV.[114] 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, as molecular correlates of phenotypic drug-resistance are poor. In 2018, WHO produced a technical report based on a systematic review of available minimum inhibitory concentration (MIC) data for phenotypically wild-type and non-wild type strains and associated sequencing of related resistance-determining genes. The report provided new recommendations for phenotypic DST of the second-line medications and modifications to breakpoints which also account for PK variability observed in clinical care.[116]

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.[117] 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.[99,118] Of note, probe-based assays including Xpert MTB/RIF and LPAs should always be confirmed with sequence based tests as well as growth-based DST. For initial evaluation of drug resistance, or confirmation of drug resistance identified by the above assays, the Centers for Disease Control and Prevention (CDC), Division of Tuberculosis Elimination, has a Molecular Detection of Drug Resistance (MDDR) service that offers rapid molecular testing for first-and second-line TB medications at no charge for persons suspected of having drug-resistant TB (See the Report of Expert Consultations on Rapid Molecular Testing to Detect Drug-Resistant Tuberculosis in the United States). State TB programs and state labs should also be consulted for resistance testing options. Several assays can be performed on cultured isolates or directly on sputum specimens.

The largest clinical experience with rapid molecular tests for rifampin resistance is with the Xpert MTB/RIF (pre-Ultra) assay. In a 2014 meta-analysis, the sensitivity of the assay for detection of rifampin resistance was 95% (95% CI, 90% to 97%) and the specificity was 98% (95% CI, 97% to 99%).[98] False-positive results for rifampin resistance with the Xpert MTB/RIF assay can occur, and sequence-based testing should be done to confirm results.[119] However, the comparator for most studies—phenotypic DST—is not an absolute gold standard.[120,121] Some isolates with rifampin resistance by the Xpert MTB/RIF assay have mutations in the *rpoB* gene, but are susceptible in phenotypic assays. Two recent analyses showed that treatment failure was more common among patients whose isolates had phenotypic susceptibility but mutations in the resistance-determining region of the *rpoB* gene than among patients whose isolates had wild type *rpoB* gene sequences.[122,123]

In low MDR TB prevalence settings such as the United States, the positive predictive value of any test for rifampin resistance is limited. Therefore, isolates with an initial reading of rifampin resistance with the Xpert MTB/RIF should undergo confirmatory testing (*rpoB* gene sequencing or phenotypic drug susceptibility testing), and in such cases, additional specimens should be obtained from the patient. Consultation with an expert in the diagnosis and treatment of MDR TB is recommended.

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 CDC as needed.

Treating Disease

Preferred and Alternative Drugs for Treatment, Including Duration of Therapy

TB among persons with advanced immunodeficiency can be a rapidly progressing and fatal illness if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens.[86] Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is warranted in patients with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.

Treatment of suspected TB for individuals with HIV is the same as for individuals without HIV and should include an initial four-drug combination of isoniazid, rifampin, ethambutol, and pyrazinamide **(AI)**. If rapid DST results indicate resistance to rifampin, with or without resistance to other drugs, an initial MDR TB regimen—including a fluoroquinolone (levofloxacin or moxifloxacin) and either an aminoglycoside or capreomycin—should be used **(BIII)** and can be adjusted as sequencing and conventional DST results become available. Directly observed therapy (DOT) is recommended for all patients with suspected HIV-related TB **(AII)**. 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 (e.g., enhanced DOT).

Drug-susceptible TB should be treated with a 2-month intensive phase of the four drugs listed above (isoniazid, rifampin, ethambutol, and pyrazinamide). 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 of treatment for uncomplicated TB **(AI)**.

Although intermittent dosing (administration less often than daily) of anti-TB treatment 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 persons with HIV.[124-132] Therefore, daily therapy given as DOT is recommended during both the intensive and continuation treatment phase **(AII)**.[130,131,133] Observational studies and meta-analyses focused primarily on the intensive phase of treatment, and thrice-weekly therapy during the continuation phase was not systematically evaluated in the context of the risk of adverse TB outcomes (treatment failure, recurrence, or acquired drug resistance).[127] Although earlier recommendations 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, there are no data substantiating the minimum number of doses needed within a specified time interval in individuals with HIV. Every effort should be made to assure 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 patients with HIV and drug-susceptible TB disease is not known. In general, the outcomes of 6-month regimens (2 months of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by 4 months of isoniazid and rifampin) given as DOT to patients with HIV have been good.[134,135] A randomized trial in the United States showed excellent and comparable outcomes of TB therapy among patients assigned to 6 months or 9 months of therapy, but the trial was underpowered.[136] Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy than among those assigned to 9-[124] or 12-month regimens.[137] However, the applicability of these two trials to low-burden settings in which ART is used, such as the United States, is uncertain. 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)**. TB meningitis should be treated for 9 to 12 months **(BII)**.

The use of a higher rifampin dose and/or addition of a fluoroquinolone to treatment for CNS TB may be beneficial, but there are limited data to support its use. A recent randomized trial that compared 9 months of standard TB therapy that included rifampin at a dose of 10 mg/kg with an intensified regimen in which levofloxacin was added and rifampicin was given at a higher dose of 15 mg/kg showed similar rates of survival, adverse events, and secondary outcomes in individuals both with and without HIV who had TB meningitis.[138] Importantly, however, rifampin doses in the two arms were highly overlapping, and standard or even modestly-increased rifampin doses do not produce rifampin concentrations in the CSF that are above rifampin's MIC against *M. tuberculosis* in many patients.[139,140] It is unclear whether even higher doses of rifampin may be more effective, but small prospective studies have found that doses as high as 35 mg/kg were well tolerated in adults, and additional studies are underway.[141,142] A PK study of 60 participants in Indonesia suggested that rifampin administered in doses equivalent to 13 mg/kg or higher given intravenously (similar to 26 mg/kg delivered orally) reduced mortality,[143] but this finding requires confirmation in a larger trial. Addition of a fluoroquinolone may improve outcomes in patients with isoniazid-monoresistant tuberculous meningitis.[138]

Adjunctive corticosteroid therapy is recommended in individuals with HIV who have TB involving the CNS **(AI)**.[81] The regimen used in trials of adjunctive corticosteroids for CNS disease were: dexamethasone (0.3–0.4 mg/kg/day for 2–4 weeks, then taper 0.1 mg/kg per week until dose of 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks).[81] Adjunctive corticosteroid therapy increases survival overall for patients with TB with CNS involvement, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV.[81,144] 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 and without HIV with tuberculous pericarditis, 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.[145] A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a non-significant reduction in constrictive pericarditis. Notably, however, <20% of patients with HIV in the trials analyzed were receiving ART.[146] There have been no trials comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations with Regard to Starting ART

Optimal management of HIV-related TB requires that both infections be addressed. Although data are conflicting whether sequential treatment of TB followed by initiation of ART is acceptable for persons with CD4 counts >220 to 250 cells/mm^3,[147,148] results from large, international, randomized trials of immediate versus delayed initiation of ART indicate that, at all CD4 counts, people with HIV without active TB disease gain substantial health benefits from immediate ART.[9,149,150] When coupled with the preponderance of data from randomized trials in persons with HIV and active TB disease, these results support the recommendation that ART should not be withheld until completion of TB treatment **(AI)**. 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 coinfected patients in the appropriate clinical setting improves survival[147] (particularly for persons with CD4 counts <50 cells/mm^3),[151] decreases the risk of additional opportunistic illnesses,[151,152] and, despite higher rates of IRIS at low CD4 counts, is not associated with higher rates of ARV or anti-TB drug related toxicity.[148]

The evidence supporting concurrent therapy comes from four trials.

The SAPIT trial randomized 642 South African adults with CD4 counts <500 cells/mm^3 and AFB smear-positive TB to start ART at either TB treatment initiation, after the intensive phase of TB therapy but before TB treatment completion, or after TB treatment completion.[147] The study was stopped early because mortality in the two integrated treatment arms was 56% lower than in the sequential treatment arm, demonstrating that ART should be started before TB completion. Notably, there was a survival benefit across the range of CD4 counts among patients enrolled, including within the stratum of baseline CD4 counts from 200 to 500/mm^3.

The CAMELIA, STRIDE (ACTG A5221), and TB-HAART trials shed further light on the optimal timing of ART during TB treatment. In CAMELIA, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 count of 25 cells/mm^3 (interquartile range [IQR], 10, 56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The mortality rate decreased from 13.77 per 100 person-years in the 8-week arm to 8.28 per 100 person-years (P = 0.002) in the 2-week arm,[153] and >95% of the study participants who survived had viral suppression.

The ACTG A5221 STRIDE study randomized 809 participants from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 count of 77 cells/mm^3 (IQR, 33,146) to immediate ART (within 2 weeks of TB treatment initiation) or early ART (8–12 weeks after TB treatment initiation).[151] A new OI or death occurred among 12.9% of participants in the immediate arm and 16.1% in the early arm by week 48 (P = 0.45). Among participants with screening CD4 count <50 cells/mm^3, 15.5% on immediate ART versus 26.6% on early ART developed AIDS or died (P = 0.02). TB-associated IRIS (TB-IRIS) was more common among participants in the immediate ART arm (11%) than in the early ART arm (5%) (P = 0.002). Viral suppression rates were similar between the arms.

The TB-HAART trial included 1,538 participants with HIV infection in South Africa, Uganda, Zambia, and Tanzania who had culture-confirmed pulmonary TB and CD4 counts ≥220 cells/mm^3 and had tolerated 2 weeks of TB treatment. Participants were randomized to early ART (initiated after 2 weeks of TB treatment) or delayed ART (until 6 months after initiation of TB treatment).[148] The median CD4 count for all participants was 367 cells/mm^3 (IQR 289, 456). The composite primary endpoint of TB treatment failure, TB recurrence, and death within 12 months of starting TB treatment occurred in 8.5% of participants in the early ART group and 9.2% in the delayed ART group (relative risk [RR] 0.91, 95% CI, 0.64–1.30; P = 0.9). Mortality rates and the incidence of grade 3 and 4 adverse events, and IRIS did not differ among the treatment groups. Patients in the early ART group had higher CD4 counts at all time points than those in the delayed ART group; no data on viral suppression were available. Unlike SAPIT, STRIDE, and CAMELIA, the TB-HAART study concluded that ART can be delayed until after 6 months of TB treatment for patients with CD4 counts >220 cells/mm^3.

The optimal approach for initiation of ART in TB meningitis remains uncertain. A randomized trial conducted in Vietnam compared ART initiation immediately (within 7 days of starting TB treatment) or until 2 months after starting TB treatment among 253 patients with HIV-related TB meningitis.[154] This study did not show a survival benefit to early ART initiation. On the contrary, mortality was similar in both study arms, and early ART was associated with more frequent and severe adverse events than deferred ART (86% vs. 75% of participants, respectively). The overall mortality rates in this study were very high (58%), likely at least in part because most participants had advanced AIDS (median baseline CD4 count was 41 cells/mm^3); it is unclear if these findings are generalizable to other settings. Many experts would recommend the initiation of ART within the first 2 to 8 weeks of starting anti-TB treatment, opting for 2 weeks in those with CD4 counts <50 cells/mm^3 in settings where close monitoring of drug-related toxicities and CNS adverse events is feasible **(AI)**.

In conclusion, ART is recommended for all persons with HIV and TB **(AI)**. For ART-naive patients, ART should be started within 2 weeks after TB treatment initiation in those with CD4 count <50 cells/mm^3 and, based on the preponderance of data, when TB meningitis is not suspected, within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts **(AI)**. Given the need to initiate five to seven new medications in a short time, patients should be offered adherence support. Rifampin-associated drug interactions should be considered when selecting the ARV drug regimen. In patients with TB meningitis and low CD4 counts, early ART may pose a risk for severe adverse effects, and an expert should be consulted, and careful monitoring provided. Early ART initiation requires close collaboration between HIV and TB care clinics, expertise in management of ART regimen selection, close monitoring, and support and adherence services for clients.

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 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 ART 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, short-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 Table 3 and 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.

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. 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, was higher with TAF/emtricitabine given with rifampicin than with TDF given alone, suggesting that TAF may be given together with rifampicin-containing TB treatment without dose adjustment.[155] Caution is urged, however, as this combination has not been tested in patients to confirm PK and virologic efficacy among patients taking full dose ART and TB regimens. Neither TDF nor TAF has been tested with rifabutin or rifapentine.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)—Efavirenz, Nevirapine, Etravirine, Doravirine, and Rilpivirine: Up to now, the preferred co-treatment regimen for HIV-related TB disease has been rifampin-based TB therapy with an ARV regimen of efavirenz 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.[156] Data on the magnitude of the change in efavirenz concentrations when co-administered with rifampin are conflicting. Early studies, largely conducted among healthy individuals without HIV infection, reported a 26% reduction in efavirenz plasma concentrations with rifampin,[157] but more recent and larger studies in PLWH and TB (including patients with higher body weight) have not shown a significant effect of rifampin-containing TB treatment on efavirenz plasma concentrations in the majority of patients.[158-160] Previous recommendations to increase the dose of efavirenz, especially in patients weighing

>60 kg, are thus not supported by high-quality data and have several disadvantages (complexity of dosing, inability to take advantage of the simplicity of the co-formulation of efavirenz, tenofovir disoproxil fumarate, and emtricitabine, and the possibility of increased neuropsychiatric side effects). A further disadvantage of increasing the dose of efavirenz coadministered with TB treatment is that slow metabolizers of efavirenz (about 20% of people of African, Thai, and 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.[161] Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[156,162] the 600 mg daily dose of efavirenz is recommended **(AII)**.

Although still used in international resource-limited settings, nevirapine is rarely used in high resourced settings, and **is not recommended** in these settings for HIV and TB co-treatment. Data from more recent studies indicate that in patients on TB therapy, co-treatment with nevirapine-based ART is associated with less satisfactory virologic outcomes and increased incidence of drug discontinuation due to adverse events than efavirenz-based ART.[163-165] Drug-drug interactions between rifampin and other NNRTIs have a more significant effect on the concentrations of the NNRTIs that limit their concomitant use. The use of rifampin or rifapentine with doravirine, etravirine or rilpivirine **is not recommended** **(AIII)** (see Table 3 and the Adult and Adolescent Antiretroviral Guidelines). Substitution of rifabutin for rifampin with appropriate dose adjustment of rifabutin might be considered for patients who require one of these NNRTIs, however, these combinations have not been evaluated in PLWH requiring treatment for active TB disease.

Integrase Inhibitors—Bictegravir, Dolutegravir, Elvitegravir, and Raltegravir: Alternatives to efavirenz-based ARV treatment for patients with HIV/TB include regimens with integrase inhibitors or protease inhibitors (PIs). One preferred alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 400 or 800 mg twice daily, with standard rifampin dosing **(BI)**.[166] Raltegravir concentrations are significantly decreased when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[167] The recently presented REFLATE TB2 trial compared efavirenz 600 mg daily to raltegravir 400 mg twice daily in PLWH undergoing TB treatment; the overall viral suppression rate at week 48 did not achieve the non-inferiority margin with this dose of raltegravir, although a previous Phase 2 randomized trial suggested virologic suppression was similar in non-comparative analyses of the raltegravir 400 and 800 mg twice daily arms.[166] These data suggest that the dose of raltegravir should be 800 mg twice daily if used with rifampin. Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without dose adjustment of either drug.[168]

Dolutegravir may be another reasonable treatment 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.[169] A recent Phase 2 randomized, non-comparative trial (INSPIRING) was conducted among ART-naive patients with HIV-associated TB and investigated dolutegravir at a dose of 50 mg twice daily during and for 2 weeks after completing rifampin-containing TB treatment. Among the 69 patients randomized to the dolutegravir arm, the results at 24 weeks were favorable with on-target PK assessments and rapid virologic response; there were no deaths, no discontinuations for IRIS or drug toxicity, and no emergence of resistance.[170] Final 48-week data are expected in 2019. A recent trial conducted among healthy volunteers without HIV infection evaluated bictegravir concentrations when given twice daily together with rifampin versus once-daily alone.[171] Bictegravir trough concentrations, even with the dose adjustment, were reduced 80%. Thus, bictegravir **should not be used** together with rifamycin-containing TB treatment **(AI)**. Similarly, elvitegravir/cobicistat should not be used together with TB treatment that contains rifamycins **(AI)**.

Protease Inhibitors with Rifampin or Rifabutin: Another alternative co-treatment regimen is rifabutin-based TB therapy with an ARV regimen including a ritonavir-boosted PI **(BIII)**. While there are no clinical trials specifically comparing rifampin- and rifabutin-containing anti-TB regimens among persons with HIV/

TB taking ART, in general, rifabutin is regarded as a reasonable substitute for rifampin for treatment of TB.[172,173] Although the dramatic effects of rifampin on serum concentrations of lopinavir may be overcome by doubling the dose of lopinavir/ritonavir,[174,175] the safety of this strategy has yet to be firmly established. High rates of hepatotoxicity were reported when dose-adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[176-178] In patients with HIV and TB, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampin-based TB treatment, but the strategy of increasing ritonavir dosing to 400 mg twice daily leads to high rates of hepatotoxicity.[175,179,180] Thus, a strategy of first increasing the dose of lopinavir/ritonavir by 50%, then increasing to full double dose is recommended **(BIII)**. Regular monitoring of transaminases is recommended when double-dose lopinavir/ritonavir is used (e.g., more frequently initially, then monthly once transaminase levels are stable on full dose).

Use of rifabutin with a boosted PI is thus preferred to use of rifampin with double-dose PI in settings where rifabutin is readily available. Co-administered rifabutin has little effect on ritonavir-boosted lopinavir[181] or atazanavir,[182] and only moderately increases concentrations of ritonavir-boosted darunavir[183] and fosamprenavir.[184] 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 to avoid dose-related toxicity, such as uveitis and neutropenia.[185] In studies of people with HIV infection, 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.[186,187] Among individuals with HIV/TB, there have been case reports of acquired rifamycin resistance with 150 mg three times weekly doses of rifabutin when co-administered with a boosted PI-based ARV regimen.[188,189] A recent study conducted in South Africa in 16 patients with HIV infection on a lopinavir/ritonavir-based ART regimen demonstrated that rifabutin administered at a dose of 150 mg daily in combination with lopinavir/ritonavir was generally safe and associated with rifabutin plasma concentrations similar to those shown to prevent acquired rifamycin resistance (i.e., rifabutin given 300 mg daily in the absence of a boosted PI).[187] A randomized clinical trial evaluating rifabutin PK and TB and ART outcomes using rifabutin 150 mg daily with lopinavir/ritonavir-based ART has been completed and results are pending. Based on available PK data, it is recommended that rifabutin should be dosed 150 mg daily in patients who are on a ritonavir-boosted PI-containing antiretroviral regimen **(BII)**. However, given that the risk of adverse events related to high levels of rifabutin's metabolite with this dosing strategy has not been firmly established, close monitoring for toxicity (especially neutropenia and uveitis) is required until larger studies provide adequate safety data. Close monitoring of adherence to ART is essential as 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.[190,191] If a rifamycin cannot be used, TB treatment duration must be extended substantially. Thus, patients with rifamycin-susceptible *M. tuberculosis* isolates should only be treated with a regimen that does not contain a rifamycin 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). 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.[192] 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.

Managing Suspected Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, incorrect or inadequate regimen prescribed, subtherapeutic drug levels due to malabsorption, super-infection with drug-resistant *M. tuberculosis*, and acquired drug-resistance.

Patients with suspected treatment failure should be evaluated with a history, physical exam, and chest radiograph to determine whether the patient has clinically responded 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 should also be reviewed. Some experts will perform therapeutic drug monitoring to determine if serum concentrations of the TB drugs are within expected ranges and dose adjust as necessary.[133,193] In addition, samples from all available sites (e.g., sputum, blood, urine) should be collected for repeat culture and drug-susceptibility testing, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or super-infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, broadening empiric TB treatment with 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

During the course of anti-TB therapy, patients with HIV who are not on ART are more likely to experience adverse events thought to be drug-related than patients without HIV.[194,195] 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,[194] 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 coadministered with anti-TB therapy.[147,148] 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 there is strong evidence that a drug reaction was caused by a specific anti-TB drug. In such situations, decisions regarding rechallenge with first-line drugs and/or substitution of second-line drugs should be made in consultation with a specialist in treating TB disease in persons with HIV.

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% to 30% of patients treated with the standard four-drug anti-TB regimen,[68,196] but many of these patients only have transient, mild elevations of ALT.[68] If the criteria for anti-TB DILI are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately. 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, an aminoglycoside, and moxifloxacin or levofloxacin)[197] 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 pre-existing 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% of patients without HIV in one randomized controlled trial of different rechallenge regimens.[197] 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. However, some experts would recommend rechallenge with pyrazinamide in patients with severe forms of TB (e.g., meningitis or disseminated TB).[198] 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 anti-TB drug rechallenge, if appropriate, relevant ARV drugs and cotrimoxazole may be restarted.

Cutaneous adverse drug reactions (CADRs) may occur with all of the first-line anti-TB drugs, notably rifampin and isoniazid;[199] many antiretroviral 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 continued. If the rash is generalized, or associated with fever or DILI, or if there is mucous membrane involvement or desquamation, all anti-TB medications, relevant ARVs, and cotrimoxazole should be stopped. When the rash is substantially improved, the TB drug 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 prevalence of drug-resistant TB globally, plus the high proportion of TB cases in the United States in people who are foreign-born, 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 (isoniazid and rifampin, in particular). 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 has not yet been published.

Growing evidence demonstrates that there is an increased risk of treatment failure associated with baseline isoniazid monoresistance,[200] particularly in patients with HIV/TB.[124] 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)**.[201,202]

Resistance to rifampin alone, or to rifampin and other drugs, substantially increases the complexity and duration of treatment. Treatment of these types of drug-resistant TB requires the use of second-line and often third-line TB medications, which are less effective, more toxic, and require 12 to 24 months of treatment.[203,204] Treatment outcomes for MDR TB are considerably worse than those for drug-susceptible TB—especially in patients with HIV/TB.[114] Consensus treatment guidelines for MDR TB are based on a review of published observational studies[205,206] and recommend use of at least five drugs with known or likely activity against the patient's isolate **(BIII)**. Until recently, such regimens included a later-generation fluoroquinolone; a second-line injectable agent (i.e., kanamycin, amikacin, or capreomycin); pyrazinamide and ethambutol (if retained susceptibility); and likely two other second-line oral medications, such as ethionamide or prothionamide, linezolid, cycloserine, or clofazimine.[203] Additional resistance to one or more of these drugs (e.g., extensively drug-resistant [XDR] TB) necessitated use of alternate or third-line agents with uncertain anti-TB activity. An intensive phase of 8 months was then followed by a continuation phase without the injectable agent for an additional 12 to 18 months.

In addition to recommendations for an all-oral MDR TB regimen, in 2016, WHO also issued guidance for programs in resource-limited settings on a standardized shorter-course regimen that includes seven anti-TB drugs and a duration of 9 to 12 months of treatment for selected patients with MDR TB.[207] The regimen composition is based on combinations evaluated as "the Bangladesh regimen,"[208] and includes kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol administered for 4 to 6 months, followed by moxifloxacin, clofazimine, pyrazinamide, and ethambutol for 5 months. Based on promising data from observational studies in predominantly persons without HIV, a randomized non-inferiority designed clinical trial (STREAM) recently compared the efficacy of an intensive, shortened, 9-month treatment regimen for MDR TB using currently available medications to the

20- to 24-month regimen. Recently published study results showed that the short-course regimen was non-inferior to the longer regimen (78.8% and 79.8% of participants with successful outcome for short- and long-term regimens, respectively). Notably, treatment outcomes in the 20- to 24-month treatment arm were considerably better than those historically reported (i.e., 54% treatment success).[209] Given the overall high success rate seen in both treatment arms, as well as the cost savings associated with the shorter regimen, WHO re-affirmed their recommendation of the short-course regimen.[210] Importantly, however, participants with HIV in the STREAM trial had more than double the risk of death compared to participants without HIV, and although this difference did not reach statistical significance, the study was not powered to detect such a difference among subgroups. This finding is particularly concerning, given that a recent observational study of patients in nine African countries receiving the short-course regimen found a statistically significantly higher mortality rate in patients with HIV than in patients without HIV.[211] Many resource-limited countries have adopted the short-course regimen in their national TB treatment programs, and variations of the shortened regimen are being evaluated in several randomized clinical trials, including in the United States. Adoption of this option may be important for patients with MDR TB who have confirmed susceptibility to fluoroquinolones and second-line injectable agents.

The field is in considerable flux as clinical trials of shorter course therapy with or without injectable agents are in progress. In late 2018, WHO issued MDR treatment guidelines recommending a fully oral regimen for most patients with rifampin-resistant TB.[212] The ranking of the second-line drugs was restructured, and bedaquiline, linezolid, and levofloxacin/moxifloxacin were placed in the highest tier (Group A), followed by clofazimine and cycloserine (Group B). All remaining drugs were placed in Group C, to complete the regimen only when drugs from Group A and B cannot be used. Notably, kanamycin and capreomycin are no longer recommended, given that the recent meta-analysis found an increased risk of treatment failure and relapse seen with their use. Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used, or in select patients eligible for the short-course regimen. Although the WHO updated recommendations are focused on crafting an initial standardized regimen in areas where access to rapid drug-susceptibility testing may be limited, based on these data and given the inordinate complexity of treatment for MDR- and XDR-TB, it is likely that these recommendations will be adopted in many countries while awaiting data from randomized clinical trials.

The treatment of MDR TB in the United States is evolving. Bedaquiline was approved in the United States for treatment of MDR TB in 2012. Initial randomized trials showed an increased number of late-occurring, unexplained deaths among the relatively small number of patients who received bedaquiline in randomized trials[213] suggesting that this drug should be used with caution and only in patients without other MDR TB treatment options while awaiting additional studies,[214] However, a meta-analysis of subsequent cohort studies that compared MDR TB regimens with and without bedaquiline showed improved survival in patients treated with regimens containing bedaquiline (adjusted hazard ratio 0.50, 95% CI, 0.41–0.61).[215] Although clinical experience with bedaquiline in the United States is still limited, experience outside the United States is rapidly expanding. Studies have revealed several important drug-drug interactions with common ARV agents. Specifically, efavirenz decreases bedaquiline levels and should not be used concurrently with bedaquiline.[216] Lopinavir/ritonavir, by contrast, increases bedaquiline plasma concentrations approximately two-fold when given at steady-state, but the clinical significance of this increase is not yet known.[217,218]

Delamanid, a new agent with a mechanism of action distinct from bedaquiline's, showed promise in early phase clinical trials.[219] Delamanid has been approved in Europe and Japan but currently is only available in the United States through a compassionate use program. A Phase 3 trial recently compared delamanid to placebo when given with an optimized background regimen to patients with MDR TB. Results of the trial showed no significant difference in treatment success with the addition of delamanid versus placebo (81% of participants in each arm).[220] However, participants in the placebo plus optimized background therapy arm had much higher rates of treatment success than expected. Given the favorable safety profile of delamanid and the high toxicity of other drugs in the background regimen, WHO reaffirmed their prior endorsement of delamanid with the caveat that it only be given as part of a longer (i.e., 20–24 month) treatment course and when a suitable regimen cannot be constructed without it.[221]

At present, there are insufficient data to support the use of WHO recommended shorter-course regimens in individuals with or without HIV in high-resource settings like the United States where full drug-susceptibility testing and individualized treatment options are available but this is likely to change in the near future. Whenever possible, treatment should be individualized based on a patient's specific drug-susceptibility testing results or treatment history. Surgical removal of TB lesions is a potential adjunctive measure in those with localized disease.[222] In the United States, treatment of MDR TB should involve an expert with experience in treating drug-resistant TB cases (if a local expert is not available, one option is to contact one of CDC's TB Centers of Excellence for Training, Education, and Medical Consultation).

Several medications for MDR TB carry considerable toxicity, including irreversible hearing loss, hypothyroidism, psychosis, and treatment-limiting gastrointestinal discomfort. Given the prolonged treatment course for MDR TB (20–24 months), patients and family members must be counseled ahead of time about possible side effects and the importance of treatment adherence. While on therapy, patients should be monitored closely for the appearance of side effects. Such screening should include serum chemistries, liver function tests, thyroid stimulating hormone, audiometry if treated with an injectable agent, and EKG monitoring if treated with bedaquiline. Sputum cultures should be performed monthly, even after culture conversion, so that any relapse and amplified resistance are detected early.

As with drug-susceptible TB, patients with HIV with drug-resistant TB (other than meningitis) should start ART as soon as possible. Despite the considerable pill burden and potential for overlapping drug toxicities, several retrospective studies and a recent prospective cohort study from South Africa have demonstrated high treatment success rates and favorable HIV outcomes with concurrent treatment.[223,224]

TB-Associated IRIS

TB-IRIS is a frequent early complication of ART in patients with recently diagnosed or undiagnosed active TB. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[225-227] 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.[228]

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in patients who are diagnosed with active TB prior to starting ART. Typically, these patients have had clinical improvement on TB treatment prior to starting ART. Within the first 1 to 4 weeks of ART (though sometimes later), they develop new or recurrent symptoms, as well as new, worsening, or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include hectic fevers, new or enlarging lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality due to paradoxical TB-IRIS is uncommon,[226,229] 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.[226,230,231] In patients with disseminated TB, hepatic TB-IRIS is common. This manifests with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.[232,233] A liver biopsy reveals a granulomatous hepatitis.[234] 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 (incidence 48% to 54%). A recent meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18% in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2% of the cases.[235] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[236-241] The syndrome lasts for 2 to 3 months on average,[230,242] but in some cases, symptoms may continue for months, and in rare cases, local manifestations may persist or recur over a year after onset.[228,242,243] 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 start of ART, especially a CD4 count <100 cells/mm^3;[239,244] high HIV viral load prior to ART;[245,246] disseminated or extrapulmonary TB;[230,238,240,244] 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.[230,237,239] Even though early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in patients with CD4 counts <50 cells/mm^3, given that this reduces risk of AIDS progression and death.[235]

The diagnosis of paradoxical TB-IRIS may be challenging, and there is no definitive confirmatory test. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms with treatment prior to ART, deterioration with inflammatory features of TB soon after starting ART, and demonstration of a response to ART (CD4 rise and/or HIV viral load reduction). In addition, and very importantly, diagnosis of paradoxical TB-IRIS requires investigations to exclude alternative causes for deterioration, particularly another OI or undetected TB drug resistance.[233]

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. 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.[247] 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,[247] observational data,[231] and clinical trials that showed reduced mortality in patients presenting with TB meningitis who were treated with corticosteroids[81] 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. Among all patients who developed TB-IRIS in the study described above, 4 weeks of prednisone treatment was insufficient in a subset. In such instances, a more gradual tapering of steroids over 2 to 3 months is recommended **(BIII)**.[247] Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms. Corticosteroids should be avoided in patients with Kaposi sarcoma, as life-threatening exacerbations can occur. There are case reports of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.[248-250]

Pre-emptive prednisone treatment has been shown to be effective in reducing the risk of paradoxical TB-IRIS in a trial conducted in South Africa.[251] This study was a randomized double-blind placebo-controlled trial in 240 ART-naive adults at high risk of paradoxical TB-IRIS treated with prednisone (40 mg/day for 2 weeks then 20 mg/day for 2 weeks) or placebo started at the time of ART initiation. High risk was defined as starting ART within 30 days of TB treatment initiation and a CD4 count ≤100/mm^3. Exclusion criteria included rifampin resistance, neurological TB, Kaposi's sarcoma, hepatitis BsAg positive, and poor clinical response to TB treatment prior to ART. The incidence of TB-IRIS was 47% in the placebo arm and 33% in the prednisone arm (RR = 0.70, 95% CI, 0.51–0.96). The intervention was not associated with harm; there was no excess risk of malignancy or severe infections. Based on these study findings, pre-emptive prednisone therapy should be offered for high-risk patients, as defined in this study, with a CD4 count ≤100/mm^3 who are starting ART in the context of recently initiated anti-TB therapy, are responding well to TB therapy, and who do not have rifampin resistance, Kaposi's sarcoma, or active hepatitis B **(BI)**.

