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 http://aidsinfo.nih.gov/contentfiles/lvguidelines/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 AIDS*info* website (http://aidsinfo.nih.gov).

Access AIDS*info* mobile site

What's New in the Guidelines

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 was published in an electronic format that could be easily updated 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 are also promptly posted). 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:

May 15, 2019

- The name of the guidelines was updated to include People-First Language. People-First Language is a way of reducing stigma and showing respect for individuals who are living with HIV by focusing on the person instead of the disease. The new title is *Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV*.
- The sections about opportunistic infections were alphabetized to make it easier to navigate the guidelines.
- The information in Tables 1, 2, and 4 were also alphabetized by opportunistic infection name.
- The name of the Isosporiasis section was updated to Cystoisosporiasis.
- The name of the Penicilliosis section was updated to Talaromycosis.
- The Preventing Exposures section was removed from the current guidelines. This section can be found in the archived versions of the guidelines.

March 28, 2019

1. ***Pneumocystis* Pneumonia:** The Panel updated references for stopping PCP prophylaxis in patients with CD4 counts between 100 and 200 cells/mm^3 and plasma viral loads below the detection limits of assays. The Panel also updated references for *Pneumocystis*-associated IRIS. Wording throughout the document was updated to improve clarity.

February 15, 2019

1. **Disseminated *Mycobacterium avium* Complex Disease:** The Panel updated the text and references throughout the section and made two key changes to their guidance:
    - Primary prophylaxis for MAC in people living with HIV who immediately initiate antiretroviral therapy is no longer recommended, regardless of CD4 cell count.
    - Guidance has been added about drug-drug interactions and dosing when using rifabutin for treatment or prevention of MAC together with newer non-nucleoside reverse transcriptase inhibitors (rilpivirine, doravirine) and integrase strand transfer inhibitors (elvitegravir/cobicistat, bictegravir).

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

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 Medical 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://aidsinfo.nih.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 AIDS*info* website (https://aidsinfo.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 AIDS*info* website (https://aidsinfo.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 AIDS*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@aidsinfo.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 August 10, 2017)

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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Bacterial Respiratory Disease (Last updated May 7, 2013; last reviewed March 13, 2019)

NOTE: Update in Progress

Epidemiology

Bacterial respiratory diseases; including sinusitis, bronchitis, otitis, and pneumonia; are among the most common infectious complications in patients with HIV infection, occurring with increased frequency at all CD4 T lymphocyte cell (CD4) counts,[1] and some data suggest that bacterial pneumonia may occur with increased severity in this population. This chapter will focus on the diagnosis, prevention, and management of bacterial pneumonia in HIV-infected patients.

Bacterial pneumonia is a common cause of HIV-associated morbidity and recurrent pneumonia (2 or more episodes within a 1-year period) is an AIDS-defining condition. The incidence of bacterial pneumonia is higher in HIV-infected individuals than in those who are not HIV infected.[2] More recently, the incidence of bacterial pneumonia in HIV-infected individuals has declined. In one study, the incidence of bacterial pneumonia declined from 22.7 episodes per 100 person-years in the era before combination antiretroviral therapy (ART) to 9.1 episodes per 100 person-years by 1997.[3-5]

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. The high rates of bacterial pneumonia in HIV-infected individuals probably result from multiple factors, including qualitative B-cell defects that impair ability to produce pathogen-specific antibody; impaired neutrophil function or numbers, or both; and factors, such as injection drug use, that are associated with underlying HIV infection. Risk factors associated with an increased risk of bacterial pneumonia include low CD4 count (< 200 cells/mm^3), no or intermittent use of ART, cigarette smoking, injection drug use, and chronic viral hepatitis.

In HIV-infected individuals, as in those who are not HIV infected, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified causes of community-acquired bacterial pneumonia.[6-12] Atypical bacterial pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila* species have been reported as infrequent causes of community-acquired bacterial pneumonia in HIV-infected individuals.[9,13]

The frequency of *Pseudomonas aeruginosa* and *Staphylococcus aureus* as community-acquired pathogens is higher in HIV-infected individuals than in those not HIV infected.[10,14] Methicillin-resistant *Staphylococcus aureus* (MRSA) infection, in particular, should be considered as a potential etiology for pneumonia, given that community outbreaks of MRSA have been seen in men who have sex with men and nasal carriage of MRSA is more common in HIV-infected individuals, particularly at lower CD4 cell counts.[15] Also, community-acquired MRSA pneumonia may not invariably be associated with preceding influenza illness.[16]

In HIV-infected patients, particularly those infected with *S. pneumoniae*, incidence of bacteremia accompanying pneumonia is increased compared with that in individuals who are not HIV infected. In one study, the estimated rate of pneumococcal bacteremia in patients with AIDS (1,094 cases per 100,000) was ~55 times that in HIV-uninfected individuals (20 cases per 100,000). This disparity narrowed but was not eliminated after the introduction of ART.[17] Other studies have highlighted the declining incidence of pneumococcal bacteremia in the era of ART.[18]

Bacterial pneumonia is associated with increased mortality in HIV-infected individuals.[10,19,20] In HIV-infected individuals with community-acquired bacterial pneumonia, a prospective, multicenter study documented CD4 count <100 cells/mm^3, radiographic progression of disease, and presence of shock as independent predictors of increased mortality.[21] In that study, multilobar infiltrates, cavitary infiltrates, and pleural effusion on baseline radiograph all were independent predictors of radiographic progression of disease.

Clinical Manifestations

Clinical and radiographic presentation of bacterial pneumonia in HIV-infected individuals is similar to that in those who are not HIV infected. Patients with pneumonias 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.[22] They are often febrile and the presence of fever, tachycardia, or hypotension can be an indicator of sepsis. Tachypnea and decreased arterial oxygen saturation indicate moderate-to-severe pneumonia and clinicians should strongly consider hospitalizing such patients.

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 in those with advanced HIV. 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 presence of cavitation may be a feature more suggestive of *P. aeruginosa* or *S. aureus*.

Disease severity and arterial oxygenation should be assessed in all patients with pneumonia. Noninvasive measurement of arterial oxygen saturation via pulse oximetry is an appropriate screening test. Arterial blood gas analysis is indicated for those with evidence of hypoxemia suggested by noninvasive assessment and for patients who have tachypnea and/or respiratory distress. Criteria developed to assess disease severity in HIV-uninfected persons, such as the Pneumonia Severity Index (PSI) (http://pda.ahrq.gov/clinic/psi/psicalc.asp) appear to be valid for HIV-infected patients, especially when used in combination with CD4 count[21,23] (discussed in further detail in Treating Disease).

Diagnosis

Guidelines for diagnosing and managing community-acquired pneumonia (CAP) in individuals who are not HIV infected also apply to those who are infected.[24] Patients with clinical symptoms and signs suggestive of CAP should have posteroanterior and lateral chest radiographs, if possible. If previous radiographs are available, they should be reviewed to assess for presence of new findings. The clinical diagnosis of bacterial pneumonia requires a demonstrable infiltrate.

Given the increased incidence of *Mycobacterium tuberculosis* in HIV-infected individuals, a tuberculosis (TB) diagnosis should always be considered in HIV-infected patients who have pneumonia. Those with clinical and radiographic findings suggestive of TB should be managed as potentially having TB (that is, with respiratory isolation if hospitalized), and two to three sputum specimens should be obtained for acid fast bacilli evaluation. 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.

Often, the differential diagnosis of pneumonia in HIV-infected individuals is broad and a confirmed microbiologic diagnosis allows clinicians to target the specific pathogen and discontinue broad spectrum antibiotic therapy and/or empiric therapy (such as empiric PCP therapy) that targets non-bacterial pathogens.

HIV-infected patients with suspected CAP should undergo investigation for specific pathogens that would significantly alter standard (empirical) management decisions when presence of such pathogens is suspected based on epidemiologic, clinical, or radiologic clues. *P. aeruginosa* should be considered in HIV-infected patients with advanced HIV disease (that is, CD4 count $\leq$50 cells/mm^3), pre-existing lung disease such

as bronchiectasis, or underlying neutropenia. It is also a consideration for HIV-infected patients who use corticosteroids, are severely malnourished, have been hospitalized in the past 90 days or reside in a health care facility or nursing home, or are on chronic hemodialysis. Because cavitary infiltrates are common in patients with *P. aeruginosa*, that radiographic finding also should prompt an investigation for this pathogen. *S. aureus* should be considered in patients with recent viral (or influenza) infection; a history of injection drug use; or severe, bilateral, necrotizing pneumonia.

Routine diagnostic tests to identify an etiologic diagnosis are optional for HIV-infected patients with suspected CAP who are well enough to be treated as outpatients, especially if the microbiologic studies cannot be performed promptly.

In contrast, a pre-treatment expectorated sputum specimen for Gram stain and culture and two blood cultures should be obtained from HIV-infected patients hospitalized for suspected CAP, particularly those who require intensive care.

Gram stain and culture of expectorated sputum should be performed only if a good-quality specimen can be obtained and quality performance measures can be met for collection, transport, and processing of samples. 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. Bronchoscopy with bronchoalveolar lavage should be considered, especially if the differential diagnosis is broad and includes pathogens such as *Pneumocystis jirovecii*.

The increased incidence of bacteremia in HIV-infected patients, especially those with low CD4 cell counts, and the high specificity of blood cultures argue for their collection in such individuals. Low sensitivity of blood cultures in persons with higher CD4 counts argues against routine collection. However, patients with HIV infection are at increased risk of infection with drug-resistant pneumococci.[25,26] Because identification of this organism could lead to changes in management, collection of blood specimens in HIV-infected patients with CAP should always be considered.

In addition to the above tests, urinary antigen tests for *L. pneumophila* and *S. pneumoniae* should be considered.

Diagnostic thoracentesis should be considered in all patients with pleural effusion, especially if concern exists for accompanying empyema, and therapeutic thoracentesis should be performed to relieve respiratory distress secondary to a moderate-to-large-sized pleural effusion.

Preventing Exposure

No effective means exist to reduce exposure to *S. pneumoniae* and *Haemophilus influenzae*, which are common in the community.

Preventing Disease

Vaccination against *S. pneumoniae* and influenza, use of combination ART, and lifestyle modifications are all important measures in preventing bacterial pneumonia. Multiple observational studies of pneumococcal polysaccharide vaccine (PPV) in the United States have reported benefits from such vaccination in HIV-infected persons.[27-32] Several studies also have documented an association between vaccination and a reduced risk of pneumococcal bacteremia.[18,32] One randomized placebo-controlled trial of PPV in Africa paradoxically found that vaccination was associated with an increased risk of pneumonia.[33] Follow-up of this cohort confirmed the increase in pneumonia in vaccinated subjects but also showed a decrease in all-cause mortality.[34]

A 13-valent pneumococcal conjugate vaccine (PCV13) has recently been recommended by the Advisory Committee on Immunization Practices for use in adults with immunocompromising conditions, including HIV infection.[35] A randomized, double-blind, placebo-controlled trial of 7-valent PCV among HIV-infected

adults 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.[36]

HIV-infected adults and adolescents who have never received any pneumococcal vaccine should receive a single dose of PCV13 regardless of CD4 count **(AI)**.[35] Patients with CD4 counts ≥200 cells/mm^3 should then receive a dose of 23-valent PPV (PPV23) at least 8 weeks later **(AII)**.[27-32,37-39] HIV-infected patients with CD4 counts <200 cells/mm^3 can be offered PPV23 at least 8 weeks after receiving PCV13 **(CIII)**; however, it may be preferable to defer PPV23 until after the CD4 count increases to >200 cells/mm^3 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;[37,39] evidence also suggests benefit for those who start ART before receiving PPV.[32]

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 **(BIII)**.[31] A third dose of PPV23 should be given at age 65 years or later, as long as 5 years have elapsed since the most recent dose and it was given before age 65 years **(BIII)**.

PCV13 should also be given in HIV-infected patients who have already received PPV23 **(AII)**. However, such patients should wait at least 1 year after their most recent dose of PPV23 before receiving a single dose of PCV13 **(BIII)**.[35] Subsequent doses of PPV23 should be given according to the schedule outlined above (i.e., at least 5 years between doses of PPV23 with no more than 3 lifetime doses).

Inactivated influenza vaccine should be administered annually during influenza season to all HIV-infected individuals **(AIII)**.[40] This recommendation is pertinent to prevention of bacterial pneumonia, which can occur as a complication of influenza. Use of live attenuated influenza vaccine is contraindicated and **is not recommended** in HIV-infected individuals **(AIII)**.

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

Several factors are associated with a decreased risk of bacterial pneumonia, including use of ART and of trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis.[20] In many studies, daily administration of TMP-SMX for PCP prophylaxis also reduced the frequency of bacterial respiratory infections.[2,41,42] This point should be considered when selecting an agent for PCP prophylaxis; however, indiscriminate use of this drug (when not indicated for PCP prophylaxis or other specific reasons) may promote development of TMP-SMX-resistant organisms. Thus, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection **(BIII)**. Similarly, clarithromycin administered daily and azithromycin administered weekly are the drugs of choice for *Mycobacterium avium* complex (MAC) prophylaxis and may be effective in preventing bacterial respiratory infections.[43,44] However, these drugs also should not be prescribed solely for preventing bacterial respiratory infection **(BIII)**.

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 malignancies. To reduce the risk of such bacterial infections, clinicians can consider taking steps to reverse neutropenia, either by stopping myelosuppressive drugs **(CIII)** or by administering granulocyte-colony stimulating factor **(CIII)**, although these interventions have not been demonstrated to be effective in HIV-infected persons.

Modifiable factors associated with an increased risk of bacterial pneumonia include smoking cigarettes and using injection drugs and alcohol.[2,38,45-47] Clinicians should encourage cessation of these behaviors, and data suggest that smoking cessation can decrease the risk of bacterial pneumonia.[48]

Treating Disease

Whether patients should be treated on an outpatient basis or admitted to the hospital depends on several factors. One study suggested that the site of care decision be dictated by considering the PSI and CD4 count together.[23] Mortality was increased in patients with higher PSI class, but even in those without an increased mortality risk by PSI, the presence of a CD4 count <200 cells/mm^3 was associated with an increased risk of death.[23] This led to the suggestion to always offer hospitalization to CAP patients with CD4 counts <200 cells/mm^3 and to use the PSI to help guide the decision in those with higher CD4 counts.[49] In fact, in one series of 118 HIV-infected patients with CAP who were hospitalized, 62% fell into PSI Classes I and II, groups that are rarely hospitalized if not HIV infected.[50] In another study, 40% of hospitalized HIV-infected patients in low-risk PSI classes had CD4 counts <200 cells/mm^3.[23]

The basic principles of treatment of community-acquired bacterial pneumonia are the same for HIV-infected patients as for those who are not HIV infected.[24] As discussed in the Diagnosis section, if specimens are to be collected for diagnosis, they should be taken before antibiotic therapy is initiated. Antibiotic therapy should be administered promptly, however, without waiting for the results of diagnostic testing.