Some clinicians 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.[230]

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.[228] 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.[228,247,252-254] Focal inflammatory manifestations such as abscesses and lymphadenitis may also develop.[255] 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 there is no clinical trial evidence 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.[256] 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.[257,258] 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.[259]

Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV: longer TB treatment regimens, administering therapy daily throughout the course of induction 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,[260,261] suggesting that this intervention decreases the risk of re-infection. However, post-treatment isoniazid is not recommended in low-burden settings such as the United States. 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 women 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 women with HIV is not recommended.[262-265] There are several studies examining the performance of the IGRAs for diagnosis of LTBI in pregnant women. In a study in pregnant women with HIV in Kenya, a positive IGRA result was associated with a 4.5-fold increased risk of developing active TB disease; in women with CD4 cell counts <250 cells/mm^3, a positive IGRA result was associated with a five-fold increased risk of maternal mortality or active TB disease and a three-fold increased risk of either active TB disease or mortality in infants.[266] Antenatal IGRA positivity has also been demonstrated to correlate with postpartum IGRA test positivity (i.e., TB infection) in women with HIV.[267] In women without HIV, the test appears to perform well but cost issues for routine screening are an area of debate.[268] If LTBI is diagnosed during pregnancy and active TB disease has been ruled out, treatment with isoniazid should be delayed until after delivery **(BI)**, given a recent clinical trial showing increased adverse pregnancy outcomes in women in high TB prevalence settings treated with isoniazid during pregnancy as compared to deferring to after delivery.[269] IPT is still recommended, however, for pregnant women whose close household contacts include a person with TB disease. Studies in individuals with HIV who are not receiving ART have been found to have a high risk of progression from LTBI to active TB disease (10% per year), and there is a high risk of maternal and infant mortality in pregnant women with HIV who have active TB disease.[270,271] However, the risk of progression from LTBI to active TB disease in individuals on ART is significantly decreased.[272] Pregnant women with HIV should be receiving ART both for their own health and for prevention of perinatal transmission. The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy. While treatment with isoniazid should be delayed until after delivery, if the risk of progression to active TB disease is considered to outweigh the risk of adverse birth outcomes with isoniazid and isoniazid is prescribed, frequent monitoring is needed.[273] Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.[274]

The diagnostic evaluation for TB disease in pregnant women is the same as for non-pregnant adults. Chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure. An increase in pregnancy complications and undesirable outcomes including preterm birth, low birthweight, and fetal growth restriction might be observed among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when TB treatment is not begun until late in pregnancy.[262-265,275-278] Congenital TB infection has been reported, although it appears relatively uncommon.[279-283] However, in one study of 107 women with active TB disease during pregnancy in South Africa, *M. tuberculosis* was detected in 16% of neonates (n = 16) tested within the first 3 weeks of life (12 by culture and 4 by smear microscopy).[284]

Treatment of TB disease for pregnant women should be the same as for non-pregnant women, but with attention to the following considerations **(BIII)**:

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently during pregnancy and the postpartum period.[285] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(CIII)**.
- 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. Experience with its use in human pregnancy is limited. Although WHO and the International Union Against Tuberculosis and Lung Diseases[286,287] have made recommendations for the routine use of pyrazinamide in pregnant women, pyrazinamide has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited.[288] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months **(AII)**. The decision regarding whether to include pyrazinamide in treatment regimens for pregnant woman should be made after consultation among obstetricians, TB specialists, and patients, considering gestational age and likely susceptibility pattern of the woman's TB strain.

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.[204] Experience using the majority of the second-line drugs for TB during pregnancy is limited.[289-292] MDR TB in pregnancy should be managed in consultation with a specialist. TB therapy should not be withheld because of pregnancy **(AIII)**. The following concerns should be considered when selecting second-line anti-TB drugs for use in pregnant women:

- Streptomycin use has been associated with a 10% rate of vestibulocochlear nerve toxicity in infants exposed to the drug *in utero*; its use during pregnancy should be avoided if possible **(AIII)**.
- Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided, if possible **(AIII)**. The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented, and these drugs might be alternatives when an aminoglycoside is required for treatment of MDR TB **(CIII)**.

- Because arthropathy has been noted in immature animals exposed to quinolones *in utero*, quinolones are typically not recommended for pregnant women or children aged <18 years **(CIII)**. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or congenital musculoskeletal abnormalities.[293,294] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII)**.[295]
- Para-aminosalicylic acid is not teratogenic in rats or rabbits.[288] 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.[296] No specific pattern of defects and no increase in rate of defects have been detected in other human studies, indicating that this agent can be used with caution, if needed **(CIII)**.
- Ethionamide has been associated with an increased risk for several anomalies in rats after high-dose exposure but not in mice and rabbits.[297-299] Case reports have documented cases of CNS defects in humans but overall experience is limited with use during human pregnancy.[300] Thus, ethionamide should be avoided unless its use is required on the basis of susceptibility testing **(CIII)**.
- No data are available from animal studies or reports of cycloserine use in humans during pregnancy.

Recommendations for Treating *Mycobacterium Tuberculosis* Infection and Disease (page 1 of 3)

Treating LTBI to Prevent TB Disease

Indications:
• 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)**
 	
Preferred Therapy:
• Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily **(AI)**
 	
Duration of Therapy:
• 9 months
 	
Alternative Therapies:
• 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 **(AII)**. **Note:** Rifapentine is only recommended for patients receiving an efavirenz- or raltegravir-based ART regimen.
  • Rifapentine Weekly Dose (maximum 900 mg)
    • *Weighing 32.1–49.9 kg:* 750 mg
    • *Weighing ≥50.0 kg:* 900 mg
• Rifampin 600 mg PO daily for 4 months **(BI)**
• For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or with public health authorities **(AII)**.

Recommendations for Treating *Mycobacterium Tuberculosis* Infection and Disease (page 2 of 3)

Treating Active TB Disease

- After collecting specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in persons 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 Table 3 (below) for TB drug dosing recommendations and to the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations of ARV drugs when used with rifampin or rifabutin.

For Drug-Sensitive TB

Intensive Phase (2 Months):

- 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.

Continuation Phase (for Drug-Susceptible TB):

- Isoniazid plus (rifampin or rifabutin) daily **(AII)**

Total Duration of Therapy:

- Pulmonary, drug-susceptible 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 w/CNS involvement: 9 to 12 months **(BII)**
- Extrapulmonary TB in other sites: 6 months **(BII)**

For Drug-Resistant TB

Empiric Therapy for Resistance to Rifamycin plus/minus Resistance to Other Drugs:

- Isoniazid plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (an aminoglycoside or capreomycin)
- Therapy should be modified once rifampin resistance is confirmed and based on drug susceptibility results to provide ≥5 active drugs.

Resistant to Isoniazid:

- (Moxifloxacin or levofloxacin) plus (rifampin or rifabutin) plus ethambutol plus pyrazinamide for 6 months **(BII)**

Resistant to Rifamycins plus/minus Other Antimycobacterial Agents:

- Therapy should be individualized based on drug susceptibility test results, clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists **(AIII)**.

Duration:

- 12 to 24 months (see the Management of Drug-Resistant TB section above for discussion of shorter course therapy)

Other Considerations in TB Management

- 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 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 table below and to the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations involving concomitant use of rifampin or rifabutin and different ARV drugs).
- If NVP is to be added to the ARV regimen of a patient who is receiving RIF, the lead-in dose for NVP should be omitted.
- Intermittent rifamycins 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
• 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. • Pre-emptive prednisone regimen: 40 mg/day for 2 weeks then 20 mg/day for 2 weeks

[a] Screening tests for LTBI include TST or IGRA; see text for details regarding these tests.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; EFV = efavirenz; IGRA = interferon-gamma release assay; LTBI = latent tuberculosis infection; NVP = nevirapine; PI = protease inhibitor; PO = orally; RAL = raltegravir; TB = tuberculosis; TST = tuberculin skin test

Table 3. 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	With HIV PIs, DOR, ETR, RPV, BIC, or EVG/c	**Not recommended**
	With TAF	Use with caution[c] at dose indicated below
	With other ARV drugs	10 mg/kg (usual dose 600 mg)
Rifabutin[a] **Note:** DOR and RPV doses need to be adjusted when used with rifabutin	With PI with COBI, TAF, BIC, or EVG/c - containing regimens	**Not recommended**
	With DTG, RAL, EFV, DOR, RPV	5 mg/kg (usual dose 300 mg)
	With HIV PIs with RTV	150 mg[d]
	With EFV	450–600 mg
Pyrazinamide	All ARVs	**Weight-Based Dosing** • *Weighing 40–55 kg:* 1,000 mg (18.2–25.0 mg/kg) • *Weighing 56–75 kg:* 1,500 mg (20.0–26.8 mg/kg) • *Weighing 76–90 kg:* 2,000 mg (22.2–26.3 mg/kg) • *Weighing >90 kg:* 2,000 mg[e]
Ethambutol	All ARVs	**Weight-Based Dosing** • *Weighing 40–55 kg:* 800 mg (14.5–20.0 mg/kg) • *Weighing 56–75 kg:* 1,200 mg (16.0–21.4 mg/kg) • *Weighing 76-90 kg:* 1,600 mg (17.8–21.1 mg/kg) • *Weighing >90 kg:* 1,600 mg[e]

[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 PK and virologic efficacy among patients taking full dose ART and TB regimens.

[d] 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 TDM when rifabutin is used with an RTV-boosted PI and adjust dose accordingly.

[e] Monitor for therapeutic response and consider TDM to assure dosage adequacy in patients weighing >90 kg.

Key: ARV = antiretroviral; ART = antiretroviral therapy; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TB = tuberculosis; TDM = therapeutic drug monitoring

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Pneumocystis Pneumonia (Last updated March 28, 2019; last reviewed October 13, 2021)

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/mm^3. 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/mm^3).[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 [PO_2] ≥70 mm Hg or alveolar-arterial PO_2 gradient [A-a] DO_2 <35 mm Hg) to moderate ([A-a] DO_2 ≥35 to <45 mm Hg) to severe ([A-a] DO_2 ≥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 **(CIII)**.

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 ≥200 cells/mm³ to ≤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 daily[45] 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 toxoplasmosis[47] 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 pentamidine[54] or dapsone[55] 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/mm^3 to >200 cells/mm^3 for >3 months **(AI)**. In observational and randomized studies whose findings support this recommendation, most patients had CD4 counts >200 cells/mm^3 for >3 months before discontinuing PCP prophylaxis.[56-65] At discontinuation of prophylaxis, the median CD4 count was >300 cells/mm^3, most participants had a CD4 cell percentage ≥14%, and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 months to 19 months.

Discontinuation of primary prophylaxis in patients with CD4 count increase to >200 cells/mm^3 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/mm^3 **(AIII)**.

A combined analysis of European cohorts,[16,66] a small randomized trial,[67] and a case series[68] found a low incidence of PCP in patients with CD4 counts between 100 cells/mm^3 and 200 cells/mm^3, who were receiving ART and had HIV plasma viral loads <50 to 400 copies/mL, and who had stopped or never received PCP prophylaxis, suggesting that primary and secondary PCP prophylaxis can be safely discontinued in patients with CD4 counts between 100 cells/mm^3 to 200 cells/mm^3 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/mm^3 to 200 cells/mm^3 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 PO_2 <70 mm Hg or PAO_2-PaO_2 ≥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 co-morbidities 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 unpredictble 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/mm^3 to >200 cells/mm^3 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/mm^3 for >3 months. At the time secondary PCP prophylaxis was discontinued, the median CD4 count was >300 cells/mm^3 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/mm^3 to 200 cells/mm^3 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/mm^3 **(AIII)** regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for patients with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 with HIV plasma viral load above detection limits of the assay used **(AIII)**. Based on results from the COHERE study, primary or secondary PCP prophylaxis may not need to be restarted in patients with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 who have had HIV plasma RNA levels below limits of detection for ≥3 to 6 months **(BII)**.[16,66]

If an episode of PCP occurs at a CD4 count >200 cells/mm^3 while a patient is on ART, it would be prudent for the patient to continue PCP prophylaxis for life, regardless of how high their CD4 cell count rises as a consequence of ART **(BIII)**. For patients in whom PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV plasma RNA levels are suppressed to below limits of detection for ≥3 to 6 months, although there are no data to support recommendations in this setting **(CIII)**.

Special Considerations 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 PO_2 <70 mm Hg or PAO_2 - PaO_2 >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/mm^3 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/mm^3 **(AI)** *or*
- CD4 percentage <14% of total lymphocyte count **(BII)** *or*
- CD4 count >200 cells/mm^3, *but* <250 cells/mm^3 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/mm^3 to ≥200 cells/mm^3 for ≥3 months in response to ART **(AI)**
- Can consider when CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months **(BII)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <100 cells/mm^3 regardless of HIV RNA **(AIII)**
- CD4 count 100–200 cells/mm^3 and HIV RNA 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)**:

- PaO_2 <70 mmHg at room air *or*
- Alveolar-arterial DO_2 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/mm^3 to >200 cells/mm^3 for >3 months as a result of ART **(BII)** *or*
- Can consider if CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months **(BII)**
- For patients in whom PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 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/mm^3 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/mm^3 regardless of HIV RNA **(AIII)**
- CD4 count 100–200 cells/mm^3 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

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Progressive Multifocal Leukoencephalopathy/JC Virus Infection

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Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] The virus has worldwide distribution, with a seroprevalence of 39% to 69% among adults.[3-6] Primary JCV infection usually occurs asymptomatically in childhood resulting in a chronic asymptomatic carrier state in most individuals. Viral DNA is detected in 20% to 30% of immunoliogically normal adults' urine.[4,7-11]

Outside the context of HIV infection, PML is rare and characteristically manifests as a complication of other immunocompromising diseases or therapies.[12-14] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab,[15] efalizumab,[16,17] and rituximab.[18] Concern has been raised about a possible increased risk of PML in HIV-infected patients treated with rituximab for non-Hodgkin lymphoma,[19,20] but no reports have yet documented PML in that setting. Chronic immunosuppression after organ transplantation is occasionally complicated by PML with a very guarded prognosis.[21]

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[22-24] and was almost invariably fatal; spontaneous remissions were rare.[25] With the widespread use of ART in the developed world, incidence of PML has decreased substantially,[26,27] and mortality in HIV-infected persons who develop the disease has declined.[28-30] Although most CNS opportunistic infections are almost wholly prevented when CD4 T-lymphocyte (CD4 cell) counts are maintained above 100 to 200 cells/mm^3 PML can still sometimes occur in patients treated effectively with ART.[2,31,32] PML can also develop in the setting of initiating ART and immune reconstitution, 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. Any region of the CNS can be involved, although some areas seem to be more favored, including the occipital lobes (with hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[12] Spinal cord involvement is rare and the optic nerves are not involved.[34] Although lesions can be multiple, one is often 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. The focal or multifocal nature of the pathology is responsible for the consistency of clinical presentations with distinct focal symptoms and signs, rather than as a more diffuse encephalopathy, or isolated dementia or behavioral syndrome, all of which are uncommon without concomitant focal findings.[35]

The time course of this 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 MRI. While rather sudden onset of a focal brain lesion can mimic strokes, the gradually progressive course should rapidly make this diagnosis unlikely with subsequent diagnostic evaluations undertaken to identify PML. Headache and fever are not characteristic of the disease, and when present may indicate presence of another opportunistic infection. Seizures develop in nearly 20% of PML patients 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 magnetic resonance imaging (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 help distinguish lesions due to PML from other pathologies, including the white matter lesions of HIV encephalitis. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident. 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 and magenetic resonance (MR) spectroscopy, may provide additional diagnostic information.[38-40] New PML lesions and the advancing edge of large lesions have high signal on diffusion-weighted imaging and 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.[41] 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. Confirming the diagnosis, however, is invaluable. Certainly for atypical cases but even for typical cases, confirmation allows physicians to initiate ART rapidly and with certainty and prevents the need to revisit the diagnosis when disease progression continues. Confirmed diagnosis also informs discussions of prognosis.

The usual first step in confirming the diagnosis is to test cerebrospinal fluid (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.[9,42] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[43] 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.[44,45] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded (e.g., by PCR analyses of CSF for varicella zoster virus and Epstein-Barr virus for varicella zoster virus encephalitis and primary CNS lymphoma, respectively). 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 labs 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.[46] Analysis of plasma samples for detection of JCV by PCR when positive are relatively specific for PML (~92% in HIV patients), while the sensitivity is less than 40% in this setting.[47]

In some instances, brain biopsy is required to establish the diagnosis. PML can usually 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.[12,48,49]

Serologic testing is generally 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 JC virus specific antibody titers[50] and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[51] but requires further prospective study.

Preventing Exposure

JCV has a worldwide distribution and, as previously noted, 20% to 60% of people exhibit serologic evidence of exposure by their late teens.[52] Currently, there is no known way to prevent exposure to the virus.

Preventing Disease

In many individuals, JCV infection is likely latent and intermittently productive, although clinically silent, in the kidney or other systemic 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 CNS.[53,54] Protection is conferred by either preventing spread to the CNS or by preventing active viral replication with effective immunosurveillance. Therefore, the only effective way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII)**.

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. In patients with PML who are not on therapy, ART should be started immediately **(AII)**. In this setting, more than half of HIV-infected PML patients experience a remission in which disease progression stops. Neurological deficits often persist, but some patients experience clinical improvement.[28,29,55-60] 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.[60] 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-to-severe disability.[61] Peripheral blood CD4 cell count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm^3 compared with patients who had higher CD4 cell counts. In other case series, worse prognosis was also associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and the presence of lesions in the brain stem.[29,32,56,57,59,60,62] Contrast enhancement on imaging may predict better outcome, as it is indicative of an immune response to the virus.[31] In PML occurring in multiple sclerosis patients, younger age, more restricted unilobar disease, and lower CSF JCV DNA copy numbers are associated with better outcomes.[63]

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 patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher than anticipated survival,64 but it has not yet been followed by a full report or structured trial. Therefore, there is no evidence supporting ART intensification for PML.

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.[65] One report found that at the beginning of the combination ART era, 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.[66] 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.[67,68]

The history of more specifically targeted treatments for PML includes many anecdotal reports of success that have not been confirmed by controlled studies. 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.[69] 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.[43,58-60,70] Thus, treatment with cidofovir is also **not recommended** **(AII)**. A lipid-ester derivative, hexadecyloxypropyl-cidofovir, recently has been reported to suppress JCV replication in cell culture,[71] but its efficacy in HIV-associated PML is unknown.

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,[72,73] drugs that block the 5HT2a receptor, including olanzapine, zisprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[74] although the rationale for this practice has been questioned.[75] Again, anecdotes about favorable outcomes[1,76-79] 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 this class of drugs **is not recommended** **(BIII)**.

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[80] 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.[81] At this time, topotecan also **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.[82] Mefloquine **cannot be recommended**.

Immunomodulatory approaches to the treatment of PML in HIV-infected patients have also 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,[83] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha **is not recommended** **(BIII)**.[84] A single report described failure of interferon-beta treatment of HIV-associated PML[85] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[15] 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.[86-88] Like the other reports, these too have not been followed up with more substantial trials. 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.[89-93]

Special Considerations with Regard to Starting ART

ART should be started in patients not on HIV treatment as soon as PML is recognized **(AII)**. For patients already on treatment who have demonstrated plasma HIV viremia and are adherent to therapy, ART should be adjusted based on plasma virus susceptibility **(AII)**.

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

Treatment response should be monitored with clinical examination and MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantitation 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. Often clinical deterioration is seen before stabilization and improvement occurs.[94] 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.

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[2,32,33,95-97] 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.[98,99] As with other presentations of IRIS, it is more likely after advanced HIV with low CD4 counts, and with greater decline in HIV viral load on initiation of ARV. This presentation has been referred to as inflammatory PML or PML-immune reconstitution inflammatory syndrome (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.[100-103] 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, but other undefined factors also may contribute to unmasked PML-IRIS.

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.[2,96,104] 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 appears justified characterized by contrast enhancement, edema or mass effect, and 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 can 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 at the standard therapeutic doses during this period **(AIII)**.

Several case reports suggest that maraviroc might be beneficial for PML-IRIS,[105] 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.[105-108]

Although some clinicians may want to use adjuvant corticosteroid therapy to treat all cases of PML regardless of whether there is evidence of IRIS, this action is not justified and should be discouraged in patients who have no evidence of substantial inflammation on contrast-enhanced neuroimaging or on pathological examination **(CIII)**. In patients whose condition worsens, imaging can be repeated to monitor for development of IRIS before initiating corticosteroids.

Managing Treatment Failure

PML remission can take several weeks and there are no strict criteria to define treatment failure. However, a working definition may be continued clinical worsening and continued detection of CSF JCV without substantial decrease within 3 months of initiating of ART. Changes in plasma HIV RNA levels and blood CD4 cell count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for the use of ART. When PML continues to worsen despite fully suppressive anti-HIV treatment, one of the unproven therapies described above can be considered, although the possibility of toxicity must be balanced against the unproven benefits of these treatments.

Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence.[58,109] 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 cell counts **(AII)**.

Special Considerations During Pregnancy

Diagnostic evaluation of PML should be the same in pregnant women as in women who are not pregnant. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen. If corticosteroid therapy is initiated during pregnancy, blood sugar monitoring should be included as insulin resistance is increased during pregnancy.

Recommendations for Preventing and Treating PML and JCV

- There is no effective antiviral therapy for preventing or treating JCV infections or PML.
- The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART.
- HIV-associated PML is often complicated by clinically significant IRIS that may require administration of corticosteroid therapy.
- In ART-naive patients who are diagnosed with PML, ART should be 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)**.

Key to Acronyms: ART = antiretroviral therapy; JCV = JC virus; PML = progressive multifocal leukoencephalopathy.

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Syphilis (Last updated December 17, 2015; last reviewed October 13, 2021)

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 immunosupression.[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 intertrigenous 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 syphilis[48] 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/mm^3 or in combination with RPR titers ≥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/mm^3), 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]/mm^3); using a higher cutoff (>20 WBC/ mm^3) 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 seroversion or a fold four 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 ≤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 (≥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 [≥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 ≥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 ceftriaxone[105] 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.

Recommendations for Treating *Treponema pallidum* Infections (Syphilis) to Prevent Disease (page 2 of 2)

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 **(AII)**

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 **(AII)**

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 **(AII)**

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 **(AII)**

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 **(AII)** +/- 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 **(AIII)**.

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 = intraveneously; MSM = men who have sex with men; PO = orally; QID = four times a day; q(n)h = every “n” hours; U = Units

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Talaromycosis (Last updated November 21, 2019; last reviewed October 13, 2021)

Epidemiology

Talaromycosis is an invasive fungal infection caused by the dimorphic fungus *Talaromyces marneffei* (formerly *Penicillium marneffei*) which is endemic in Southeast Asia (in northern Thailand, Vietnam, and Myanmar), East Asia (in southern China, Hong Kong, and Taiwan), and South Asia (in northeastern India) (see the geographic distribution of talaromycosis in Figure 1).[1-4] *Talaromyces marneffei* was formerly classified under the *Penicillium* subgenus *Biverticillium* based on morphological characteristics. In 2011, the subgenus *Biverticillium* was found to form a monophyletic group with *Talaromyces* that is distinct from *Penicillium*, and was taxonomically unified with the *Talaromyces* genus.[5] Hence, *Penicillium marneffei* was changed to *Talaromyces marneffei*, and the disease penicilliosis is now called talaromycosis.

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/mm^3.[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 saprozoonotic 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. marneffei*;[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/mm^3.[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/mm^3 who have traveled to or have lived in talaromycosis-endemic areas and present with a systemic infection involving the reticuloendothelial system (i.e., lymph nodes, liver, spleen, and bone marrow).

Skin lesions in talaromycosis 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 25ºC to 30ºC, 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 32ºC to 37ºC, the fungus makes the morphological transition from a mold to a yeast, producing tan colored colonies without a red diffusible pigment. In laboratory media, only the transitional sausage-shaped cells can be seen microscopically. The round-to-oval yeast cells are only seen in natural tissue.[1]

Culture yield is the highest from bone marrow (100%), followed by skin lesions (90%) and blood (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/mm^3 to 50 cells/mm^3, 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/mm^3. 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. marneffei*.

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/mm^3 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/mm^3.[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/mm^3 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/mm^3, 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/mm^3 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 China[51-54] 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 Thailand[53] 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/mm^3 or ≥ 50 cells/mm^3), 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/mm^3 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 µg/mL for itraconazole and >1 µg/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 mortality[55] 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/mm^3.[60]

Therefore, secondary prophylaxis for talaromycosis can be discontinued in patients who are ART adherent and have CD4 counts >100 cells/mm^3 for at least 6 months **(BII)**.

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/mm^3 **(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 every12 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 Talaromycosis

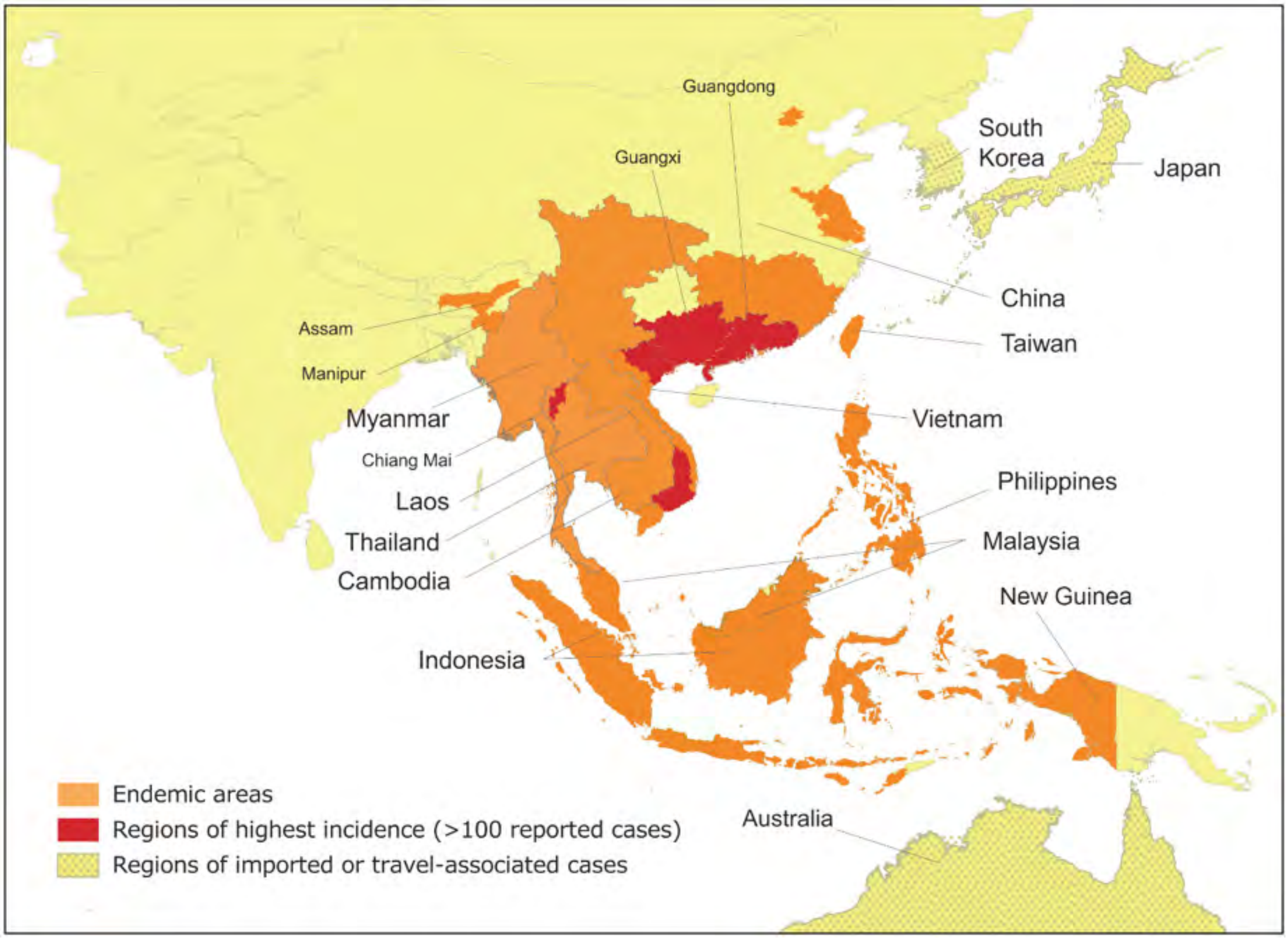

Figure courtesy of Dr. Thuy Le, Division of Infectious Diseases and International Health, Duke University School of Medicine

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Toxoplasma gondii Encephalitis (Last updated July 25, 2017; last reviewed October 13, 2021)

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 tomography[13] or single-photon emission computed tomography scanning[14] 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/µL for more than 3 months **(AI)**. Multiple observational studies[31-33] 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/µL to >200 cells/µL 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/µL. 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/µL 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/µL. Thus, the recommendation specifies discontinuing prophylaxis after an increase to >200 cells/µL. When CD4 counts are >200 cells/µL 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 PCP[71] **(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 Therappy

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/µL 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/mm^3 **(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/mm^3 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/µL 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/µL, and recurrent TE can be debilitating and potentially life-threatening, maintenance therapy should be reintroduced if the CD4 count decreases to <200 cells/µL **(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 congential 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, spiramcyin 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). Spiramcyn 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 are no studies published to date link 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/mm[3] **(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/mm[3] for >3 months in response to ART **(AI)**; *or*
- Can consider if CD4 count is 100-200 cells/mm[3] 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/mm[3] **(AIII)**

Recommendations for Preventing and Treating *Toxoplasma gondii* Encephalitis (page 2 of 2)

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 pyrimethamineb-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] (BII), *or*
- Atovaquone[b] 1500 mg PO BID + sulfadiazined **(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/mm^3 for >6 months in response to ART **(BI)**

Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance

- CD4 count <200 cells/mm^3 **(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 administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

[b] Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

[c] Pyrimethamine and leucovorin doses: Same 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

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Varicella-Zoster Virus Diseases

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Epidemiology

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella-zoster virus (VZV), mostly due to primary VZV infection, known as varicella (or chickenpox).[1] A varicella vaccine became available in the United States in 1995; most children born in the United States after 2005 are immune to varicella as a result of vaccination.[2] Reactivation of latent VZV results in herpes zoster (shingles). In the general population, the incidence of herpes zoster is about 3.6 cases per 1,000 person-years, with much higher incidence seen among elderly and immunocompromised individuals. Before the availability of antiretroviral therapy (ART), the incidence of herpes zoster was more than 15-fold higher among adults with HIV than among age-matched controls without HIV.[3,4] Herpes zoster can occur in adults with HIV at any CD4 T lymphocyte (CD4) cell count, but with CD4 counts <200 cells/mm^3, the risk of disease is higher.[5-8] In addition, HIV viremia is associated with an increased risk for incident herpes zoster.[9] ART has been shown to reduce the incidence of herpes zoster in adults with HIV, presumably because of immune restoration, although the risk of herpes zoster remains threefold higher in adults with HIV than in the general population.[7,10-13] Several studies have demonstrated that the risk of herpes zoster in adults with HIV is increased in the 6-month period immediately after initiation of ART, possibly because of an immune reconstitution inflammatory syndrome (IRIS)-related mechanism.[7,10,13,14]

Clinical Manifestations

Varicella rash tends to have a central distribution, with lesions first appearing on the head, then the trunk, and finally the extremities, evolving through stages of macules, papules, vesicles, pustules, and crusts. The rash is characterized by rapid evolution of lesions during the initial 8 to 12 hours after onset, by successive crops of new lesions, and by the presence of lesions in different stages of development. New vesicle formation continues for 2 to 4 days, accompanied by pruritus, fever, headache, malaise, and anorexia.[15] Primary varicella can cause substantial morbidity in adolescents and adults with HIV. Visceral dissemination, especially VZV pneumonitis, is well documented.[15] Because most adults with HIV in the United States are VZV seropositive, primary varicella is an uncommon occurrence in this population.