Empiric Antibiotic Therapy by Treatment Setting and Severity of Diseases

Outpatient Treatment

HIV-infected individuals who are being treated as outpatients should receive an oral beta-lactam plus an oral macrolide **(AII)** or an oral respiratory fluoroquinolone **(AII)**. Preferred beta-lactams are high-dose amoxicillin or amoxicillin-clavulanate; alternatives are cefpodoxime or cefuroxime. Preferred macrolides are azithromycin or clarithromycin. Doxycycline is an alternative to the macrolide **(CIII)**. Preferred oral respiratory fluoroquinolones are moxifloxacin or levofloxacin.

An oral respiratory fluoroquinolone (moxifloxacin or levofloxacin) should be used in patients who are allergic to penicillin **(AII)**.

Respiratory fluoroquinolones also are active against *M. tuberculosis*. Thus, patients with TB who are treated with fluoroquinolone monotherapy may have an initial but misleading response that could delay diagnosis of TB and initiation of appropriate multidrug TB therapy and increase risk of drug-resistant TB and TB transmission. Fluoroquinolones, therefore, 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. Increasing rates of pneumococcal resistance suggest that empirical therapy with a macrolide alone **cannot be routinely recommended (BIII)**. Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia, but macrolides can be used as part of a combination regimen.

Non-Intensive Care Unit Inpatient Treatment

HIV-infected individuals who are being treated as inpatients should receive an intravenous (IV) beta-lactam plus a macrolide **(AII)** or an IV respiratory fluoroquinolone **(AII)**. Preferred beta-lactams are ceftriaxone, cefotaxime, or ampicillin-sulbactam. Preferred macrolides are azithromycin and clarithromycin. Doxycycline is an alternative to the macrolide **(CIII)**. Preferred respiratory fluoroquinolones are moxifloxacin or levofloxacin. Clinical and Laboratory Standards Institute and U.S. Food and Drug Administration changes in the penicillin breakpoints for treatment of non-meningitis pneumococcal disease imply that clinicians can consider treatment with IV penicillin in HIV-infected patients confirmed to have pneumococcal pneumonia **(BIII)**.[51]

In patients who are allergic to penicillin, an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) should be used **(AII)**.

Because of the activity of fluoroquinolones against *M. tuberculosis* and the dangers of monotherapy in those with TB, as previously discussed, 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.

Increasing rates of pneumococcal resistance suggest that empirical therapy with a macrolide alone **cannot be recommended routinely (BIII)**. Patients who are receiving a macrolide for MAC prophylaxis should never receive macrolide monotherapy for empiric treatment of bacterial pneumonia, but macrolides can be used as part of a combination regimen.

Intensive Care Unit Treatment

Intensive care unit patients should not receive empiric monotherapy, even with a fluoroquinolone, because the efficacy of this approach has not been established. 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 intensive care unit.[52] Patients with severe pneumonia who require intensive care should be treated with an IV beta-lactam plus either IV azithromycin **(AII)** or an IV respiratory fluoroquinolone (moxifloxacin or levofloxacin [750 mg/day]) **(AII)**. 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)**.

The majority of CAP pathogens can be treated adequately with recommended empiric regimens. The increased incidence of *P. aeruginosa* and *S. aureus* (including community-acquired MRSA) as causes of CAP are exceptions. Both of these pathogens occur in specific epidemiologic patterns with distinct clinical presentations, for which empiric antibiotic coverage may be warranted. Diagnostic tests (sputum Gram stain and culture) are likely to be of high yield for these pathogens, allowing early discontinuation of empiric treatment if results are negative.

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 **(BIII)**. Preferred beta-lactams are piperacillin-tazobactam, cefepime, imipenem, or meropenem. Alternatives are an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and azithromycin **(BIII)** or an antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone **(BIII)**. In patients who are allergic to penicillin, aztreonam can be used in place of the beta-lactam **(BIII)**.

Empiric Staphylococcus aureus Treatment

In patients who have risk factors for *S. aureus* infection, including community-acquired MRSA, vancomycin or linezolid should be added to the antibiotic regimen **(BIII)**. Although not routinely recommended, the addition of clindamycin (to vancomycin, but not to linezolid) may be considered if severe necrotizing pneumonia is present to minimize bacterial toxin production **(CIII)**.

Pathogen-Directed Therapy

When the etiology of the pneumonia has been identified on the basis of reliable microbiological methods, antimicrobial therapy should be modified and directed at that pathogen.

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 (PaO_2) >60 mm Hg.[24]

Special Considerations Regarding When to Start Antiretroviral Therapy

The presence of acute opportunistic infection (OI), including bacterial pneumonia, increases the urgency of

starting ART. In one randomized, controlled trial, use of ART early in the course of OIs, including bacterial infections, led to less AIDS progression and death compared with later onset of therapy.[53] Therefore, in patients not already on ART, ART should be initiated early in the course of bacterial pneumonia **(AI)**.

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

The clinical response to appropriate antimicrobial therapy is similar in HIV-infected patients and individuals who are not HIV infected.[54] 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. The presence of advanced HIV infection, CD4 count <100 cells/mm^3, and *S. pneumoniae* etiology were predictors of needing >7 days to reach clinical stability, whereas those patients receiving ART tended to become clinically stable sooner.[49] Usually, radiographic improvement lags behind clinical improvement.

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with bacterial respiratory disease and treatment with ART in HIV-infected patients.

Managing Treatment Failure

Patients who fail to respond to appropriate antimicrobial therapy should undergo further evaluation to search for other infectious and noninfectious causes of pulmonary dysfunction. The possibility of TB should always be considered in HIV-infected patients with pulmonary disease.

Preventing Recurrence

HIV-infected patients should receive pneumococcal and influenza vaccine 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.

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 as in women who are not pregnant, with certain exceptions. Clarithromycin is not recommended as the first-line agent among macrolides because of an increased risk of birth defects seen in some animal studies. Two studies, each involving at least 100 women with first-trimester exposure to clarithromycin, did not document a clear increase in or specific pattern of birth defects, although an increased risk of spontaneous abortion was noted in one study.[55,56] 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. However, studies evaluating quinolone use in pregnant women did not find an increased risk of birth defects or musculoskeletal abnormalities.[57,58] Thus, when indicated, quinolones can be used in pregnancy for serious respiratory infections **(CIII)**.[59]

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. Aminoglycosides can be used as needed. A theoretical risk of fetal renal or eighth nerve damage exists with exposure during pregnancy, but this finding has not been documented in humans, except with streptomycin (10% risk) and kanamycin (2% risk). 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)**. Although its safety during the first

trimester has not been evaluated, no adverse consequences have been reported among newborns whose mothers were inadvertently vaccinated during pregnancy. Inactivated influenza vaccine also can be administered during pregnancy, and the vaccine is recommended for all pregnant women during influenza season **(AIII)**. Live attenuated influenza vaccine should not be used in HIV-infected persons **(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 Bacterial Respiratory Diseases (page 1 of 3)

Preventing *Streptococcus pneumoniae* Infections

Indications for Pneumococcal Vaccination:

- All HIV-infected persons regardless of CD4 count

Vaccination Recommendations:

For Individuals Who Have Not Received Any Pneumococcal Vaccination:

Preferred Vaccination:

- One dose of PCV13 **(AI)**, followed by:
- For patients with CD4+ count ≥200 cells/μL: PPV23 should be given at least 8 weeks after receiving PCV13 **(AII)**; *or*
- For patients with CD4 count <200 cells/μL: PPV23 can be offered at least 8 weeks after receiving PCV13 **(CIII)** or can await increase of CD4 count to >200 cells/μL on ART **(BIII)**

Alternative Vaccination:

- One dose of PPV23 **(BII)**

For Individuals Who Have Previously Received PPV23:

- One dose of PCV13 should be given at least 1 year after the last receipt of PPV23 **(AII)**

Re-vaccination of PPV

- A dose of PPV23 is recommended for individuals 19–64 years old if ≥5 years have elapsed since the first dose of PPV **(BIII)**
- Another dose should be given for individuals 65 years or older, if at least 5 years have elapsed since previous PPV23 dose **(BIII)**

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 HIV-infected persons during influenza season **(AIII)**

Vaccination:

- Inactivated influenza vaccine per recommendation of the season **(AIII)**

Note: Live attenuated influenza vaccine is **contraindicated** in HIV-infected persons **(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.

Empiric Outpatient Therapy (Oral)

Preferred Therapy:

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

- A fluoroquinolone[a] **(AII)**, especially for patients with penicillin allergies
  - Levofloxacin[a] 750 mg PO once daily **(AII)**, *or*
  - Moxifloxacin[a] 400 mg PO once daily **(AII)**

Alternative Therapy:

- A beta-lactam **(AII)** + doxycycline **(CIII)**

Duration of Therapy:

- For most patients: 7–10 days; a minimum of 5 days. The patient should be afebrile for 48–72 hours, and should be clinically stable before discontinuation of therapy

Empiric Therapy for Non-ICU Hospitalized Patients

Preferred Therapy:

- An IV beta-lactam + a macrolide (azithromycin or clarithromycin) **(AII)**, *or*
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
- An IV fluoroquinolone[a] **(AII)**, especially for patients with penicillin allergies
  - Levofloxacin[a] 750 mg IV once daily **(AII)**, *or*
  - Moxifloxacin[a] 400 mg IV once daily **(AII)**

Alternative Therapy:

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

Empiric Therapy for ICU Patients

Preferred Therapy:

- An IV beta-lactam + IV azithromycin **(AII)**, *or*
- An IV beta-lactam + (levofloxacin[a] IV 750 mg once daily or moxifloxacin[a] 400mg IV daily) **(AII)**
  - *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam

Alternative Therapy:

For Penicillin-Allergic Patients:

- Aztreonam (IV) + an IV respiratory fluoroquinolone (moxifloxacin 400 mg per day or levofloxacin 750 mg per day) **(BIII)**

Empiric Therapy for Patients at Risk of Pseudomonas Pneumonia

Preferred Therapy:

- An IV antipneumococcal, antipseudomonal beta-lactam + (ciprofloxacin IV [400 mg q8–12h] or levofloxacin IV 750 mg/day) **(BIII)**
  - *Preferred beta-lactams:* piperacillin-tazobactam, cefepime, imipenem, or meropenem

Alternative Therapy:

- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + IV azithromycin **(BIII)**, *or*
- An IV antipneumococcal, antipseudomonal beta-lactam + an IV aminoglycoside + an IV antipneumococcal fluoroquinolone (moxifloxacin [400 mg/day] or levofloxacin [750 mg/day]) **(BIII)**

For Penicillin-Allergic Patients:

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

Empiric Therapy for Patients at Risk of Staphylococcus aureus Pneumonia:

- Vancomycin IV or linezolid (IV or PO) should be added to the baseline regimen **(BIII)**.
- 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 **(CIII)**.

Other Considerations

- Empiric therapy with a macrolide alone is not routinely recommended because of increasing pneumococcal resistance **(BIII)**.
- Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia.

Recommendations for Preventing and Treating Bacterial Respiratory Diseases (page 3 of 3)

- Once the pathogen has been identified by reliable microbiologic methods, antibiotics should be modified to treat the pathogen **(BIII)**.
- For patients begun on IV antibiotic therapy, switching to PO should be considered when patient is clinically improved and able to tolerate oral medications.
- Antibiotics chemoprophylaxis is generally not recommended because of the potential for development of drug resistance microorganisms and drug toxicities.

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

Key to Acronyms: PCV13 = 13-Valent Pneumococcal Conjugate Vaccine; CD4 = CD4 T lymphocyte cell; PPV 23 = 23-Valent Pneumococcal Polysaccharide Vaccine; ART = antiretroviral therapy; IM = intramuscularly; PO = Orally; IV = Intravenously; MAC = *Mycobacterium avium* complex

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Bartonellosis (Last updated May 7, 2013; last reviewed March 13, 2017)

Epidemiology

Bartonella species cause infections that include cat scratch disease, retinitis, trench fever, relapsing bacteremia, endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis.[1] The latter two manifestations occur only in individuals who are immunocompromised. BA is caused by either *Bartonella quintana* or *Bartonella henselae*.[1,2] Twenty-four species and three subspecies of *Bartonella* have been isolated and are officially recognized (http://www.bacterio.cict.fr/b/bartonella.html), and eight have been isolated from humans. However, only *B. henselae* and *B. quintana* infections have been identified in HIV-infected patients.[2] BA most often occurs late in HIV infection, in patients with median CD4 T lymphocyte (CD4 cell) counts <50 cells/mm^3.[2] In HIV-infected patients, bartonellosis is often a chronic illness, lasting for months to years, with BA lesions and intermittent bacteremia.

Development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in patients with HIV infection.[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* in humans. To avoid exposure to *B. quintana*, HIV-infected patients should avoid body lice and, if infected, treat the infestation. 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] Control of cat flea infestation and avoidance of cat scratches are therefore critical strategies for preventing *B. henselae* infections in patients who are HIV infected.

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* can cause bacillary peliosis hepatis. 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 late-stage AIDS and should be considered in the differential diagnosis of patients with fever and CD4 counts <100 cells/mm^3.[4] *Bartonella* is a relatively common cause of culture-negative endocarditis in immunocompetent and immunocompromised humans and is most commonly caused by *B. quintana* and, less frequently, *B. henselae*.[5]

Diagnosis

Diagnosis 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 serologic test was developed at Centers for Disease Control and Prevention[7] and is also available at some state health labs. In addition, several private laboratories offer serological testing, but none of these private laboratory tests has been evaluated for sensitivity or specificity with sera from HIV-infected patients with culture-documented *Bartonella* infection. 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 for months or even >1 year. Note that 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 correlate with resolution and recrudescence of *Bartonella* infection.

Bartonella species can be isolated (with difficulty) from blood, using ethylenediaminetetraacetic acid (EDTA) tubes. The organisms have been isolated from tissue in only a few laboratories because of the fastidious nature of *Bartonella*.[2] Polymerase chain reaction methods have been developed for identification and speciation of *Bartonella* but are not widely available.

Preventing Exposure

HIV-infected patients, 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 HIV-infected individuals 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)**.

Preventing Disease

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

Treating Disease

All HIV-infected patients with *Bartonella* infection should receive antibiotic treatment **(AII)**. Guidelines for treatment of *Bartonella* infections have been published.[8] No randomized, controlled clinical trials have evaluated antimicrobial treatment of bartonellosis in HIV-infected patients. Erythromycin and doxycycline have been used successfully to treat BA, peliosis hepatis, bacteremia, and osteomyelitis and are considered first-line treatment for bartonellosis on the basis of reported experience in case series **(AII)**.[1,2] Therapy should be administered for ≥3 months **(AII)**. Doxycycline, with or without a rifamycin, is the treatment of choice for bartonellosis infection involving the central nervous system (CNS) **(AIII)**. For severe *Bartonella* infections, combination therapy using erythromycin or doxycycline with a rifamycin is recommended **(BIII)**; intravenous therapy may be needed initially **(AIII)**. Treatment of confirmed *Bartonella* endocarditis should include doxycycline with the addition of gentamicin for 2 weeks (if tolerated); a rifamycin can be substituted for gentamicin in the setting of renal insufficiency **(BII)**.[8]

Clarithromycin or azithromycin treatment has been associated with clinical response and either of these can be an alternative therapy *Bartonella* infections (except for endocarditis or CNS infections) **(BIII)**. Azithromycin is recommended for patients who are less likely to comply with the more frequent dosing schedule for doxycycline or erythromycin. A third-generation cephalosporin, ceftizoxime,[9] was used successfully to treat *Bartonella* in a pregnant HIV-infected woman, but because there are no other data, a macrolide is the drug of first choice. Penicillins and first-generation cephalosporins have no *in vivo* activity and should not be used for treatment of bartonellosis **(BII)**. Quinolones and trimethoprim-sulfamethoxazole (TMP-SMX) have variable *in vitro* activity and an inconsistent clinical response in case reports and are not recommended **(BIII)**.

Special Consideration with Regard to Starting ART

Antiretroviral-naive patients with *Bartonella* CNS or ophthalmic lesions should probably be treated with doxycycline and a rifamycin for 2 to 4 weeks before instituting antiretroviral therapy **(CIII)**.

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

Patients should have anti-*Bartonella* IgG antibody titers checked at the time of diagnosis and, if positive, should be followed with sequential titers every 6 to 8 weeks until a four-fold decrease is documented. This test is available at the Centers for Disease Control and Prevention and several large commercial labs. Patients treated with oral doxycycline should be cautioned about pill-associated ulcerative esophagitis that occurs most often when a dose is taken with only a small amount of liquid or at night just before retiring.[10] Photosensitivity also can occur during doxycycline treatment. Adverse effects associated with macrolides include nausea, vomiting, abdominal pain, and elevations of liver transaminase levels. Serious side effects can occur during treatment with rifamycins, including hypersensitivity reactions (including thrombocytopenia, interstitial nephritis, and hemolytic anemia), and hepatitis. Administration of rifamycins strongly induces the cytochrome P450 enzyme system, which is an important consideration when other medications, including many ARV drugs, are taken simultaneously.

Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with Bartonellosis and treatment with ART in HIV-infected persons.

Managing Treatment Failure

Among patients who fail to respond to initial treatment, 1 or more of the second-line alternative regimens should be considered **(AIII)**, again with treatment duration of ≥3 months. For patients with positive or increasing antibody titers, treatment should continue until a fourfold decrease is documented.

Preventing Recurrence

If a relapse occurs after a minimum 3-month course of primary treatment, long-term suppression of infection with doxycycline or a macrolide is recommended, as long as the CD4 count remains <200 cells/mm^3 **(AIII)**.

Long-term suppression can be discontinued after the patient has received at least 3 to 4 months of therapy and when the CD4 count remains >200 cells/mm^3 for ≥6 months **(CIII)**. Some specialists would discontinue therapy only if the *Bartonella* titers have also decreased by four-fold **(CIII)**.

Special Considerations During Pregnancy

Infection with *Bartonella bacilliformis* in immunocompetent patients during pregnancy has been associated with increased complications and risk of death.[11] No data are available on the effect of *B. henselae* or *B. quintana* infections in pregnant women with concomitant HIV infection.

The approach to diagnosis of *Bartonella* infections in pregnant women is the same as in non-pregnant women. Erythromycin treatment should be used **(AIII)** rather than tetracyclines 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[9] or ceftriaxone may have efficacy against *Bartonella* in pregnant women who are HIV infected, but it should be considered second-line therapy after a macrolide. First- and second-generation cephalosporins **are not recommended** because of their lack of efficacy against *Bartonella* **(AII)**.

Recommendations for Treating *Bartonella* Infections

Preferred Therapy

For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis:

- Doxycycline 100 mg PO or IV q12h **(AII)**, *or*
- Erythromycin 500 mg PO or IV q6h **(AII)**

For Infections Involving the CNS:

- Doxycycline 100 mg PO or IV q12h +/- rifampin 300 mg PO or IV q12h **(AIII)**

For Confirmed Bartonella Endocarditis:

- (Doxycycline 100 mg IV q12h + gentamicin 1 mg/kg IV q8h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**, *or*
- For patients with renal insufficiency: (doxycycline 100 mg IV q12h + rifampin 300 mg IV or PO q12h) x 2 weeks, then continue with doxycycline 100 mg IV or PO q12h **(BII)**

For Other Severe Infections

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

Alternative Therapy for Bartonella Infections (Not for Endocarditis or CNS Infections):

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

Duration of Therapy:

- At least 3 months

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

Other Considerations

- Rifampin is a potent hepatic enzyme inducer and may lead to significant interaction with many drugs; including ARV agents (see Table 5 for dosing recommendations)

Key to Abbreviations: 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 October 18, 2017; last reviewed October 18, 2017)

Epidemiology

Oropharyngeal and esophageal candidiasis are common in HIV-infected patients.[1,2] The vast majority of such infections are caused by *Candida albicans*, although infections caused by non-*albicans Candida* 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-*albicans Candida* 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 HIV-infected patients with 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 HIV-infected women, *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 rarely refractory to azole therapy.

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) 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 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 two weeks of therapy is recommended for oropharyngeal candidiasis; two to three weeks of therapy is recommended for esophageal disease.[15]

Using topical agents to treat oropharyngeal candidiasis reduces systemic drug exposure, diminishes 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 equivalent as shown in a multicenter, randomized study.[16] Nystatin suspension or pastilles four times daily remains an additional alternative **(BII)**.[17]

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[18] is also as effective as fluconazole and generally better tolerated than itraconazole solution, although both posaconazole and itraconazole have more drug-drug interactions compared to 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.[18] A new solid oral delayed-release tablet formulation of posaconazole is now available, which exhibits less variable absorption compared to the oral suspension.[19] Whether it offers any advantage for the treatment of oropharyngeal candidiasis is unknown and it currently is indicated only for prophylaxis of invasive *Apsergillus* and *Candida* infection.[20] 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- 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 two-week course of the newer triazole isavuconazole, given orally at an initial loading dose of 200 mg, followed by 50 mg; or a loading dose fo 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 compared to fluconazole and the other isavuconazole regimens.[21] 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.[22,23] Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis **(AI)**. Although other pathogens (e.g., cytomegalovirus, herpes simplex virus esophagitis) can mimic the symptoms 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 HIV-infected women, 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 (CDC).

Special Considerations with Regard to Starting ART

There are no special considerations regarding initiation of ART in patients with mucocutaneous candidiasis. Specifically, there is as yet 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 with ART has not yet been reported for mucocutaneous candidiasis in HIV-infected patients. 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 HIV-infected patients with oral or esophageal candidiasis, typically those with CD4 cell 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)**.[24] Again, although the new solid delayed-release tablet formulation has been recently made available, it is not known if 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 4 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 HIV-infected patients with CD4 counts <150 cells/mm^3 documented a significantly lower number of episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (3 times a week) compared 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) is not recommended by most HIV specialists for recurrent oropharyngeal or vulvovaginal candidiasis unless patients have frequent or severe recurrences **(BIII)** because therapy for acute disease is effective, mortality associated with mucocutaneous disease is low, potential exists for drug interactions and for the development of antifungal-resistant *Candida*, and prophylaxis is costly.

If recurrences are frequent or severe, oral fluconazole can be used as suppressive therapy for either oropharyngeal **(BI)**, esophageal **(BI)**, or vulvovaginal **(BII)** candidiasis.[11-13] Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII)**.[25] The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in HIV-infected patients who are severely immunocompromised. Several important factors should be taken into account when making the decision to use secondary prophylaxis. These 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.[26]

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. On the basis of experience with other opportunistic infections, it would be reasonable to discontinue secondary prophylaxis when the CD4 count has risen 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 or vaginal candidiasis in pregnancy, when possible **(AIII)**. Although single-dose, episodic treatment with oral fluconazole has not been associated with birth defects in humans,[27] its use has not been widely endorsed.[28] 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.[29] A report from a national cohort register in Denmark found an increased hazard ratio 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.[30] An increased hazard ratio 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, 95% 1.89–8.90) was noted with fluconazole doses above 300 mg. On the basis of these data, substitution of amphotericin B for high-dose 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 has been shown to be teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so these data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole,[31] but experience is limited. Human data are not available for posaconazole; however, the drug was associated with skeletal abnormalities in rats and was embryotoxic in rabbits when given at doses that produced plasma levels equivalent to those seen in humans. Voriconazole is considered a Food and Drug Administration Category D drug because of its association with cleft palate and renal defects seen in rats, as well as embryotoxicity seen in rabbits. Human data on the use of voriconazole are not available, so use in the first trimester is not recommended. Multiple anomalies have been seen in animals exposed to micafungin, and ossification defects have been seen with use of anidulafungin and caspofungin.[32] 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 HIV-infected women who become pregnant **(AIII)**.

Recommendations for Treating Mucosal Candidiasis (page 1 of 2)

Treating Mucosal Candidiasis

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

Preferred Therapy:

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

Alternative Therapy:

- Clotrimazole troches 10 mg PO 5 times daily **(BI)**, *or*
- Miconazole mucoadhesive buccal tablet 50 mg: Apply to mucosal surface over the canine fossa once daily (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 BID for one day, then 400 mg daily **(BI)**, *or*
- Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily **(BII)**

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 BID **(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*
- Caspofungin 50 mg IV daily **(BI)**, *or*
- Micafungin 150 mg IV daily **(BI)**, *or*
- Anidulafungin 100 mg IV for one dose, then 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 1 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)**

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

Recommendations for Treating Mucosal Candidiasis (page 2 of 2)

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 3 times weekly **(BI)**

Esophageal Candidiasis:

- Fluconazole 100–200 mg PO daily **(BI)**
- Posaconazole oral suspension 400 mg PO BID **(BII)**

Vulvovaginal Candidiasis:

- Fluconazole 150 mg PO once weekly **(BII)**

Other Considerations

- Chronic or prolonged use of azoles might promote development of resistance.
- Systemic azoles may have significant drug-drug interactions with ARV drugs and other drugs for treatment of OI; refer to Table 5 for dosing recommendations. Consider therapeutic drug monitoring if prolonged use is indicated.

Key to Acronyms: ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; IV = intravenous; OI = opportunistic infection; PO = orally; QID = four times daily

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Chagas Disease (Last updated August 8, 2018; last reviewed September 13, 2017)

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 November 10, 2016; last reviewed June 14, 2017)

Epidemiology

Coccidioidomycosis is caused by a soil-dwelling fungus that consists of two species, *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in HIV-infected individuals have been reported in the areas in which the disease is highly endemic.[1] 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] Recently, cases of coccidioidomycosis that appeared to be acquired in eastern Washington state have been reported.[3] Whether this is anomalous or is a manifestation of an expanding area of endemicity is not clear at this time. In some instances, coccidioidomycosis has been diagnosed in patients with HIV infection well outside the known endemic regions. These have presumably been the result of reactivation of a previously acquired infection.

The risk of developing symptomatic coccidioidomycosis after infection is increased in HIV-infected patients who have CD4 T lymphocyte (CD4) counts <250 cells/mm^3 or who have been diagnosed with AIDS.[4] The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[5,6]

Clinical Manifestations

Lack of suppression of HIV replication and lower CD4 cell counts are associated with the severity of the presentation of coccidioidomycosis.[6] Four common syndromes of coccidioidomycosis have been described in HIV-infected patients: focal pneumonia, diffuse pneumonia, extrathoracic involvement including meningitis, and positive coccidioidal serology tests without evidence of localized infection.[7] In addition, patients with HIV infection may develop dissemination to other extrathoracic sites, including the bones and joints.

Focal pneumonia is most common in patients with CD4 counts ≥250 cells/mm^3. This diagnosis can be difficult to distinguish from a bacterial community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[8,9] However, coccidioidomycosis may present with hilar or mediastinal adenopathy, upper lobe infiltrates, night sweats, and peripheral blood eosinophilia, all of which are uncommon in bacterial pneumonia. The syndromes other than focal pneumonia usually occur in more immunosuppressed patients. Diffuse pulmonary disease presents with fever and dyspnea and can be difficult to clinically distinguish from *Pneumocystis* pneumonia.[10] Hypoxemia may be severe and serological tests are frequently negative at the time of presentation. Routine bacterial cultures from pulmonary secretions frequently reveal *Coccidioides* after an incubation time of less than one week. Meningitis presents with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile demonstrates low glucose levels with elevated protein and a lymphocytic pleocytosis. In addition, immunosuppressed patients with HIV infection may present with elevated coccidioidal serological titers without evidence of disease. A study in the era prior to potent ART described 13 patients, all with CD4 counts <350 cells/mm^3 and positive coccidioidal serologic tests. Five patients subsequently developed clinical illness at a median CD4 count of 10 cells/mm^3.[11]

Diagnosis

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of spherules on histopathological examination of infected tissue. Blood cultures are positive in a minority of patients, usually those with diffuse pulmonary disease. Cultures of the CSF are positive in fewer than one-third of patients with coccidioidal meningitis. Unlike other endemic mycoses, *Coccidioides* grows relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a non-pigmented mould may be observed in as few as 3 days and can be confirmed as *Coccidioides* by gene probe. *Coccidioides* growing on an agar plate is a significant laboratory hazard because of the risk of inhalation of dislodged arthroconidia. Laboratory personnel should be alerted to the possibility of *Coccidioides* at the time the specimen is sent to the laboratory, and the plate lid securely taped.[12] Identification of the fungus should be

performed in biosafety level 3 (BSL 3) containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test associated with a compatable clinical syndrome. Patients with past coccidioidal infection without disease activity usually have negative serological tests. The nomenclature and variety of coccidioidal serological tests can be confusing.[13] The original assays examined two reactions. The first was the development of a precipitate in a tube when incubated with a heat-stable coccidioidal antigen preparation. This has been termed "tube precipitin" or TP response. It is due to an IgM antibody reaction, is not titratable, not useful in the diagnosis of meningitis, and is positive early in disease. If performed by immunodiffusion, it is termed IDTP. The second reaction originally detected the loss of serum complement activity in the presence of a heat-labile coccidioidal antigen preparation. This is called "complement-fixing" or CF, is due to an IgG response, is titratable, and its detection in the CSF is indicative of meningitis. CF antibody responses can also be measured by immunodiffusion (IDCF). In general, elevated CF titers suggest clinically active disease. Several companies offer enzyme immunoassays (EIAs). They appear to be similar to IDTP and IDCF with the following caveats. The IgM EIA has been associated with false positive results and the IgG EIA is not titratable. Both CF and EIA tests appear to be more sensitive than immunodiffusion assays. All coccidioidal serologic tests are positive less frequently in HIV infected patients with low CD4 cell counts than in those who are immunocompetent.[14] It is strongly recommended that clinical samples for serological testing be sent to laboratories with expertise in performing these assays.

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[15] serum[16] and other body fluids in samples from individuals with active coccidioidomycosis. It is most useful in diagnosing extrathoracic disseminated coccidioidomycosis. A recent study suggests that detection of coccidioidal antigen in the cerebrospinal fluid has a very high sensitivity and specificity for diagnosing coccidioidal meningitis.[17]

Preventing Exposure

HIV-infected individuals cannot completely avoid activities involving exposure to infection while living in or visiting areas where *Coccidioides* is endemic. They should, however, avoid extensive exposure to disturbed soil, such as at building excavation sites, and they should stay inside during dust storms **(BIII)**.