Herpes zoster manifests as a painful cutaneous eruption in a dermatomal distribution, often preceded by prodromal pain. The most common sites for herpes zoster are the thoracic dermatomes (40% to 50% of cases), followed by cranial nerve (20% to 25%), cervical (15% to 20%), lumbar (15%), and sacral (5%) dermatomes.[16] Skin changes begin with an erythematous maculopapular rash, followed by the appearance of clear vesicles and accompanied by pain, which may be severe. New vesicle formation typically continues for 3 to 5 days, followed by lesion pustulation and scabbing. Crusts typically persist for 2 to 3 weeks. About 20% to 30% of people with HIV have one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes. The probability of a recurrence of herpes zoster within 1 year of the index episode is approximately 10%.[5,17] Approximately 10% to 15% of people with HIV report post-herpetic neuralgia as a complication following herpes zoster.[5,18]

When herpes zoster involves the nasociliary branch of the trigeminal nerve, the eye can be affected (herpes zoster ophthalmicus [HZO]), resulting in keratitis (inflammation of the cornea) or anterior uveitis (inflammation of the iris and anterior ciliary body) or both. Vesicles on the tip of the nose (Hutchinson sign) are a clue that the nasociliary branch is involved. With corneal involvement, there may be an initial brief period during which the corneal epithelium is infected with VZV, but the major problem is inflammation of the corneal stroma, which can result in scarring, neovascularization, or necrosis with loss of vision. Stromal keratitis can be chronic. Once it occurs, VZV-associated anterior uveitis also tends to be chronic and can result in increased intraocular pressure or glaucoma, scarring of intraocular tissues, and cataract.

Stromal keratitis and anterior uveitis may not develop immediately after the appearance of skin vesicles on the forehead and scalp; therefore, patients with normal eye examinations initially should receive follow-up eye examinations, even after the skin lesions heal. Antiviral treatment of herpes zoster at the onset of cutaneous lesions reduces the incidence and severity of ophthalmic involvement.

Some patients with HZO may develop late dendriform lesions of the corneal epithelium that contain virus and will respond rapidly to systemic or topical anti-herpetic medications. These lesions are usually painful. In one study, the median time from onset of HZO to development of late dendriform lesions was 5 months, and the risk of recurrences decreased over time.[19] The frequency with which these late infectious lesions occur has not been determined.

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN occurs almost exclusively[22] in patients with AIDS with CD4 counts <100 cells/mm^3. In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of occlusive retinal vasculitis, and multiple discrete peripheral lesions that manifest initially as yellow foci of retinal opacification in the outer retinal layers.[23] PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.[24] Both ARN and PORN are associated with high rates of loss of vision.

People with HIV who have CD4 counts <200 cells/mm^3 are at highest risk of herpes zoster–related complications, including disseminated herpes zoster.[20] The central nervous system (CNS) is a target organ for herpes zoster dissemination in patients coinfected with HIV. Various VZV-related neurologic syndromes occur in people with HIV, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.[21]

Diagnosis

Varicella and herpes zoster are typically distinctive in appearance and usually can be diagnosed clinically. Varicella also can be diagnosed retrospectively by documenting seroconversion (i.e., immunoglobulin G [IgG] antibody negative to positive). In immunocompromised persons, varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); a history of VZV exposure, a rash that began with a dermatomal pattern, and VZV serologic testing to assess prior VZV infection may be helpful to distinguish disseminated herpes zoster from varicella. When lesions are atypical or difficult to distinguish from those due to other potential etiologies (including herpes simplex virus [HSV]), swabs of vesicular fluid from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase chain reaction (PCR). Additionally, scabs may be adequate specimens for PCR testing. PCR of lesions is the most sensitive and specific method for diagnosis of VZV infections. Histopathology and PCR (of blood or fluids, such as cerebrospinal fluid or vitreous humor) can aid with diagnosis of VZV infections of visceral organs (e.g., pneumonitis, encephalitis, retinitis).[25]

Preventing Exposure

People with HIV who are susceptible to VZV (i.e., people who have no history of chickenpox or shingles, who are seronegative for VZV, and who have no history of vaccination against VZV) should avoid exposure to individuals with varicella or herpes zoster **(CIII)**.

Household contacts of people with HIV without evidence of immunity to VZV should be vaccinated to prevent acquisition of varicella and potential transmission of wild-type VZV to susceptible contacts with HIV **(BIII)**.

Preventing Disease

Vaccination to Prevent Primary Infection (Varicella)

The live attenuated varicella vaccine (Varivax®) has been documented to be safe and immunogenic in children with HIV who have relatively preserved immune systems (CD4 percentage ≥15%)[26-29] and is recommended for this population of children with HIV.[30] Varicella vaccination of children with HIV also reduces the risk of subsequent herpes zoster.[29,31]

VZV-seronegative adults are potential candidates for varicella vaccination. Some experts would serologically screen adults with HIV without a history of prior varicella or varicella vaccination for VZV IgG. However, the value of this approach may be limited by the lack of sensitivity of commercially available VZV antibody assays (particularly for vaccine-induced antibody).[32,33] No studies have evaluated the vaccine in adolescents or adults with HIV, but many experts recommend varicella vaccination (2 doses, administered 3 months apart) for VZV-susceptible people with HIV aged ≥8 years with CD4 counts ≥200 cells/mm^3 **(BIII)**.[34] If varicella vaccination results in disease caused by vaccine virus (a rare event), therapy with acyclovir is recommended **(AIII)**. Administration of varicella vaccine to more severely immunocompromised people with HIV (CD4 counts <200 cells/mm^3) is **<u>contraindicated</u>** **(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 **<u>is not recommended</u>** **(AIII)**.

Post-Exposure Prophylaxis to Prevent Primary Infection (Varicella)

For people with HIV who are susceptible to VZV, post-exposure prophylaxis following known or suspected VZV exposure is recommended **(AII)**. After close contact with a person who has active varicella or herpes zoster, adolescents and adults with HIV who are susceptible to VZV (particularly those with CD4 counts <200 cells/mm^3) should receive VariZIG as soon as possible (preferably within 96 hours), but up to 10 days after exposure **(AIII)**.[36] Given the cost of obtaining VariZIG, it is reasonable to check VZV serology before administering VariZIG to people who do not have a clinical history of chickenpox or shingles and no documentation of varicella vaccination **(AIII)**. The risk of VZV transmission is greater with exposure to varicella than localized herpes zoster. In the United States, VariZIG is commercially available from a broad network of specialty distributers (listed at: www.varizig.com). The duration of protection from VariZIG is at least 3 weeks. Patients receiving monthly infusions of high-dose intravenous immune globulin (IVIG >400 mg/kg) are likely to be protected and probably do not require VariZIG if they received a dose of IVIG <3 weeks before VZV exposure. A 5- to 7-day course of post-exposure acyclovir or valacyclovir beginning 7 to 10 days after exposure is recommended by some experts to prevent varicella among VZV-susceptible adolescents or adults with HIV, but this intervention has not been studied in these populations **(BIII)**.[37] Among VZV-susceptible immunocompetent children, post-exposure varicella vaccination has been shown to reduce the risk for varicella and is more effective than pre-emptive therapy with antiviral drugs; however, the efficacy of post-exposure varicella vaccination for people with HIV has not been studied and **is not recommended.**

Antiviral Prophylaxis to Prevent Re-Activation Disease (Herpes Zoster)

Long-term administration of anti-VZV drugs to individuals with HIV to prevent episodes of herpes zoster is not routinely recommended **(AII)**. However, in a randomized, placebo-controlled study in Africa that evaluated daily acyclovir prophylaxis (acyclovir 400 mg orally [PO] twice a day) administered to people with HIV/HSV-2 coinfection who were not taking ART, acyclovir prophylaxis reduced the rate of herpes zoster by 62%.[38] Acyclovir did not prevent recurrent zoster episodes in patients with prior history of herpes zoster.[38] People with HIV who are taking suppressive anti-herpes medications (i.e., acyclovir, valacyclovir, or famciclovir) for other indications—such as prevention of genital herpes—may receive some additional benefit in reduction of risk of herpes zoster, but the relative risk reduction in people who are receiving ART is unknown.

Vaccination to Prevent Reactivation Disease (Herpes Zoster)

One 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 $AS01_B$ (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 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, and to date ACIP has not recommended the use of RZV in people with HIV. A Phase 1/2 randomized, placebo-controlled study enrolled 94 adults with HIV receiving ART[43] with CD4 count ≥200 cells/mm^3, 14 adults receiving ART with CD4 count <200 cells/mm^3, and 15 ART-naive adults with CD4 count ≥500 cells/mm^3. The participants' median age was 46 years. Participants received the vaccine in three doses administered at 0, 2, and

6 months. The vaccine increased humoral and cell-mediated immunity to VZV gE after two doses, including among people with CD4 counts <200 cells/mm^3. The most common side effects included pain at the injection sites (98.6% of participants, 16.4% Grade 3), fatigue (75.3%, 16.4% Grade 3), myalgia (74.0%, 13.7% Grade 3), and headache (64.4%, 8.2% Grade 3). No vaccine-related severe adverse events occurred during follow-up. Based on these very limited data in people with HIV, the vaccine appears safe and immunogenic. No efficacy data are available for the RZV among people with HIV.

Given that the risk of herpes zoster is high among people with HIV, and the vaccine appears safe, experts recommend administration of RZV to people with HIV aged ≥50 years, following the FDA-approved schedule for persons without HIV (intramuscular [IM] dose at 0 and 2 months) **(AIII)**.

No data identify the optimal timing of vaccination for persons who have a CD4 count <200 cells/mm^3 or who are not suppressed virologically on ART. Following initiation of ART, some experts would administer the RZV vaccination series after CD4 count recovery **(CIII)**, and others would administer the series after virologic suppression was achieved **(CIII)**. No efficacy data guide RZV vaccination in people with HIV aged <50 years given the following:

- Clinical trial experience demonstrating safety in immunocompetent persons <50 years is limited, *and*
- The duration of protection is not known.

Thus, at this time, RZV **is not recommended** for people with HIV aged <50 years. RZV is not a treatment for 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 is 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.

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)**.[15,48,49] 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)**.[50]

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)**.[51] 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;[52,53] **(AIII)** however, many ophthalmologists and infectious disease specialists will continue oral antiviral therapy for much longer. Many experts would also include an intravitreous injection of ganciclovir as part of the initial induction therapy. Additional intravitreous injections can be given if there is concern for lack of treatment response, but injections should not be more frequent than twice weekly **(BIII)**.Use of oral valaciclovir instead of IV acyclovir for initial treatment has been reported. This approach should be used with caution because serum drug levels with oral treatment will not be as high as those achieved with IV administration **(CIII)**. Involvement of an experienced ophthalmologist in the management of patients with VZV ocular disease is strongly recommended **(AIII)**.

Optimal antiviral therapy for PORN remains undefined and should be managed in consultation with an experienced ophthalmologist **(AIII)**.[54-56] 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.[24,55,57] 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)**.[57,58] 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.[7,13,14,59,60] 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)**.[61] 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.[62] 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.[62] 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 with CD4 counts ≥200 cells/mm³, administer primary varicella vaccination (Varivax™) in two doses (0.5 mL SQ) 3 months apart (**CIII**). • 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 <u>contraindicated</u> (**AIII**).
Post-Exposure Prophylaxis of VZV Primary Infection *Indications* • Close contact with a person who has active varicella or herpes zoster, and • Susceptible to VZV (i.e., no history of varicella vaccination, no history of varicella or herpes zoster, or known to be VZV seronegative) *Preferred Prophylaxis* • VariZIG 125 IU/10 kg (maximum of 625 IU) IM, administered as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster (**AIII**) • If post-exposure VariZIG has been administered, wait ≥5 months before varicella vaccination (**CIII**). **Note:** Patients receiving monthly high-dose IVIG (i.e., >400 mg/kg) are likely protected against VZV and probably do not require VariZIG if the last dose of IVIG they received was administered <3 weeks before VZV exposure. *Alternative Prophylaxis (Begin 7 to 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.
Preventing Herpes Zoster (Shingles)

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections
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 ≥50 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 to10 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

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections
• 7 to10 days; longer duration should be considered if lesions resolve slowly *Herpes Zoster Ophthalmitis (HZO)* Late dendriform lesions of the corneal epithelium should be treated with systemic or topical anti-herpetic medications (AIII). Extensive Cutaneous Lesion or Visceral Involvement • Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident (AII). • Switch to oral therapy (valacyclovir 1 g 3 times a day, famciclovir 500 mg 3 times a day, or acyclovir 800 mg PO 5 times daily to complete a 10- to 14-day course) when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving (BIII). *Acute Retinal Necrosis (ARN)* • Acyclovir 10mg/kg IV every 8 hours for 10 to 14 days, followed by valacyclovir 1 g PO 3 times a day for ≥14 weeks (AIII). In addition, an intravitreous injection of ganciclovir (2 mg/0.05mL) 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 cell; 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

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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 Living with HIV section.

(Last reviewed and updated December 10, 2021)

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/µL (**BIII**)	Fluconazole 400 mg PO daily (**BIII**)	
Histoplasma capsulatum infection	CD4 count ≤150 cells/µL and at high risk because of occupational exposure or live 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.	
Mycobacterium avium complex (MAC) disease	CD4 Count <50 cells/mm³ **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**), *or* Clarithromycin 500 mg PO BID (**AI**), *or* Azithromycin 600 mg PO twice weekly (**BIII**)	Rifabutin (dose adjusted based on concomitant ART)[a] (**BI**); rule out active TB before starting rifabutin.

Opportunistic Infections	Indication	Preferred	Alternative
Mycobacterium tuberculosis infection (TB) (i.e., treatment of latent TB infection [LTBI])	Positive screening test for LTBI,[b] with no evidence of active TB, and no prior treatment for active TB or LTBI (AI), *or* Close contact with a person with infectious TB, with no evidence of active TB, regardless of screening test results (AI)	(INH 300 mg plus pyridoxine 25–50 mg) PO daily for 9 months (AII), *or* 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).	Rifapentine (see dose below) PO plus INH 900 mg PO plus pyridoxine 50 mg PO once weekly for 12 weeks (AII) **Note:** Rifapentine is recommended only for persons receiving RAL or an EFV-based ART regimen *Rifapentine Weekly Dose* *Weighing 32.1 to 49.9 kg* • 750 mg *Weighing >50 kg* • 900 mg, *or* • Rifampin 600 mg PO daily for 4 months (BI), *or* • For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or public health authorities (AII).
Pneumocystis Pneumonia (PCP)	CD4 count <200 cells/mm^3 (AI), *or* CD4 <14% (BII), *or* If ART initiation must be delayed, CD4 count ≥200 cells/mm^3, but <250 cells/mm^3 and if monitoring of CD4 cell count every 3 months is not possible (BII) **Note:** Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII).	TMP-SMX[c] 1 DS tablet PO daily (AI), *or* TMP-SMX[c] 1 SS tablet daily (AI)	• TMP-SMX[c] 1 DS PO three times weekly (BI), *or* • Dapsone[d] 100 mg PO daily or 50 mg PO BID (BI), *or* • Dapsone[d] 50 mg PO daily with (pyrimethamine[e] 50 mg plus leucovorin 25 mg) PO weekly (BI), *or* • (Dapsone[d] 200 mg plus pyrimethamine[e] 75 mg plus leucovorin 25 mg) PO weekly (BI); *or* • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month (BI), *or* • Atovaquone 1,500 mg PO daily (BI), *or* • (Atovaquone 1,500 mg plus pyrimethamine[e] 25 mg plus leucovorin 10 mg) PO daily (CIII)

Opportunistic Infections	Indication	Preferred	Alternative
Syphilis	For individuals exposed to a sex partner with a diagnosis of primary, secondary, or early latent syphilis within the past 90 days (AII), *or* 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)	Benzathine penicillin G 2.4 million units IM for 1 dose (AII)	For penicillin-allergic patients: • Doxycycline 100 mg PO BID for 14 days (BII), *or* • Ceftriaxone 1 g IM or IV daily for 8–10 days (BII), *or* • Azithromycin 2 g PO for 1 dose (BII)—**not recommended** for men who have sex with men or pregnant people (AII)
Talaromycosis (Penicilliosis)	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— • Who reside in the highly endemic regions* in northern Thailand, northern or southern Vietnam, or southern China (BI), *or* • Who are from countries outside of the endemic region, and must travel to the region (BIII) * Particularly in highland regions during the rainy and humid months	For persons who reside in endemic areas, itraconazole 200 mg PO once daily (BI). 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).	For persons who reside in endemic areas, fluconazole 400 mg PO once weekly (BII). 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).
Toxoplasma gondii encephalitis	Toxoplasma IgG-positive patients with CD4 count <100 cells/µL (AII) **Note:** All regimens recommended for primary prophylaxis against toxoplasmosis also are effective as PCP prophylaxis.	TMP-SMX[a] 1 DS PO daily (AII)	• TMP-SMX[c] 1 DS PO three times weekly (BIII), *or* • TMP-SMX[c] 1 SS PO daily (BIII), *or* • Dapsone[d] 50 mg PO daily plus (pyrimethamine[e] 50 mg plus leucovorin 25 mg) PO weekly (BI), *or* • (Dapsone[d] 200 mg plus pyrimethamine[e] 75 mg plus leucovorin 25 mg) PO weekly (BI), *or* • Atovaquone 1500 mg PO daily (CIII), *or* • (Atovaquone 1500 mg plus pyrimethamine[e] 25 mg plus leucovorin 10 mg) PO daily (CIII)

[a] Refer to the Drug-Drug Interactions section in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations.

[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 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 Systems for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Opportunistic Infection Guidelines.

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; EFV = efavirenz; G6PD = glucose-6-phosphate dehydrogenase; 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 AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 1 of 21) (Last updated July 1, 2021; last reviewed April 14, 2021)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections	**Empiric therapy pending definitive diagnosis**	Diagnostic fecal specimens should be obtained before initiation of empiric antibiotic therapy. If culture is positive, antibiotic susceptibilities should be performed to inform antibiotic choices given increased reports of antibiotic resistance. If a culture independent diagnostic test is positive, reflex cultures for antibiotic susceptibilities should also be done. Empiric antibiotic therapy is indicated for advanced HIV patients (CD4 count <200 cells/µL or concomitant AIDS-defining illnesses), with clinically severe diarrhea (≥6 stools/day or bloody stool) and/or accompanying fever or chills. Empiric Therapy: • Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)** Therapy should be adjusted based on the results of diagnostic work-up. For patients with chronic diarrhea (>14 days) without severe clinical signs, empiric antibiotics therapy is not necessary, can withhold treatment until a diagnosis is made.	Empiric Therapy: • Ceftriaxone 1 g IV q24h **(BIII)**, *or* • Cefotaxime 1 g IV q8h **(BIII)**	Oral or IV rehydration (if indicated) should be given to patients with diarrhea **(AIII)**. Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including *Clostridium-difficile*-associated diarrhea **(BIII)**. If no clinical response after 3-4 days, consider follow-up stool culture with antibiotic susceptibility testing or alternative diagnostic tests (e.g., toxin assays, molecular testing) to evaluate alternative diagnosis, antibiotic resistance, or drug-drug interactions. IV antibiotics and hospitalization should be considered in patients with marked nausea, vomiting, diarrhea, electrolyte abnormalities, acidosis, and blood pressure instability.
	Campylo-bacteriosis	For Mild Disease and If CD4 Count >200 cells/µL: • No therapy unless symptoms persist for more than several days **(CIII)** For Mild-to-Moderate Disease Disease (If Susceptible): • Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)**, *or* • Azithromycin 500 mg PO daily **(BIII)** (Note**:** Not for patients with bacteremia **(AIII)**) For *Campylobacter* Bacteremia: • Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(BIII)** + an aminoglycoside **(BIII)** Duration of Therapy: • *Gastroenteritis:* 7–10 days **(AIII)** (5 days with azithromycin) • *Bacteremia:* ≥14 days **(BIII)** • *Recurrent bacteremia:* 2–6 weeks **(BIII)**	For Mild-to-Moderate Disease (If Susceptible): • Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or* • Moxifloxacin 400 mg (PO or IV) q24h **(BIII)** Add an aminoglycoside to fluoroquinolone in bacteremic patients **(BIII)**.	Oral or IV rehydration if indicated **(AIII)**. Antimotility agents should be avoided **(BIII)**. If no clinical response after 5–7 days, consider follow-up stool culture, alternative diagnosis, or antibiotic resistance. There is an increasing rate of fluoroquinolone resistance in the United States (24% resistance in 2011). The rationale of addition of an aminoglycoside to a fluoroquinolone in bacteremic patients is to prevent emergence of quinolone resistance. Effective ART may reduce the frequency, severity, and recurrence of campylobacter infections.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

<table>
<tr><th colspan="2">Opportunistic Infection</th><th>Preferred Therapy</th><th>Alternative Therapy</th><th>Other Comments</th></tr>
<tr><td rowspan="3">Bacterial Enteric Infections, continued</td><td>Clostridium difficile Infection (CDI)</td><td>Vancomycin 125 mg (PO) QID for 10–14 days (AI)

For severe, life-threatening CDI, see text and references for additional information.</td><td><u>For mild, outpatient disease:</u>

Metronidazole 500 mg (PO) TID for 10–14 days (CII).</td><td>Recurrent CDI:

Treatment is the same as in patients without HIV infection. Fecal microbiota therapy may be successful and safe to treat recurrent CDI in HIV-infected patients (CIII). See text and references for additional information.</td></tr>
<tr><td rowspan="2">Salmon-ellosis</td><td colspan="2">All HIV-infected patients with salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20-100 fold) and mortality (by up to 7-fold) compared to HIV-negative individuals (AIII).</td><td rowspan="2">Oral or IV rehydration if indicated (AIII).

Antimotility agents should be avoided (BIII).

The role of long-term secondary prophylaxis in patients with recurrent Salmonella bacteremia is not well established. Must weigh benefit against risks of long-term antibiotic exposure (BIII).

Effective ART may reduce the frequency, severity, and recurrence of salmonella infections.</td></tr>
<tr><td>• Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h, if susceptible (AIII)

<u>Duration of Therapy</u>:

For gastroenteritis without bacteremia:
• If CD4 count ≥200 cells/µL: 7–14 days (BIII)
• If CD4 count <200 cells/µL: 2–6 weeks (BIII)

For gastroenteritis with bacteremia:
• If CD4 count ≥200 cells/µL: 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/µL: 2–6 weeks (BIII)

<u>Secondary Prophylaxis Should Be Considered For</u>:
• Patients with recurrent Salmonella gastroenteritis +/- bacteremia (CIII), or
• Patients with CD4 <200 cells/µL with severe diarrhea (CIII)</td><td>• Levofloxacin 750 mg (PO or IV) q24h (BIII), or
• Moxifloxacin 400 mg (PO or IV) q24h (BIII), or
• TMP 160 mg-SMX 800 mg (PO or IV) q12h (BIII), or
• Ceftriaxone 1 g IV q24h (BIII), or
• Cefotaxime 1 g IV q8h (BIII)</td></tr>
</table>

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 3 of 21)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections, *continued*	**Shigellosis**	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)** <u>Duration of Therapy</u>: • *Gastroenteritis:* 7–10 days **(AIII)** (if azithromycin is used, treat for 5 days) • *Bacteremia:* ≥14 days **(BIII)** • *Recurrent Infections:* up to 6 weeks **(BIII)** **Note:** Increased resistance of *Shigella* to fluoroquinolones is occurring in the United States. Avoid 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 HIV-infected individuals should be performed routinely.	• Levofloxacin 750 mg (PO or IV) q24h **(BIII)**, *or* • Moxifloxacin 400 mg (PO or IV) q24h **(BIII)**, *or* • TMP 160 mg-SMX 800 mg (PO or IV) q12h **(BIII)** (Note**:** *Shigella* 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**:** azithromycin is not recommended for patients with bacteremia **[AIII]**) **Note:** Azithromycin-resistant *Shigella spp* has been reported in HIV-infected MSM.	Therapy is indicated both to shorten duration of illness and prevent spread of infection **(AIII)**. Given increasing antimicrobial resistance and limited data showing that antibiotic therapy limits transmission, antibiotic treatment may be withheld in patients with CD4 >500 cells/mm^3 whose diarrhea resolves prior to culture confirmation of *Shigella* infection **(CIII)**. Oral or IV rehydration if indicated **(AIII)**. Antimotility agents should be avoided **(BIII)**. If no clinical response after 5–7 days, consider follow-up stool culture, alternative diagnosis, or antibiotic resistance. Effective ART may decrease the risk of recurrence of *Shigella* infections.
Bartonellosis		<u>For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis</u>: • Doxycycline 100 mg PO or IV q12h **(AII)**, *or* • Erythromycin 500 mg PO or IV q6h **(AII)** <u>CNS Infections</u>: • (Doxycycline 100 mg +/- RIF 300 mg) PO or IV q12h **(AIII)** <u>Confirmed *Bartonella* Endocarditis</u>: • (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) for 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)** <u>Other Severe Infections</u>: • (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) q12h **(BIII)**, *or* • (Erythromycin 500 mg PO or IV q6h) +/- RIF 300 mg PO or IV q12h **(BIII)** <u>Duration of Therapy</u>: • At least 3 months **(AII)**	<u>For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis</u>: • Azithromycin 500 mg PO daily **(BIII)** • Clarithromycin 500 mg PO BID **(BIII)** <u>Confirmed *Bartonella* Endocarditis but with Renal Insufficiency</u>: • (Doxycycline 100 mg IV + RIF 300 mg PO or IV) q12h for 2 weeks, then continue with doxycycline 100 mg IV or PI q12h **(BII)**	When RIF is used, take into consideration the potential for significant interaction with ARV drugs and other medications (see Table 5 for dosing recommendations). If relapse occurs after initial (>3 month) course of therapy, long-term suppression with doxycycline or a macrolide is recommended as long as CD4 count <200 cells/µL **(AIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 4 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Candidiasis (Mucocutaneous)	For Oropharyngeal Candidiasis; Initial Episodes (for 7–14 Days) *Oral Therapy:* • Fluconazole 100 mg PO daily **(AI)** For Esophageal Candidiasis (for 14–21 Days): • Fluconazole 100 mg (up to 400 mg) PO or IV daily **(AI)**, *or* • Itraconazole oral solution 200 mg PO daily **(AI)** For Uncomplicated Vulvo-Vaginal Candidiasis: • Oral fluconazole 150 mg for one dose **(AII)**, *or* • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days **(AII)** For Severe or Recurrent Vulvo-Vaginal Candidiasis: • Fluconazole 100–200 mg PO daily for ≥7 days **(AII)**, *or* • Topical antifungal ≥7 days **(AII)**	For Oropharyngeal Candidiasis; Initial Episodes (for 7–14 Days) *Oral Therapy:* • Itraconazole oral solution 200 mg PO daily **(BI)**, *or* • Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily **(BI)** *Topical Therapy:* • Clotrimazole troches, 10 mg PO five times daily **(BI)**, *or* • Miconazole mucoadhesive buccal 50-mg tablet; apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet) **(BI)**, *or* • Nystatin suspension 4–6 mL four times a day or 1–2 flavored pastilles four to five times daily **(BII)** • Gentian violet (0.00165%) topical application twice daily **(BI)** For Esophageal Candidiasis (for 14–21 Days): • Voriconazole 200 mg PO or IV twice a day **(BI)**, *or* • Isavuconazole 200 mg PO as a loading dose, followed by 50 mg PO daily **(BI)**, *or* • Isavuconazole 400 mg PO as a loading dose, followed by 100 mg PO daily **(BI)**, *or* • Isavuconazole 400 mg PO once weekly **(BI)**, *or* • Anidulafungin 100 mg IV 1 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)** For Uncomplicated Vulvo-Vaginal Candidiasis: • Itraconazole oral solution 200 mg PO daily for 3–7 days **(BII)** For Azole-Refractory *Candida glabrata* Vaginitis: • Boric acid vaginal suppository 600 mg once daily for 14 days	Chronic or prolonged use of azoles may promote development of resistance. Higher relapse rate for esophageal candidiasis seen with echinocandins than with fluconazole use. Suppressive therapy usually not recommended **(BIII)** unless patients have frequent or severe recurrences. If Decision is to Use Suppressive Therapy *Oropharyngeal Candidiasis:* • Fluconazole 100 mg PO daily or three times weekly **(BI)**; *or* • Itraconazole oral solution 200 mg PO daily **(CI)** *Esophageal Candidiasis:* • Fluconazole 100–200 mg PO daily **(BI)**; *or* • Posaconazole 400 mg PO twice a day **(BII)** *Vulvo-Vaginal Candidiasis:* • Fluconazole 150 mg PO once weekly **(CII)**