Preventing Disease

Primary antifungal prophylaxis (i.e. prophylaxis for individuals with negative serologic tests for *Coccidioides*) is of little benefit to patients with low CD4 cell counts who live in regions where *Coccidioides* is endemic[5] and it **is not recommended (AIII)**. Yearly or twice-yearly serological testing for coccidioidomycosis is reasonable for serologically negative HIV-infected individuals who live in regions endemic for coccidioidomycosis. Testing is also advised for individuals who have traveled to or lived in endemic areas in the past. Both IgM and IgG antibody testing using either an EIA or immunodiffusion technique are recommended. A new positive test suggests possible active disease in patients with low CD4 cell counts[11] and further clinical evaluation should be undertaken. 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 CD4 counts <250 cells/mm^3 **(AIII)**. This should be continued until the CD4 count is ≥250 cells/mm^3 and ART has fully suppressed HIV replication **(BIII)**. Outside endemic regions, routine testing does not appear to be useful and **should not be performed (CIII)**.

Treating Disease

Initial therapy with a triazole antifungal agent given orally is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII)**. When prescribing triazoles, it should be noted that all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with drugs that are principally based on CYP 3A4 enzyme for metabolism. Therapeutic drug monitoring and dosage

adjustments, may be necessary. Clinicians should refer to Table 5 for dosage guidance when triazoles are used with other drugs for treatment of OI, and to the antiretroviral treatment guidelines for interaction recommendations with ARV, especially when used with ritonavir- or cobicistat-containing regimens.

Without concomitant interacting drugs, fluconazole should be given as 400 mg daily **(AII)**, while itraconazole should be given in divided doses of 200 mg two to three times daily **(BII)**.[18,19] Itraconazole is preferred for those who have bone or joint disease **(AI)**.[20] Serum itraconazole levels should be measured after reaching steady state at 2 weeks to ensure adequate absorption. Data are limited for treatment with posaconazole[21,22] and voriconazole, but these agents are useful for patients who fail to respond to fluconazole or itraconazole **(BII)**. The dose of voriconazole is 200 mg twice daily after a loading dose of 400 mg twice daily for the first day **(AIII)**. Trough serum levels should be measured to ensure efficacy and avoid toxicity; a level of 1-5 mg/L 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 **(BII)**,[22] but the current extended-release tablet formulation is better tolerated by patients and provides more reliable absorption and serum levels. There is no established dosage with the tablet formulation for coccidioidomycosis but 300 mg daily is reasonable **(BIII)**. There are no published data on the use of the newly approved triazole antifungal isavuconazole for coccidioidomycosis in patients with HIV infection. Among nine patients with pulmonary disease without HIV infection, initial therapy with isavuconazole resulted in complete or partial success in 5 (56%).[23]

Patients with HIV infection and positive coccidioidal serologies but without clinical illness should be treated with antifungal therapy as previously described in the same manner as patients with focal pneumonia **(AII)**. For patients with CD4 cell counts <250/mm^3 who are not receiving suppressive antiretroviral therapy, fluconazole 400 mg daily should be given and continued until the CD4 cell count is ≥250/mm^3 and HIV RNA suppression has been achieved **(AIII)**. For those with CD4 cell counts already ≥250/mm^3 and on suppressive antiretroviral therapy, close clinical follow-up is recommended **(BIII)**.

Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or are severely ill with extrathoracic disseminated disease **(AII)**.[19] Most experience has been with the deoxycholate formulation, using an initial dose of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are no reported studies that have used lipid formulations of amphotericin B for the treatment of coccidioidomycosis, but these are likely to be as effective as the deoxycholate formulation and should be considered as an equivalent initial therapy, particularly if there is underlying renal dysfunction **(AIII)**. An initial daily dose 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 (fluconazole or itraconazole) 400 mg daily at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII)**.[19]

Treatment of patients with coccidioidal meningitis requires consultation with a specialist **(AIII)**. Therapy should begin with a triazole antifungal. IV or oral fluconazole at a dose of 400 to 800 mg daily is preferred **(AII)**,[24] but itraconazole also has been successfully used (BII).[25] Therapy with posaconazole **(CIII)**[22,26] or voriconazole **(BIII)**[27-29] has been described in individual cases. 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)**. If intrathecal therapy is required, it should be administered by someone very experienced in this technique.

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

Monitoring the CF antibody titer is useful in assessing response to therapy, and it should be measured every 12 weeks. A rise suggests recurrence or worsening of clinical disease and should prompt reassessment of management. As indicated previously, all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain ARV agents and other anti-infective agents. Table 5 lists such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

The immune reconstitution inflammatory syndrome (IRIS) has been infrequently reported in HIV-infected persons with concomitant coccidioidomycosis.[30-32] Because of this, delaying initiation of potent antiretroviral therapy while treating coccidioidomycosis is not recommended **(AIII)**.

Managing Treatment Failure

Patients with severe coccidioidomycosis who fail treatment with fluconazole or itraconazole should have their treatment changed to IV amphotericin B, either deoxycholate or a lipid formulation **(AIII)**. For patients who are not severely ill, posaconazole **(BII)** 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 Table 5). Posaconazole has fewer known drug interactions with ARV medications than does voriconazole.

Therapy after Immune Reconstitution

Patients with peripheral blood CD4 lymphocyte counts ≥250/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[33] Moreover, a prospective study has demonstrated that the severity of coccidioidomycosis is less in those with lower HIV RNA and higher CD4 cell counts.[6] Given these facts, in HIV-infected patients with undetectable HIV RNA on potent ARV therapy who have a CD4 ≥250/mm^3, coccidioidomycosis should be managed no differently than it is in the general population **(AII)**.

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

Prevention of Relapse

Relapse occurs in 25% to 33% of HIV-uninfected patients who have diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis[34,35] and may occur in HIV-infected patients with CD4 counts ≥250 cells/mm^3 on potent ART[36]. Continued monitoring during coccidiomycosis therapy and after such therapy has been discontinued with clinical follow-up, serial chest radiographs and coccidioidal serology every 3 to 6 months should be performed. Because relapses have been reported in 80% of patients with meningitis in whom triazoles have been discontinued,[37] therapy for coccidioidal meningitis should be continued for life **(AII)**.

Special Considerations During Pregnancy

Women are generally at less risk than men for severe coccidioidomycosis and disease does not appear to worsen in women with prior coccidioidomycosis during pregnancy. However, coccidioidomycosis is likely to be severe and disseminated if infection is acquired during the second or third trimester of pregnancy.[38]

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[39] A recent systematic review and meta-analysis of cohort or case–control studies reporting fetal outcomes after exposure to any dose of fluconazole used in the first trimester of pregnancy found an increased risk of heart defects[40] but did not find an increase in the rate of overall malformations or in craniofacial defects. One registry-based cohort study (included in the systematic review)[41] and a more recent large population-based case-control study[42] specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

In addition in a nation-wide cohort study from Denmark oral fluconazole in pregnancy was associated with an increase risk of spontaneous abortion compared to unexposed women or those with topical azole exposure only.[42] Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short

term exposure. Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, 150 mg dose to treat vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[43,44] However, in general, all azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. One problematic area is coccidioidal meningitis, in which the only alternative treatment to triazole antifungals is IV or intrathecal amphotericin B. For 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.[45] Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies; for voriconazole, these occurred at doses lower than recommended for humans. There are no adequately controlled studies in humans. These drugs **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.

Recommendations for Treating Coccidiodomycosis (page 1 of 2)

Treating Mild Infections (Such As Focal Pneumonia or asymptomatic patients with positive serology and CD4 count <250 cells/mm^3)

Preferred Therapy:

- Fluconazole 400 mg PO once daily **(BII)***, *or*
- Itraconazole 200 mg PO twice daily **(BII)***

Alternative Therapy (For Patients Who Failed To Respond To Fluconazole Or Itraconazole):

- Voriconazole 200 mg PO twice daily after a loading dose of 400 mg twice on first day **(BIII)***; *or*
- Posaconazole (delayed release tablet) 300 mg PO daily after a loading dose of 300 mg twice daily for one day, then 300 mg once daily* **(BIII)*** *or*
- Posaconazole (oral suspension) 400 mg PO twice daily **(BII)***

Treating Bone or Joint Infections

Preferred Therapy:

- Itraconazole 200 mg PO twice daily **(AI)***

Alternative Therapy:

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

Treating Severe, Non-Meningeal Infection (Diffuse Pulmonary or Severely Ill Patients with Extrathoracic Disseminated Disease)—Acute Phase

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 add a triazole (either fluconazole 400 mg daily or itraconazole 200 mg twice daily, with itraconazole preferred for bone or joint disease) to amphotericin B therapy and continue the triazole once amphotericin B is stopped **(BIII)**

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

Preferred Therapy:

- Fluconazole 400–800 mg PO daily **(AII)**; IV if patient unable to take orally.

Recommendations for Treating Coccidiodomycosis (page 2 of 2)

Alternative Therapy:

- Itraconazole 200 mg PO twice to three-times daily* **(BII)**, *or*
- Voriconazole 200–400 mg PO twice daily after loading dose* **(BIII)**, *or*
- Posaconazole (delayed release tablet) loading dose of 300 mg twice daily on first day, then 300 mg once daily* **(CIII)**, *or*
- Posaconazole (oral suspension) 400 mg PO twice daily* **(CIII)**, *or*
- Intrathecal amphotericin B **(AIII)** when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by a clinician experienced in this technique.

Duration of Therapy

*Focal Coccidioidal Pneumonia, or Asymptomatic Patients with Positive Serology and CD4 Count <250 cells/mm^3, Therapy Can Be Stopped If **(AII)**:*

- Clinically responded to ≥6 months of antifungal therapy (for patients with focal pneumonia), *and*
- CD4 count ≥250 cells/mm^3, and
- Receiving effective ART with virologic suppression, *and*
- Continued monitoring for recurrence should be performed using serial chest radiograph and coccidioidal serology every six to twelve months.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

- Relapse can occur in 25% to 33% of HIV-seronegative patients, and can occur in HIV patients with CD4 count >250 cells/mm^3
- Therapy 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 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.

* It should be noted that all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with drugs that are principally based on CYP 3A4 enzyme for metabolism. Therapeutic drug monitoring and dosage adjustments, may be necessary. Clinicians should refer to Table 5 for dosage guidance when triazoles are used with other drugs for treatment of OI, and to the antiretroviral treatment guidelines for interaction recommendations with ARV, especially when used with efavirenz, ritonavir- or cobicistat-containing regimens.

Key to Acronyms: CD4 = CD4 T lymphocyte cell; CSF = cerebrospinal fluid; IgG = immunogloblulin G; IgM = immunoglobulin M; IV = intravenous; PO = orally

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Cryptococcosis (Last updated August 17, 2016; last reviewed June 14, 2017)

Epidemiology

Most HIV-associated cryptococcal infections are caused by *Cryptococcus neoformans*, but occasionally *Cryptococcus gattii* is the etiology. *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 HIV-infected patients in developed countries were diagnosed with disseminated cryptococcosis.[1] Current estimates indicate that every year, nearly 1 million cases of cryptococcal meningitis are diagnosed worldwide and the disease accounts for more than 600,000 deaths.[2] With the availability of effective ART, the incidence of the disease has declined substantially in areas with ART access, and most new infections are being recognized in patients recently diagnosed with HIV infection.[3] Most cases are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/μL.

Clinical Manifestations

In HIV-infected patients, cryptococcosis commonly presents as a subacute meningitis or meningoencephalitis with fever, malaise, and headache.[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.

Cryptococcosis usually is disseminated when diagnosed in an HIV-infected patient. Any organ of the body can be involved, and skin lesions may show myriad different manifestations, including umbilicated skin lesions mimicking 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 mimic *Pneumocystis* pneumonia.

Diagnosis

Analysis of cerebrospinal fluid (CSF) generally demonstrates mildly elevated levels of serum protein, low-to-normal glucose concentrations, and pleocytosis consisting mostly of lymphocytes. Some HIV-infected patients will have very few CSF inflammatory cells, but a Gram's stain preparation, or an India ink preparation if available, may demonstrate numerous yeast forms. The opening pressure in the CSF may be elevated, with pressures ≥25 cm H_2O occurring in 60% to 80% of patients.[4,5]

Cryptococcal disease can be diagnosed through culture, CSF microscopy, or by cryptococcal antigen (CrAg) detection. In patients with HIV-related cryptococcal meningitis, 55% of blood cultures and 95% of CSF cultures are positive and visible colonies can be detected within 7 days. Cryptococcus may be occasionally identified on a routine Gram stain preparation of CSF. India ink staining of CSF demonstrates encapsulated yeast in 60% to 80% of cases, but many laboratories in the United States no longer perform this test. CSF CrAg is usually positive in patients with cryptococcal meningoencephalitis. Serum CrAg is usually positive in both meningeal and non-meningeal infections and may be present weeks to months before symptom onset.[6] A positive serum CrAg should prompt a lumbar puncture to rule out meningeal disease. Three methods exist for antigen detection: latex agglutination, enzyme immunoassays, and lateral flow assay (a newly developed dipstick test). Testing for the antigen in the serum is a useful initial screening tool in diagnosing cryptococcosis in HIV-infected patients,[7] and it may be particularly useful when a lumbar puncture is delayed or refused.

Preventing Exposure

Cryptococcus is ubiquitous in the environment. HIV-infected patients cannot completely avoid exposure to

C. neoformans or *C. gattii*. Limited epidemiological evidence suggests that exposure to aged bird droppings may increase risk of infection.

Preventing Disease

The incidence of cryptococcal disease is low among HIV-infected patients in the United States. However, a recent report from the United States indicates that among HIV-infected patients with peripheral blood CD4 counts ≤100 cells/μL, the prevalence of cryptococcal antigenemia, a harbinger of disease, was 2.9%, and prevalence was 4.3% for those with CD4 counts ≤50 cells/μL.[8] Routine testing for serum CrAg in newly diagnosed HIV-infected persons with no overt clinical signs of meningitis is recommended by some experts for patients whose CD4 counts are ≤100 cells/μL and particularly in those with CD4 counts ≤50 cells/μL. A positive test should prompt CSF evaluation for meningitis.

Prospective, controlled trials indicate that prophylactic fluconazole or itraconazole can reduce the frequency of primary cryptococcal disease in patients who have CD4 counts <100 cells/μL.[9,10] However, in the United States, primary prophylaxis in the absence of a positive serum cryptococcal antigen test is not recommended because of the relative infrequency of cryptococcal disease, lack of survival benefit associated with prophylaxis, possibility of drug interactions, potential antifungal drug resistance, and cost **(BII)**. Patients with isolated cryptococcal antigenemia without meningitis can be treated similarly to patients with focal pulmonary cryptococcosis (see below).

Treating Disease

Treating cryptococcosis consists of three phases: induction, consolidation, and maintenance therapy. For induction treatment for 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 has been the preferred formulation at a dose of 0.7 to 1.0 mg/kg daily. However, there is a growing body of evidence that lipid formulations of amphotericin B are effective for disseminated cryptococcosis, particularly in patients who experience clinically significant renal dysfunction during therapy or who are likely to develop it. The non-comparative CLEAR study demonstrated a 58% response rate in HIV-infected patients treated with amphotericin B lipid complex at mean dose of 4.4 mg/kg daily.[11] In a Dutch and Australian study, a 3-week course of liposomal amphotericin B (4 mg/kg daily) resulted in more rapid sterilization of CSF than amphotericin B deoxycholate (0.7 mg/kg daily).[12] A recently published comparison of amphotericin B deoxycholate (0.7 mg/kg daily), and liposomal amphotericin B (AmBisome®) (3 mg/kg or 6 mg/kg daily) showed similar efficacy for the three regimens, but nephrotoxicity was lower with 3 mg/kg daily liposomal amphotericin B.[13]

Amphotericin B formulations should be combined with flucytosine at a dose of 100 mg/kg daily in 4 divided doses for ≥2 weeks in patients with normal renal function, and this is the preferred regimen for primary induction therapy **(AI)**. Based on available clinical trial data, a daily dose of 3 to 4 mg/kg of liposomal amphotericin B is the recommended amphotericin B formulation **(AI)**. Amphotericin B deoxycholate at a dose of 0.7 mg/kg daily is equally efficacious **(AI)** and can be used if cost is an issue and the risk of renal dysfunction is low. Amphotericin B lipid complex at a dose of 5 mg/kg daily can be used as an alternative amphotericin B preparation, although fewer data are available to support its use **(BII)**.

When using flucytosine, serum levels of flucytosine, if this assay is available, should be obtained 2 hours post-dose after 3 to 5 doses have been administered. Serum levels should be between 25 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 amphotericin B during acute treatment is associated with more rapid sterilization of CSF.[14-17] A recent randomized clinical trial also showed that the combination of amphotericin B deoxycholate at a dose of 1.0 mg/kg daily combined with flucytosine was associated with improved survival compared to the same dose of amphotericin B without flucytosine.[18]

Amphotericin B deoxycholate in combination with 400 mg of fluconazole daily was inferior to amphotericin B in combination with flucytosine for clearing *Cryptococcus* from CSF.[19] However, in 2 randomized trials, amphotericin B plus 800 mg of fluconazole daily compared favorably with amphotericin B alone.[19,20] Therefore, amphotericin B deoxycholate alone or combined with fluconazole at 800 mg daily **(BI)** or lipid-formulation amphotericin B alone or combined with fluconazole at 800 mg daily **(BIII)** may be viable options in some circumstances but are less preferable alternatives than lipid-formulation amphotericin B combined with flucytosine **(BI)**.

Fluconazole (400 mg daily) combined with flucytosine is also a potential alternative to amphotericin B regimens **(BII)**.[21] Some experts would use 800 mg daily **(BIII)**. Fluconazole alone, based on early fungicidal activity, is inferior to amphotericin B[22] for induction therapy and is recommended only for patients who cannot tolerate or do not respond to standard treatment. If it is used for primary induction therapy, the starting daily dose should be 1200 mg **(CI)**.[23]

After at least 2 weeks of successful induction therapy—defined as substantial clinical improvement and a negative CSF culture after repeat lumbar puncture—amphotericin B and flucytosine can be discontinued and follow-up or consolidation therapy initiated with fluconazole at 400 mg daily **(AI)**. This therapy should continue for at least 8 weeks **(AI)**.[14,15,24] Subsequently, the fluconazole should be reduced to 200 mg daily and continued as chronic maintenance therapy to complete at least 1 year of azole therapy (see the Preventing Recurrence section below).[25] Itraconazole, at the same dosage as fluconazole, can be used as an alternative **(CI)**, but it is clearly inferior to fluconazole.[24] Limited data are available for the newer triazoles, voriconazole and posaconazole, as either primary or maintenance therapy for patients with cryptococcosis. Most of the data on use of these extended-spectrum triazole antifungals have been reported for treatment of refractory cases, with success rates of approximately 50%.[26,27] At this time, the role of posaconazole and voriconazole in the management of cryptococcosis is not established. Voriconazole should be used cautiously with HIV protease inhibitors and efavirenz.

Non-central-nervous-system (CNS), extrapulmonary cryptococcosis, and diffuse pulmonary disease should be treated similarly to CNS disease **(BIII)**. For mild-to-moderate symptoms and focal pulmonary infiltrates, treatment with fluconazole (400 mg daily for 12 months) combined with effective ART is appropriate **(BIII)**. Treatment is the same for patients with an isolated positive serum cryptococcal antigen test **(BIII)**. **All patients should have their CSF sampled to rule out CNS disease.**

Special Considerations with Regard to Starting ART

Optimal timing for ART initiation in patients with acute cryptococcal meningitis is controversial. One randomized, controlled trial that included 35 patients with cryptococcal meningitis suggested that ART was safe when started within the first 14 days of diagnosis.[28] A subsequent study from Africa demonstrated significantly worse outcomes in 54 patients started on ART within 72 hours of cryptococcal meningitis diagnosis compared with those in which ART was delayed for at least 10 weeks.[29] However, in the latter study, cryptococcal meningitis was managed with fluconazole alone, and ART consisted of nevirapine, stavudine, and lamivudine. Neither fluconazole alone nor the latter ART regimen are recommended as preferred initial treatment in the United States. A randomized clinical trial conducted at 2 sites in Africa among hospitalized patients with acute cryptococcal meningitis[30] compared patients with cryptococcal meningitis who were started on ART within 1 to 2 weeks (median 8 days) after fungal diagnosis with patients in whom ART was deferred until 5 weeks (median 36 days) after diagnosis. In contrast to the other African study, this study used deoxycholate amphotericin B (0.7–1.0 mg/kg daily) plus 800 mg of fluconazole daily during the induction phase of antifungal treatment. There was a significant increase in 6-month mortality in the early ART group compared with the deferred ART group (45% vs 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 was even greater between the early ART group and the deferred ART group if the CSF white cell count was <5 cells/μL ($P = 0.008$). While the excess of deaths in the early ART group was attributed to cryptococcosis, it is unclear if they were directly due to meningitis and its sequelae or due to immune reconstitution inflammatory syndrome (IRIS).

Based on the studies cited above and on expert opinion, it is prudent to delay initiation of ART at least until after completion of antifungal induction therapy (the first 2 weeks) and possibly until the total induction/consolidation phase (10 weeks) has been completed. Delay in ART may be particularly important in those with evidence of increased intracranial pressure or in those with low CSF white blood cell counts. Hence, the timing of ART administration should be considered between 2 and 10 weeks after the start of antifungal therapy with the precise starting dates based on individual conditions and local experience **(BIII)**. If effective ART is to begin prior to 10 weeks, the treating physicians should be prepared to aggressively address complications caused by IRIS, such as elevated intracranial pressure (ICP).

For other forms of cryptococcosis, where the risk of IRIS appears to be much lower, the optimal time to begin ART and antifungal therapy is not clear. However, it would seem prudent to delay initiation of ART by 2 to 4 weeks after starting antifungal therapy **(BIII)**.

All the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

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

ICP elevations can cause clinical deterioration despite a microbiologic response, and they are more likely to occur if the CSF opening lumbar pressure is ≥25cm H_2O[4,14] when obtained in the lateral decubitus position with good manometrics assured. In 1 large clinical trial, increased ICP was associated with 93% of deaths during the first 2 weeks of therapy and 40% of deaths during weeks 3 to 10.[4] Although it is uncertain which patients with high opening lumbar pressures will deteriorate, those with symptoms and signs of ICP require immediate clinical intervention.

Lumbar opening pressure should be measured in all patients with cryptococcal meningitis at the time of diagnosis. Measures to decrease ICP should be used for all patients with confusion, blurred vision, papilledema, lower extremity clonus, or other neurologic signs of increased pressure. Drainage of CSF via lumbar puncture is recommended for initial management. One approach is to remove a volume of CSF (typically 20–30 mL) that at least halves the opening pressure[31] and repeat daily until symptoms and signs consistently improve. CSF shunting through a lumbar drain or ventriculostomy should be considered for patients who cannot tolerate repeated lumbar punctures or in whom signs and symptoms of cerebral edema persist after multiple lumbar taps **(BIII)**. Corticosteroids and mannitol have been shown to be ineffective in managing ICP and **are not recommended (AIII)**. Acetazolamide **should not be used** as therapy for increased ICP management since it may cause hyperchloremic acidosis and does not result in a decrease in ICP **(AI)**.[32] A randomized study compared a 6-week course of a tapering dose of dexamethasone among 451 Asian and African patients with HIV infection and cryptococcal meningitis who received amphotericin B deoxycholate plus fluconazole as the induction antifungal regimen. Compared to those receiving placebo, there was no improvement in survival at 10 weeks and dexamethasone was associated with more adverse events.[33] These data support the recommendation that corticosteroids should not routinely be used during induction therapy for HIV-associated cryptococcal meningitis unless they are being used for IRIS **(AI)**.

After the first 2 weeks of treatment, many experts would advocate a repeat lumbar puncture to ensure that viable organisms have been cleared from the CSF. Even in patients who have clinical improvement, positive CSF cultures after 2 weeks of therapy are predictive of future relapse and less favorable outcomes. In such cases, some experts would continue amphotericin B plus flucytosine until the CSF cultures are negative **(BIII)**. Monitoring titers of cryptococcal polysaccharide antigen in serum or CSF is of no value in determining response to therapy and **is not recommended**. If new symptoms or clinical findings occur later, a repeat lumbar puncture, with measurement of opening lumbar pressure and CSF culture, should be performed.

Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline appears to reduce the risk of nephrotoxicity during amphotericin B treatment. Thirty minutes before infusion,

acetaminophen (650 mg) and diphenhydramine (25–50 mg) or hydrocortisone (50–100 mg) typically are administered in an attempt to ameliorate infusion-related adverse reactions **(BIII)**, but data supporting these practices are scant. Meperidine (25–50 mg titrated during infusion) is effective for preventing and treating amphotericin B-associated rigors **(BII)**.

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 and the therapeutic range is between 25 and 100 mg/L. Alternatively, frequent (i.e., at least biweekly) blood counts can be performed to detect development of cytopenia. Patients treated with flucytosine also should be monitored for hepatotoxicity and gastrointestinal toxicities.

An estimated 30% of HIV-infected patients with cryptococcal meningitis experience IRIS after initiation or reinitiation of effective ART.[34,35] Patients who have cryptococcal IRIS are more likely to be antiretroviral naive, have higher HIV RNA levels, and have less CSF inflammation on initial presentation.[36] The risk of IRIS may be decreased in those with negative CSF cultures at the time of antiretroviral initiation.[37] Distinguishing IRIS from treatment failure may be difficult. In general, cryptococcal IRIS presents with worsening clinical disease despite microbiological evidence of effective antifungal therapy,[36,38] whereas treatment failure is associated with continued positive cultures. The appropriate management strategy for IRIS is to continue both ART and antifungal therapy and reduce elevated ICP, if present **(AII)**. In patients with severe symptoms of IRIS, some specialists recommend a brief course of glucocorticosteroids **(CIII)**, but data-based management strategies have not been developed.

The risk of IRIS appears to be much lower with other forms of cryptococcosis; IRIS may present as lymphadenitis, cutaneous abscesses, or bony lesions.[39] Management is similar to that for IRIS associated with cryptococcal meningitis, including continuing ART, initiating or continuing antifungal therapy **(AIII)**, and considering glucocorticoids **(CIII)**.

Managing Treatment Failure

Treatment failure is defined as a lack of clinical improvement and continued positive cultures after 2 weeks of appropriate therapy, including management of increased ICP; or as a relapse after an initial clinical response, defined as recurrence of symptoms with a positive CSF culture after ≥4 weeks of treatment. Direct primary fluconazole resistance with *C. neoformans* has been reported in the United States but is uncommon.[40] Therefore, susceptibility testing is not routinely recommended for intial management of cryptococcosis. Isolates collected to evaluate for persistence or relapse should, however, be checked for susceptibility and compared with the original isolate. While clinical data are lacking, strains with minimum inhibitory concentrations against fluconazole ≥16 µg/mL in patients with persistent disease or relapse may be considered resistant.[41]

Optimal therapy for patients with treatment failure has not been established. Patients who fail to 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 it until a clinical response occurs. 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 deoxycholate formulation in this setting[12,13,42] and should be considered when initial treatment with other regimens fails **(AII)**.

Higher doses of fluconazole in combination with flucytosine also may be useful **(BIII)**. Echinocandins have no activity against *Cryptococcus* spp. and **are not recommended** for clinical management of cryptococcosis **(AII)**. The newer triazoles—posaconazole and voriconazole—have activity against *Cryptococcus* spp. *in vitro* and may have a role in salvage therapy, but probably offer no specific advantages over fluconazole unless *in vitro* susceptibility testing indicates fluconazole resistance. Most clinical failures are a result of inadequate induction therapy, drug interactions that interfere with treatment, or the development of IRIS and are not due to drug resistance.

Preventing Recurrence

When to Start Chronic Suppressive Therapy

Patients who have completed the first 10 weeks of induction and consolidation therapy for acute cryptococcosis should be given chronic maintenance or suppressive therapy with 200 mg of fluconazole daily **(AI)**. Itraconazole is inferior to fluconazole for preventing relapse of cryptococcal disease **(CI)**.[24]

When to Stop Chronic Suppressive Therapy

Only a small number of patients have been evaluated for relapse after successful antifungal therapy for cryptococcosis and discontinuation of secondary prophylaxis while on ART. In a European study, recurrence of cryptococcosis was not seen among 39 subjects on potent ART whose antifungal therapy was discontinued. In this cohort, when maintenance therapy was stopped, the median CD4 cell count was 297 cells/μL, the median HIV RNA concentration was <500 copies/mL, and the median time on potent ART was 25 months.[43] 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 having achieved a CD4 count >100 cells/μL with a sustained undetectable HIV RNA level for 3 months on potent ART.[44] Given these data and inference from data on discontinuation of secondary prophylaxis for other HIV-associated opportunistic infections, it is reasonable to discontinue chronic antifungal maintenance therapy for cryptococcosis in patients whose CD4 cell counts are ≥100 cells/μL, who have undetectable viral loads on ART for >3 months, and who have received a minimum of 1 year of azole antifungal chronic maintenance therapy after successful treatment of cryptococcosis **(BII)**.[45] Secondary prophylaxis should be reinitiated if the CD4 count decreases again to <100 cells/μL **(AIII)**.

Special Considerations During Pregnancy

The diagnosis of cryptococcal infections during pregnancy is similar to that in non-pregnant adults. Treatment should be initiated promptly after a diagnosis is confirmed. It should be emphasized that the postpartum period may be a high-risk period for the development of IRIS.

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

Flucytosine was teratogenic in animal studies, and human experience is limited to case reports and small series. Therefore, its use should be considered only when the benefits outweigh its risks to the fetus **(CIII)**.