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 5 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Chagas Disease (American Trypanosomiasis)	For Acute, Early Chronic, and Re-Activated Disease: • Benznidazole 5–8 mg/kg/day PO in 2 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)	For Acute, Early Chronic, and Reactivated Disease: • Nifurtimox 8–10 mg/kg/day PO for 90–120 days **(CIII)** (not commercially available in the U.S., contact the CDC Drug Service at drugservice@cdc.gov or (404) 639-3670, or the CDC emergency operations center at (770) 488-7100)	Treatment is effective in reducing parasitemia and preventing clinical symptoms or slowing disease progression. It is ineffective in achieving parasitological cure. Duration of therapy has not been studied in HIV-infected patients. Initiate or optimize ART in patients undergoing treatment for Chagas disease, once they are clinically stable **(AIII)**.
Coccidioidomycosis	Clinically Mild Infections (e.g., Focal Pneumonia): • Fluconazole 400 mg PO daily **(BII)**, *or* • Itraconazole 200 mg PO BID **(BII)** Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)** • Lipid formulation amphotericin B 4-6 mg/kg IV daily **(AIII)** • Duration of therapy: continue until clinical improvement, then switch to an azole **(BIII)** Meningeal Infections: • Fluconazole 400–800 mg IV or PO daily **(AII)** Chronic Suppressive Therapy: • Fluconazole 400 mg PO daily **(AII)**, *or* • Itraconazole 200 mg PO BID **(AII)**	Mild Infections (Focal Pneumonia): *For Patients Who Failed to Respond to Fluconazole or Itraconazole:* • Posaconazole 200 mg PO BID **(BII)**, *or* • Voriconazole 200 mg PO BID **(BIII)** Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): • 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 **(BIII)**. Meningeal Infections: • Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID **(BII)**, *or* • Posaconazole 200 mg PO BID **(BIII)**, *or* • Voriconazole 200–400 mg PO BID **(BIII)**, *or* • Intrathecal amphotericin B deoxycholate, when triazole antifungals are ineffective **(AIII)** Chronic Suppressive Therapy: • Posaconazole 200 mg PO BID **(BII)**, *or* • Voriconazole 200 mg PO BID **(BIII)**	Some patients with meningitis may develop hydrocephalus and require CSF shunting. Therapy should be continued indefinitely in patients with diffuse pulmonary or disseminated diseases because relapse can occur in 25%–33% of HIV-negative patients. It can also occur in HIV-infected patients with CD4 counts >250 cells/µL **(BIII)**. Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of HIV-infected patients after discontinuation of triazole therapy **(AII)**. Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bi-directional. Refer to Table 5 for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and reduce concentration-related toxicities. Intrathecal amphotericin B should only be given in consultation with a specialist and administered by an individual with experience with the technique.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 6 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Community-Acquired Pneumonia (CAP)	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available **(BIII)**. Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy. Empiric Outpatient Therapy: • A PO beta-lactam plus a PO macrolide (azithromycin or clarithromycin) **(AII)** *Preferred Beta-Lactams:* • High-dose amoxicillin or amoxicillin/clavulanate *Alternative Beta-Lactams:* • Cefpodoxime or cefuroxime, *or* • Levofloxacin 750 mg PO once daily **(AII)**, *or* moxifloxacin 400 mg PO once daily **(AII)**, especially for patients with penicillin allergies. Empiric Therapy for Hospitalized Patients with Non-Severe CAP: • An IV beta-lactam plus a macrolide (azithromycin or clarithromycin) **(AI)** *Preferred Beta-Lactams:* • Ceftriaxone, cefotaxime, or ampicillin-sulbactam • Levofloxacin 750 mg IV once daily **(AI)**, *or* moxifloxacin, 400 mg IV once daily **(AI)**, especially for patients with penicillin allergies. Empiric Therapy for Hospitalized Patients with Severe CAP: • An IV beta-lactam plus IV azithromycin **(AI)**, *or* • An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(AI)** *Preferred Beta-Lactams:* • Ceftriaxone, cefotaxime, or ampicillin-sulbactam	Empiric antibiotic therapy should be initiated promptly for patients presenting with clinical and radiographic evidence consistent with bacterial pneumonia. The recommendations listed are suggested empiric therapy. The regimen should be modified as needed once microbiologic results are available **(BIII)**. Providers must also consider the risk of opportunistic lung infections (e.g., PCP, TB), which may alter the empiric therapy. Empiric Outpatient Therapy: • A PO beta-lactam plus PO doxycycline **(CIII)** *Preferred Beta-Lactams:* • High-dose amoxicillin or amoxicillin/clavulanate *Alternative Beta-Lactams:* • Cefpodoxime or cefuroxime Empiric Therapy for Hospitalized Patients with Non-Severe CAP: • An IV beta-lactam plus doxycycline **(CIII)** Empiric Therapy for Hospitalized Patients with Severe CAP *For Penicillin-Allergic Patients:* • Aztreonam IV plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)** Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia: • An IV antipneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus azithromycin **(BII)**, *or* • An IV antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)** *For Penicillin-Allergic Patients:* • Replace the beta-lactam with aztreonam **(BIII)**.	Duration: • For most patients, 5–7 days. • Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics. • Longer duration is often required if severe CAP or bacteremia is present, and particularly if due to *S. pneumoniae* or complicated *S. aureus* pneumonia. Fluoroquinolones should be used with caution in patients in whom TB is suspected but is not being treated. Empiric therapy with a macrolide alone is not routinely recommended, because of increasing pneumococcal resistance (up to 30%) **(BIII)**. Patients receiving a macrolide for MAC prophylaxis may have bacterial resistance to macrolide due to chronic exposure. For patients begun on IV antibiotic therapy, switching to PO should be considered when they are clinically improved and able to tolerate oral medications. Antibiotic chemoprophylaxis is generally not recommended because of the potential for developing drug resistance and drug toxicities **(AI)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 7 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Community-Acquired Pneumonia (CAP), continued	Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia: • An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every 8–12 hours or levofloxacin 750 mg IV once daily) **(AI)** *Preferred Beta-Lactams:* • Piperacillin-tazobactam, cefepime, imipenem, or meropenem Empiric Therapy for Patients at Risk for Methicillin-Resistant *Staphylococcus aureus* Pneumonia: • Add vancomycin IV or linezolid (IV or PO) to the baseline regimen **(AII)** • Addition of clindamycin to vancomycin (but **not** to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production **(CII)**.		
Cryptococcosis	Cryptococcal Meningitis *Induction Therapy (2 weeks, followed by consolidation therapy):* • Liposomal amphotericin B 3–4 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)** (Note: Flucytosine dose should be adjusted in patients with renal dysfunction.) • Amphotericin B deoxycholate 0.7-1.0 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)** (if cost is an issue and the risk of renal dysfunction is low), *or* • If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative **(BIII)**. *Consolidation Therapy (for at least 8 weeks **(AI)**, followed by maintenance therapy):* • 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)**;	Cryptococcal meningitis *Induction Therapy (for at least 2 weeks, followed by consolidation therapy):* • Amphotericin B lipid complex 5 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(BII)**, *or* • Liposomal amphotericin B 3-4 mg/kg IV daily + fluconazole 800-1,200 mg PO or IV daily **(BIII)**, *or* • Fluconazole 1,200 mg PO or IV daily + flucytosine 25 mg/kg PO QID **(BII)**, *or* • Fluconazole 800 mg PO or IV daily + flucytosine 25 mg/kg PO QID **(BIII)**, *or* • Amphotericin B deoxycholate 0.7-1.0 mg/kg IV daily + fluconazole 800-1,200 mg PO or IV daily **(BI)**, *or* • Liposomal amphotericin B 3-4 mg/kg IV daily **(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 QID for 1 week followed by fluconazole 1,200 mg PO once daily **(BIII)**; *or* • Fluconazole 1,200 mg PO or IV daily **(CI)**	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 25–100 mcg/mL) or at least twice weekly monitoring of complete blood counts for cytopenia. Dosage should be adjusted in patients with renal insufficiency **(BII)**. In resource limited settings, induction of 1 week of amphotericin B deoxycholate with flucytosine followed by high dose fluconazole is preferred **(BIII)**. Opening pressure should always be measured when an LP is performed **(AII)**. Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure. Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(AIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptococcosis *continued*	duration of consolidation therapy should be 8 weeks from the time of negative CSF culture **(AI)**. *Maintenance Therapy:* • Fluconazole 200 mg PO daily for ≥ 1 year from initiation of antifungal therapy **(AI)** For Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease or Patients with Isolated Asymptomatic Antigenemia Without Meningitis and Serum CrAg. ≥ 1:640 by LFA: • Treatment same as for cryptococcal meningitis **(BIII)** Non-CNS Cryptococcosis with Mild-to-Moderate Symptoms and Focal Pulmonary Infiltrates, or Patients with Isolated Asymptomatic Antigenemia Without Meningitis and Serum CrAg ≤ 1:320 by LFA): • Fluconazole, 400 to 800 mg PO daily for 10 weeks, followed by 200 mg daily for a total of 6 months **(BIII)**	*Consolidation Therapy (for at least 8 weeks **(AI)**, followed by maintenance therapy):* • If patient's CSF culture remains positive at the end of 2 weeks, but not ill enough to be hospitalized, continue flucytosine for an additional 2 weeks with fluconazole 1,200 mg daily, before starting single drug consolidation regimen. • Itraconazole 200 mg PO BID for 8 weeks—less effective than fluconazole **(CI)** *Maintenance Therapy:* • No alternative therapy recommendation	Some specialists recommend a brief course of tapering dose of corticosteroid for management of severe IRIS symptoms **(BIII)**.
Cryptosporidiosis	• Initiate or optimize ART for immune restoration to CD4 count >100 cells/µL **(AII)**, *and* • Aggressive oral or IV rehydration and replacement of electrolyte loss **(AIII)**, *and* • Symptomatic treatment of diarrhea with anti-motility agents **(AIII)**.	No therapy has been shown to be effective without ART. Trial of these agents may be used in conjunction with, but not instead of, ART: • Nitazoxanide 500–1,000 mg PO BID for 14 days **(CIII)**, *or* • Paromomycin 500 mg PO QID for 14–21 days **(CIII)** • With optimized ART, symptomatic treatment and rehydration and electrolyte replacement	Tincture of opium may be more effective than loperamide in management of diarrhea **(CII).**
Cytomegalovirus (CMV) Disease	**CMV Retinitis** Induction Therapy (followed by Chronic Maintenance Therapy): *For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea):* • Ganciclovir 5 mg/kg q12h IV or Valganciclovir 900 mg PO BID or for 14–21 days **(AI)** (some prefer IV ganciclovir initially and transition to PO valganciclovir when there is evidence of clinical response) **with or without** • Intravitreal injections of ganciclovir (2mg) or foscarnet (2.4mg) to rapidly achieve high intraocular concentration, continue weekly until lesion inactivity is achieved **(AIII)**; plus	**CMV Retinitis** *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:* *Alternative Systemic Induction Therapy (followed by Chronic Maintenance Therapy):* • Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h 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)**.	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)**. 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. The ganciclovir ocular implant, which is effective for treatment of CMV retinitis is no longer available.

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cytomegalovirus (CMV) Disease, continued	*For Peripheral Lesions –* • Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily **(AI)** Maintenance Therapy – • Valganciclovir 900 mg PO daily **(AI)** for 3-6 months until ART induced immune recovery **CMV Esophagitis or Colitis:** • Ganciclovir 5 mg/kg IV q12h; may switch to valganciclovir 900 mg PO q12h once the patient can tolerate oral therapy **(BI)** • Valganciclovir 900 mg PO q12h 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)**. Well-Documented, Histologically Confirmed CMV Pneumonia: • 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)**. • The optimal duration of therapy and the role of oral valganciclovir have not been established. CMV Neurological Disease ***Note: Treatment should be initiated promptly.*** • Ganciclovir 5 mg/kg IV q12h + (foscarnet 90 mg/kg IV q12h or 60 mg/kg IV q8h) 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.	(Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid.) *Chronic Maintenance (for 3-6 months until ART induced immune recovery):* • 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)** CMV Esophagitis or Colitis: • Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h **(BI)** for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance, *or* • Valganciclovir 900 mg PO q12h in milder disease and if able to tolerate PO therapy **(BII)**, *or* • 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)**.	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)**. IRU may develop in the setting of immune reconstitution. Treatment of IRU • Periocular, intravitreal, or short courses of systemic steroid **(BIII)**. Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART **(BIII)**.

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Hepatitis B Virus (HBV) Disease	ART is recommended for all HIV/ HBV-co-infected patients regardless of CD4 cell count **(AII)**. ART regimen should include 2 drugs that are active against both HBV and HIV, such as [tenofovir 300 mg + emtricitabine 200 mg (or lamivudine 300 mg)] PO once daily (+ additional drug (s) for HIV) **(AIII)**. Duration: Continue treatment indefinitely **(CIII)**	For Patients Who Refuse or Are Unable to Take ART or Who Are HIV Long-Term Non-Progressors: • HBV treatment is indicated for patients with elevated ALT and HBV DNA >2,000 IU/mL significant liver fibrosis, advanced liver disease or cirrhosis. **(AI)** • Peginterferon alfa-2a 180 µg SQ once weekly for 48 weeks **(CIII)**, *or* • Peginterferon alfa-2b 1.5 µg/kg SQ once weekly for 48 weeks **(CIII)** If Tenofovir Cannot Be Used as Part of HIV/HBV Therapy (Because of Current or High Risk of Renal Dysfunction): • Use a fully suppressive ART regimen without tenofovir, and with the addition of entecavir (dose adjustment according to renal function) **(BIII).**	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 resistance HIV **(AI)**. Cross-resistance to emtricitabine or telbivudine should be assumed in patients with suspected or proven lamivudine-resistance. When changing ART regimens, continue agents with anti-HBV activity **(BIII)**. If anti-HBV therapy is discontinued and a flare occurs, therapy should be re-instituted because it can be potentially life-saving **(AIII)**.
Hepatitis C Virus (HCV) Disease	The field of HCV drug development is evolving rapidly, with a number of investigational drugs currently at late stage clinical trials, and some will soon be approved for use. Clinicians should refer to the most recent HCV treatment guidelines (http://www.hcvguidelines.org) for the most up-to-date recommendations.		
Herpes Simplex Virus (HSV) Disease	Orolabial Lesions (for 5–10 Days): • Valacyclovir 1 g PO twice a day **(AIII)**, *or* • Famciclovir 500 mg PO twice a day **(AIII)**, *or* • Acyclovir 400 mg PO three times a day **(AIII)** Initial or Recurrent Genital HSV (for 5–14 Days): • Valacyclovir 1 g PO twice a day **(AI)**, *or* • Famciclovir 500 mg PO twice a day **(AI)**, *or* • Acyclovir 400 mg PO three times a day **(AI)** Severe Mucocutaneous HSV: • 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.	For Acyclovir-Resistant HSV *Preferred Therapy:* • Foscarnet 80–120 mg/kg/day IV in two to three divided doses until clinical response **(AI)** *Alternative Therapy **(CIII)**:* • IV cidofovir (dosage as in CMV retinitis), *or* • Topical trifluridine 1% three times a day, *or* • Topical cidofovir 1% once daily, *or* • Topical imiquimod 5% three times weekly, *or* • Topical foscarnet 1% five times daily Duration of Therapy: • 21–28 days or longer	Patients with HSV infection can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences. 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 the AiCuris Pritelivir website.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 11 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Herpes Simplex Virus (HSV) Disease *continued*	Chronic Suppressive Therapy *For Patients with Severe Recurrences of Genital Herpes **(AI)** or Patients Who Want to Minimize Frequency of Recurrences **(AI)***: • 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	Moderately Severe to Severe Disseminated Disease *Induction Therapy:* • For at least 2 weeks or until clinically improved • Liposomal amphotericin B 3 mg/kg IV daily **(AI)** *Maintenance Therapy:* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day **(AII)** Less Severe Disseminated Disease *Induction and Maintenance Therapy:* •Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day **(AII)** *Duration of Therapy:* • At least 12 months Meningitis *Induction Therapy (4–6 weeks):* • Liposomal amphotericin B 5 mg/kg/day **(AIII)** *Maintenance Therapy:* • Itraconazole 200 mg PO twice a day to three times a day for ≥12 months and until resolution of abnormal CSF findings **(AII)** Long-Term Suppression Therapy: *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)**:* • Itraconazole 200 mg PO daily **(AIII)**	Moderately Severe to Severe Disseminated Disease *Induction Therapy (for at least 2 weeks or until clinically improved):* • Amphotericin B lipid complex 5 mg/kg IV daily **(AIII)**, *or* Alternatives to Itraconazole for Maintenance Therapy or Treatment of Less Severe Disease: • 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)** Meningitis (these recommendations are based on limited clinical data for patients with intolerance to itraconazole): • 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)** Long-Term Suppression 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)**	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 ARV efficacy and reduce concentration-related toxicities. Random serum concentration of itraconazole between 1-2 mcg/mL is recommended. Frequency and severity of toxicities increase when concentration is >4 mcg/mL. Acute pulmonary histoplasmosis in HIV-infected patients with CD4 counts >300 cells/mm³ should be managed as non-immunocompromised host **(AIII)**.

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Human Herpesvirus-8 Diseases *(Kaposi Sarcoma [KS], Primary Effusion Lymphoma [PEL], Multicentric Castleman's Disease [MCD])*	Mild To Moderate KS (localized involvement of skin and/or lymph nodes): • Initiate or optimize ART **(AII)** Advanced KS [visceral **(AI)** or disseminated cutaneous KS **(BIII)**]: • Chemotherapy (per oncology consult) + ART • Liposomal doxorubicin first line chemotherapy **(AI)** Primary Effusion Lymphoma: • Chemotherapy (per oncology consult) + ART **(AIII)** • PO valganciclovir or IV ganciclovir can be used as adjunctive therapy **(CIII)**. MCD Therapy Options (in consultation with specialist, depending on HIV/HHV-8 status, presence of organ failure, and refractory nature of disease): ART **(AIII)** along with one of the following: • Valganciclovir 900 mg PO BID for 3 weeks **(CII)**, *or* • Ganciclovir 5 mg/kg IV q12h for 3 weeks **(CII)**, *or* • Valganciclovir PO or Ganciclovir IV + zidovudine 600 mg PO q6h for 7–21 days **(CII)** • Rituximab +/- Prednisone **(CII)** • Monoclonal antibody targeting IL-6 or IL-6 receptor **(BII)** Concurrent KS and MCD • Rituximab + liposomal doxorubicin **(BII)**	MCD • Rituximab (375 mg/m^2 given weekly for 4–8 weeks) may be an alternative to or used adjunctively with antiviral therapy **(CII)**.	• Corticosteroids should be avoided in patients with KS, including those with KS-IRIS **(AIII)** • Corticosteroids are potentially effective as adjunctive therapy for MCD, but should be used with caution, esp. in patients with concurrent KS. • Patients who received rituximab for MCD may experience subsequent exacerbation or emergence of KS.
Human Papillomavirus (HPV) Disease	**Treatment of Condyloma Acuminata (Genital Warts)**		HIV-infected patients may have larger or more numerous warts and may not respond as well to therapy for genital warts when compared to HIV-uninfected individuals. Topical cidofovir has activity against genital warts, but the product is not commercially available **(CIII)**. Intralesional interferon-alpha is usually not recommended because of high cost, difficult administration, and potential for systemic side effects **(CIII)**. The rate of recurrence of genital warts is high despite
	Patient-Applied Therapy for Uncomplicated External Warts That Can Be Easily Identified by Patients: • Podophyllotoxin (e.g., podofilox 0.5% solution or 0.5% gel): Apply to all lesions BID 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)**, *or* • Imiquimod 5% cream: Apply to lesion at bedtime and remove in the morning on 3 non-consecutive nights weekly for up to 16 weeks, until lesions are no longer visible. Each treatment should be washed	Provider-Applied Therapy for Complex or Multicentric Lesions, or Lesions Inaccessible to Patient: *Applied Therapy:* • 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)**, *or* • Trichloroacetic acid or bichloroacetic acid cauterization: 80%–90% aqueous solution, apply to wart only, allow to dry until	

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 13 of 21)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Human Papillomavirus (HPV) Disease *continued*		with soap and water 6–10 hours after application **(BII)**, *or* • Sinecatechins 15% ointment: Apply to affected areas TID for up to 16 weeks, until warts are completely cleared and not visible **(BIII)**.	a white frost develops. Repeat weekly for up to 6 weeks, until lesions are no longer visible **(BIII)**, *or* • Surgical excision **(BIII)** or laser surgery **(CIII)** to external or anal warts, *or* • Podophyllin resin 10%–25% in tincture of benzoin: Apply to all lesions (up to 10 cm^2), then wash off a few hours later, repeat weekly for up to 6 weeks until lesions are no longer visible **(CIII)**.	treatment in HIV-infected patients. 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.
Isosporiasis (Cystoisosporiasis)		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)** • Can start with BID 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 mal-absorption. Chronic Maintenance Therapy (Secondary Prophylaxis): • In patients with CD4 count <200/µL, TMP-SMX (160 mg/800 mg) PO TIW **(AI)**	For Acute Infection: • Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily **(BIII)**, *or* • Ciprofloxacin 500 mg PO BID for 7 days **(CI)** as a second line alternative Chronic Maintenance Therapy (Secondary Prophylaxis): • TMP-SMX (160 mg/800 mg) PO daily or (320 mg/1,600 mg) three times weekly **(BIII)** • Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily **(BIII)** • Ciprofloxacin 500 mg three times weekly **(CI)** as a second-line alternative	Fluid and electrolyte management in patients with dehydration **(AIII)**. Nutritional supplementation for malnourished patients **(AIII)**. Immune reconstitution with ART may result in fewer relapses **(AIII)**.
Leish-maniasis	**Visceral**	For Initial Infection: • 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)** • To achieve total dose of 20–60 mg/kg **(AII)** Chronic Maintenance Therapy (Secondary Prophylaxis); Especially in Patients with CD4 Count <200 cells/µL: • Liposomal amphotericin B 4 mg/kg every 2–4 weeks **(AII)**, *or* • Amphotericin B lipid complex **(AII)** 3 mg/kg every 21 days **(AII)**	For Initial Infection: • Other lipid formulation of amphotericin B, dose and schedule as in Preferred Therapy, *or* • Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 g **(BII)**, *or* • Sodium stibogluconate (pentavalent antimony) **(BII)** 20 mg/kg IV or IM daily for 28 days. • Miltefosine - if 30-44 kg: 50 mg BID; if (*insert actual >/= sign*)45 kg, 50 mg TID - for 28 days. Chronic Maintenance Therapy (Secondary Prophylaxis): • Sodium stibogluconate 20 mg/kg IV or IM every 4 weeks **(BII)**	ART should be initiated or optimized **(AIII)**. For sodium stibogluconate, contact the CDC Drug Service at (404) 639-3670 or drugservice@cdc.gov. For miltefosine – can be accessed via http://www.impavido.com/

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 14 of 21)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Leish-maniasis	**Cutaneous**	• Liposomal amphotericin B 2–4 mg/kg IV daily for 10 days **(BIII)**, *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg **(BIII)**, *or* • Sodium stibogluconate 20 mg/kg IV or IM daily for 3–4 weeks **(BIII)** <u>Chronic Maintenance Therapy</u>: May be indicated in immunocompromised patients with multiple relapses **(CIII)**	<u>Possible Options Include</u>: • Oral miltefosine (can be obtained via a treatment IND), *or* • Topical paromomycin, *or* • Intralesional sodium stibogluconate, *or* • Local heat therapy No data exist for any of these agents in HIV-infected patients; choice and efficacy dependent on species of *Leishmania*.	None.
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 hospitalized for evaluation, initiation of treatment, and observation **(AIII)**. 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, region of infection, and the likely drug susceptibility of the infected species, and can be found at http://www.cdc.gov/malaria.	When suspicion for malaria is low, antimalarial treatment should not be initiated until the diagnosis is confirmed.	For treatment recommendations for specific regions, clinicians should refer to the following web link: http://www.cdc.gov/malaria/ or call the CDC Malaria Hotline: (770) 488-7788: M–F 8 AM–4:30 PM ET, or (770) 488-7100 after hours
Microsporidiosis		<u>For GI Infections Caused by *Enterocytozoon bienuesi*</u>: • Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 **(AII)**; *plus* • Manage severe dehydration, malnutrition, and wasting by fluid support **(AII)** and nutritional supplement **(AIII)** <u>For Intestinal and Disseminated (Not Ocular) Infections Caused by Microsporidia Other Than *E. bienuesi* and *Vittaforma corneae*</u>: • Albendazole 400 mg PO twice daily **(AII)**, continue until CD4 count >200 cells/mm^3 for >6 months after initiation of ART **(BIII)** <u>For Disseminated Disease Caused by *Trachipleistophora* or *Anncaliia*</u>: • Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily **(CIII)**	<u>For GI Infections Caused by *E. bienuesi*</u>: • 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 cell counts **(CIII)**.	Anti-motility agents can be used for diarrhea control if required **(BIII)**. Fumagillin is available in France as FLISINT® 20 mg capsules. Only available as compassionate use; see the Sanofi Compassionate Use/Managed Access Program website.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 15 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Microsporidiosis *continued*	For Ocular Infection: • Topical fumagillin bicylohexylammonium (Fumidil B) eye drops 3 mg/mL in saline (fumagillin 70 μg/mL): two drops every 2 hours for 4 days, then two drops four times daily (investigational use only in United States) **(BII)** plus albendazole 400 mg PO twice daily, for management of systemic infection **(BIII)** *If CD4 count >200 cells/mm³:* • Continue until symptoms resolved **(CIII)**. *If CD4 count ≤200 cells/mm³:* • Continue until resolution of ocular symptoms **and** CD4 count increases to >200 cells/mm³ for >6 months in response to ART **(BIII)**.		
Mycobacterium avium **Complex (MAC) Disease**	At Least 2 Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance: • Clarithromycin 500 mg PO BID **(AI)** + ethambutol 15 mg/kg PO daily **(AI)**, *or* • If drug interaction or intolerance precludes the use of clarithromycin, (azithromycin 500–600 mg + ethambutol 15 mg/kg) PO daily **(AII)** Duration: • 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	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)**. Third or Fourth Drug Options May Include: • Rifabutin 300 mg PO daily (dose adjustment may be necessary based on drug interactions) **(CI)**, *or* • A fluoroquinolone such as moxifloxacin 400 mg PO daily **(CIII)** or levofloxacin 500 mg PO daily **(CIII)**, *or* • An injectable aminoglycoside such as amikacin 10–15 mg/kg IV daily **(CIII)** or streptomycin 1 g IV or IM daily **(CIII)**	Testing of susceptibility to clarithromycin and azithromycin is recommended **(BIII)**. NSAIDs can be used for moderate to severe symptoms attributed to IRIS **(CIII)**. If IRIS symptoms persist, short course (i.e., 4 weeks–8 weeks) systemic corticosteroid (equivalent to 20–40 mg prednisone) can be used **(CII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 16 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
***Mycobacterium tuberculosis* (TB) Disease**	After collecting specimen for culture and molecular diagnostic tests, empiric TB treatment should be started in individuals with clinical and radiographic presentation suggestive of TB **(AIII)**. Refer to Table 3 for dosing recommendations. Initial Phase (2 Months, Given Daily by DOT) **(AI)**: • INH (plus pyridoxine) plus (RIF or RFB) plus PZA plus EMB **(AI)**. Continuation Phase (Duration Depends on Site and Severity of Infection [as noted below]): • INH (plus pyridoxine) plus (RIF or RFB) daily **(AI)** Total Duration of Therapy (For Drug-Susceptible TB) *Pulmonary, Drug-Susceptible TB:* • 6 months **(BII)** *Pulmonary TB with Positive Culture After 2 Months of TB Treatment, or Severe Cavitary or Disseminated Extrapulmonary TB:* • 9 months **(BII)** *Extra-Pulmonary TB with CNS Infection:* • 9–12 months **(BII)** *Extra-Pulmonary TB in Other Sites:* • 6 months **(BII)**	If rapid **drug susceptibility testing** (DST) indicates resistance to rifampin with or without other drugs: • INH (plus pyridoxine) plus EMB plus PZA plus (moxifloxacin or levofloxacin) plus an aminoglycoside, *or* • Capreomycin **(BIII)**; adjust regimen as conventional DST become available Treatment for Drug Resistant TB *Resistant to INH:* • (Moxifloxacin or levofloxacin) plus (RIF or RFB) plus EMB plus PZA plus for 6 months **(BII)** Resistant to Rifamycins Plus or Minus Other Drugs: • Therapy should include at least 5 active drugs, individualized based on DST results, clinical and microbiological responses, and with close consultation with experienced specialists **(AIII)**.	DOT is recommended for all patients **(AII)**. All patients with HIV and TB should be started on ART. Refer to text for recommendations on when to start ART while on TB treatment. All rifamycins may have significant pharmacokinetic interactions with ARV drugs, please refer to the Drug-Drug Interactions section in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations. Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART. Adjunctive corticosteroids improve survival for TB with CNS involvement **(AI)**. See text for drug, dose, and duration recommendations. Paradoxical IRIS that is not severe can be treated with NSAIDs without a change in TB or HIV therapy **(BIII)**. See text for prednisone dosing recommendations for pre-emptive treatment or management of IRIS.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 17 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
***Pneumocystis* Pneumonia (PCP)**	Patients who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX **(BIII)**. Duration of PCP treatment: 21 days **(AII)** For Moderate to Severe PCP: • TMP-SMX: (TMP 15–20 mg 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)**. For Mild to Moderate PCP: • TMP-SMX: (TMP 15–20 mg and SMX 75–100 mg)/kg/day, given PO in 3 divided doses **(AI)**, *or* • TMP-SMX: (160 mg/800 mg or DS) two tablets PO three times daily **(AI)** Secondary Prophylaxis, After Completion of PCP Treatment: • TMP-SMX DS: 1 tablet PO daily **(AI)**, *or* • TMP-SMX (80 mg/400 mg or SS): 1 tablet PO daily **(AI)**	For Moderate-to-Severe PCP: • Pentamidine 4 mg/kg IV daily infused over ≥60 minutes **(AI)**; can reduce dose to 3 mg/kg IV daily in the event of toxicities **(BI)**, *or* • 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)** For Mild-to-Moderate PCP: • Dapsone 100 mg PO daily plus TMP 5 mg/kg PO TID **(BI)**, *or* • Primaquine 30 mg (base) PO daily plus (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) **(BI)**, *or* • Atovaquone 750 mg PO twice daily with food **(BI)** Secondary Prophylaxis, After Completion of PCP Treatment: • TMP-SMX DS: 1 tablet PO three times weekly **(BI)**, *or* • Dapsone 100 mg PO daily **(BI)**, *or* • Dapsone 50 mg PO daily with (pyrimethamine[a] 50 mg plus leucovorin 25 mg) PO weekly **(BI)**, *or* • (Dapsone 200 mg plus pyrimethamine[a] 75 mg plus leucovorin 25 mg) PO weekly **(BI)**, *or* • Aerosolized pentamidine 300 mg monthly via Respirgard II™ nebulizer **(BI)**, *or* • Atovaquone 1,500 mg PO daily **(BI)**, *or* • (Atovaquone 1,500 mg plus pyrimethamine[a] 25 mg plus leucovorin 10 mg) PO daily **(CIII)**	Indications for Adjunctive Corticosteroids **(AI)**: • PaO_2 <70 mmHg at room air, *or* • Alveolar-arterial DO_2 gradient >35 mmHg Prednisone Doses (Beginning as Early as Possible and Within 72 Hours of PCP Therapy) **(AI)**: • Days 1–5: 40 mg PO twice daily • Days 6–10: 40 mg PO daily • Days 11–21: 20 mg PO daily IV methylprednisolone can be administered as 75% of prednisone dose. Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP **(BIII)**. 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. Patients who are receiving pyrimethamine[a]/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis **(AII)**. 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)**. TMP-SMX should be permanently discontinued in patients with possible or definite Stevens-Johnson Syndrome or toxic epidermal necrosis **(AII)**.

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Progressive Multifocal Leukoencephalopathy (PML)/JC Virus Infections	There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse the immunosuppression caused by HIV. Initiate ART immediately in ART-naive patients **(AII)**. Optimize ART in patients who develop PML in phase of HIV viremia on ART **(AIII)**.	None.	Corticosteroids may be used for PML-IRIS characterized by contrast enhancement, edema or mass effect, and with clinical deterioration **(BIII)** (see text for further discussion).
Syphilis (*Treponema pallidum* Infection)	<u>Early Stage (Primary, Secondary, and Early-Latent Syphilis)</u>: • Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)** <u>Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis)</u>: • Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AII)** <u>Late-Stage (Tertiary–Cardiovascular or Gummatous Disease)</u>: • Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AII)** (Note: rule out neurosyphilis before initiation of benzathine penicillin, and obtain infectious diseases consultation to guide management) <u>Neurosyphilis (Including Otic or Ocular Disease)</u>: • 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 3 doses after completion of IV therapy **(CIII)**	<u>Early Stage (Primary, Secondary, and Early-Latent Syphilis)</u>: *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: azithromycin is not recommended for men who have sex with men or pregnant women **(AII)**) <u>Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis)</u>: *For penicillin-allergic patients* • Doxycycline 100 mg PO BID for 28 days **(BIII)** <u>Neurosyphilis</u>: • Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO QID for 10–14 days **(BII)** +/- benzathine penicillin G 2.4 million units IM weekly for 3 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)**	The efficacy of non-penicillin alternatives has not been evaluated in HIV-infected patients and they should be used only with close clinical and serologic monitoring. Combination of procaine penicillin and probenecid **<u>is not recommended</u>** for patients who are allergic to sulfa-containing medications **(AIII)**. 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.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 19 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Talaromycosis (Penicilliosis)	Induction Therapy: • Liposomal amphotericin B 3–5 mg/kg/day IV **(AI)** *Duration:* • 2 weeks **(AI)**, followed by consolidation therapy Consolidation Therapy: • Itraconazole 200 mg PO twice daily for 10 weeks **(AI)**, followed by chronic maintenance therapy Chronic Maintenance Therapy: • Itraconazole 200 mg PO once daily, until CD4 count >100 cells/mm^3 for ≥6 months **(AII)**	Induction Therapy: • Amphotericin B deoxycholate 0.7 mg/kg/day IV for 2 weeks (if liposomal amphotericin B is not available) **(AI)** *If Amphotericin B is Not Available:* • 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)** *Duration:* • 2 weeks **(BII)** followed by consolidation therapy with itraconazole (preferred) or voriconazole Consolidation Therapy: • Voriconazole 200 mg PO twice daily for 10 weeks **(BII)**, followed by chronic maintenance therapy Chronic Maintenance Therapy: • Itraconazole should be used **(AII)**. Chronic maintenance therapy with voriconazole has not been studied.	Itraconazole is not recommended as induction therapy for talaromycosis **(AI)**. ART can be initiated as early as 1 week after initiation of treatment for talaromycosis **(BIII)**. 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. 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 >0.5 mcg/mL and >1.0 mcg/mL respectively.

***Toxoplasma gondii* Encephalitis**	Treatment of Acute Infection **(AI)**:
	• Pyrimethamine[a] 200 mg PO 1 time, followed by weight-based therapy:
	  • If <60 kg, pyrimethamine[a] 50 mg PO once daily + sulfadiazine 1,000 mg PO q6h + leucovorin 10–25 mg PO once daily
	  • If ≥60 kg, pyrimethamine[a] 75 mg PO once daily + sulfadiazine 1,500 mg PO q6h + leucovorin 10–25 mg PO once daily
	• Leucovorin dose can be increased to 50 mg daily or BID.
	Duration for Acute Therapy:
	• At least 6 weeks **(BII)**; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks
	• After completion of acute therapy, all patients should be initiated on chronic maintenance therapy
		Treatment of Acute Infection:
		• Pyrimethamine[a] (leucovorin)* + clindamycin 600 mg IV or PO q6h **(AI)**, *or*
		• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO BID **(BI)**, *or*
		• Atovaquone 1,500 mg PO BID with food + pyrimethamine[a] (leucovorin)* **(BII)**, *or*
		• Atovaquone 1,500 mg PO BID with food + sulfadiazine 1,000–1,500 mg PO q6h (weight-based dosing, as in preferred therapy) **(BII)**, *or*
		• Atovaquone 1,500 mg PO BID with food **(BII)**, *or*
		Chronic Maintenance Therapy:
		• Clindamycin 600 mg PO q8h + (pyrimethamine[a] 25–50 mg + leucovorin 10–25 mg) PO daily **(BI)**, *or*
		• TMP-SMX DS 1 tablet BID **(BII)**, *or*
			If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be utilized 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)**.
			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.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 20 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Toxoplasma gondii **Encephalitis** *continued*	Chronic Maintenance Therapy: • Pyrimethamine[a] 25–50 mg PO daily + sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) + leucovorin 10–25 mg PO daily **(AI)**	• TMP-SMX DS 1 tablet once daily **(BII)**; *or* • Atovaquone 750–1,500 mg PO BID + (pyrimethamine[a] 25 mg + leucovorin 10 mg) PO daily **(BII)**, *or* • Atovaquone 750–1,500 mg PO BID + sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) **(BII)**, *or* • Atovaquone 750–1,500 mg PO BID with food **(BII)** * Pyrimethamine[a] and leucovorin doses are the same as for preferred therapy.	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)**. If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP **(AII)**.

Varicella-Zoster Virus (VZV) Disease	Primary Varicella Infection (Chickenpox)
	Uncomplicated Cases:
	• Initiate as soon as possible after symptom onset and continue for 5 to 7 days:
	  • Valacyclovir 1 g PO three times a day **(AII)**, *or*
	  • Famciclovir 500 mg PO three times a day **(AII)**
	Severe or Complicated Cases:
	• Acyclovir 10 mg/kg IV every 8 hours for 7–10 days **(AIII)**
	• May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement **(BIII).**
	Herpes Zoster (Shingles)
	Acute Localized Dermatomal:
	• For 7–10 days; consider longer duration if lesions are slow to resolve
	• Valacyclovir 1 g PO three times a day **(AII)**, *or*
	• Famciclovir 500 mg three times a day **(AII)**
	Extensive Cutaneous Lesion or Visceral Involvement:
	• Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident **(AII)**
	• May switch to PO therapy (valacyclovir, famciclovir, or acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV), to complete a 10–14-day course **(BIII)**.
		Primary Varicella Infection (Chickenpox)
		Uncomplicated Cases (For 5-7 Days):
		• Acyclovir 800 mg PO 5 times a day **(BII)**
		Herpes Zoster (Shingles)
		Acute Localized Dermatomal:
		• For 7–10 days; consider longer duration if lesions are slow to resolve
		• Acyclovir 800 mg PO 5 times a day **(BII)**
			In managing VZV of the eyes, consultation with an ophthalmologist experienced in management of VZV retinitis **is strongly recommended** **(AIII)**.
			Duration of therapy for VZV retinitis is not well defined, and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses.
			Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) **(AIII)**.
			In patients with herpes zoster ophthalmicus who have stromal keratitis and anterior uveitis, topical corticosteroids to reduce inflammation may be necessary. The role of ART has not been established in these cases.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 21 of 21)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Varicella-Zoster Virus (VZV) Disease continued	ARN: • Acyclovir 10 mg/kg IV every 8 hours for 10–14 days, followed by valacyclovir 1 g PO three times a day for >14 weeks **(AIII)**, *plus* • Intravitreal ganciclovir 2 mg/0.05 mL twice weekly for 1-2 doses **(BIII)** PORN: • Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg IV every 12 hours **(AIII)**, *plus* • ≥1 intravitreal antiviral injection: ganciclovir 2 mg/0.05 mL or foscarnet 1.2 mg/0.05 mL twice weekly **(AIII)** • Initiate or optimize ART **(AIII)**		

[a] Refer to Daraprim Direct for information on accessing pyrimethamine.

Key to Acronyms: ACTG = AIDS Clinical Trials Group; ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; ATV/r = ritonavir-boosted atazanavir; BID = twice a day; BIW = twice weekly; BOC = boceprevir; CD4 = CD4 T lymphocyte cell; CDC = The Centers for Disease Control and Prevention; CFU = colony-forming unit; CNS = central nervous system; CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; ddI = didanosine; DOT = directly-observed therapy; DS = double strength; EFV = efavirenz; EMB = ethambutol; g = gram; G6PD = Glucose-6-phosphate dehydrogenase; GI = gastrointestinal; ICP = intracranial pressure; ICU = intensive care unit; IM = intramuscular; IND = investigational new drug; INH = isoniazid; IRIS = immune reconstitution inflammatory syndrome; IRU = immune reconstitution uveitis; IV = intravenous; LP = lumbar puncture; mg = milligram; mmHg = millimeters of mercury; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NSAID = non-steroidal anti-inflammatory drugs; PegIFN = Pegylated interferon; PI = protease inhibitor; PO = oral; PORN = progressive outer retinal necrosis; PZA = pyrazinamide; qAM = every morning; QID = four times a day; q(n)h = every "n" hours; qPM = every evening; RBV = ribavirin; RFB = rifabutin; RIF = rifampin; SQ = subcutaneous; SS = single strength; TID = three times daily, TVR = telaprevir; TMP-SMX = trimethoprim-sulfamethoxazole; ZDV = zidovudine

Evidence Rating:

Strength of Recommendation:

A: Strong recommendation for the statement

B: Moderate recommendation for the statement

C: Optional recommendation for the statement

Quality of Evidence for the Recommendation:

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints

II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes

III: Expert opinion

In cases where there are no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected patients exist that can plausibly guide management decisions for patients with HIV/AIDS, the data will be rated as III but will be assigned recommendations of A, B, C depending on the strength of recommendation.

Table 3. Dosing Recommendations for Anti-TB Drugs for Treatment of Active Drug Sensitive TB

(Last updated September 27, 2019; last reviewed September 27, 2019)

TB Drug	ARV Drugs	Daily Dose
Isoniazid	All ARVs	5 mg/kg (usual dose 300 mg)
Rifampin[a,b]	With HIV PIs, DOR, ETR, RPV, BIC, or EVG/c	**<u>Not recommended</u>**
Note: DTG, RAL, and MVC doses need to be adjusted when used with rifampin	With TAF	Use with caution[c] at dose indicated below
	With other ARV drugs	10 mg/kg (usual dose 600 mg)
Rifabutin[a]	With PI with COBI, TAF, BIC, or EVG/c -containing regimens	**<u>Not recommended</u>**
Note: DOR and RPV doses need to be adjusted when used with rifabutin	With DTG, RAL, EFV, DOR, RPV	5 mg/kg (usual dose 300 mg)
	With HIV PIs with RTV	150 mg[d]
	With EFV	450–600 mg
Pyrazinamide	All ARVs	**Weight-Based Dosing** • *Weighing 40–55 kg:* 1,000 mg (18.2–25.0 mg/kg) • *Weighing 56–75 kg:* 1,500 mg (20.0–26.8 mg/kg) • *Weighing 76–90 kg:* 2,000 mg (22.2–26.3 mg/kg) • *Weighing >90 kg:* 2,000 mg[e]
Ethambutol	All ARVs	**Weight-Based Dosing** • *Weighing 40–55 kg:* 800 mg (14.5–20.0 mg/kg) • *Weighing 56–75 kg:* 1,200 mg (16.0–21.4 mg/kg) • *Weighing 76-90 kg:* 1,600 mg (17.8–21.1 mg/kg) • *Weighing >90 kg:* 1,600 mg[e]

[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 PK and virologic efficacy among patients taking full dose ART and TB regimens

[d] 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 TDM when rifabutin is used with an RTV-boosted PI and adjust dose accordingly.

[e] Monitor for therapeutic response and consider TDM to assure dosage adequacy in patients weighing >90 kg.

Key: ARV = antiretroviral; ART = antiretroviral therapy; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; MVC = maraviroc; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TB = tuberculosis; TDM = therapeutic drug monitoring

Table 4. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents (page 1 of 3) (Last updated July 1, 2021; last reviewed April 14, 2021)

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 *Salmonella* infection and after response to ART with sustained viral suppression and CD4 counts >200 cells/µL **(CII)**	No recommendation
Bartonellosis	Not applicable	Not applicable	• Received at least 3–4 months of treatment, *and* • CD4 count >200 cells/µL for ≥6 months **(CIII)** Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by four-fold **(CIII)**.	No recommendation
Candidiasis (Mucocutaneous)	Not applicable	Not applicable	If used, reasonable to discontinue when CD4 count >200 cells/µL **(AIII)**.	No recommendation
Coccidioidomycosis	CD4 count ≥250 cells/µL for ≥6 months **(CIII)**	Restart at CD4 count <250 cells/µL **(BIII)**	Only for patients with focal coccidioidal pneumonia **(AII)**: • Clinically responded to ≥12 months antifungal therapy, with CD4 count >250 cells/mm^3, and receiving effective ART. • Should continue monitoring for recurrence with serial chest radiographs and coccidioidal serology. For patients with diffuse pulmonary **(BIII)**, disseminated non-meningeal **(BIII)**, or meningeal diseases **(AII)**: For meningeal diseases **(AII)**: Suppressive therapy should be continued indefinitely, even with increase in CD4 count on ART.	No recommendation
Cryptococcal Meningitis	Not applicable	Not applicable	If the following criteria are fulfilled **(BII)**: • Completed initial (induction and consolidation) therapy, *and* • Received at least 1 year of antifungal therapy, *and* • Remain asymptomatic of cryptococcal infection, *and* CD4 count ≥100 cells/µL, and with suppressed plasma HIV RNA in response to ART	CD4 count <100 cells/µL **(AIII)**

Table 4. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents (page 2 of 3)

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
Cytomegalovirus Retinitis	Not applicable	Not applicable	• CMV treatment for at least 3 to 6 months; and with CD4 count >100 cells/µL 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/µL **(AIII)**
***Histoplasma capsulatum* 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)**	If the following criteria **(AI)** are fulfilled: • Received azole therapy for >1 year, *and* • Negative fungal blood cultures, *and* • Serum or urine *Histoplasma* antigen below the level of quantification, *and* • Undetectable HIV viral load, *and* • CD4 count ≥150 cells/mm^3 for ≥6 months in response to ART	CD4 count <150 cells/ mm^3 **(BIII)**
***Isospora belli* Infection**	Not applicable	Not applicable	Sustained increase in CD4 count to >200 cells/µL for >6 months in response to ART and without evidence of *I. belli* 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/µL for 3–6 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/µL for >6 months in response to ART.	No recommendation
***Mycobacterium avium* 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)**: • Completed ≥12 months of therapy, *and* • No signs and symptoms of MAC disease, *and* Have sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART.	CD4 count <100 cells/ mm^3 **(AIII)**

Table 4. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in HIV-Infected Adults and Adolescents (page 3 of 3)

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
***Pneumocystis* 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–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 ≥3months–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 cell count rises as a consequence of ART **(BIII)**.	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)**.
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)**
***Toxoplasma gondii* Encephalitis**	CD4 count increased to >200 cells/µL for >3 months in response to ART **(AI)** Can consider when CD4 count 100-200 cells/µL if HIV RNA remain below limits of detection for at least 3-6 months **(BII)**	CD4 count <100 cells/µL, **(AIII)** CD4 count 100-200 cells/µL and with HIV RNA above detection limit of the assay **(AIII)**.	Successfully completed initial therapy, rSuccessfully completed initial therapy, receiving maintenance therapy and remain free of signs and symptoms of TE, and CD4 count >200 cells/µL for >6 months in response to ART **(BI)**.	CD4 count <200 cells/µL **(AIII)**

Key to Acronyms: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; TE = *Toxoplasma* encephalitis

Evidence Rating:

Strength of Recommendation:

A: Strong recommendation for the statement
B: Moderate recommendation for the statement
C: Optional recommendation for the statement

Quality of Evidence for the Recommendation:

I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
III: Expert opinion

In cases where there are no data for the prevention or treatment of an OI based on studies conducted in HIV-infected populations, but data derived from HIV-uninfected patients exist that can plausibly guide management decisions for patients with HIV/AIDS, the data will be rated as III but will be assigned recommendations of A, B, C depending on the strength of recommendation.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 1 of 15) (Last updated October 22, 2019; last reviewed October 22, 2019)

This table lists the known, predicted, or suspected PK interactions between drugs used for the treatment or prevention of HIV-associated OIs. Many of the drugs listed in this table may also interact with 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 rationale for these recommendations are summarized below:

Do not coadminister.

There is either strong evidence or strong likelihood that the drug-drug 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.

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 Antibiotics-Related Interactions

Rifamycin antibiotics are potent inducers of Phase 1 and Phase 2 drug metabolizing reactions. Studies have demonstrated that with daily doses of rifampin, enzyme induction increases over a week or more. Based on limited data, larger doses of rifampin (e.g., 1,200 mg) appear to produce the same maximum induction as lower doses, but more rapidly. Single doses of rifampin may not produce significant induction. In general, rifabutin as a CYP3A4 inducer is about 40% of the potency of rifampin, but this can vary by substrate and enzymatic reaction. In general, daily rifapentine (for active TB disease) is at least as potent an inducer as rifampin. However, the potential of drug interactions with once weekly rifapentine (prescribed with isoniazid for latent TB infection) is not well studied, and may result in reduced exposure of drugs that are CYP3A4 substrates. When using a rifamycin antibiotic with a potential interacting drug is necessary, close monitoring for clinical efficacy of the coadministered agent is advised.

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 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 2 of 15)

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.
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	↑ artemether and lumefantrine possible	Use with caution. Monitor for artemether and lumefantrine toxicities.
	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.
Atovaquone	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	↔ atovaquone (based on interaction data for atovaquone oral solution with ATV/r)	No dosage adjustment necessary.
	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.**

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 3 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Atovaquone/ Proguanil	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	↓ atovaquone and proguanil AUC (when coadministered with ATV/r or LPV/r)	Consider alternative drug for malaria prophylaxis.
Bedaquiline	Clarithromycin	↑ bedaquiline expected	**Do not coadminister.** Consider azithromycin in place of clarithromycin.
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	↑ bedaquiline expected	Coadministration should be avoided, if possible. Consider alternative HCV regimen.
	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 coadministration is required for >14 days, weigh the benefits of therapy against the risks of bedaquiline toxicities. If coadministered, monitor for bedaquiline toxicities.
	Posaconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Rifabutin[a]	↔ bedaquiline	If coadministered, monitor for rifabutin toxicities.
	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]	No data ↓ 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]	No data ↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 4 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
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 co-administered, monitor for chloroquine toxicities.
	Isavuconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Itraconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Posaconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Rifabutin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifampin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifapentine[a]	↓ 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
	Daclatasvir	↑ daclatasvir expected	Decrease daclatasvir dose to 30 mg once daily.
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	↑ clarithromycin and paritaprevir expected ↑ ombitasvir and dasabuvir possible	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Elbasvir/Grazoprevir	↑ elbasvir and grazoprevir expected	Coadministration should be avoided, if possible. If coadministered, monitor closely for hepatotoxicity. Consider azithromycin in place of clarithromycin.
	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.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 5 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Clarithromycin, continued	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); consider monitoring itraconazole concentration 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.
	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, monitoring clarithromycin and rifabutin concentrations, and monitoring 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	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for rifapentine toxicities; consider monitoring clarithromycin and rifapentine concentrations and adjusting doses accordingly.
	Voriconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
Daclatasvir	Clarithromycin	See Clarithromycin	See Clarithromycin
	Erythromycin	↑ daclatasvir possible	No dosage adjustment. Monitor for daclatasvir toxicities.
	Fluconazole	↑ daclatasvir possible	No dosage adjustment. Monitor for daclatasvir toxicities.
	Isavuconazole	↑ daclatasvir possible	Dose not established. Monitor for daclatasvir toxicities.
	Itraconazole	↑ daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Posaconazole	↑ daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Rifabutin[a]	↓ daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitor for therapeutic efficacy.
	Rifampin[a]	Daclatasvir AUC ↓ 79%	**Do not coadminister.**
	Rifapentine[a]	↓ daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitor for therapeutic efficacy.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 6 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Daclatasvir, continued	TDF	TFV AUC ↑ 10%	No dosage adjustment.
	Voriconazole	↑ daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
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.
	Rifapentine[a]	↓ dapsone expected	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
Dasabuvir/ Ombitasvir/ Paritaprevir/ Ritonavir	Artemether/ Lumefantrine	See Artemether/lumefantrine	See Artemether/Lumefantrine
	Atovaquone (oral solution)	See Atovaquone (oral solution)	See Atovaquone (oral solution)
	Atovaquone/ Proguanil	See Atovaquone/Proguanil	See Atovaquone/Proguanil
	Bedaquiline	See Bedaquiline	See Bedaquiline
	Clarithromycin	See Clarithromycin	See Clarithromycin
	Erythromycin	↑ erythromycin and paritaprevir expected ↑ ombitasvir and dasabuvir possible	Coadministration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Isavuconazole	Isavuconazole ↑ 96% and RTV AUC ↓ 31% (when studied with LPV/r) ↑ or ↓ paritaprevir, ombitasvir, and dasabuvir possible	Coadministration should be avoided, if possible. If coadministered, monitor for isavuconazole toxicity and HCV regimen-associated toxicities and efficacy.
	Itraconazole	↑ itraconazole and paritaprevir expected ↑ ombitasvir and dasabuvir possible	Itraconazole doses >200 mg/day are not recommended unless dosing is guided by itraconazole concentration. Monitor for itraconazole- and HCV regimen-associated toxicities.
	Mefloquine	RTV AUC ↓ 31% (based on study with RTV 200 mg twice daily)	Monitor for HCV antiviral activity.
	Posaconazole	↑ posaconazole and paritaprevir expected ↑ ombitasvir and dasabuvir possible	Monitor for posaconazole- and HCV regimen-associated toxicities. Monitor posaconazole concentration and adjust dose if necessary.
	Rifabutin[a]	↑ rifabutin expected ↓ paritaprevir possible	Coadministration should be avoided, if possible. With coadministration, decrease rifabutin dose to 150 mg/day and monitor rifabutin concentration. Monitor HCV regimen for efficacy.
	Rifampin[a]	↓ paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	**Do not coadminister.**
	Rifapentine[a]	↓ paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	**Do not coadminister.**
	Voriconazole	Voriconazole AUC ↓ 39% (when given with RTV 100 mg twice daily) ↑ paritaprevir expected	Coadminister only if the benefits outweigh the risk. Monitor voriconazole concentration to guide dosage adjustments.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 7 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Doxycycline	Atovaquone	See Atovaquone	See Atovaquone
	Rifabutin[a]	No data ↓ 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]	No data ↓ doxycycline possible	Monitor closely for doxycycline efficacy or consider alternative therapy.
Elbasvir/ Grazoprevir	Clarithromycin	See Clarithromycin	See Clarithromycin
	Erythromycin	↑ elbasvir and grazoprevir expected	Coadministration should be avoided, if possible. If coadministered, monitor closely for hepatotoxicity. Consider azithromycin in place of erythromycin.
	Isavuconazole	↑ elbasvir and grazoprevir expected	Coadministration should be avoided, if possible. If coadministered, monitor closely for hepatotoxicity.
	Itraconazole	↑ elbasvir and grazoprevir expected	Coadministration should be avoided, if possible. If coadministered, monitor closely for hepatotoxicity.
	Posaconazole	↑ elbasvir and grazoprevir expected	Coadministration should be avoided, if possible. If coadministered, monitor closely for hepatotoxicity.
	Rifabutin[a]	↓ elbasvir and grazoprevir possible	Coadministration should be avoided if possible. Consider alternative HCV regimen.
	Rifampin[a]	Grazoprevir AUC ↓ 7% and C_{24h} ↓ 90% ↓ elbasvir expected	**Do not coadminister.**
	Rifapentine[a]	↓ elbasvir and grazoprevir expected	**Do not coadminister.**
	Voriconazole	↑ elbasvir and grazoprevir expected	Coadministration should be avoided if possible. If coadministered, monitor closely for hepatotoxicity.
Erythromycin	Artemether/ Lumefantrine	See Artemether/Lumefantrine	See Artemether/Lumefantrine
	Bedaquiline	See Bedaquiline	See Bedaquiline
	Chloroquine	See Chloroquine	See Chloroquine
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	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.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 8 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Erythromycin, continued	Mefloquine	↑ mefloquine possible	**Do not coadminister.** Consider azithromycin in place of erythromycin.
	Posaconazole	↑ erythromycin expected	**Do not coadminister.** Consider azithromycin in place of erythromycin.
	Quinine	↑ quinine expected ↑ erythromycin possible	**Do not coadminister.** Consider azithromycin in place of erythromycin.
	Rifabutin[a]	↓ erythromycin possible ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy or rifabutin toxicities.
	Rifampin[a]	↓ erythromycin expected	Consider azithromycin in place of erythromycin. If co-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
	Daclatasvir	See Daclatasvir	See Daclatasvir
	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. Consider monitoring rifabutin concentration; 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	Coadminsitration should be avoided, if possible. Consider alternative agents.
	Rifampin[a]	Glecaprevir AUC ↓ 88% Pibrentasvir AUC ↓ 87%	**Do not coadminister.**
	Rifapentine[a]	↓ glecaprevir and pibrentasvir possible	**Do not coadminister.** Consider alternative agents.
	TDF	TFV AUC ↑ 29% when coadministered as EFV/TDF/FTC	Use usual dose. Monitor renal function or consider TAF.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 9 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Glecaprevir/ Pibrentasvir, continued	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
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	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 anti-fungal activity and rifabutin toxicity.
	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
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	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; monitor itraconazole concentration and adjust dose accordingly.

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 10 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Itraconazole, continued	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).
Ledipasvir/ Sofosbuvir	Rifabutin[a]	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**
	Rifampin[a]	Ledipasvir AUC ↓ 59% Sofosbuvir AUC ↓ 72%	**Do not coadminister.**
	Rifapentine[a]	↓ ledipasvir and sofosbuvir expected	**Do not coadminister.**
	TAF	Ledipasvir AUC ↑ 79% (when given with EVG/c/TAF/FTC)	No dosage adjustment.
	TDF	TFV AUC ↑ 98% (when given with EFV/FTC) TFV AUC ↑ 40% (when given with RPV/FTC) TFV AUC ↑ 50% (when given with DRV/r/FTC)	Monitor for TDF toxicities. Consider TAF in place of TDF.
Linezolid	Rifabutin[a]	↓ linezolid possible	Monitor for linezolid efficacy.
	Rifampin[a]	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy.
	Rifapentine[a]	↓ linezolid possible	Monitor for linezolid efficacy.
Mefloquine	Artemether/ Lumefantrine	See Artemether/Lumefantrine	See Artemether/Lumefantrine
	Clarithromycin	See Clarithromycin	See Clarithromycin
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Erythromycin	See Erythromycin	See Erythromycin
	Fluconazole	See Fluconazole	See Fluconazole
	Isavuconazole	See Isavuconazole	See Isavuconazole
	Itraconazole	See Itraconazole	See Itraconazole
	Posaconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Rifabutin[a]	↓ mefloquine possible	Monitor for mefloquine efficacy.
	Rifampin[a]	Mefloquine AUC ↓ 68%	**Do not coadminister.** Use alternative antimalarial drug or rifabutin.
	Rifapentine[a]	↓ 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

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 11 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Posaconazole, continued	Chloroquine	See Chloroquine	See Chloroquine
	Clarithromycin	See Clarithromycin	See Clarithromycin
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	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, monitor posaconazole and rifabutin concentrations 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, monitor posaconazole concentration and adjust dose accordingly; monitor for clinical response.
	Rifapentine[a]	↓ posaconazole expected	Coadministration should be avoided, if possible. If coadministered, monitor posaconazole concentration and adjust dose accordingly; monitor clinical response.
Quinine	Clarithromycin	See Clarithromycin	See Clarithromycin
	Erythromycin	See Erythromycin	See Erythromycin
	Fluconazole	See Fluconazole	See Fluconazole
	Itraconazole	See Itraconazole	See Itraconazole
	Posaconazole	See Posaconazole	See Posaconazole
	Rifabutin[a]	↓ quinine possible ↑ rifabutin possible	Monitor for quinine efficacy. Monitor rifabutin concentration and toxicity.
	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

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 12 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Rifabutin[a], continued	Clarithromycin	See Clarithromycin	See Clarithromycin
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Dapsone	See Dapsone	See Dapsone
	Doxycycline	See Doxycycline	See Doxycycline
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	Erythromycin	See Erythromycin	See Erythromycin
	Fluconazole	See Fluconazole	See Fluconazole
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir
	Isavuconazole	See Isavuconazole	See Isavuconazole
	Itraconazole	See Itraconazole	See Itraconazole
	Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir
	Linezolid	See Linezolid	See Linezolid
	Mefloquine	See Mefloquine	See Mefloquine
	Posaconazole	See Posaconazole	See Posaconazole
	Quinine	See Quinine	See Quinine
	Sofosbuvir	↓ sofosbuvir expected	**Do not coadminister.**
	Sofosbuvir/Velpatasvir +/- Voxilaprevir	↓ velpatasvir, voxilaprevir, and sofosbuvir expected	**Do not coadminister.**
	TAF	↓ TAF expected	**Do not coadminister.**
	Voriconazole	Voriconazole AUC ↓ 79% Rifabutin AUC ↑ 4-fold	**Do not coadminister.** Consider alternative antifungal and/or antimycobacterial agent(s). If coadministration is absolutely necessary, monitor voriconazole and rifabutin concentrations to guide therapy.
Rifampin[a]	Artemether/ Lumefantrine	See Artemether/Lumefantrine	See Artemether/Lumefantrine
	Atovaquone	See Atovaquone	See Atovaquone
	Bedaquiline	See Bedaquiline	See Bedaquiline
	Caspofungin	See Caspofungin	See Caspofungin
	Chloroquine	See Chloroquine	See Chloroquine
	Clarithromycin	See Clarithromycin	See Clarithromycin
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dapsone	See Dapsone	See Dapsone
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Doxycycline	See Doxycycline	See Doxycycline
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	Erythromycin	See Erythromycin	See Erythromycin
	Fluconazole	See Fluconazole	See Fluconazole
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 13 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Rifampin[a], continued	Isavuconazole	See Isavuconazole	See Isavuconazole
	Itraconazole	See Itraconazole	See Itraconazole
	Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir
	Linezolid	See Linezolid	See Linezolid
	Mefloquine	See Mefloquine	See Mefloquine
	Posaconazole	See Posaconazole	See Posaconazole
	Quinine	See Quinine	See Quinine
	Sofosbuvir	Sofosbuvir AUC ↓ 72%	**Do not coadminister.**
	Sofosbuvir/Velpatasvir +/- Voxilaprevir	Sofosbuvir AUC ↓ 72% Velpatasvir AUC ↓ 82% Voxilaprevir AUC ↓ 73%	**Do not coadminister.**
	TAF	**TAF plus Rifampin:** • 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 efficacy. **Note:** FDA labeling recommends not to coadminister.
	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
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dapsone	See Dapsone	See Dapsone
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Doxycycline	See Doxycycline	See Doxycycline
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir
	Erythromycin	See Erythromycin	See Erythromycin
	Fluconazole	See Fluconazole	See Fluconazole
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir
	Isavuconazole	See Isavuconazole	See Isavuconazole
	Itraconazole	See Itraconazole	See Itraconazole
	Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir
	Linezolid	See Linezolid	See Linezolid
	Mefloquine	See Mefloquine	See Mefloquine
	Posaconazole	See Posaconazole	See Posaconazole

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 14 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Rifapentine[a], continued	Quinine	See Quinine	See Quinine
	Sofosbuvir	↓ sofosbuvir expected	**Do not coadminister.**
	TAF	↓ TAF expected	**Do not coadminister.**
	Sofosbuvir/Velpatasvir +/- Voxilaprevir	↓ sofosbuvir, velpatasvir, and voxilaprevir expected	**Do not coadminister.**
	Voriconazole	↓ voriconazole expected	**Do not coadminister.** Consider alternative antifungal and/or antimycobacterial agent(s).
Sofosbuvir	Rifabutin[a]	See Rifabutin	See Rifabutin
	Rifampin[a]	See Rifampin	See Rifampin
	Rifapentine[a]	See Rifapentine	See Rifapentine
Sofosbuvir/ Velpatasvir +/- Voxilaprevir	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	TFV AUC ↑ 35% to 40% (when given with EVG/c/FTC or RPV/FTC) TFV AUC ↑ 81% (when given with EFV/FTC and SOF/VEL) TFV AUC ↑ 39% (when given with DRV/r/FTC and SOF/VEL/VOX)	Monitor for TDF toxicities. Consider TAF in place of TDF.
Tenofovir Alafenamide	Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir
	Rifabutin[a]	See Rifabutin	See Rifabutin
	Rifampin[a]	See Rifampin	See Rifampin
	Rifapentine[a]	See Rifapentine	See Rifapentine
	Sofosbuvir/Velpatasvir +/- Voxilaprevir	See Sofosbuvir/Velpatasvir +/- Voxilaprevir	See Sofosbuvir/Velpatasvir +/- Voxilaprevir
Tenofovir Disoproxil Fumarate	Daclatasvir	See Daclatasvir	See Daclatasvir
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir
	Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir	See Ledipasvir/Sofosbuvir
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir +/- Voxilaprevir	See Sofosbuvir/Velpatasvir +/- Voxilaprevir
Voriconazole	Artemether/ Lumefantrine	See Artemether/Lumefantrine	See Artemether/Lumefantrine
	Bedaquiline	See Bedaquiline	See Bedaquiline
	Chloroquine	See Chloroquine	See Chloroquine
	Clarithromycin	See Clarithromycin	See Clarithromycin
	Daclatasvir	See Daclatasvir	See Daclatasvir
	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir	See Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir
	Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir	See Elbasvir/Grazoprevir

Table 5. Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections (page 15 of 15)

Primary Drug	Interacting Agent	Effect on Primary and/ or Concomitant Drug Concentrations	Recommendations
Voriconazole, continued	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] Rifamycin antibiotics are potent inducers of Phase 1 and Phase 2 drug-metabolizing reactions. Studies have demonstrated that with daily doses of rifampin, enzyme induction increases over a week or more. Based on limited data, larger doses of rifampin (e.g., 1,200 mg) appear to produce the same maximum induction as lower doses, but more rapidly. Single doses of rifampin may not produce significant induction. In general, rifabutin is about 40% as potent a CYP3A4 inducer as rifampin, but this can vary by substrate and enzymatic reaction. In general, daily rifapentine (for active TB disease) is at least as potent an inducer as rifampin. However, the potential of drug interactions with once weekly rifapentine (for latent TB infection, along with isoniazid) is not well studied, and may result in reduced exposure of drugs that are CYP3A4 substrates. When a rifamycin antibiotic is given with a potential interacting drug, close monitoring for clinical efficacy of the coadministered agent is advised.