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 of ≥400 mg/day or more through or beyond the first trimester of pregnancy.[46] 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.[47,48] Based on the reported birth defects, the FDA has changed the pregnancy category for fluconazole from C to D for any use other than a single, low dose for treatment of vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Use of fluconazole in the first trimester should be considered only if the benefits clearly outweigh risks. For pregnant women, amphotericin should be continued throughout the first trimester. After the first trimester, switching to oral fluconazole may be considered, if clinically appropriate.

Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[49,50] However, in general azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs

should be avoided in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Treating Cryptococcosis (page 1 of 2)

Treating Cryptococcal Meningitis

Treatment for cryptococcosis consists of 3 phases: induction, consolidation, and maintenance therapy.

Induction Therapy (For At Least 2 Weeks, Followed by Consolidation Therapy)

Preferred Regimens:

- Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO QID **(AI)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO QID **(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 daily plus flucytosine 25 mg/kg PO QID **(BII)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800 mg PO or IV daily **(BIII)**; *or*
- Amphotericin B (deoxycholate 0.7-1.0 mg/kg IV daily) plus fluconazole 800 mg PO or IV daily **(BI)**; *or*
- Liposomal amphotericin B 3–4 mg/kg IV daily alone **(BI)**; *or*
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily alone **(BI)**; *or*
- Fluconazole 400 mg PO or IV daily plus flucytosine 25 mg/kg PO QID **(BII)**; *or*
- Fluconazole 800 mg PO or IV daily plus flucytosine 25 mg/kg PO QID **(BIII)**; *or*
- Fluconazole 1200 mg PO or IV daily alone **(CI)**

Consolidation Therapy (For At Least 8 Weeks, Followed by Maintenance Therapy)

- To begin after at least 2 weeks of successful induction therapy (defined as substantial clinical improvement and a negative CSF culture after repeat LP)

Preferred Regimen:

- Fluconazole 400 mg PO or IV once daily **(AI)**

Alternative Regimen:

- Itraconazole 200 mg PO BID **(CI)**

Maintenance Therapy

Preferred Regimen:

- Fluconazole 200 mg PO for at least 1 year **(AI)**—see below for recommendation of when to stop maintenance therapy

Stopping Maintenance Therapy

*If the Following Criteria are Fulfilled **(BII)**:*

- Completed initial (induction, consolidation) therapy, and at least 1 year on maintenance therapy, *and*
- Remains asymptomatic from cryptococcal infection, *and*
- CD4 count ≥100 cells/μL for ≥3 months and suppressed HIV RNA in response to effective ART

Restarting Maintenance Therapy:

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

Treating Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease:

- Same treatment as for CNS disease **(BIII)**

Treating Non-CNS Cryptococcosis Focal Pulmonary Disease and Isolated Cryptococcal Antigenemia:

- Fluconazole 400 mg PO daily for 12 months **(BIII)**

Recommendations for Preventing and Treating Cryptococcosis (page 2 of 2)

Other Considerations:

- Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF, decreased risk for subsequent relapse, and improved survival.
- When flucytosine is used, serum levels (if available) should be monitored (2 hours post-dose, after 3–5 doses) and drug concentration should be between 25–100 mg/L).
- Opening pressure should always be measured when a LP is performed. Repeated LPs or CSF shunting are essential to effectively manage symptomatic increased ICP.
- In a randomized, controlled trial, a 6-week course of tapering doses of dexamethasone as adjunctive therapy for cryptococcal meningitis did not improve 10-week survival when compared to placebo, and resulted in a higher rate of adverse events. Corticosteroids should not be routinely used during induction therapy unless it is used for management of IRIS **(AI)**.
- Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(BII)**.
- Infection due to *C. gattii* should be treated similarly to *C. neoformans* **(BIII)**.
- 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 to Acronyms: BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system; CSF = cerebrospinal fluid; ICP = intracranial pressure; IV = intravenous; LP = lumbar puncture; PO = orally; QID = four times a day

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Cryptosporidiosis (Last updated June 17, 2013; last reviewed March 13, 2019)

NOTE: Update in Progress

Epidemiology

Cryptosporidiosis is caused by various species of the protozoan parasite *Cryptosporidium*, which infect the small bowel mucosa and, if symptomatic, typically cause 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 of <100 cells/μL[1]—is associated with the greatest risk for prolonged, severe, or extraintestinal cryptosporidiosis. 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]

Cryptosporidiosis remains a common cause of chronic diarrhea in AIDS patients in developing countries, with up to 74% of diarrheal stools demonstrating the organism.[3] In developed countries with low rates of environmental contamination and where potent antiretroviral therapy (ART) is widely available, cryptosporidiosis has decreased and occurs at an incidence of <1 case per 1000 person-years in patients with AIDS.[4] Infection occurs through ingestion of *Cryptosporidium* oocysts. Viable oocysts in feces can be transmitted directly through contact with infected humans or animals, particularly those with diarrhea. Oocysts can contaminate recreational water sources such as swimming pools and lakes, and public water supplies and may persist despite standard chlorination (see Appendix: Food and Water-Related Exposures). Person-to-person transmission 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. Severity can range from asymptomatic to profuse, cholera-like diarrhea. More severe symptoms tend to occur in immune-suppressed patients, whereas transient diarrhea alone is typical in hosts 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 cell counts.[5-8] Pulmonary infections also have been reported,[9,10] and may be under-recognized.[11]

Diagnosis

Diagnosis of cryptosporidiosis can be made by microscopic identification of the oocysts in stool or tissue with acid-fast staining or direct immunofluorescence, which offers better sensitivity.[12] Immunofluorescence is estimated to be 10 times more sensitive than acid-fast staining and is now the gold standard for stool examination. Concentration methods (i.e., formalin ether or formalin-ethyl acetate) and flotation methods (i.e., Sheather's sucrose or sodium chloride) may facilitate diagnosis, but they are very labor intensive and not routinely used in clinical laboratories. Antigen-detection by enzyme-linked immunosorbent assay or immunochromatographic tests also are useful, with sensitivities reportedly ranging from 66% to 100%, depending on the specific test. Molecular methods such as polymerase chain reaction (PCR) are even more sensitive,[13] detecting as few as five oocysts in spiked stool samples and nearly double the number of cases identified by microscopic methods. Cryptosporidial enteritis also can be diagnosed from small sections from intestinal biopsy.

A single stool specimen is usually adequate for diagnosis in individuals with profuse diarrheal illness, whereas repeat stool sampling is recommended for those with milder disease.

Preventing Exposure

HIV-infected individuals should be educated and counseled about the different ways that *Cryptosporidium* can be transmitted **(BIII)**. Modes of transmission include having direct contact with infected adults, diaper-aged children, and infected animals; coming into contact with contaminated water during recreational activities; drinking contaminated water; and eating contaminated food.

Detailed prevention recommendations related to food and water exposures (including methods for removing *Cryptosporidium* from drinking water), pet exposures, and travel-related exposures can be found in Appendix A: Recommendations to Help HIV-infected Patients Avoid Exposure to, or Infection from, Opportunistic Pathogens.

Scrupulous handwashing can reduce the risk of diarrhea in HIV-infected individuals, including diarrhea caused by *Cryptosporidium*.[14] HIV-infected patients should be advised to wash their hands after potential contact with human feces (including after diapering small children). Hand-washing also should be recommended in association with the following activities: after handling pets or other animals, gardening or having other contact with soil; before preparing food or eating; and before and after sex **(BIII)**. HIV-infected patients should avoid unprotected sex, especially practices that could lead to direct (e.g., oral-anal) or indirect (e.g., penile-anal) contact with feces. They should be advised to use barriers such as condoms and dental dams during sex to reduce such exposures **(BIII)**.

HIV-infected individuals—particularly those with CD4 counts <200 cells/μL—should avoid direct contact with diarrhea or stool from pets **(BIII)**. Gloves should be worn when handling feces or cleaning areas that might have been contaminated by feces from pets **(BIII)**. They 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 premises such as farms or petting zoos where these animals are housed or exhibited.

HIV-infected individuals should not drink water directly from lakes or rivers **(AIII)**. Waterborne infection also can result from swallowing water during recreational activities. HIV-infected individuals should be made aware that lakes, rivers, and salt water beaches and 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 that impose a community advisory to boil water, boiling water for at least 1 minute will eliminate the risk for cryptosporidiosis **(AIII)**. Using submicron personal-use water filters (home/office types) or bottled water also may reduce the risk of infection from municipal and well water **(BII)**.

For persons with low CD4 cell counts, the magnitude of the risk of acquiring cryptosporidiosis from drinking water in a non-outbreak setting is uncertain, and available data are inadequate to recommend that all HIV-infected persons boil water or avoid drinking tap water in non-outbreak settings. However, HIV-infected individuals should consider drinking only filtered water **(CIII)**, despite the complexities involved in selecting appropriate products, the lack of enforceable standards for removal of oocysts, the costs of the products, and the logistic difficulty of using these products consistently. Note that ice made from contaminated tap water also can be a source of infection.

HIV-infected patients with low CD4 cell counts should be cautious about eating raw oysters because cryptosporidial oocysts can survive in oysters for longer than 2 months and have been found in oysters taken from certain commercial oyster beds **(CIII)**. In the hospital setting, standard precautions for use of gloves and for hand-washing after removal of gloves should be sufficient to prevent transmission of cryptosporidiosis from an infected patient to a susceptible HIV-infected individual **(BIII)**. Because of the potential for fomite transmission, some specialists recommend that HIV-infected patients, especially individuals who are severely immunocompromised, not share a room with a patient with cryptosporidiosis **(CIII)**.

HIV-infected individuals who travel to developing countries should be warned to avoid drinking tap water or

using tap water to brush their teeth **(BIII)**. Ice that is not made from bottled water and consumption of raw fruits or vegetables that could have been washed in tap water should also be avoided **(BIII)**. HIV-infected individuals also should avoid other sources of *Cryptosporidium* oocysts as much as possible **(BIII)**. These include working directly 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 used and practices for good hand hygiene observed.

Preventing Disease

Because chronic cryptosporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of combination ART before the patient becomes severely immunosuppressed should prevent this disease **(AII)**. Rifabutin and possibly clarithromycin, when taken for *Mycobacterium avium complex* prophylaxis, have been found to protect against cryptosporidiosis.[15,16] Data are insufficient, however, to warrant a recommendation for using 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/μL usually leads to resolution of clinical cryptosporidiosis[17-21] and is the mainstay of treatment. Therefore, patients with cryptosporidiosis should be started on ART as part of the initial management of their infection **(AII)**. HIV protease inhibitors (PIs) can inhibit *Cryptosporidium in vitro* and in animal models, and some experts believe that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[22,23] 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)**.[24] 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. Severe diarrhea can exceed >10 L/day among patients with AIDS, often requiring intensive support. Oral rehydration should be pursued aggressively with oral rehydration solutions **(AIII)**.

Patients with biliary tract involvement may require endoscopic retrograde choledocoduodenoscopy for diagnosis. They may also benefit from sphincterotomy and/or stenting.[25]

Several agents have been investigated in small, randomized controlled clinical trials of HIV-infected adults, including nitazoxanide, paromomycin, spiramycin, bovine hyperimmune colostrum, and bovine dialyzable leukocyte extract. No pharmacologic or immunologic therapy directed specifically against *Cryptosporidium* has been shown to be consistently effective when used without ART.[19]

Nitazoxanide is an orally administered nitrothiazole benzamide with *in vivo* activity against a broad range of helminths, bacteria, and protozoa.[26,27] It is approved by the U.S. Food and Drug Administration for treatment of cryptosporidiosis in children and adults. When administered for 3 days at 500 mg twice daily to HIV-uninfected adults with cryptosporidiosis, nitazoxanide resulted in higher rates of diarrhea resolution and oocyst-free stools than placebo.[26] In one study, HIV-infected adults with cryptosporidiosis with CD4 counts >50 cells/μL were treated with nitazoxanide 500 to 1000 mg twice daily for 14 days; they experienced substantially higher rates of parasitological cure and resolution of diarrhea than those in the placebo group.[27] This finding was not confirmed, however, in two randomized trials in children.[28,29] Data from a compassionate use program before the advent of potent ART, which included primarily white male adults with median CD4 counts less than 50 cells/μL, 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.[30] 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, a trial

of nitazoxanide or other anti-parasitic drugs in conjunction with ART, but never instead of ART, can be considered **(CIII)**.

Paromomycin is a non-absorbable aminoglycoside indicated for the treatment of intestinal amebiasis but not specifically approved for cryptosporidiosis. It is effective in high doses for the treatment of cryptosporidiosis in animal models.[31] A meta-analysis of 11 published studies of paromomycin in humans reported a response rate of 67%; however, relapses were common, with long-term success rates of only 33%.[25] Two randomized trials comparing paromomycin with placebo among patients with AIDS and cryptosporidiosis showed that the drug had limited effectiveness in patients with AIDS,[32,33] and a meta-analysis of the two trials found the drug was not significantly more effective than placebo at reducing diarrheal frequency or parasite burden, but that analysis was limited by the small sample size and methodologic problems.[19] One case series suggested a better response rate in patients receiving paromomycin along with ART.[34] Paromomycin may be used instead of nitazoxanide along with, 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 their infection **(AII)**. PIs can inhibit *Cryptosporidium in vitro* and in animal models, thus some authorities feel that PI-based ART is preferable in patients with documented cryptosporidiosis **(CIII)**.[22,23]

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. Total parenteral nutrition may be indicated in certain patients **(CIII)**. Immune reconstitution inflammatory syndrome (IRIS) has not been described in association with treatment of cryptosporidiosis.

Managing treatment failure

Supportive treatment and optimization of ART to achieve full virologic suppression are the only feasible approaches to managing treatment failure **(AIII)**.

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.[35] Nitazoxanide is not teratogenic in animals but no human data on use in 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, a recent study identified an increased risk of congenital malformations, and specifically hypospadias, among 683 women with exposure to loperamide early in pregnancy.[36] 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)**.

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:

- Initiate or optimize ART for immune restoration to CD4 count >100 cells/mm^3 **(AII)**.
- 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 as an anti-diarrheal agent **(CIII)**.

Alternative Management Strategies:

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 500–1000 mg PO BID with food for 14 days **(CIII)** + optimized ART, symptomatic treatment, and rehydration and electrolyte replacement, *or alternatively*
- Paromomycin 500 mg PO QID for 14 to 21 days (**CIII)** + optimized ART, symptomatic treatment and rehydration and electrolyte replacement

Other Considerations:

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

Key to Acronyms: ART = antiretroviral therapy; IV = intraveneously; PO = orally; BID = twice a day; QID = four times a day

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Cystoisosporiasis (Formerly Isosporiasis) (Last updated September 10, 2015; last reviewed September 13, 2017)

NOTE: Update in Progress

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 November 4, 2015; last reviewed January 27, 2017)

Epidemiology

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes virus family that can cause disseminated or localized end-organ disease in HIV-infected patients with advanced immunosuppression. Most clinical disease occurs in individuals previously infected with CMV (seropositive) and therefore represents either re-activation of latent infection or re-infection with a novel strain.