Key to Symbols:

↑ = increase

↓ = decrease

↔ = no change

Key: 14-OH = active metabolite of clarithromycin; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; AUC = area under the curve; C_{24h} = concentration at 24 hours post dose; C_{min} = minimum concentration; C_{SS} = concentration at steady state; CYP3A4 = Cytochrome P450 3A4; des-Rbt = desacetyl rifabutin; DHA = dihydroartemisinin; DRV/r = darunavir/ritonavir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; HCV = hepatitis C virus; LPV/r = lopinavir/ritonavir; OI = opportunistic infection; PK = pharmacokinetic; RPV = rilpivirine; RTV = ritonavir; SOF = sofosbuvir; $T_{1/2}$ = half-life; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TFV= tenofovir; TFV-DP = tenofovir diphosphate; VEL = velpastavir; VOX = voxilaprevir

Table 6. Common or Serious Adverse Reactions Associated with Systemically Administered Drugs Used to Treat Opportunistic Infections (page 1 of 6) (Last updated October 22, 2019; last reviewed October 22, 2019)

Drug(s)	Common or Serious Adverse Reactions
Acyclovir	Crystalluria associated with high doses, dehydration, or pre-existing renal impairment; nephrotoxicity secondary to obstructive urolithiasis, particularly after high dose rapid IV infusion; neurotoxicity (e.g., agitation, confusion, hallucination, seizure, coma) with high doses, especially in patients with renal impairment and/or older patients; thrombophlebitis at peripheral IV infusion site; nausea; vomiting; headache
Adefovir	Nausea, asthenia, nephrotoxicity (especially in patients with underlying renal insufficiency or predisposing comorbidities, or in patients who are currently taking nephrotoxic drugs)
Albendazole	Nausea, vomiting, hepatotoxicity, hypersensitivity reaction, dizziness, headache, reversible alopecia **Rarely:** Granulocytopenia, agranulocytosis, pancytopenia
Amikacin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), neuromuscular blockade (associated with rapid infusion of large aminoglycoside doses), pain upon IM injection
Amoxicillin/Clavulanate and Ampicillin/Sulbactam	Diarrhea, nausea, vomiting, abdominal pain, *Clostridium difficile*-associated diarrhea and colitis, hypersensitivity reactions (immediate or delayed reactions, including anaphylaxis), bone marrow suppression, drug fever, neurotoxicity (seizure) at high doses (especially in patients with renal dysfunction)
Amphotericin B Deoxycholate and Lipid Formulations	Nephrotoxicity, infusion-related reactions (e.g., fever, chills, rigors, back pain, hypotension), hypokalemia, hypomagnesemia, anemia, thrombophlebitis, nausea, vomiting Lower incidence of nephrotoxicity and infusion-related reactions with liposomal formulations.
Anidulafungin	Generally well-tolerated. Hepatotoxicity, histamine-related infusion reactions (flushing, rash, pruritus, hypotension, and dyspnea are rare when infusion rate <1.1 mg/min), hypokalemia, diarrhea
Artemether/Lumefantrine	Generally well-tolerated. Rash, pruritus, nausea, vomiting, abdominal pain, anorexia, diarrhea, arthralgia, myalgia, dizziness, asthenia, headache, QTc prolongation **Rarely:** Hemolytic anemia
Artesunate	Generally well-tolerated. Bradycardia, dizziness, nausea and vomiting, skin rash, pruritus, postartemisinin delayed hemolysis, QTc prolongation
Atovaquone	Rash, nausea, vomiting, diarrhea, hepatotoxicity, headache, hyperglycemia, fever
Atovaquone/Proguanil	Pruritus, rash, nausea, vomiting, abdominal pain, diarrhea, anorexia, erythema multiforme, asthenia, dizziness, headache, oral ulcers, hepatotoxicity
Azithromycin	Nausea, vomiting, diarrhea, hepatotoxicity, ototoxicity (with prolonged use), rash, urticaria, pruritus, abdominal pain, *C. difficile*-associated diarrhea **Rarely:** Torsades de Pointes (greatest risk in patients with underlying QTc prolongation)
Aztreonam	Diarrhea, thrombophlebitis, neutropenia, increased liver enzymes, *C. difficile*-associated diarrhea **Rarely:** Hypersensitivity reaction
Benznidazole	Photosensitivity, allergic dermatitis, paresthesia, peripheral neuropathy, nausea, vomiting, abdominal pain, anorexia, weight loss, bone marrow suppression
Bedaquiline	Nausea, arthralgia, headache, QTc prolongation, elevated transaminases
Capreomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), pain upon IM injection
Caspofungin	Generally well-tolerated. Fever, thrombophlebitis, histamine-related infusion reactions (flushing, rash, pruritus, facial swelling, hypotension, dyspnea), hypokalemia, anemia, headache, hepatotoxicity, diarrhea

Table 6. Common or Serious Adverse Reactions Associated with Systemically Administered Drugs Used to Treat Opportunistic Infections (page 2 of 6)

Drug(s)	Common or Serious Adverse Reactions
Ceftriaxone	Generally well-tolerated. Cholelithiasis, urolithiasis, pancreatitis, rash, diarrhea, drug fever, hemolytic anemia, *C. difficile*-associated diarrhea and colitis, injection-site reactions after IM injections
Cephalosporins **See above for Ceftriaxone**	Hypersensitivity reaction, rash, nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, bone marrow suppression, hemolytic anemia **Rarely:** CNS toxicities (e.g., seizure, confusion) mostly seen with high doses used in patients with renal insufficiency or elderly patients without dose adjustment
Chloroquine and Hydroxychloroquine	Headache, pruritus, skin pigmentation, nausea, vomiting, abdominal pain, diarrhea, anorexia, photosensitivity, visual disturbances including blurry vision and retinal toxicity, auditory disturbances, QTc prolongation, cardiomyopathy, bone marrow suppression, hemolysis (associated with G6PD deficiency), hypersensitivity reaction (including TEN, SJS, and EM), hepatitis, neuropsychiatric changes (including extrapyramidal reactions and suicidal behavior), convulsive seizures, severe hypoglycemia (which may require adjustment of antidiabetic medications) **Rarely:** Neuromyopathy (which may occur with long-term use)
Cidofovir	Nephrotoxicity, proteinuria, ocular hypotony, anterior uveitis/iritis, neutropenia, metabolic acidosis (including Fanconi's syndrome), diarrhea, asthenia, fever, headache, alopecia, anemia Side effects most likely related to co-administration with probenecid are rash, nausea, vomiting, anorexia.
Ciprofloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with age >60 and concomitant steroid use), photosensitivity, hypoglycemia, peripheral neuropathy, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures, and mental health side effects (e.g., disorientation, agitation, memory impairment, delirium) **Rarely:** Aortic dissection
Clarithromycin	Hepatotoxicity, ototoxicity (with high doses or prolonged use), headache, nausea, vomiting, abdominal cramps, diarrhea, *C. difficile*-associated diarrhea and colitis, rash, QTc prolongation, dysgeusia
Clindamycin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, rash, arrhythmia associated with rapid IV infusion, metallic taste (with IV infusion), thrombophlebitis, abnormal liver function tests
Clotrimazole (Troche)	Generally well-tolerated. Nausea, vomiting, anorexia, metallic taste **Rarely:** Increase in serum transaminases
Cycloserine	Neuropsychiatric toxicities (e.g., headache, somnolence, lethargy, vertigo, tremor, dysarthria, irritability, confusion, paranoia, psychosis), seizures (particularly in patients with history of chronic alcoholism), allergic dermatitis, rash
Dapsone	Methemoglobinemia, hemolytic anemia (especially in patients with G6PD deficiency), neutropenia, dermatologic reactions (including rash), sulfone syndrome (fever, exfoliative dermatitis, lymphadenopathy, hepatic necrosis, hemolysis), peripheral neuropathy, hepatotoxicity, drug-induced lupus erythematosus, nephrotic syndrome, phototoxicity
Daclatasvir	Fatigue, headache, nausea, anemia, bradycardia (when co-administered with sofosbuvir and amiodarone)
Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir	Hepatotoxicity, nausea, pruritus, rash, insomnia, fatigue, asthenia, dyspnea (associated with ribavirin co-administration)
Doxycycline	Photosensitivity reaction, nausea, vomiting, diarrhea, esophageal ulceration, thrombophlebitis (with IV infusion), intracranial hypertension, *C. difficile*-associated diarrhea and colitis, tissue hyperpigmentation **Rarely:** Hepatotoxicity

Table 6. Common or Serious Adverse Reactions Associated with Systemically Administered Drugs Used to Treat Opportunistic Infections (page 3 of 6)

Drug(s)	Common or Serious Adverse Reactions
Elbasvir/Grazoprevir	Fatigue, headache, nausea, ALT elevations, anemia (when given with ribavirin)
Emtricitabine	Generally well-tolerated. Headache, nausea, skin hyperpigmentation, diarrhea, rash
Entecavir	Generally well-tolerated. Headache, fatigue, dizziness, nausea
Erythromycin	Nausea, vomiting, diarrhea, abdominal pain, anorexia, rash, hepatotoxicity, cholestatic jaundice, ototoxicity (hearing loss, tinnitus), rash, QTc prolongation and cardiac arrhythmia, *C. difficile*-associated diarrhea and colitis, thrombophlebitis (with IV infusion)
Ethambutol	Optic neuritis (dose dependent), peripheral neuropathy, headache, nausea, vomiting, anorexia
Ethionamide	Dose-dependent gastrointestinal side effects (nausea, vomiting, diarrhea, abdominal pain, metallic taste, anorexia), dizziness, drowsiness, depression, postural hypotension, hepatotoxicity, hypothyroidism (with or without goiter), gynecomastia, impotence, hypoglycemia
Famciclovir	Generally well-tolerated. Headache, nausea, vomiting, diarrhea, nephrotoxicity (in patients with underlying renal disease)
Flucytosine	Concentration-dependent bone marrow suppression (anemia, neutropenia, thrombocytopenia), diarrhea, nausea, vomiting, rash, hepatotoxicity
Fluconazole	Hepatotoxicity, rash, nausea, vomiting, diarrhea, abdominal discomfort, reversible alopecia (with doses ≥400 mg/day for >2 months), QTc prolongation
Foscarnet	Nephrotoxicity, electrolyte imbalances (e.g., hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, hypokalemia), penile ulceration, nausea, vomiting, anorexia, headache, seizure (associated with electrolyte imbalances), anemia, injection-site associated thrombophlebitis
Fumagillin (Investigational)	**Oral Therapy:** Neutropenia, thrombocytopenia, vertigo, nausea, vomiting, diarrhea, anorexia, abdominal cramps **Ocular Therapy:** Minimal systemic effect or local effect
Ganciclovir	Neutropenia, thrombocytopenia, anemia, injection-site-associated thrombophlebitis, increased serum creatinine, carcinogenic and teratogenic potential, impaired fertility, neuropathy
Glecaprevir/Pibrentasvir	Generally well tolerated with only 0.1% discontinuation due to adverse reaction in clinical trials. Mild headache, fatigue, nausea, diarrhea
Imipenem/Cilastatin	Hypersensitivity reaction (immediate or delayed); nausea; vomiting; diarrhea; *C. difficile*-associated diarrhea and colitis; thrombophlebitis; headache; bone marrow suppression; drug fever; CNS effects (seizure, myoclonus, and confusion) especially with higher doses, in patients with underlying CNS disorders, or with renal insufficiency
Interferon-Alfa and Peginterferon-Alfa	Flu-like syndrome (e.g., fever, headache, fatigue, myalgia), neuropsychiatric disorders (e.g., depression, suicidal ideation), neutropenia, anemia, thrombocytopenia, thyroid dysfunction, injection-site reactions, alopecia, nausea, anorexia, diarrhea, weight loss, development or exacerbation of autoimmune disorders, ocular effects (e.g., retinal hemorrhage, retinal artery or vein obstructions, and cotton wool spots)
Isavuconazonium Sulfate	Hepatotoxicity, cholelithiasis, infusion-related reaction (hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia), hypersensitivity reaction (e.g., anaphylaxis, rash, SJS), nausea, vomiting, diarrhea, headache, hypokalemia, dyspnea, cough. Adverse events primarily reported in immunocompromised patients.
Isoniazid	Hepatotoxicity, peripheral neuropathy, optic neuritis, psychosis, diarrhea, nausea **Rarely:** Psychosis
Itraconazole	Hepatotoxicity, congestive heart failure, edema, hypokalemia, nausea, vomiting, diarrhea, abdominal pain, rash, QTc prolongation, neuropathy
Lamivudine	Generally well-tolerated. Nausea, vomiting.
Ledipasvir/Sofosbuvir	Fatigue, headache, asthenia (most common), nausea, diarrhea, insomnia, mild transient asymptomatic lipase elevation, mild bilirubin elevation

Table 6. Common or Serious Adverse Reactions Associated with Systemically Administered Drugs Used to Treat Opportunistic Infections (page 4 of 6)

Drug(s)	Common or Serious Adverse Reactions
Levofloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with age >60 years and concomitant steroid use), photosensitivity, hypoglycemia, peripheral neuropathy, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in older patients, or in patients with renal dysfunction), seizures, and mental health side effects (e.g., disorientation, agitation, memory impairment, delirium) **Rarely:** Aortic dissection
Linezolid	Anemia, neutropenia, thrombocytopenia (especially with treatment lasting longer than 2–4 weeks), peripheral neuropathy, 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), diarrhea, headache, nausea, vomiting **Rarely:** Lactic acidosis
Mefloquine	Depression, psychosis, anxiety, rash (reports of TEN and SJS), nausea, vomiting, diarrhea, epigastric pain, agitation, dizziness, headache, insomnia, abnormal dreams, QTc prolongation, arrhythmias (extrasystole, sinus bradycardia), agranulocytosis/aplastic anemia
Meropenem	Generally well-tolerated. Hypersensitivity reaction (immediate or delayed), nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, headache, bone marrow suppression, drug fever
Micafungin	Generally well-tolerated. Histamine-related infusion reactions (e.g., flushing, rash, pruritus, hypotension, dyspnea) may occur, but these are rare if infusion lasts over 1 hour; anaphylaxis and anaphylactoid reaction, hepatotoxicity, thrombophlebitis, nausea, vomiting, diarrhea, hypokalemia **Rarely:** Hemolysis
Miconazole Buccal Tablets	Dysgeusia, diarrhea, nausea, vomiting, upper abdominal pain, headache, local reactions (oral discomfort, burning, pain, tongue/mouth ulceration, gingival pruritus, swelling, dry mouth) **Rarely:** Hypersensitivity reaction (may occur in patients with known hypersensitivity reaction to milk product concentrate)
Miltefosine	Nausea, vomiting, diarrhea, headache, motion sickness, leukocytosis, thrombocytosis, nephrotoxicity, retinal degeneration, elevated transaminases and bilirubin, teratogenic potential, impaired fertility
Moxifloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with age >60 years and concomitant steroid use), photosensitivity, hypoglycemia, peripheral neuropathy, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients or in patients with renal dysfunction), seizures, and mental health side effects such as disorientation, agitation, memory impairment, delirium **Rarely:** Aortic dissection
Nifurtimox	Anorexia, weight loss, nausea, vomiting, abdominal pain, headache, dizziness, mood changes, insomnia, myalgia, peripheral neuropathy, rash, pruritus, memory loss
Nitazoxanide	Generally well-tolerated. Nausea, vomiting, diarrhea, abdominal pain, headache
Nystatin (Oral Preparations)	Unpleasant taste, nausea, vomiting, anorexia, diarrhea **Rarely:** Hypersensitivity reaction
Paromomycin	Nausea, vomiting, cramps, anorexia, rash, headache **Rarely:** Nephrotoxicity and ototoxicity (inflammatory bowel disease and renal insufficiency may increase risk)

Table 6. Common or Serious Adverse Reactions Associated with Systemically Administered Drugs Used to Treat Opportunistic Infections (page 5 of 6)

Drug(s)	Common or Serious Adverse Reactions
Penicillin G	**All Penicillin G Preparations:** Hypersensitivity reactions (immediate or delayed reactions, including anaphylaxis), bone marrow suppression, nausea, vomiting, diarrhea, *C. difficile*-associated diarrhea and colitis, drug fever **Benzathine Penicillin G and Procaine Penicillin G:** IM injection-site reactions (pain and erythema), procaine neuropsychiatric reactions (with high dose), neurovascular damage (due to inadvertent intravascular instead of IM injection) **Aqueous Crystalline Penicillin G (IV):** Thrombophlebitis, neurotoxicity at high doses, especially in patients with renal dysfunction
Pentamidine	**IV Infusion:** Nephrotoxicity, infusion-related hypotension, thrombophlebitis, QTc prolongation, arrhythmias (including Torsades de Pointes), pancreatitis, hypoglycemia, hyperglycemia, diabetes mellitus, hepatotoxicity, electrolyte abnormalities, leucopenia, thrombocytopenia **Aerosolized Therapy:** Bronchospasm, cough, dyspnea, tachypnea, metallic taste **Rarely:** Pancreatitis
Pentavalent Antimony (Sodium Stibogluconate)	Nausea, vomiting, abdominal pain, anorexia, headache, hepatotoxicity, arthralgia, myalgia, cardiac toxicity with >20 mg/kg dose (prolonged QTc and T wave inversion), rash, thrombophlebitis, leukopenia, anemia, thrombocytopenia **Rarely:** Pancreatitis
Posaconazole	Nausea, vomiting, diarrhea, abdominal pain, headache, hepatotoxicity, hypokalemia, QTc prolongation, rash **IV Infusion:** Thrombophlebitis, cyclodextrin accumulation (especially in patients with eGFR <50 mL/min, but an observational study did not show an increased risk of nephrotoxicity)
Piperacillin-Tazobactam	Generally well-tolerated. Hypersensitivity reaction, rash, diarrhea, nausea, vomiting, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, impaired platelet aggregation, seizure (with high doses used in patients with renal insufficiency) **Rarely:** Thrombocytopenia
Primaquine	Methemoglobinemia, hemolytic anemia (especially in patients with G6PD deficiency), leukopenia, neutropenia, abdominal cramps, nausea, vomiting, QTc prolongation, pruritus, rash, dizziness
Pyrazinamide	Hepatotoxicity, hyperuricemia, arthralgia, myalgia, nausea, vomiting, rash
Pyrimethamine	Neutropenia, thrombocytopenia, megaloblastic anemia, rash
Quinidine Glucuronate	QTc prolongation, lightheadedness, nausea, vomiting, diarrhea, abdominal pain, drug-induced SLE, headache, rash, hemolysis (with G6PD deficiency), hepatotoxicity, heartburn/esophagitis, cinchonism (tinnitus, vertigo, blurred vision)
Quinine	Headache, nausea, vomiting, diarrhea, cinchonism (tinnitus, vertigo, blurred vision), hypersensitivity reaction, hypoglycemia, thrombocytopenia, QTc prolongation
Ribavirin	Hemolytic anemia, dyspnea, hyperbilirubinemia, fatigue, myalgia, headache, nausea, vomiting, anorexia, dyspepsia, rash, dry cough, teratogenicity, hypersensitivity reaction, hepatotoxicity
Rifabutin	Hepatotoxicity, anterior uveitis (dose dependent), red-orange discoloration of body fluids, rash, arthralgia, neutropenia, nausea, vomiting, abdominal pain, diarrhea, anorexia
Rifampin	Hepatotoxicity (cholestatic hepatitis), red-orange discoloration of body fluids, thrombocytopenia, hemolytic anemia, rash, hypersensitivity reactions with flu-like syndrome, nausea, vomiting, anorexia, abdominal pain, flatulence, diarrhea, renal failure, headache, confusion
Rifapentine	Hypersensitivity reaction, hepatotoxicity, anemia, lymphopenia, neutropenia, arthralgia, conjunctivitis, headache, vomiting, nausea, diarrhea, rash, pruritus, anorexia and lymphadenopathy, red-orange discoloration of body fluids, *C. difficile*-associated diarrhea and colitis

Table 6. Common or Serious Adverse Reactions Associated with Systemically Administered Drugs Used to Treat Opportunistic Infections (page 6 of 6)

Drug(s)	Common or Serious Adverse Reactions
Sofosbuvir	Generally well-tolerated. Fatigue, headache, nausea, insomnia, anemia, bilirubin elevation (associated with ribavirin co-administration), asymptomatic CK elevation and lipase elevation, pancytopenia, depression (associated with Peg-IFN co-administration)
Streptomycin	Nephrotoxicity, ototoxicity (both hearing loss and vestibular toxicity are possible), neuromuscular blockade (associated with rapid infusion of large aminoglycoside doses), pain upon IM injection
Sulfadiazine	Rash (including SJS, EM, and TEN), anemia, neutropenia, thrombocytopenia, crystalluria (with or without urolithiasis), renal insufficiency, nausea, vomiting, drug fever, hepatotoxicity, headache, peripheral neuritis, tinnitus, vertigo, insomnia
Tafenoquine	Dizziness, nausea, vomiting, headache, hypersensitivity reactions, decreased hemoglobin, methemoglobinemia, hemolytic anemia (associated with G6PD deficiency; may cause harm to fetuses and breastfeeding infants who are GDPD deficient), psychiatric adverse reactions (in patients with history of psychiatric illness)
Telavancin	Taste disturbance, nausea, vomiting, diarrhea, red-man syndrome with rapid infusion (flushing, urticaria, pruritus, rash), nephrotoxicity, QTc prolongation, headache, dizziness, *C. difficile*-associated colitis
Telbivudine	Generally well-tolerated. Nausea, vomiting, abdominal pain, increase in creatine kinase, headache, dizziness, fatigue, diarrhea, myopathy, myalgia, cough, fever, dyspepsia, abdominal pain
Tenofovir DF	Renal insufficiency, proximal renal tubulopathy (with hypophosphatemia, hypouricemia, normoglycemic glycosuria), decrease in bone mineral density, nausea
Tenofovir Alafenamide	Lower incidence of renal or bone toxicities than with tenofovir DF
Tetracycline	Photosensitivity, tooth discoloration when taken by infants and children aged <8 years, reduced skeletal development, pruritus, esophageal ulceration, nausea, vomiting, diarrhea, hepatotoxicity, rash, increased BUN, intracranial hypertension
Trimethoprim-Sulfamethoxazole	Rash (including SJS, EM, and TEN), photosensitivity, anemia, neutropenia, thrombocytopenia, hepatotoxicity, dose dependent increase in serum creatinine (without change in GFR), interstitial nephritis, nausea, vomiting, crystalluria (in patients with inadequate hydration), hyperkalemia (more common with high-dose TMP), drug fever
Valacyclovir	Generally well-tolerated. Nausea; vomiting; headache; crystalluria (with high dose or in patients with renal impairment); neurotoxicity (e.g., agitation, confusion, hallucination, seizure, coma) with high doses, especially in patients with renal impairment; abdominal pain
Valganciclovir	Neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, confusion, pyrexia, tremor, acute renal failure, carcinogenic and teratogenic potential, impaired fertility
Vancomycin	Infusion-related reactions (associated with infusion rate and can include flushing, hypotension, and rash), thrombophlebitis, rash, neutropenia, ototoxicity (associated with excessive concentration), nephrotoxicity (associated with high daily dose and high trough concentrations) **Rarely:** Thrombocytopenia
Velpatasvir/Sofosbuvir	Generally well tolerated. Headache, fatigue, and anemia (associated with ribavirin co-administration)
Voriconazole	Visual disturbances (associated with initial dosing), optic neuritis (associated with >28 days treatment), skin photosensitivity, hepatotoxicity, fever, nausea, rash, vomiting, chills, tachycardia, QTc prolongation, peripheral edema, headache, delirium, hallucination, encephalopathy (associated with trough >5.5 mcg/mL), fluorosis and periostitis with high dose and/or prolonged use, cyclodextrin accumulation (associated with use of IV formulation in patients with CrCl <50 mL/min, but an observational study did not show an increased risk of nephrotoxicity) **Rarely:** Peripheral neuropathy

Key: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; CNS = central nervous system; CrCl = creatinine clearance; eGFR = estimated glomerular filtration rate; EM = erythema multiforme; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; IM = intramuscular; IV = intravenous; Peg-IFN = peginterferon alpha; SJS = Stevens-Johnson syndrome; SLE = systemic lupus erythematosus; TEN = toxic epidermal necrolysis

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 1 of 8) (Last updated October 22, 2019; last reviewed October 22, 2019)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	Dose
Acyclovir	**IV Dose** *Serious HSV:* • 5 mg/kg IV every 8 hours *VZV Infections:* • 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/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
Amikacin For mycobacterial infections	IV 15 mg/kg per day *or* 25 mg/kg three times per week	Use with caution in patients with renal insufficiency and family history of ototoxicity.	Adjust dose based on serum concentrations with target peak concentration 35–45 mcg/mL and trough concentration <4 mcg/mL. Administer dose after HD on day of dialysis.
Amphotericin B	0.7–1.0 mg/kg IV per day (amphotericin B deoxycholate) *or* 3–6 mg/kg IV per day (lipid formulation)	N/A	No dosage adjustment necessary; consider alternative antifungals if renal insufficiency occurs during therapy despite adequate hydration.
Capreomycin	15 mg/kg IV or IM per day	Use with caution in patients with renal insufficiency.	Adjust dose based on serum concentrations with target peak concentration 35–45 mcg/mL and trough concentration <4 mcg/mL. Administer dose after HD on day of dialysis.
Chloroquine (Base)	**For Treatment of Acute Malaria:** • 1 g (600 mg base) PO for 1 dose, followed by 500 mg (300 mg base) PO at 6, 24, and 48 hours (for a total dose of 1,500 mg)	<10	50% of dose
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 *or* CrCl <55 mL/min *or* Proteinuria ≥100 mg/dL (≥2 +)	Cidofovir **is not recommended**.
		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 *or* Proteinuria ≥3 +	Discontinue therapy

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 2 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	Dose
Ciprofloxacin	500–750 mg PO every 12 hours *or* 400 mg IV every 8–12 hours	30–50	500–750 mg PO every 12 hours *or* 400 mg IV every 12 hours
		<30	250–500 mg PO every 24 hours *or* 400 mg IV every 24 hours
		HD or PD	250–500 mg PO every 24 hours *or* 200–400 mg IV every 24 hours; administer after HD or PD on day of dialysis.
Clarithromycin	500 mg PO every 12 hours	30–60	Usual dose except when used with an HIV PI or with COBI, then reduce dose by 50%.
		<30	250 mg PO twice daily *or* 500 mg PO once daily If used with an HIV PI or COBI, reduce dose by 75% (or consider using azithromycin as alternative).
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	50–80	Usual dose; consider monitoring serum concentration and toxicities.
		<50 (not on HD)	Monitor serum concentrations (target peak concentration 20–35 mcg/mL) and adjust dose accordingly. Use with caution in patients with ESRD who are not on dialysis.
		HD	250 mg PO once daily or 500 mg PO three times per week; monitor serum cycloserine concentration (target peak concentration 20–35 mcg/mL).
Emtricitabine (FTC)	One 200–mg tablet PO once daily *or* 240 mg solution PO once daily	30–49	**Oral Tablets:** 200 mg every 48 hours **Oral Solution:** 120 mg every 24 hours
		15–29	**Oral Tablets:** 200 mg every 72 hours **Oral Solution:** 80 mg every 24 hours
		<15 or HD (administer dose after dialysis)	**Oral Tablets:** 200 mg every 96 hours **Oral Solution:** 60 mg every 24 hours
Emtricitabine/Tenofovir Alafenamide (FTC/TAF) (FDC Trade Name: Descovy) **Note:** Please refer to product information for dosing recommendations for other ARV FDC products containing FTC/TAF.	One (FTC 200 mg/TAF 25 mg) tablet PO once daily	<30	Coformulated tablet **is not recommended**.

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 3 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	**Dose**
Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) (FDC Trade Name: Truvada) **Note:** Please refer to product information for dosing recommendations for other ARV FDC products containing FTC/TDF.	One (FTC 200 mg/TDF 300 mg) tablet PO daily	30–49	1 tablet PO every 48 hours (monitor for worsening renal function or consider switching to TAF)
		<30 or HD	**<u>Do not use</u>** coformulated tablet in patients with CrCl <30 mL/min. 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	30 to <50	**Usual Renal Dose Adjustment:** • 0.25 mg PO every 24 hours, *or* • 0.5 mg PO every 48 hours **3TC-Refractory or Decompensated Liver Disease:** • 0.5 mg PO every 24 hours, *or* • 1 mg PO every 48 hours
		10 to <30	**Usual Renal Dose Adjustment:** • 0.15 mg PO every 24 hours, *or* • 0.5 mg PO every 72 hours **3TC-Refractory or Decompensated Liver Disease:** • 0.3 mg PO every 24 hours, *or* • 1 mg PO every 72 hours
		<10 or HD or CAPD (administer after HD or CAPD on dialysis day)	**Usual Renal Dose Adjustment:** • 0.05 mg PO every 24 hours, *or* • 0.5 mg PO once every seven days **3TC-Refractory or Decompensated Liver Disease:** • 0.1 mg PO every 24 hours, *or* • 1 mg PO once every seven days
Ethambutol	**For MAI:** 15 mg/kg PO daily **For MTB:** 15–25 mg/kg PO daily (See Table 3 for additional MTB dosing recommendations.)	<30 or HD	Usual dose PO three times weekly (in patients on HD, give dose after dialysis) Consider 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
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

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 4 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	**Dose**
Fluconazole	200–1,200 mg PO or IV every 24 hours (dose and route of administration depends on type of OI)	≤50	50% of dose every 24 hours
		HD	Administer full dose after HD on days of dialysis
Flucytosine	25 mg/kg PO every 6 hours TDM is recommended for all patients to guide optimal dosing (target peak serum concentration 2 hours after dose: 30–80 mcg/mL).	21–40	25 mg/kg PO every 12 hours
		10–20	25 mg/kg PO every 24 hours
		<10	25 mg/kg PO every 48 hours
		HD	25–50 mg/kg PO every 48–72 hours; administer dose after HD
Foscarnet	**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	**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 (3TC)	300 mg PO every 24 hours	30–49	150 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 dialysis day
Lamivudine/Tenofovir Disoproxil Fumarate (3TC/TDF) (FDC Trade Names: Cimduo or Temixys) **Note:** Please refer to product information for dosing recommendations for other ARV FDC products containing 3TC/TDF.	One (3TC 300 mg/TDF 300 mg) tablet PO every 24 hours	<50	Coformulated tablet **is not recommended**.
Ledipasvir/Sofosbuvir	One (ledipasvir 90 mg/sofosbuvir 400 mg) tablet PO once daily	<30	Co-formulated tablet **is not recommended**. No dose has been established because of up to 20-fold higher sofosbuvir metabolite observed at this level of renal impairment.

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 5 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	Dose
Levofloxacin	500 mg (low dose) or 750-1,000 mg (high dose) IV or PO daily	20–49	**Low Dose:** 500 mg once, then 250 mg every 24 hours, IV or PO **High Dose:** 750 mg every 48 hours IV or PO
		<20 or CAPD or HD (administer dose after HD or CAPD on days of dialysis)	**Low Dose:** • 500 mg once, then 250 mg every 48 hours, IV or PO • Dose can be adjusted based on serum concentrations. **High Dose:** 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
Peginterferon Alfa-2b	1.5 mcg/kg SQ once weekly	30–50	Reduce dose by 25%
		10–29 and HD	Reduce dose by 50%
Penicillin G (Potassium or Sodium)	**Neurosyphilis, Ocular Syphilis, or Otosyphilis:** • 3–4 million units IV every 4 hours, *or* • 18–24 million units IV daily as continuous infusion	10–50	2–3 million units every 4 hours *or* 12–18 million units as continuous infusion
		<10	2 million units every 4–6 hours *or* 8–12 million units as continuous infusion
		HD or CAPD	2 million units every 6 hours *or* 8 million units as continuous infusion
Pentamidine	4 mg/kg IV every 24 hours	10–50	3 mg/kg IV every 24 hours
		<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. Monitor posaconazole concentrations (target trough concentration >1.25 mcg/mL). IV posaconazole **is not recommended** by the manufacturer because of potential toxicity due to accumulation of sulfobutylether cyclodextrin (vehicle of IV product). However, an observational study did not find worsening in renal function in patients with CrCl <50 ml/min given sulfobutylether cyclodextrin. Switch patients with CrCl <50 ml/min to oral posaconazole when feasible.
Pyrazinamide	See Table 3 for weight-based dosing guidelines.	<30 or HD	25–35 mg/kg/dose three times per week; administer dose after HD on dialysis days

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 6 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	Dose
Quinidine Gluconate (Salt) **Note:** 10 mg quinidine gluconate salt = 6.25 mg quinidine base	10 mg/kg (salt) IV over one to two hours, then 0.02 mg/kg/min (salt) IV for up to 72 hours or until able to take oral meds	<10	75% of usual dose
		HD	75% of usual dose; some clinicians recommend supplementation with 100–200 mg IV after HD on days of dialysis. Consider TDM for all patients to optimize dosing.
Quinine Sulfate	650 mg salt (524 mg base) PO every 8 hours	<10 or HD	650 mg once, then 325 mg PO every 12 hours
Ribavirin	**For Genotypes 1 and 4:** 1,000–1,200 mg PO per day in two divided doses (based on weight; see Table 2 for full dosing recommendation) **For Genotypes 2 and 3:** 400 mg PO twice daily	30–50	Alternate dosing 200 mg PO and 400 mg PO every other day
		<30 or HD	200 mg PO daily (based on limited data)
Rifabutin	5 mg/kg PO daily (usually 300 mg PO daily) See Table 3 and Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage adjustment based on interactions with ARVs.	<30	Consider 50% of dose once daily if toxicity is suspected. Monitor serum concentration and adjust dose as needed.
Rifampin	10 mg/kg PO daily (usually 600 mg PO daily)	<30 or HD	600 mg once daily, or 600 mg three times per week
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 *or* 25 mg/kg IM or IV three times per week	Use with caution in patients with renal insufficiency.	Adjust dose based on serum concentrations. Administer dose after dialysis on day of dialysis.
Sulfadiazine	1,000–1,500 mg PO every 6 hours (1,500 mg every 6 hours for patients >60 kg)	10–50	1,000–1,500 mg PO every 12 hours (ensure adequate hydration)
		<10 or HD	1,000–1,500 mg PO every 24 hours; administer dose after HD on days of dialysis
Telavancin	10 mg/kg IV every 24 hours	31-50	7.5 mg/kg IV every 24 hours (decreased clinical cure rate with CrCl <50 ml/minute; use with caution)
		10-30	10 mg/kg IV every 48 hours (decreased clinical cure rate with CrCl <50 ml/minute; use with caution)
		<10	Insufficient clinical data to recommend routine use. Use with caution due to decreased clinical cure rate with CrCl <50 mL/minute. If no other option, consider 10 mg/kg every 48 hours IV or 10 mg/kg IV post-HD three times a week (based on observational study [n = 10]).

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 7 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	Dose
Telbivudine	600 mg PO daily	30–49	**Oral Tablets:** 600 mg PO every 48 hours **Oral Solution:** 400 mg PO every 24 hours
		<30	**Oral Tablets:** 600 mg PO every 72 hours **Oral Solution:** 200 mg PO every 24 hours
		HD	**Oral Tablets:** 600 mg PO every 96 hours; administer dose after dialysis. **Oral Solution:** 120 mg PO every 24 hours; administer dose after HD on dialysis day
Tenofovir Alafenamide (TAF)	25 mg PO daily	<15	**<u>Not recommended</u>**
		<15 on HD	No dosage adjustment required. Administer dose after HD on dialysis days.
Tenofovir Disoproxil Fumarate (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	**<u>Not recommended</u>**
		HD	300 mg PO once weekly; administer dose after dialysis
Tetracycline	250 mg PO every 6 hours Consider using doxycycline in patients with renal dysfunction.	10–49	250 mg PO every 12–24 hours
		<10	250 mg PO every 24 hours
		HD	250 mg PO every 24 hours; administer dose after dialysis
Trimethoprim/ Sulfamethoxazole (TMP-SMX)	**For PCP Treatment:** • 5 mg/kg (of TMP component) IV every 6-8 hours, *or* • Two TMP-SMX DS tablets PO every 8 hours	15–30	5 mg/kg (TMP) IV every 12 hours, or two TMP-SMX DS tablets PO every 12 hours
		<15	5 mg/kg (TMP) IV every 24 hours, or one TMP-SMX DS tablet PO every 12 hours (or two TMP-SMX DS tablets every 24 hours)
		HD	5 mg/kg/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: • One TMP-SMX DS tablet PO daily; • One TMP-SMX DS tablet PO three times per week; *or* • One TMP-SMX SS tablet PO daily	15–30	Reduce dose by 50%
		<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

Table 7. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency (page 8 of 8)

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl (mL/min)*	**Dose**
Trimethoprim/ Sulfamethoxazole (TMP-SMX), continued	**For TE Chronic Maintenance Therapy:** • One TMP-SMX DS tablet twice daily, *or* • One TMP-SMX DS tablet daily	15–30	Reduce dose by 50%
		<15	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; dose after HD on dialysis days
Valganciclovir	**Induction Therapy:** 900 mg PO twice daily **Maintenance Therapy:** 900 mg PO once daily	40–59	**Induction:** 450 mg PO twice daily **Maintenance:** 450 mg PO daily
		26–39	**Induction:** 450 mg PO daily **Maintenance:** 450 mg PO every 48 hours
		10–25	**Induction:** 450 mg PO every 48 hours **Maintenance:** 450 mg PO twice weekly
		<10 and not on dialysis	**Induction: Not recommended** **Maintenance: Not recommended**
		HD **Note:** Clinical efficacy of these doses has not been established.	**Induction:** 200 mg (oral powder formulation) PO three times per week after HD **Maintenance:** 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 sulfobutylether cyclodextrin (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. Adjust dose based on serum concentrations.

Key: 3TC = lamivudine; ARV = antiretroviral; CAPD = continuous ambulatory peritoneal dialysis; CMV = cytomegalovirus; COBI = cobicistat; CrCl = creatinine clearance; DS = double strength, 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; PD = peritoneal dialysis; PCP = Pneumocystis pneumonia; PI = protease inhibitor; PO = orally; SCr = serum creatinine; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TMP-SMX = trimethoprim-sulfamethoxazole; VZV = varicella zoster virus

* Creatinine Clearance Calculation	
Male:	Female:
$\frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine})}$	$\frac{(140 - \text{age in years}) \times (\text{weight in kg}) \times (0.85)}{72 \times (\text{serum creatinine})}$

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 1 of 8) (Last updated February 11, 2020; last reviewed February 11, 2020)

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 *P. falciparum* 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, *Toxoplasma gondii*, malaria infections
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), *Chlamydia trachomatis* 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 *T. cruzi* in pregnancy. Seek expert consultation if acute or symptomatic infection in pregnancy requiring treatment.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 2 of 8)

Drug	FDA Category[a]	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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 *Candida* or *Aspergillus* 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 (meningocele, 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
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 *Toxoplasma*
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 *Candida*. No increase in adverse pregnancy outcomes with vaginal use.	Oral or vaginal *Candida* 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.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 3 of 8)

Drug	FDA Category[a]	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During 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.
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 *Candida* 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.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 4 of 8)

Drug	FDA Category[a]	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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.
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 *in utero* therapy.	Drug-resistant TB

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 5 of 8)

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 *T. cruzi* in 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 **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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 6 of 8)

Drug	FDA Category[a]	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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**
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 *P. falciparum* 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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 7 of 8)

Drug	FDA Category[a]	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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. Report exposures during pregnancy to the Ribavirin Pregnancy Registry (1-800-593-2214).
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.
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 *in utero* 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.
Sofusbuvir/ 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 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 8 of 8)

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

Figure: Recommended Immunization Schedule for Adults and Adolescents with HIV Infection (Last updated August 7, 2019; last reviewed October 13, 2021)

NOTE: Update in Progress

Revision of this section is currently underway, to reflect the Panel's recommendations on the use of newer vaccines in persons with HIV. This section will have guidance that is similar to the Advisory Committee on Immunization Practices (ACIP) which is the accepted standard in the United States but is likely to make recommendations additionally in areas where ACIP is silent. (These immunization schedules are available at www.cdc.gov/vaccines/schedules/hcp/index.html. Detailed information on these and other vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/index.html). Readers should consult individual pathogen chapters for additional guidance beyond the ACIP recommendations presented here.

Table 2 Recommended Adult Immunization Schedule by Medical Condition and Other Indications United States, 2019

<table>
<tr><th rowspan="2">Vaccine</th><th rowspan="2">Pregnancy</th><th rowspan="2">Immuno-compromised (excluding HIV infection)</th><th colspan="2">HIV infection CD4 count</th><th rowspan="2">Asplenia, complement deficiencies</th><th rowspan="2">End-stage renal disease, on hemodialysis</th><th rowspan="2">Heart or lung disease, alcoholism[1]</th><th rowspan="2">Chronic liver disease</th><th rowspan="2">Diabetes</th><th rowspan="2">Health care personnel[2]</th><th rowspan="2">Men who have sex with men</th></tr>
<tr><th><200</th><th>≥200</th></tr>
<tr><td>IIV or RIV</td><td colspan="11">1 dose annually</td></tr>
<tr><td>or</td><td colspan="11"></td></tr>
<tr><td>LAIV</td><td colspan="5">CONTRAINDICATED</td><td colspan="4">PRECAUTION</td><td colspan="2">or
1 dose annually</td></tr>
<tr><td>Tdap or Td</td><td>1 dose Tdap each pregnancy</td><td colspan="10">1 dose Tdap, then Td booster every 10 yrs</td></tr>
<tr><td>MMR</td><td colspan="3">CONTRAINDICATED</td><td colspan="8">1 or 2 doses depending on indication</td></tr>
<tr><td>VAR</td><td colspan="3">CONTRAINDICATED</td><td colspan="8">2 doses</td></tr>
<tr><td>RZV (preferred)</td><td>DELAY</td><td></td><td></td><td></td><td colspan="7">2 doses at age ≥50 yrs</td></tr>
<tr><td>or</td><td colspan="4"></td><td colspan="7">or</td></tr>
<tr><td>ZVL</td><td colspan="3">CONTRAINDICATED</td><td></td><td colspan="7">1 dose at age ≥60 yrs</td></tr>
<tr><td>HPV Female</td><td>DELAY</td><td colspan="3">3 doses through age 26 yrs</td><td colspan="6">2 or 3 doses through age 26 yrs</td><td></td></tr>
<tr><td>HPV Male</td><td></td><td colspan="3">3 doses through age 26 yrs</td><td colspan="6">2 or 3 doses through age 21 yrs</td><td>2 or 3 doses through age 26 yrs</td></tr>
<tr><td>PCV13</td><td></td><td colspan="10">1 dose</td></tr>
<tr><td>PPSV23</td><td colspan="11">1, 2, or 3 doses depending on age and indication</td></tr>
<tr><td>HepA</td><td colspan="11">2 or 3 doses depending on vaccine</td></tr>
<tr><td>HepB</td><td colspan="11">2 or 3 doses depending on vaccine</td></tr>
<tr><td>MenACWY</td><td colspan="11">1 or 2 doses depending on indication, then booster every 5 yrs if risk remains</td></tr>
<tr><td>MenB</td><td>PRECAUTION</td><td colspan="10">2 or 3 doses depending on vaccine and indication</td></tr>
<tr><td>Hib</td><td></td><td>3 doses HSCT[3] recipients only</td><td colspan="9">1 dose</td></tr>
</table>

- Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection
- Recommended vaccination for adults with an additional risk factor or another indication
- Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
- Delay vaccination until after pregnancy if vaccine is indicated
- Contraindicated—vaccine should not be administered because of risk for serious adverse reaction
- No recommendation

1. Precaution for LAIV does not apply to alcoholism. **2.** See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. **3.** Hematopoietic stem cell transplant.

evidence of immunity to varicella (documented receipt of 2 doses of VAR, born in the United States before 1980, diagnosis of varicella or zoster by a healthcare provider, or laboratory evidence of immunity). Those with a CD4 cell count <200 cells/µL should not receive VAR.

5. Herpes zoster vaccination

There is no recommendation for herpes zoster vaccine (HZV) for adults and adolescents with a CD4 cell count ≥200 cells/µL. Those with a CD4 cell count <200 cells/µL should not receive HZV.

6. Human papillomavirus vaccination

Administer a 3-dose series of human papillomavirus (HPV) vaccine at 0, 1–2, and 6 months to adults and adolescents through age 26 years. Pregnant women are not recommended to receive HPV vaccine.

7. Pneumococcal vaccination

Administer 1 dose of 13-valent pneumococcal conjugate vaccine (PCV13) followed by 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 2 months later. Administer a second dose of PPSV23 at least 5 years after the first dose of PPSV23. If the most recent dose of PPSV23 was administered before age 65 years, at age 65 years or older, administer another dose of PPSV23 at least 5 years after the last dose of PPSV23.

8. Hepatitis A vaccination

Administer a 2-dose series of single antigen hepatitis A vaccine (HepA) at 0 and 6–12 months or 0 and 6–18 months, depending on the vaccine, or a 3-dose series of combined hepatitis A and hepatitis B vaccine (HepA-HepB) at 0, 1, and 6 months to adults and adolescents who may not have a specific risk but wants protection against hepatitis A infection. Administer a HepA-containing vaccine series to adults and adolescents at risk which includes chronic liver disease, receive clotting factor concentrates, men who have sex with men, inject illicit drugs, and travel in countries with endemic hepatitis A.

9. Hepatitis B vaccination

Administer a 3-dose series of single-antigen hepatitis B vaccine (HepB) or combined hepatitis A and hepatitis B vaccine (HepA-HepB) at 0, 1, and 6 months.

10. Meningococcal vaccination

Administer a 2-dose primary series of serogroup A, C, W, and Y meningococcal vaccine (MenACWY) at least 2 months apart, and revaccinate every 5 years. Serogroup B meningococcal vaccine (MenB) is not routinely recommended. Young adults and adolescents age 16 through 23 years (preferred age range is 16 through 18 years) may receive MenB (a 2-dose series of MenB-4C at least 1 month apart or a 3-dose series of MenB-FHbp at 0, 1–2, and 6 months) based on individual clinical decision.

11. *Haemophilus influenzae* type b vaccination

Adults and adolescents with HIV infection are not routinely recommended to receive *Haemophilus influenzae* type b vaccine (Hib). Administer Hib to those with asplenia, hematopoeitic stem cell transplant, and other indications.

Immunizations for Preventable Diseases in Adults and Adolescents Living with HIV

(Last updated: November 18, 2021; last reviewed: October 13, 2021)

Overview

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

- Many live virus vaccines are contraindicated in PWH.
    - For any CD4 T lymphocyte (CD4) cell count
        - Live attenuated influenza (LAIV)
    - For CD4 count <200 cells/mm^3 or uncontrolled HIV
        - Measles
        - Mumps
        - Rubella
        - Varicella (VAR)
        - Live attenuated typhoid Ty21a
        - Yellow fever
- The following have specific recommendations related to HIV status:
    - 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.

- Recombinant zoster vaccine (RZV, Shingrix) is recommended in this NIH/IDSA/CDC guideline for all PWH age 18 years and older. ACIP currently has no recommendation regarding the use of RZV in PWH.

Specific Immunizations

COVID-19 Vaccine

People with HIV appear to be at increased risk for severe outcomes with COVID-19 compared with those without HIV.[1-5] A recent review of 22 previous studies found that PWH had a 24 percent higher risk of infection and a 78 percent higher risk of death from COVID-19 than people without HIV.[6]

Individuals ages 12 and older should be vaccinated for COVID-19 regardless of their CD4 count or HIV viral load because the potential benefits outweigh the potential risks.[7,8] Those with severe immunosuppression may have a diminished immune response to the vaccine.[8,9] Routine serologic testing following vaccination is not recommended[10] because anti-spike protein antibodies have not been shown to correlate with immune response. Repeat vaccination is not recommended for individuals who received vaccination with lower CD4 counts and now have had immune reconstitution. Guidance regarding booster vaccination is evolving.

The U.S. Food and Drug Administration issued an Emergency Use Authorization to permit the emergency use of three vaccines[11-13]: the Comirnaty® Pfizer-BioNTech COVID-19 vaccine (Pfizer-BioNTech), the Moderna COVID-19 vaccine, and the Janssen COVID-19 vaccine. Pfizer-BioNTech is the only authorized vaccine for individuals ages 12 through 17. Many of the COVID-19 vaccine trials have included PWH; however, safety and efficacy in this specific subgroup have not been reported fully. The National Institute of Allergy and Infectious Diseases recently announced a new trial that will analyze the immune response to COVID-19 vaccines and outcomes in individuals with and without immune deficiencies and dysregulations.[14] Despite limited data, currently available information suggests vaccines permitted for emergency use in the United States are safe for people with HIV.

On April 23, 2021, the ACIP reaffirmed its interim recommendation for the use of the Janssen COVID-19 vaccine in all persons aged ≥18 years.[14] Women aged <50 years should be aware of the increased risk for a rare adverse event, thrombotic thrombocytopenia syndrome, and that other COVID-19 vaccines are available—the Moderna and Pfizer-BioNTech vaccines.[15,16]

Following vaccination, everyday preventive actions (i.e., social or physical distancing, wearing masks consistently, avoiding crowded areas, using proper hand hygiene) are recommended to continue to protect against COVID-19.[17] Vaccination of household members and close contacts of PWH is encouraged to provide further protection from infection.

Given currently available data, COVID-19 vaccination is recommended for all people with HIV because the benefits outweigh the potential risks.[7,18] COVID-19 is a rapidly evolving situation, and updates will be posted as new data become available.

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- or four-dose series (0, 1, and 6 months or days 0, 7, 21–30, and 12 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) **(AIII).**
- Assess antibody response 1 to 2 months after completion of the series. If negative, revaccinate

when CD4 count is >200 cells/mm^3 **(BIII).**

- PWH presenting with CD4 cell count <200 cells/mm^3 with ongoing risk for HAV should be immunized and assessed for antibody response 1 to 2 months after completion of the series. For PWH without risk factors, waiting for CD4 >200 cells/mm^3 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/mm^3 **(BIII).**

For pre-exposure prophylaxis (travel)

- For PWH 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 PWH 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 PWH who are non-immune to HBV (surface antibody titer negative) and do not have chronic HBV infection (surface antigen negative), administer a three-dose series of single antigen hepatitis B vaccine (Recombivax® or Engerix®) or combined HepA-HepB at 0, 1, and 6 months (alternate dosing intervals are available) **(AII).**
- A novel recombinant hepatitis B vaccine that uses a toll-like receptor 9 immunostimulatory adjuvant (HepBCpG, Heplisav-B®) is now available. Observational data in individuals with HIV suggest superior response rates. A randomized controlled trial of Heplisav-B in PWH is enrolling currently. If a two-dose vaccine at 0 and 1 month is preferred, Heplisav-B® is an option for vaccinating PWH **(CIII).**
- PWH presenting with CD4 cell count <200 cells/mm^3 with ongoing risk for HBV should be immunized and assessed for antibody response 1 to 2 months after completion of the series. For PWH without risk factors, waiting for CD4 >200 cells/mm^3 is an option.
- Assess antibody response to hepatitis B surface antibody (anti-HBs) 1 to 2 months after completion of the vaccine series.
- For PWH who do not respond to a complete HepB vaccination series, administer a four-dose revaccination series using double doses **(BI)** or consider Heplisav-B® **(CIII).**
- For individuals with isolated hepatitis B core antibody (anti-HBc), vaccinate with one standard dose of HBV vaccine and check anti-HBs titers 1 to 2 months afterward. 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 (single-dose or double-dose) followed by anti-HBs testing **(BII).** If titers are not available, then give a complete vaccine series followed by anti-HBs testing.

For post-exposure prophylaxis

- For exposed persons who have been vaccinated previously with a complete HepB vaccine series and have documented antibody response, no additional vaccine is needed.
- For exposed persons who have received a complete HepB vaccine series without documentation of antibody response, administer a single dose of HepB vaccine.
- For exposed persons 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 PWH 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 PWH. Ideally, the series should be initiated at age 11 or 12 years but may be started as early as age 9 years. For all PWH aged 13 to 26 years who were not vaccinated previously, regardless of gender, administer three doses of the recombinant HPV nonavalent vaccine at 0, 1 to 2, and 6 months. The two-dose series is **not recommended** in PWH **(AIII).**
- For PWH 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.
- For pregnant persons, delay HPV vaccination until after delivery; pregnancy testing is not routinely recommended before administering HPV vaccine.
- 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 Recommendations[19]

- For all adults and adolescents with HIV, administer age-appropriate inactivated influenza vaccine or recombinant influenza vaccine annually **(AI).**
- For pregnant PWH, administer inactivated influenza or recombinant vaccine at any time during pregnancy **(AI).**
- The LAIV administered via nasal spray **is contraindicated** in PWH **(AIII).**
- High-dose and adjuvanted influenza vaccines also are approved as options for PWH aged 65 years or older **(AIII).**

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,[20,21] the frequent emergence of antigenic variants through antigenic drift[22] (i.e., point mutations and recombination events within a subtype) is the virologic basis for seasonal epidemics and necessitates revaccination each season.[23]

Some studies of influenza have noted higher hospitalization rates[24-27] and increased mortality[27,28] among PWH; however, these findings have not been observed in all settings.[29] Increased morbidity may be greatest for PWH not on antiretrovirals (ARV) or with advanced disease. PWH 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, PWH with minimal AIDS-related symptoms and normal or near-normal CD4 counts who receive inactivated influenza vaccine develop adequate antibody responses.[30-32] Among persons with low CD4 counts or who have advanced HIV disease, inactivated influenza vaccine might not induce protective antibody titers.[32-34] In one study, markers of inflammation in older people (≥60 years) with HIV were associated with lower post-vaccination influenza antibody titers.[35] In people with HIV, a second dose of vaccine does not improve immune response,[33,36] and intradermal influenza vaccine dosing did not improve the immune response compared with intramuscular dosing.[37]

Two clinical studies have evaluated influenza vaccine efficacy in PWH. In an investigation of an influenza A outbreak at a residential facility for PWH,[24] vaccination was most effective at preventing influenza-like illness among persons with >100 CD4 cells/mm^3 and among those with HIV RNA <30,000 copies/mL. In a randomized placebo-controlled trial conducted in South Africa among 506 PWH, including 349 persons on ARV treatment and 157 who were ARV treatment-naive, efficacy of trivalent inactivated influenza vaccine for prevention of culture- or RT-PCR–confirmed influenza illness was 75 percent (95% confidence interval, 9% to 96%).[38]

Several clinical studies also have evaluated the immunogenicity of influenza vaccine in PWH. In a randomized study[39] comparing the immunogenicity of high-dose (60 µg of antigen per strain) versus standard-dose (15 µg of antigen per strain) trivalent inactivated influenza vaccine among 195 adults with HIV aged ≥18 years (10% of whom had CD4 counts <200 cells/mm^3), 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 inactivated influenza vaccine was no more immunogenic than the standard dose among the recipients with HIV.[40]

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.[19] 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.[41] One study in PWH assessed the effectiveness of a two-dose regimen of inactivated influenza virus vaccine and found that the second dose of vaccine did not significantly increase the frequency or magnitude of antibody responses.[36] Based on this study, influenza booster immunizations are not recommended for PWH.

Many licensed injectable influenza vaccine options are available, with no recommendation favoring one product over another.[19] Information on currently available influenza vaccines is obtainable through the CDC recommendation, "Prevention and Control of Seasonal Influenza with Vaccines." Adults aged ≥65 years can receive standard inactivated influenza vaccine, high-dose inactivated influenza vaccine,[42] adjuvanted inactivated influenza vaccine,[43] or recombinant influenza vaccine,[44] each of which has been studied in this age group.

Influenza vaccines are either trivalent (two influenza A components and one influenza B component) or quadrivalent (two A components and two B components) with formulations that change from season to season. Although quadrivalent live attenuated influenza vaccine (LAIV4) was available during the 2018 to 2019 influenza season, it **is contraindicated** for people with HIV because of the paucity of safety data and the availability of alternative vaccines.[19] Although unintentional administration of LAIV4 to adults with HIV has been well tolerated,[45] it is not recommended for PWH.

Inactivated influenza vaccine can be administered to persons 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 persons with a CD4 count ≥200 cells/mm^3 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 had no laboratory evidence of immunity or disease) **(AIII).**
- The MMR vaccine **is contraindicated** during pregnancy.
- Persons of childbearing potential who get the MMR vaccine should wait 4 weeks before getting pregnant.
- For pregnant persons 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/mm^3 **(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 PWH with CD4 count <200 cells/mm^3 **(AIII).**

For post-exposure prophylaxis

- For measles exposure of non-immune individuals with CD4 count >200 cells/mm^3, administer the MMR vaccine within 72 hours of exposure **or** immunoglobulin (IG) within 6 days of exposure. Do not administer the MMR vaccine and IG simultaneously.

- For measles exposure of non-immune individuals with CD4 count <200 cells/mm^3 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 persons with advanced HIV.[46] 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 domestically[47] and globally,[48] PWH 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/mm^3 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 PWH.

Several studies from the 1990s found that approximately 90 percent to 95 percent of adults with HIV were immune to measles.[49-51] In these studies, serostatus did not vary by CD4 count, suggesting PWH retained protective immunity even in the context of advanced disease. However, in a more recent study, the measles seroprevalence rate was 70.3 percent.[52] Similarly, PWH appear to retain immunity to mumps and rubella even after acquisition of HIV.[52]

MMR vaccine **is contraindicated** for PWH with CD4 count <200 cells/mm^3 because MMR vaccine is a live attenuated formulation that has been linked to fatal cases of measles-associated pneumonitis following administration to PWH with low CD4 counts.[53,54] For PWH with CD4 count ≥200 cells/mm^3, the vaccine has been shown to be safe, although antibody response may be lower than for patients without HIV.[52,55,56]

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

Meningococcal Vaccine

Summary of Recommendations

- Administer quadrivalent meningococcal conjugate vaccine, either MenACWY-D (Menactra®) or MenACWY-CRM (Menveo®), to all PWH age ≥2 months **(AIII).**
- For PWH 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. Two quadrivalent meningococcal conjugate vaccines targeted against serogroups A, C, Y, and W-135 (MenACWY-D or MenACWY-CRM) are licensed for use in the United States and are recommended for all adolescents aged 11 to 18 years and persons 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 PWH. Studies have shown a 5- to 24-fold increased risk of meningococcal disease in PWH compared with persons without HIV; low CD4 count and high HIV viral load are associated with increased risk.[57] The average annual incidence rate of invasive meningococcal disease (IMD) was 0.39 cases per 100,000 persons. PWH with lower CD4 counts are at higher risk of invasive disease.[58]

The safety and immunogenicity of MenACWY-D vaccine have been evaluated only in PWH aged 11 to 24 years. Patients with CD4% ≥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 PWH who received one dose of vaccine, 21 percent to 63 percent developed an antibody titer of ≥1:128 at 72 weeks after vaccination. Antibody responses at 72 weeks in individuals with CD4% <15% were less robust,[59] with only 6 percent to 28 percent achieving titers ≥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 PWH, and clinical outcome data for both vaccines in PWH are lacking.

For PWH aged ≤56 years, either conjugate vaccine (MenACWY-D [Menactra®] or MenACWY–CRM [Menveo®]) is recommended. The meningococcal polysaccharide vaccine (MPSV4, [Menomune®]) is the only *licensed* vaccine for persons ≥56 years of age; however, the efficacy of MPSV4 in PWH has not been evaluated. Therefore, Menactra® or Menveo® 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®; PWH 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.[60]

Pneumococcal Vaccine

See the "Preventing Disease" section in Bacterial Pneumonia for detailed guidance for immunization against pneumococcal disease, as well as the evidence summary.

Summary of Recommendations

- For PWH aged <65 years, administer 13-valent pneumococcal conjugate vaccine (PCV13) **(AI)**, followed by a dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later **(AII)**. Administer a second dose of PPSV23 at least 1 year after PCV13 and at least 5 years after the first dose of PPSV23 **(BIII)**.
- For PWH aged ≥65 years, administer PCV13 if they have not already received it and a dose of PPSV23 at least 8 weeks after PCV13 and at least 5 years after the last dose of PPSV23. For PWH who have received PPSV23 previously, administer PCV13 **(AII)** at least 1 year after the last 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 PWH, administer one dose of Tdap during each pregnancy, preferably between 27 weeks and 36 weeks gestation **(AIII)**.
- For adolescent and adult PWH 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.[61,62] For persons with CD4 counts >300 cells/mm^3, antibody response to tetanus vaccination is similar to the general population, whereas response to diphtheria remains diminished.[61-63] 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. Tetanus vaccination has been linked to transient upregulation of HIV replication,[32,64] but no studies suggest any negative effect on HIV disease progression, and the potential risk of increased HIV replication should not impact timing of immunization.

Persons 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

- PWH 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 PWH who are varicella non-immune with CD4 count ≥200 cells/mm^3, administer two doses of VAR 3 months apart **(BIII).**
- VAR is **contraindicated** for PWH with CD4 count <200 cells/mm^3 **(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 PWH aged ≥18 years, administer RZV, two doses at 0 and 2 months **(AIII).**
- Consider delaying vaccination until the patient is virologically suppressed on antiretroviral therapy **(CIII)** and wait for CD4 count >200 cells/mm^3 to maximize response to vaccine **(CIII).**
- If PWH has already received attenuated zoster vaccine live (ZVL), revaccination with an RZV two-dose series should be given.