End-organ disease caused by CMV occurs in patients with advanced immunosuppression, typically those with CD4 T lymphocyte cell (CD4) counts <50 cells/mm^3, who are either not receiving or have failed to respond to antiretroviral therapy (ART).[1-3] Other risk factors include previous opportunistic infections (OIs), a high level of CMV viremia (most often measured by polymerase chain reaction [PCR]), and high plasma HIV RNA levels (>100,000 copies/mL).

Before potent ART, an estimated 30% of patients with AIDS experienced CMV retinitis sometime between the diagnosis of AIDS and death.[1-3] The incidence of new cases of CMV end-organ disease has declined by ≥95% with the advent of ART.[4,5] For those with established CMV retinitis, recurrence of active lesions occurs at a rate substantially lower than that seen in the pre-ART era. However, even for those with immune recovery sufficient to discontinue anti-CMV therapy, that is, CD4+ counts >100 cells/mm^3, relapse of the retinitis occurs at a rate of 0.03/person-year and occasionally can occur at CD4 counts as high as 1,250 cells/mm^3.[6] Therefore, whether anti-CMV therapy is continued or not, regular ophthalmologic follow-up is needed.

Clinical Manifestations

Retinitis is the most common clinical manifestation of CMV end-organ disease in HIV-infected patients. It occurs as unilateral disease in two-thirds of patients at presentation, but disease ultimately is 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 pre-ART era.[6]

Peripheral retinitis may be asymptomatic or present with floaters, scotomata, or peripheral visual field defects. Central retinal lesions or lesions impinging on the macula or optic nerve are associated with decreased visual acuity or central field defects. CMV retinitis is a full-thickness necrotizing retinitis, and the characteristic ophthalmologic appearance is that of fluffy, yellow-white retinal lesions, with or without intraretinal hemorrhage, with little inflammation of the vitreous unless immune recovery with ART intervenes.[1] Blood vessels near the lesions may appear to be sheathed. Occasionally, CMV retinitis lesions, particularly peripheral lesions, may have a more granular appearance.

In the absence of ART or specific anti-CMV therapy, retinitis invariably progresses, usually within 10 to 21 days after presentation. Progression of retinitis occurs in fits and starts and causes a characteristic brushfire pattern, with a granular, white leading edge advancing before an atrophic gliotic scar.[7]

Colitis occurs in 5% to 10% of patients with AIDS and CMV end-organ disease.[2] The most frequent clinical manifestations are weight loss, anorexia, abdominal pain, debilitating diarrhea, and malaise. In the colon, and especially in the cecum, CMV can produce perforation and present as an acute abdomen. If CMV colitis is present, computed tomography may show colonic thickening. 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. Colitis and esophagitis may cause fever.

CMV pneumonitis is extremely uncommon. CMV is detected frequently in the bronchoalveolar lavage but is

a bystander most of the time and should trigger a search for a more likely causative agent.

CMV neurologic disease includes dementia, ventriculoencephalitis, and polyradiculomyelopathies.[8] Patients with dementia caused by CMV encephalitis typically have lethargy, confusion, and fever. Cerebrospinal fluid (CSF) typically demonstrates lymphocytic pleocytosis (although a mixture of neutrophils and lymphocytes might be evident), low-to-normal glucose levels, and normal-to-elevated protein levels. 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-related neurologic disease. CMV polyradiculomyelopathy causes a Guillian-Barre–like syndrome characterized by 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 100–200 neutrophils/μL and some erythrocytes) accompanied by hypoglycorrhachia and elevated protein levels.

Diagnosis

CMV viremia can be detected by PCR, antigen assays, or culture and is usually, but not invariably, present in end-organ disease. Viremia as detected by one of these assays can be present in disease-free patients with low CD4 cell counts—that is, in the absence of end-organ disease.[8-13] 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. A negative serum or plasma PCR assay also does not rule out CMV end-organ disease.

Of note, patients with CMV retinitis have CMV DNA detected in the vitreous in around 80% of cases, but in only 70% in the blood, with the remaining cases diagnosed by clinical criteria plus response to therapy.[14,15] CMV PCR can be particularly useful in assessing CSF or vitreous or aqueous humor specimens; a positive result is highly suggestive that CMV is the cause of end-organ disease. However, PCR assays are not standardized; therefore, sensitivity, specificity, and interassay comparability are not clearly delineated.

Presence of serum antibodies to CMV is not diagnostically useful, although a negative immunoglobulin G antibody level indicates that CMV is unlikely to be the cause of the disease process.

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, diagnosis may be difficult and PCR of aqueous or vitreous specimens for CMV and other pathogens—especially herpes simplex virus, varicella zoster virus, and toxoplasmosis—can be useful for establishing the diagnosis.

CMV colitis is usually diagnosed based on demonstration of mucosal ulcerations on endoscopic examination, combined with with histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions.[2,16] CMV esophagitis is diagnosed by presence of ulcers of the distal esophagus and biopsy evidence of intranuclear inclusion bodies in the endothelial cells with an inflammatory reaction at the edge of the ulcer.[2] Specimens may contain many inclusion bodies or rare, isolated inclusion bodies. The significance of such inclusion bodies is determined by clinical judgment plus the presence or absence of other plausible etiologies.

Culturing CMV 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 have positive cultures in the absence of clinical disease.[13]

The diagnosis of CMV pneumonitis is difficult and 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.[11]

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.[3,9,12]

Preventing Exposure

HIV-infected patients who belong to groups with relatively low seroprevalence rates for CMV and, therefore, cannot be presumed to be seropositive may be tested for antibody to CMV **(BIII)**. That includes individuals who have not had contact with men who have sex with men or used injection drugs, and patients without extensive exposure to children in day care centers. HIV-infected adolescents and adults should be advised that CMV is shed in semen, cervical secretions, and saliva and that latex condoms must always be used during sexual contact to reduce the risk of exposure to CMV as well as other sexually transmitted pathogens **(AII)**.

HIV-infected adults and adolescents who are CMV-seronegative and provide child care (or are parents of children in day care facilities) should be informed that they are at increased risk of acquiring CMV infection **(BI)**. Risk of acquiring CMV infection can be diminished with optimal hygienic practices, such as handwashing and use of latex gloves **(AIII)**. HIV-infected adolescents, and adults who are seronegative for CMV and who require blood transfusion should be given only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations **(BIII)**.

Preventing Disease

CMV end-organ disease is best prevented using ART to maintain the CD4 count >100 cells/mm^3. Before ART was widely available, daily use of oral ganciclovir (no longer marketed in the United States) for primary prophylaxis significantly reduced incidence of CMV disease in a randomized, placebo-controlled trial.[17] However, such prophylactic therapy never became standard of care because of the cost, toxicity, and number-needed-to-treat to reduce disease. More recently, another randomized, placebo-controlled trial addressed whether valganciclovir (the current standard oral agent for treatment of CMV disease) 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) in the era of modern ART.[18] This study failed to show a benefit for such preventive therapy; therefore, valganciclovir primary prophylaxis **is not recommended** either in patients who will be receiving ART, or in patients who will not be receiving ART **(AI)**.

The primary method for preventing severe CMV disease is recognizing the early manifestations of the disease and instituting proper therapy. Patients should be made aware of the implications of increased floaters in the eye and should be advised to assess their visual acuity regularly using simple techniques, such as reading newsprint **(BIII)**. In the pre-modern ART era, some specialists recommended ophthalmologic examinations every 3 ro 4 months for patients with CD4 cells <50 cells/mm^3, as 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.

Treating Disease

CMV retinitis should ideally be treated with the active participation of an opthalmologist who is familiar with the diagnosis and management of retinal disease.

Oral valganciclovir **(AI)**, intravenous (IV) ganciclovir **(AI)**, IV ganciclovir followed by oral valganciclovir **(AI)**, IV foscarnet **(AI)**, and IV cidofovir **(BI)** are all effective treatments for CMV retinitis.[7,19-26] The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approxiamately 6 months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis **(AIII)**. The choice of initial therapy for CMV retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment **(AIII)**. 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] Prevention of contralateral eye involvement, visceral disease, and the benefits on survival should be considered when choosing among oral, IV, and local options. Given the evident benefits of systemic treatment, when medically and logistically feasible, treatment regimens for CMV retinitis should include a systemic component. There have been few comparative trials comparing 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. Thus, clinical judgment must be used when choosing a regimen.[21-25] Early clinical trials were conducted with oral ganciclovir, a preparation with poor bioavailability that is no longer marketed in the United States. In these guidelines, valganciclovir has replaced oral ganciclovir in recommendations even though the best data in some situations come from early trials with oral ganciclovir.

In studies conducted in the pre-ART era,[23] ganciclovir intraocular implant (no longer available) plus oral ganciclovir was superior to once-daily IV ganciclovir for treatment of CMV retinitis. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, HIV specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions (within 1500 microns of the fovea) **(AIII)**. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications.[19] For patients with small peripheral lesions, oral valganciclovir alone often is adequate **(AI)**.

Because ART can control CMV retinitis without anti-CMV therapy in patients who develop substantial immune recovery, some clinicians may consider not treating small peripheral CMV lesions with anti-CMV therapy in ART-naive patients who are initiating ART. However, this strategy has multiple potential drawbacks: ART can take 3 to 6 months to fully control HIV replication and stimulate sufficient immune recovery to control the retinitis. 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 there is sufficient immune recovery 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 patients with CMV retinitis and immune compromise.[13,20,26,28] In addition data from the ART era demonstrate that the use of systemic therapy for patients with CMV retinitis is associated with decreased retinitis progression, contralateral eye involvement, and visceral disease, as well as a reduction in mortality.[27] Moreover, some reports in the current era indicate that only 50% of some patient populations with CMV retinitis will experience immune recovery sufficient to meet criteria for discontinuation of anti-CMV therapy.[29] Therefore, even in ART-naive patients with small peripheral lesions, treatment with systemic anti-CMV therapy, such as oral valganciclovir for the first 3 to 6 months until ART has induced immune recovery will be beneficial **(AII)**. Systemic therapy is given twice daily for the first 14 to 21 days (induction) followed by once daily dosing (maintenance) until immune reconstitution occurs (see When to Stop Maintenance Therapy below).

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. Some HIV specialists would withhold therapy for mild disease if ART is to be initiated soon or can be optimized **(CIII)**. IV ganciclovir generally is the therapy of choice, therapy can be switched to oral valganciclovir once the patient can tolerate oral medications **(BI)**; foscarnet can be used as an alternative if ganciclovir-related toxicity is treatment limiting or in unusual 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)**. Optimizing ART is important, as in all types of CMV disease **(BIII)**. The optimal duration of therapy

and the role of oral valganciclovir have not been established.

Special Considerations with Regard to Starting Antiretroviral Therapy

Visual impairment caused by complications of immune reconstitution inflammatory syndrome (IRIS), such as macular edema, may occur in patients who have active CMV retinitis and those who have had CMV retinitis in the recent or distant past. One historical controlled study suggested a substantial increase in immune reconstitution uveitis (IRU, described below) in association with immediate as opposed to deferred initiation of ART (71% vs. 31%),[30] suggesting that a delay in therapy until retinitis was controlled might be beneficial in reducing the likelihood or severity of IRU. However, this strategy must be weighed against the potential for occurrence of other OIs if ART initiation is delayed.

CMV replication usually is controlled within 1 to 2 weeks after anti-CMV therapy is initiated, and in the current era, the rate of clinically significant IRU following initiation of ART appears to be low (approximately 0.04 per person-year).[29] Most experts would not delay ART for more than 2 weeks after starting anti-CMV therapy for retinitis or for 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 through a dilated pupil 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. The purpose of such examinations is to evaluate efficacy of treatment and to detect complications such as retinal detachment. Monthly fundus photographs, using a standardized technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse. For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months, but clinicians should be aware that relapses and other 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 hematopoietic growth factors.[31,32] Adverse effects of foscarnet include nephrotoxicity, and electrolyte abnormalities; seizures occur, characteristically in the context of renal insufficiency, and anemia.

In patients receiving ganciclovir or foscarnet, complete blood counts, serum electrolytes (including potassium, magnesium, calcium, and phosphorus), and renal function should be monitored twice weekly during induction and at least once weekly during maintenance therapy **(AIII)**. Cidofovir is associated with dose-related nephrotoxicity, neutropenia, uveitis, and hypotony. In patients receiving IV cidofovir, blood urea nitrogen and creatinine levels should be tested and urinalysis performed before each infusion; drug administration is contraindicated if renal dysfunction or significant proteinuria is detected. IV cidofovir requires prehydration and oral probenecid before administration. Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony even when organ dysfunction does not appear to include retinitis. Intraocular injections can be associated with bacterial or fungal infections, hemorrhage, or retinal detachment.

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 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.[33-37] The estimated incidence of IRU is 0.02/person-year after immune recovery.[38] Ocular complications of IRU include macular edema and development of epiretinal membranes, which can cause loss of vision.

Treatment of IRU usually consists of some type of corticosteroid therapy. The benefit of anti-CMV therapy is unclear.[33,39] Many experts would use both corticosteroids and anti-CMV therapy **(CIII)**. Data are insufficient on which to base a recommendation regarding the preferred route of corticosteroid administration; periocular, intravitreal, and oral administration all have been reported to be potentially successful. When oral corticosteroids are used, a short course rather than chronic therapy usually is recommended **(BIII)**.[40] IRU can occur even 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.

Early after the initiation of ART, patients remain at risk for development of CMV retinitis.[41] Development of CMV retinitis in the setting of recent ART initiation should be treated with systemic anti-CMV therapy, similarly to any patient with CMV retinitis, and continuing the same ART regimen **(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 relapse is most likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART.42 Treatment failure also may be a result of inadequate anti-CMV drug levels in the eye or CMV drug resistance. Many experts believe that early relapse is most often caused by the limited intraocular penetration of systemically administered drugs.[39,43,44]

When relapse occurs in patients receiving maintenance therapy, retinitis usually can be controlled with re-induction with the same drug as used for maintenance followed by re-institution of maintenance therapy, although results are likely to be seen for progressively shorter periods with each relapse **(BIII)**.[45] 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 multiple relapses of retinitis **(CIII)**.[45] That drug combination, however, is associated with substantial toxicity.

Drug resistance occurs in patients receiving long-term anti-CMV therapy.[46-49] Rates of approximately 25% per person-year were reported in the pre-ART era[46,50,51] and reported rates are similar for ganciclovir, foscarnet, and cidofovir.[46,47] In the ART era, the rate of resistance appears to be lower (approximately 5% per person-year).[52] 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.[48,53-57] 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[55] and occasionally to foscarnet.[56] Although early relapse typically is not a result of resistance, later relapse may be. Because patients with resistant CMV are most likely to have mutations in the CMV UL97 gene, and because a limited number of mutations are responsible for most drug resistance, susceptibility testing in peripheral blood using a CMV DNA PCR assay and sequencing for CMV UL97 mutations or using a point mutation assay[58,59] may be reasonable for patients who relapse on therapy.[60] Virus in the eye and in the blood are identical in more than 90% of cases;14 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, but not all, cases.[61]

Sequencing the UL97 gene from PCR-amplified specimens from blood can be accomplished in less than 48 hours, correlates well with conventional drug susceptibility testing and clinical outcomes,[60] and therefore has clinical utility for patients in whom therapy has failed. Conventional methods of culture and susceptibility testing and viral sequencing often are not available in clinical laboratories because they are too time-consuming or costly. By themselves, peripheral blood CMV viral load measurements have poor positive predictive value for treatment failure. UL97 mutants usually respond to foscarnet, as do some UL54 mutants. Patients with high-level ganciclovir-resistant isolates will require a switch to alternative therapy.[62] Many clinicians will treat with a series of intravitreal injections of foscarnet and/or systemic foscarnet **(CIII)**.