Table 1: Recommended Adult Immunization Schedule by Medical Condition and Other Indications

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
COVID-19	All persons regardless of CD4 count or viral load (AIII)	PWH should receive COVID-19 vaccines regardless of their CD4 count or HIV viral load (AIII). • Pfizer-BioNTech: aged ≥12 years, 0.3 mL IM 2 doses (0, 21 days) • Moderna: aged ≥18 years, 0.5 mL IM, 2 doses (0, 28 days) • Janssen (Johnson & Johnson): aged ≥18 years, 0.5 mL, 1 dose	People with advanced HIV or untreated HIV who received a 2-dose series of one of the mRNA COVID-19 vaccines should receive a third dose of that vaccine at >28 days after the second dose (AIII). Many experts define advanced HIV as patients with CD4 <200 cells/mm^3 or <14%. Recommendations regarding an additional dose for Janssen (Johnson & Johnson) vaccine are pending.	No difference in recommendations.
Hepatitis A virus (HAV)	HAV susceptible with HIV infection (AIII)	2-dose series of either single antigen vaccine: • Havrix®: 1.0 mL IM (0, 6–12 months) (AII) OR • Vaqta®: 1.0 mL IM (0, 6–18 months) (AIII) Alternative for individuals susceptible to both HAV and HBV: • Twinrix®: 1.0 mL IM o 3-dose series (0, 1, 6 months) (AII) o 4-dose series (0, 7, 21–30 days, 12 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).	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 persons who are non-immune.		

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
Hepatitis B virus (HBV)	HBV susceptible and never vaccinated (i.e., anti-HBs <10 mIU/mL)	Patients may receive any of the following single-antigen vaccines: • Recombivax®: 3-dose series (0, 1, 6 months) 10 µg in 1.0 mL IM **(AII)** OR • Engerix®: 3-dose series (0, 1, 6 months) 20 µg in 1.0 mL IM **(AII)** OR • Double dose Recombivax® (20 µg) or Engerix® (10 µg) 4-dose series (0, 1, 2, 6 months) **(BI)** OR • Heplisav®: 2-dose series (0, 1 month) 20 µg in 0.5 mL IM **(CIII)** Alternative for individuals susceptible to both HAV and HBV: • Twinrix®: 1.0 mL IM o 3-dose series (0, 1, 6 months) **(AIII)** o 4-dose series (0, 7, 21–30 days, 12 months) **(AIII)**	Assess antibody response (anti-HBs) 1–2 months after completion of the series. Vaccinate individuals with isolated anti-HBc with 1 standard dose of HepB **(BIII)** 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 (single dose or double dose) followed by anti-HBs testing **(BII)**. Safety and efficacy of Heplisav® has not yet been studied in PWH. If a 2-dose vaccine is preferred, Heplisav® is an option. If a significant delay occurs between doses, there is no need to restart the series.	No difference in recommendations.
	Vaccine nonresponder (if anti-HBs <10 mIU/mL after 3-dose series)	May consider 4-dose double dose of either Recombivax® or Engerix® **(BI)**. Repeat 3-dose revaccination series of either Recombivax® or Engerix® **(BIII)**. May consider delaying repeat vaccination until after the CD4 count is ≥200 cells/mm^3 **(CIII)**.		

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Post-exposure prophylaxis	For exposed persons who have been previously vaccinated with complete series and have documented antibody response, no additional vaccine needed. For exposed persons who have received complete series without documentation of antibody response, administer a single dose of HepB vaccine. For exposed persons who have not received a vaccine or have not received the complete series, administer or complete the HepB vaccine series and administer a dose of HBIG at a separate anatomical site as soon as possible after exposure (ideally within 24 hours, but up to 7 days after percutaneous exposure and up to 14 days after sexual exposure).		
Human papillomavirus (HPV)	Adults and adolescents through age 26	Recombinant 9-valent human papillomavirus vaccine (Gardasil 9®): 0.5 mL IM 3-dose series (0, 1, 6 months)	If a significant delay occurs between doses, there is no need to restart the series. Routine vaccination is not recommended for persons ages 27–45 years. 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	Delay until after pregnancy.	

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
		define who might benefit or how cost effective this approach might be (CIII).		
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 either trivalent or quadrivalent, with formulations that change from season to season. In addition to standard IIV formulations, adults age ≥65 years may use high-dose IIV (Fluzone® High-Dose) and adjuvanted IIV (FLUAD™). Persons age ≥18 years also may use (Flublok® Quadrivalent). For persons 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).	No difference in recommendations.
Measles, mumps, and rubella (MMR)	CD4 count ≥200 cells/mm³ and no evidence of immunity to measles, mumps, or rubella	2-dose series of MMR vaccine at least 1 month apart (AIII). MMR is contraindicated if CD4 count <200 cells/mm³. MMR vaccine is contraindicated during pregnancy.	Evidence of immunity to MMR: • birth date before 1957, or • documentation of receipt of MMR, or • laboratory evidence of immunity or disease for each pathogen For pregnant persons without immunity to rubella, after pregnancy administer 2 doses of MMR vaccine at least 1 month apart if CD4 count >200 cells/mm³ (AIII).	No difference in recommendations.

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Post-exposure prophylaxis	For measles non-immune individuals with CD4 counts >200 cells/µl, administer MMR vaccine within 72 hours of exposure or IG within six days of exposure. Do not administer MMR vaccine and IG simultaneously. For measles non-immune individuals with CD4 counts <200 cells/µl or those who are pregnant, administer IG.		
Meningococcus serogroup A, C, W, Y (MenACWY)	Not received any polyvalent meningococcal vaccine	Menactra® or Menveo® • 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. MenB vaccine is not routinely recommended; only recommended if at increased risk (see "Meningococcus serogroup B" below).	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	Did not receive any pneumococcal vaccine	PCV13 (Prevnar®) • 0.5 mL IM × 1 (AI) Followed at least 8 weeks later by • PPV23 (Pneumovax®): o 0.5 mL IM × 1 (AII)	Administer PCV13 to all PWH, regardless of CD4 count (AII). In those who received PCV13 when their CD4 count was <200 cells/mm³, some experts may choose to defer PPV23 until CD4 count is >200 cells/mm³ to optimize vaccine efficacy (BIII).	No difference in recommendations.
	Received PPV23 previously	Give 1 dose of PCV13 at least 1 year after the last receipt of PPV23 (AII).		

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
	Revaccination: • If age 19–64 years and ≥5 years since the first PPV23 dose • If age ≥65 years and if ≥5 years since the previous PPV23 dose	Repeat PPV23 five (5) years after the first, then another dose at or after age 65 (BIII).		
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)		
	Previously vaccinated with 1–2 doses of vaccine	Give remaining doses of vaccine at recommended intervals (CIII).		

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
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. 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/mm³ with no evidence of immunity to varicella	2-dose series of VAR 3 months apart (BIII) VAR **is contraindicated** if CD4 count <200 cells/mm³ (AIII).	Evidence of immunity to varicella: • 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®) regardless of CD4 count for PWH	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/mm³ (CIII) to maximize immunologic response to the vaccine. **Do not give** RZV during an acute episode of herpes zoster (AIII).	RZV is FDA approved for prevention of herpes zoster in adults >50 years **and** in adults >18 years who are or will be at increased risk of herpes zoster due to immunodeficiency or immunosuppression. No current ACIP recommendations exist for use of RZV in PWH.

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 *Salmonella* serotype typhi infection (travel, intimate exposure to a chronic carrier, occupational exposure) Revaccination only if continued or renewed exposure to *Salmonella 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 persons 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**).	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.

Vaccine	Indication	Recommendations	Additional Comments	ACIP Recommendations
		YF vaccine **is contraindicated** for persons with CD4 counts <200 cells/mm^3. This recommendation is based on a theoretic increased risk for encephalitis in this population **(AII).**	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; PPV23 = 23-valent pneumococcal polysaccharide vaccine; PWH = persons 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

<table>
<tr><th rowspan="2">VACCINE</th><th rowspan="2">All persons</th><th colspan="4">Where varies by age</th><th colspan="2">Where varies by CD4 cell count (cells/mm^3)</th></tr>
<tr><th>13–26 years</th><th>27–49 years</th><th>50–64 years</th><th>> 65 years</th><th>< 200</th><th>> 200</th></tr>
<tr><td>COVID-19</td><td>1–2 doses (varies by formulation)</td><td></td><td></td><td></td><td></td><td>Third dose if primary series was mRNA vaccine</td><td></td></tr>
<tr><td>Hepatitis A</td><td>2–3 doses (varies by formulation)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Hepatitis B</td><td>2–3 doses (varies by formulation)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Human papillomavirus (HPV)</td><td></td><td>3 doses</td><td>3 doses</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Influenza</td><td>1 dose annually</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Measles, mumps, rubella (MMR)</td><td></td><td></td><td></td><td></td><td></td><td>Contraindicated</td><td>2 doses if born after 1956 or nonimmune</td></tr>
<tr><td>Meningococcal A,C,W,Y conjugate (MenACWY)</td><td>2 doses, booster every 5 years</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Meningococcal B (MenB)</td><td>2–3 doses (varies by formulation)</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pneumococcal conjugate (PCV13)</td><td>1 dose</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Pneumococcal polysaccharide (PPSV23)</td><td></td><td colspan="3">2 doses, 5 years apart</td><td>1 dose</td><td></td><td></td></tr>
<tr><td>Tetanus, diphtheria, pertussis (Tdap/Td)</td><td>Tdap once, then Td or Tdap booster every 10 years</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Varicella (VAR)</td><td></td><td></td><td></td><td></td><td></td><td>Contraindicated</td><td>2 doses</td></tr>
<tr><td>Zoster recombinant (RZV)</td><td></td><td></td><td></td><td colspan="2">2 doses</td><td></td><td></td></tr>
</table>

- (Green) Recommended for all adults and adolescents with HIV who meet the age requirement or lack documentation of vaccination or evidence of past infection
- (Blue) Recommended vaccination based on shared decision-making
- (Yellow) Recommended for adults and adolescents with HIV with another risk factor (medical, occupational, or other indication) or in select circumstances
- (Red) Contraindicated

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

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Appendix A. List of Abbreviations (Last updated May 7, 2013; last reviewed October 13, 2021)

Acronym/Abbreviation	Definition
ABGs	arterial blood gasses
ACTG	AIDS Clinical Trials Group
AFB	acid-fact bacilli
AIN	anal intraepithelial neoplasia
ALT	alanine aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
ARV	antiretroviral
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	atypical squamous cells—cannot exclude high grade cervical squamous intraepithelial lesion
ASC-US	atypical squamous cells of uncertain significance
AST	serum aspartate aminotransferase
AUC	area under the curve
BA	bacillary angiomatosis
BAL	bronchoalveolar lavage
BID	twice a day
BIW	twice a week
CAP	community-acquired pneumonia
CAPD	continuous ambulatory peritoneal dialysis
CD4	CD4 T lymphocyte cell
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile*-associated infection
CES-D	Center for Epidemiologic Studies Depression Scale
CFU	colony-forming unit
CIA	chemiluminescence immunoassays
CIN	cervical intraepithelial neoplasia
C_{max}	maximum concentration
C_{min}	minimum concentration
CMV	cytomegalovirus
CNS	central nervous system
CPE	central nervous system penetration effectiveness
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CT	computed tomography

CYP3A4	Cytochrome P450 3A4
DAAs	direct acting antiviral agents
DOT	directly observed therapy
DS	double strength
EDTA	ethylenediaminetetraacetic acid
EIAs	enzyme immunoassays
EM	erythema multiforme
FDA	Food and Drug Administration
FTA-ABS	fluorescent treponemal antibody absorbed
g	gram
G6PD	Glucose-6-phosphate dehydrogenase
GFR	glomerular filtration rate
GI	gastrointestinal
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV-8	human herpesvirus-8
HPA	hypothalamic-pituitary-adrenal
HPV	human papillomavirus
HSIL	high grade cervical squamous intraepithelial lesion
HSV	herpes simplex virus
HSV-1	herpes simplex virus 1
HSV-2	herpes simplex virus 2
ICP	intracranial pressure
ICU	intensive care unit
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
IGRA	interferon-gamma release assays
IM	intramuscular
IND	investigational new drug
IRIS	immune reconstitution inflammatory syndrome
IRU	immune recovery uveitis
IV	intravenous
IVIG	intravenous immunoglobulin
JCV	JC virus
KS	Kaposi Sarcoma
LEEP	loop electrosurgical excision procedure
LP	lumbar puncture
LSIL	low grade squamous intraepithelial lesion

LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MAI	*Mycobacterium avium intracellulare*
MCD	multicentric Castleman's disease
MDR TB	multi-drug-resistant tuberculosis
mg	milligram
mmHg	millimeters of mercury
MSM	men who have sex with men
MTB	*Mycobacterium tuberculosis*
NAA	nucleic acid amplification
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitors
NSAID	non-steroidal anti-inflammatory drugs
NVP	nevirapine
OI	opportunistic infection
PCP	*Pneumocystis* pneumonia
PCR	polymerase chain reaction
PEL	primary effusion lymphoma
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PO	orally
PORN	Progressive Outer Retinal Necrosis
PPV	polysaccharide vaccine
PSI	pneumonia severity index
q(n)h	every "n" hours
qAM	every morning
QID	four times a day
qPM	every evening
RPR	rapid plasma reagin
RVR	rapid virological response
SCr	serum creatinine
SJS	Stevens-Johnson syndrome
SLE	systemic lupus erythematosus
SQ	subcutaneous
SS	single strength
STD	sexually transmitted disease
SVR	sustained virologic response
TB	tuberculosis
TDM	therapeutic drug monitoring
TE	*Toxoplasma* encephalitis

TEN	toxic epidermal necrolysis
TID	three times daily
TIW	three times weekly
TP-PA	*T. pallidum* particle agglutination
TST	tuberculin skin test
ULN	upper limit of normal
VAIN	vaginal intra-epithelial neoplasia
VDRL	Venereal Disease Research Laboratory
VIII	vestibulocochlear
VIN	vulvar intraepithelial neoplasia
VZV	varicella zoster virus
WBC	white blood cell
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis

Abbreviation	**Drug Name**
3TC	lamivudine
5-FU	fluorouracil
ATV/r	ritonavir-boosted atazanavir
BCA	bichloroacetic acid
BOC	boceprevir
COBI	cobicistat
ddA-TP	dideoxyadenosine triphosphate
ddI	didanosine
DHA	dihydroartemisinin
EFV	efavirenz
EMB	ethambutol
EVG	elvitegravir
FTC	emtricitabine
INH	isoniazid
MVC	maraviroc
PCV13	13-valent pneumococcal conjugate vaccine
PegIFN	peginterferon alfa
PI	protease inhibitor
PPV23	23-valent pneumococcal polysaccharides vaccine
PZA	pyrazinamide
RAL	raltegravir
RBV	ribavirin
RFB	rifabutin
RIF	rifampin

RPT	rifapentine
SMX	sulfamethoxazole
TCA	trichloroacetic acid
TDF	tenofovir disoproxil fumarate
TMP	trimethoprim
TMP-SMX	trimethoprim-sulfamethoxazole
TVR	telaprevir
ZDV	zidovudine

Appendix B. Panel Roster and Financial Disclosures

(Last updated: December 16, 2021)

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
Leadership	Constance Benson	*University of California, San Diego, School of Medicine*	Gilead Sciences	Research Support (paid to institution)
	John Brooks	*Centers for Disease Control and Prevention*	None	N/A
	Shireesha Dhanireddy	*University of Washington, School of Medicine*	None	N/A
	Henry Masur	*National Institutes of Health*	None	N/A
	Alice Pau	*National Institutes of Health*	None	N/A
Section Review Group	Lydia Barakat	*Yale University, School of Medicine*	None	N/A
	Thomas Campbell*	*University of Colorado Denver, School of Medicine*	None	N/A
	Ellen Kitchell	*The University of Texas Southwestern Medical School*	None	N/A
	Susana Lazarte	*The University of Texas Southwestern Medical Center*	Gilead Sciences	Research Support (paid to institution)
	Rodrigo Mauricio Burgos	*University of Illinois at Chicago, College of Pharmacy*	OptumRx	Consultant
			Merck Janssen Vaccines & Prevention B.V. ModernaTX, Inc.	Research Support (paid to institution)
	Paul Pham	*Johns Hopkins University, School of Medicine, Westview Urgent Care Medi Center*	Gilead Sciences AbbVie	Equity interest
	Gregory Robbins	*Massachusetts General Hospitala*	AIDS Clinical Trial Group Leonard Meron Biosciences Gilead Sciences Emergent Biosolutions Biotech USA, Inc.	Research Support (paid to institution)

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
			inVentiv Health	Research Support (paid to individual)
	Anandi Sheth	*Emory University, School of Medicine*	None	N/A
	William Short	*University of Pennsylvania, Perlman School of Medicine*	ViiV Healthcare Gilead Sciences	Scientific Advisory Board
	Ronald Wilcox	*Health Resources and Services Administration*	None	N/A
Bacterial Enteric Infections	Anna Bowen	*Centers for Disease Control and Prevention*	None	N/A
	Paul Pham	*Johns Hopkins University, School of Medicine and Westview Urgent Care Medi Center*	Gilead Sciences AbbVie	Equity Interest
	Susan Tuddenham	*Johns Hopkins University, School of Medicine*	None	N/A
	Cynthia Sears*	*Johns Hopkins University, School of Medicine*	Janssen Bristol Myers Squibb	Research Support (paid to institution)
	Brian Zanoni	*Emory University, School of Medicine*	Accordant Health Services	Consultant
Bartonellosis	Nesli Basgoz	*Harvard Medical School*	Allergen	Equity Interest
	Bruno Chomel	*University of California, Davis, School of Medicine*	None	N/A
	James Kirby	*Harvard Medical School*	None	N/A
	Jane Koehler	*University of California, San Francisco, School of Medicine*	None	N/A
	Stacey Rose*	*Baylor College of Medicine*	None	N/A

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
Candidiasis	Michail Lionakis*	*National Institutes of Health*	None	N/A
	Michael Mansour	*Massachusetts General Hospital*	GenMark Diagnostics	Scientific Advisory Board
			Genetech Thermo Fisher Scientific	Research Support (paid to institution)
			Sorrento Therapeutics	Equity Interest
			Vericel Pulsethera NED Biosystems Day Zero Diagnostics Clear Creek Bio	Consultant
	Jeniel Nett	*University of Wisconsin–Madison, School of Medicine and Public Health*	None	N/A
	Sanjay Revankar	*Wayne State University, School of Medicine*	Merck	Consultant
	Jack Sobel	*Wayne State University, School of Medicine*	None	N/A
Community-Acquired Pneumonia	Sushma Cribbs	*Emory University, School of Medicine and Department of Veterans Affairs*	None	N/A
	Kristina Crothers*	*University of Washington, School of Medicine*	None	N/A
	Miwako Kobayashi	*Centers for Disease Control and Prevention*	None	N/A
	Robert Miller	*University College London, England*	None	N/A
	Michael Niederman	*Weill Cornell Medicine*	Pfizer Merck AbbVie N8 Medical Shionogi Thermo-Fisher	Scientific Advisory Board
			IQVIA	Data Safety Monitoring Board
			Shionogi	Research Support (paid to

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			Company	Relationship
			Merck Bayer	institution)
	Maria Rodriguez-Barradas	*Michael E. DeBakey Veterans Affairs Medical Center and Baylor College of Medicine*	None	N/A
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	Michele Hlavsa	*Centers for Disease Control and Prevention*	None	N/A
	Nagalingeswaran Kumarasamy	*Brown University, Warren Alpert Medical School*	None	N/A
	Honorine Ward	*Tufts University, School of Medicine*	None	N/A
	Louis Weiss*	*Albert Einstein College of Medicine*	None	N/A
	Clinton White	*The University of Texas Medical Branch*	None	N/A
	Lihua Xiao	*Centers for Disease Control and Prevention*	None	N/A
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	Thuy Le	*Duke University, School of Medicine*	Gilead Sciences	Research Support (paid to institution)
	Rojelio Mejia	*Baylor College of Medicine*	Romark Laboratories	Research Support (paid to institution)
	Edward Mitre*	*Uniformed Services University of the Health Sciences, F. Edward Hebert School of Medicine*	None	N/A
	Susan Montgomery	*Centers for Disease Control and Prevention*	None	N/A
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			Company	Relationship
	Laura Cooley	*Centers for Disease Control and Prevention*	None	N/A
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	Marion Peters	*Northwestern University, Feinberg School of Medicine*	Aligos Antios	Scientific Advisory Board
	Chloe Thio*	*Johns Hopkins University, School of Medicine*	Allovir	Scientific Advisory Board
Hepatitis C Virus	Meena Bansal	*Mount Sinai, Icahn School of Medicine*	None	N/A
	Arthur Kim	*Harvard Medical School*	Kintor Pharmaceuticals	Data Monitoring Committee
	Nina Kim	*University of Washington, School of Medicine and School of Public Health*	Gilead FOCUS grant	Research Support (paid to institution)
	Susanna Naggie	*Duke University, School of Medicine*	Vir Biotechnology	Equity Interest
			Vir Biotechnology Bio Marin Theratechnologies	Scientific Advisory Board
			AbbVie Gilead Sciences	Research Support (paid to institution)
			FHI360 PRA/BMS	Adjudication Committee
	Mark Sulkowski	*Johns Hopkins University, School of Medicine*	Arbutus Assembly Bio Atea Antios AbbVie Gilead Sciences Virion	Scientific Advisory Board
			AbbVie Assembly Bio Gilead Sciences Janssen Contrafect	Research Support (paid to institution)

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			Company	Relationship
			EigerBio	
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	David Wyles*	*Denver Health Medical Center and University of Colorado Denver, School of Medicine*	Gilead Sciences	Research Support (paid to institution)
Herpes (HHV-8/CMV)	Gary Holland	*University of California Los Angeles, David Geffen School of Medicine*	None	N/A
	Christine Johnston	*University of Washington, School of Medicine*	Gilead Sciences AbbVie	Consultant
	Warren Phipps*	*University of Washington, School of Medicine*	None	N/A
	Ramya Ramaswami	*National Institutes of Health*	Celgene/BMS EMD-Serano Janssen CTI Biopharma Merck	Research Support (paid to institution)
	Shannon Ross	*The University of Alabama at Birmingham, School of Medicine*	None	N/A
Herpes (HSV/VZV)	Christine Durand	*Johns Hopkins University, School of Medicine*	AbbVie Gilead Sciences GlaxoSmithKline	Research Support (paid to institution)
			Gilead Sciences	Grant Review Committee, Honorarium
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			BioCryst	Data Safety Monitoring Board
	Gary Holland	*University of California, Los Angeles, David Geffen School of Medicine*	None	N/A
	Christine Johnston	*University of Washington, School of Medicine*	Gilead Sciences AbbVie	Consultant

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
	Shannon Ross	*The University of Alabama at Birmingham, School of Medicine*	None	N/A
	Nicholas Van Wagoner*	*The University of Alabama at Birmingham, School of Medicine*	None	N/A
Human Papillomavirus	Darron Brown	*Indiana University, School of Medicine*	Pfizer Johnson & Johnson Novavax Lilly	Equity Interest
			PDS Biotechnologies	Scientific Advisory Board
			Merck	Research Support (paid to institution)
	Susan Cu-Uvin*	*Brown University, Warren Alpert Medical School*	United Nations Population Fund	Research Support (paid to institution)
	Mark Einstein	*Rutgers New Jersey Medical School*	AstraZeneca Inovio Iovance Johnson & Johnson Pfizer VBL Therapeutics	Research Support (paid to institution)
			Becton-Dickerson Douglas Inovio Merck Papivax PDS Biotechnologies	Consulting fee (paid to institution)
	Lauri Markowitz	*Centers for Disease Control and Prevention*	None	N/A
	L. Stewart Massad	*Washington University in St. Louis, School of Medicine*	None	N/A
	Anna-Barbara Moscicki	*University of California Los Angeles, School of Medicine*	Merck	Scientific Advisory Board
	Joel Palefsky	*University of California, San Francisco, School of Medicine*	Merck	Research Support (paid to institution)
	Elizabeth Stier	*Boston University*	None	N/A

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
		Medical Center		
	Howard Strickler	*Albert Einstein College of Medicine*	Arbor Vista MTM Laboratories/ Ventura-Roche BD Diagnostics	Research Support (paid to institution)
	John Weiser	*Centers for Disease Control and Prevention*	None	N/A
	Timothy Wilkin	*Weill Cornell Medicine*	Merck	Scientific Advisory Board
			Merck ViiV Healthcare	Research Support (paid to institution)
Immunizations	Shireesha Dhanireddy*	*University of Washington, School of Medicine*	None	N/A
	Robyn Neblett Fanfair	*Centers for Disease Control and Prevention*	None	N/A
	Philip Peters	*Centers for Disease Control and Prevention*	None	N/A
	Daniel Solomon	*Harvard Medical School*	None	N/A
Invasive Mycoses	Neil Ampel	*University of Arizona, College of Medicine*	None	N/A
	David Boulware	*University of Minnesota Medical School*	Appili Therapeutics Matinas BioPharma	Research Support (paid to institution)
	Richard Hamill	*Baylor College of Medicine*	None	N/A
	Carol Kauffman*	*University of Michigan Medical School and Veterans Affairs Ann Arbor Healthcare System*	Cidara Laboratoires SMB S.A.	Data Safety Monitoring Board
	Marisa Miceli	*University of Michigan Medical School*	SCYNEXIS F2G Mayne	Research Support (paid to institution)
			SCYNEXIS	Data Safety Monitoring Board
			Astellas	Consulting
	Peter Pappas	*The University of Alabama at Birmingham, School of Medicine*	Astellas Pharma Merck	Research Support (paid to institution)
			Cidara Therapeutics	Scientific Advisory Board

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
			SCYNEXIS	Advisory Board (Research Support)
	John Perfect	*Duke University, School of Medicine*	Pfizer	Scientific Advisory Board
Mycobacterium avium Complex	Jacqueline Achkar	*Albert Einstein College of Medicine*	None	N/A
	Constance Benson*	*University of California San Diego, School of Medicine*	Gilead Sciences	Research Support (paid to institution)
	Maura Manion	*National Institutes of Health*	None	N/A
Mycobacterium tuberculosis	James Brust*	*Albert Einstein College of Medicine*	None	N/A
	Kelly Dooley	*Johns Hopkins University, School of Medicine*	None	N/A
	Neela Goswami	*Centers for Disease Control and Prevention*	None	N/A
	Scott Heysell	*University of Virginia, School of Medicine*	None	N/A
	Gary Maartens	*University of Cape Town, South Africa, Faculty of Health Sciences*	ViiV Healthcare	Marketing Advisory Board
	Graeme Meintjes	*University of Cape Town, South Africa, Faculty of Health Sciences*	None	N/A
	Sarita Shah	*Centers for Disease Control and Prevention*	None	N/A
	Timothy Sterling	*Vanderbilt University Medical Center*	None	N/A
Pharmacology	Kelly Dooley	*Johns Hopkins University, School of Medicine*	None	N/A
	Jomy George	*National Institutes of Health*	None	N/A
	Emily Heil	*University of Maryland, School of Pharmacy*	Lexi-Comp	Consultant
	Safia Kuriakose	*National Institutes of Health*	None	N/A
	Alice Pau*	*National Institutes of Health*	None	N/A

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
	Charles Peloquin	*University of Florida, College of Pharmacy*	None	N/A
	Jason Schafer	*Jefferson College of Pharmacy, Thomas Jefferson University*	Merck ViiV Healthcare	Scientific Advisory Board
			Merck Gilead Sciences	Research Support (paid to institution)
PML/JCV	Shruti Agnihotri	*The University of Alabama at Birmingham, School of Medicine*	Moderna Pfizer Gilead Sciences Johnson & Johnson	Equity interest
	Paola Cinque	*San Raffaele Scientific Institute, Milan, Italy*	Janssen	Consultant
			Cellevolve	Scientific Advisory Board
			Gilead Sciences ViiV Healthcare	Research Support (paid to institution)
	David Clifford*	*Washington University in St. Louis, School of Medicine*	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	*National Institutes of Health*	Nouscom AG Keires AG PDC*line Pharma Life Sciences Partners CV	Equity interest
	Christina Marra	*University of Washington, School of Medicine*	None	N/A
	Jose M. Miro	*Hospital Clinic-IDIBAPS, University of Barcelona, Spain*	None	N/A
Pneumocystis Pneumonia	Kristina Crothers	*University of Washington, School of*	None	N/A

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
		Medicine		
	Hansjakob Furrer	*Universitatsspital Bern, Switzerland*	Gilead Sciences ViiV Healthcare	Research Support (paid to institution)
	Jannik Helweg-Larsen	*Rigshospitalet, Copenhagen University, Denmark*	None	N/A
	Aley Kalapila	*Emory University, School of Medicine*	None	N/A
	Joseph Kovacs*	*National Institutes of Health*	Matinas BioPharma Merck	Research Support (paid to institution)
	Robert Miller	*University College London, England*	None	N/A
	Alison Morris	*University of Pittsburgh Medical School*	None	N/A
	Sean Wasserman	*University of Cape Town, South Africa, Faculty of Health Sciences*	None	N/A
Pregnancy	Jean Anderson	*Johns Hopkins University, School of Medicine*	DKBmed	Research Support (paid to institution)
	Katherine Bunge	*UPMC Magee-Womens Hospital*	None	N/A
	Nahida Chakhtoura*	*National Institutes of Health*	None	N/A
	Oluwatosin Goje	*Cleveland Clinic, Lerner College of Medicine*	SCYNEXIS Organicare, LLC	Consultant
			SCYNEXIS	Scientific Advisory Board
			SCYNEXIS	Research Support (paid to institution)
	Brenna Hughes	*Duke University, School of Medicine*	Merck	Scientific Advisory Board
	Sylvia LaCourse	*University of Washington, School of Medicine and School of Public Health*	Merck	Research Support (paid to institution)
	Gweneth Lazenby	*Medical University of South Carolina*	None	N/A
	Rodney Wright	*Albert Einstein College of Medicine*	None	N/A
Syphilis	Laura Bachmann	*Centers for Disease Control and Prevention, National Center for HIV,*	None	N/A

Section	Member	Institution	Financial Disclosure	
			Company	Relationship
		Viral Hepatitis, STD and TB Prevention, Division of STD Prevention		
	Khalil Ghanem	*Johns Hopkins University, School of Medicine*	None	N/A
	Lisa Hollier	*Baylor College of Medicine*	None	N/A
	Edward W. Hook	*The University of Alabama at Birmingham, School of Medicine*	Visby Diagnostics	Scientific Advisory Board
	Arlene Sena	*The University of North Carolina at Chapel Hill, School of Medicine*	None	N/A
	Brad Stoner	*Washington University in St. Louis, School of Medicine*	None	N/A
	Kimberly Workowski*	*Emory University, School of Medicine*	None	N/A
Toxoplasma gondii	Sarita Boyd	*U.S. Food and Drug Administration*	None	N/A
	Felicia Chow	*University of California, San Francisco, School of Medicine*	None	N/A
	Joseph Kovacs*	*National Institutes of Health*	Matinas BioPharma Merck	Research Support (paid to institution)
	Janaki Kuruppu	*National Institutes of Health*	None	N/A
	Leon Lai	*Washington Hospital Center*	None	N/A
	Jose M. Miro	*Hospital Clinic-IDIBAPS, University of Barcelona, Spain*	None	N/A
	Daniel Podzamczer	*Fight AIDS and Infectious Disease Foundation, Hospital Germans Trias i Pujol, Badalona, Spain*	Janssen Gilead Sciences ViiV Healthcare	Consultant
			Gilead Sciences MSD	Research Support (paid to institution)

Key: * = Section Group Lead

Note: Members are required to update disclosures annually and to notify guideline staff of any relevant changes in status during the interim.