Preventing Recurrence

When to Start Maintenance Therapy

With regard to CMV retinitis, after induction therapy, chronic maintenance therapy should be continued,[8,12,19,22,63] until immune reconstitution occurs as a result of ART **(AI)**. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Intravitreal therapy alone will not protect against contralateral or extraocular disease, however: oral or intravenous therapy must be administered to prevent disease in the contralateral eye until immune reconstitution has occurred. Repetitive intravitreous injections of fomivirsen also have been demonstrated to be effective in randomized clinical trials, but that drug, is no longer available in the United States.

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

Repetitive intravitreous injections of ganciclovir or of foscarnet have appeared to be effective for maintenance therapy of CMV retinitis in uncontrolled case series. Because of the risk of hypotony and uveitis, and the substantially increased risk of immune recovery uveitis with intravitreal cidofovir, intravitreal administration of cidofovir should be reserved for extraordinary cases.[64]

CMV retinitis requires a chronic regimen until an increase in CD4 cell count to >100 cells/mm^3 in response to ART has been sustained for 3 to 6 months **(AI)**.[65]

After resolution of the acute CMV syndrome, and after initiation of effective ART, chronic maintenance therapy is not routinely recommended for CMV gastrointestinal disease, pneumonitis, and central nervous system disease unless there is concurrent retinitis or relapses have occurred **(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)**.[4,66-72] Such decisions should be made in consultation with an ophthalmologist. A 3% relapse 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 (relapses have been reported at CD4 cell counts of 1250 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 **(BII)**.

Relapse of CMV retinitis occurs frequently in patients whose anti-CMV maintenance therapies have been discontinued and whose CD4 counts have decreased to <50 cells/mm^3.[73] Therefore, reinstitution of maintenance therapy should occur when the CD4 count has decreased to <100 cells/mm^3 **(AIII)**.

Special Considerations During Pregnancy

The diagnostic considerations among pregnant women are the same as for non-pregnant women. Indications for treatment of CMV infection during pregnancy are the same as for nonpregnant HIV-infected adults **(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 as discussed should then be started after the first trimester.

Ganciclovir is embryotoxic among rabbits and mice and teratogenic (i.e., cleft palate, anophthalmia, aplastic kidney and pancreas, and hydrocephalus) in rabbits.[74-76] Safe use in human pregnancy after organ

transplantation has been reported,[74,75] and use in late pregnancy to treat fetal CMV infection in non-HIV-infected women has also been reported.[77]

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.[78] 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 studies, and ease of use of the various drugs, valganciclovir is recognized as the treatment of choice during pregnancy **(BIII)**. No experience has been reported with the use of valganciclovir in human pregnancy, but concerns are expected to be the same as with ganciclovir. 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 different CMV strains during pregnancy[79] can all lead to in utero transmission and congenital CMV. Although about one-third of newborns acquire congenital CMV infection after primary infection, only approximately 1% to 2% of newborns acquire CMV after a recurrent infection in HIV-uninfected women. Because >90% of HIV-infected pregnant women are CMV antibody positive in the majority of studies, the risk for symptomatic infection in the fetus is expected to be low.[80-84] However, recent studies of HIV-exposed infants suggest that rates of congenital CMV may be increased, ranging from 2% to 7%,[85,86] with higher rates in babies born to mothers with CD4 <200 cells/mm^3 and in HIV-infected infants. Maternal ART in pregnancy has been associated with decreased rates of perinatal/early postnatal CMV and occurrence of related clinical symptoms among HIV-infected and HIV-exposed infants.[87]

Up to 90% of infants who are symptomatic at birth will have serious long-term problems, including hearing loss, visual impairment, mental retardation and/or cognitive impairment, but only 5% to 15% of asymptomatic newborns are at risk for serious long-term impairment. However, asymptomatic congenital CMV infection is associated with late-onset hearing loss in non-HIV-infected children.[88] In women with CMV disease in pregnancy, the fetus should be monitored by periodic ultrasound after 20 weeks gestation, although from studies in HIV-uninfected populations, only about 5% to 25% of infected newborns have ultrasound evidence of congenital infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, and echogenic fetal bowel). Any ultrasound findings suspicious for congenital CMV infection should prompt consideration of invasive testing (i.e., amniocentesis) for definitive diagnosis. Although invasive fetal testing was associated with increased rates of perinatal HIV transmission in early studies,[89] more recent data suggests that risk may be minimal in women on effective ART and with undetectable HIV-RNA levels.[89-91] Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended.

If fetal CMV infection is confirmed, there is no standard therapy for *in utero* treatment. A non-randomized trial of CMV hyperimmune globulin suggested potential benefit of passive immunotherapyfor treatment of acute fetal CMV infection, with decreased incidence of having a symptomatic newborn at birth[92] and regression of fetal cerebral abnormalities.[93] 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.94 A larger placebo-controlled trial of CMV hyperimmune globulin currently is underway at NICHD Maternal Fetal Units across the United States [ClinicalTrials.gov Identifier NCT01376778].

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 (page 1 of 2)

Preventing CMV Disease

- CMV end-organ disease is best prevented by using ART to maintain CD4 count >100 cells/mm^3.

Managing CMV Retinitis

- The choice of initial therapy for CMV retinitis should be individualized, based on location and severity of the lesion(s), the level of immunosuppression, and other factors (e.g., concomitant medications, ability to adhere to treatment) **(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.

Initial Therapy Followed by Chronic Maintenance Therapy—For Immediate Sight Threatening Lesions (within 1500 microns of the fovea)

Preferred Therapy:

- Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) for 1–4 doses over a period of 7–10 days to provide higher intraocular levels of drug and faster control of the infection until steady state intraocular ganciclovir concentrations are achieved **(AIII)**; *plus*
- Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg once daily **(AI)**

Alternative Therapy

- Intravitreal injections as listed above **(AIII)**; *plus* one of the following systemic 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*
  - Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h **(AI)**, *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) **(BI)**.

  Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid

For Peripheral Lesions

- Administer one of the systemic antiviral therapy listed above 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 corticosteroid or a short course of systemic steroid (BIII).

Stopping Chronic Maintenance Therapy for CMV Retinitis:

- CMV treatment for at least 3–6 months, **and** lesions are inactive, **and** with CD4 count >100 cells/mm^3 for 3 to 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 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/mm^3 **(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*
- For mild cases: If ART can be initiated or optimized without delay, withholding CMV therapy may be considered **(CIII)**.

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 = intraveneously; q(n)h = every "n" hours

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

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 IU/mL, no further vaccination is needed, but if the titer is <100 IU/mL, a complete series of HBV vaccine should be completed followed by anti-HBs testing **(BII)**.[55] The cut-off of 100 IU/mL is used in this situation because one study demonstrated that 100% of patients with isolated anti-HBc who achieved a titer of 100 IU/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 IU/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 IU/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 IU/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 IU/mL, no further vaccination is needed, but if the titer is <100 IU/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 IU/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 July 25, 2017)

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 September 17, 2015; last reviewed January 27, 2017)

Epidemiology

Infections with human herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) are common, with a seroprevalence of HSV-1 among adults in the United States of approximately 60% and a seroprevalence of HSV-2 among persons aged ≥12 years of 17%.[1] Approximately 70% of HIV-infected persons are HSV-2 seropositive and 95% are seropositive for either HSV-1 or HSV-2.[2] In most persons, HSV infections are unrecognized clinically. However, regardless of the clinical severity of infection, shedding on mucosal surfaces occurs frequently and can result in transmission. HSV-2 infection increases the risk of HIV acquisition two- to three-fold, and HSV-2 reactivation results in increases in HIV RNA levels in blood and genital secretions of coinfected patients.

Clinical Manifestations

Orolabial herpes (e.g., cold sores, fever blisters) is the most common manifestation of HSV-1 infection. Classic manifestations include a sensory prodrome in the affected area, rapidly followed by the evolution of lesions from papule to vesicle, ulcer, and crust stages on the lip. The course of illness in untreated patients is 5 to 10 days. Lesions recur 1 to 12 times per year and can be triggered by sunlight or physiologic stress.

Genital herpes is the most common manifestation of HSV-2 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 genital skin (e.g., the penile shaft, thighs, pubis). Local symptoms might include a sensory prodrome consisting of pain and pruritis. Mucosal disease is occasionally accompanied by dysuria or vaginal or urethral discharge. Inguinal lymphadenopathy is common with genital herpes, particularly in primary infection.[3] These classic manifestations occur in some patients, but most individuals with genital herpes have mild and atypical lesions that are often unrecognized, not brought to medical attention, and cannot reliably be diagnosed by physical examination. HSV is a significant cause of proctitis in men who have sex with men with HIV infection and may not be associated with external anal ulcers.[4] In profoundly immunocompromised patients, extensive, deep, nonhealing ulcerations can occur. These lesions have been reported most often in those with CD4 T-lymphocyte (CD4) cell counts of <100 cells/μL and also may be associated with acyclovir-resistant HSV.[5] In addition, atypical presentations such as hypertrophic genital HSV,[6,7] which mimics neoplasia and requires biopsy for diagnosis, may be seen in persons with HIV infection.

An episode of genital HSV-1 disease is indistinguishable from genital HSV-2 disease, but genital HSV-1 recurrences and viral shedding occur less often than with genital HSV-2 infection.

Non-mucosal HSV infections, such as HSV keratitis, HSV encephalitis, HSV hepatitis, and herpetic whitlow, are similar in presentation to manifestations 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, especially in persons with HIV infection, a laboratory diagnosis should be pursued in all cases.[8] HSV DNA polymerase chain reaction (PCR), and viral culture are preferred methods for diagnosis of mucocutaneous HSV lesions caused by HSV. PCR is the most sensitive method. The virus detected in genital lesions should be typed because of the prognostic significance—HSV-1 recurs less frequently than HSV-2 in the genital area. Type-specific serologic assays are commercially available and can be used for diagnosis in asymptomatic individuals or those with atypical lesions. Because of the poor sensitivity and specificity of clinical diagnosis,

the extensive interactions between HIV and HSV-2, and the availability of effective therapy for HSV-2, routine type-specific serologic screening for HSV-2 for persons with HIV infection can be considered. 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 Centers for Disease Control and Prevention sexually-transmitted disease treatment guidelines.[9]

Preventing Exposure

The majority of persons with HIV infection have HSV-1 and HSV-2 infections. However, prevention of acquisition of HSV is important for those who are uninfected. Persons with HIV infection who are HSV-2 seronegative should consider asking their partners to be tested using 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)**.[10] Consistent use of latex condoms reduced HSV-2 acquisition from women to men and from men to women, and their use should be encouraged for prevention of transmission of HSV-2 and other sexually transmitted pathogens **(AII)**.[11,12] Persons with HIV infection should specifically avoid sexual contact when their partners have overt (genital or orolabial) herpetic lesions **(AII)**. However, most sexual transmission of HSV occurs during asymptomatic viral shedding.

The use of suppressive antiviral therapy (i.e., valacyclovir 500 mg once daily) in persons without HIV infection with symptomatic genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 48%.[13] However, in HIV-1/HSV-2-seropositive persons not on antiretroviral therapy, suppressive acyclovir (400 mg twice daily) did not prevent HSV-2 transmission to HSV-2 seronegative partners.[14] Suppressive anti-HSV therapy is not recommended to prevent HSV-2 transmission in persons with HIV infection who are not on ART **(AI)**.

Preventing Disease

Prophylaxis with antiviral drugs to prevent primary HSV infection is not recommended **(AIII)**. Although preexposure prophylaxis (PrEP) with vaginal tenofovir and oral tenofovir or tenofovir/emtricitabine has been associated with reduced risk of HSV-2 acquisition in clinical trials in HIV-negative persons[15,16], vaginal and oral tenofovir for prevention of HSV-2 has not been studied in persons with HIV infection. The dose, duration, timing, and efficacy of antiviral prophylaxis after known or suspected exposure to HSV have not been evaluated. No vaccine for prevention of HSV infection is available.

Treating Disease

Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur or with daily suppressive therapy to prevent recurrences. The management plan for genital HSV-2 disease in persons with HIV infection should include consideration of several factors, such as frequency and severity of HSV recurrences, and risk for genital ulcer disease (GUD) when initiating ART. Episodic treatment for individual recurrences does not influence the natural history of genital HSV-2 infection.

Patients with orolabial lesions can be treated with oral acyclovir, valacyclovir, or famciclovir for 5 to 10 days **(AIII)**. Genital HSV episodes should be treated with oral acyclovir, valacyclovir, or famciclovir for 5 to 10 days **(AI)**. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir **(AIII)**.[5,17] Patients can be switched to oral antiviral therapy after their lesions have begun to regress. Therapy should be continued until the lesions have completely healed. Disseminated disease due to HSV is rare in persons with HIV infection, although HSV necrotizing retinitis can occur, which may be difficult to distinguish clinically from retinitis caused by varicella-zoster virus (VZV).

Special Considerations with Regard to Starting Antiretroviral Therapy

In most instances, orolabial HSV should not influence the decision about when to start antiretroviral therapy (ART). Persons with HIV infection receiving ART who have had immune reconstitution often have

improvement in the frequency and severity of their clinical episodes of genital herpes. However, immune reconstitution does not reduce the frequency of genital HSV shedding.[18] Chronic cutaneous or muscosal HSV that is refractory to therapy and visceral or disseminated cases of HSV disease (which are uncommon) would be indications to hasten the initiation of ART **(CIII)**.

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

Acyclovir, valacyclovir, and famciclovir are occasionally associated with nausea or headache. No laboratory monitoring is needed in patients receiving episodic or suppressive therapy unless they have advanced renal impairment. 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. Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in persons with HIV infection treated with high-dose (8 g/day) valacyclovir, but has not been reported at conventional doses recommended for therapy of HSV infection.[19]

HSV-2 shedding and genital ulcer disease can increase in the first 6 months after initiation of ART, particularly in those with low CD4 cell count.[20,21] 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).[22]

Managing Treatment Failure

Treatment failure as a result of resistance to antivirals should be suspected if lesions do not begin to resolve within 7 to 10 days after initiation of 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)**.[23] 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)**.[24,25] IV cidofovir is a potential alternative **(CIII)**. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer may be required **(CIII)**.

Preventing Recurrence

Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences **(AI)**.[8,26] Suppressive therapy for HSV may be continued indefinitely, without regard for improved CD4 cell count, although need for continuation should be addressed on an annual basis, particularly if immune reconstitution has occurred **(BIII)**. In persons starting ART with CD4 cell counts <250 cells/mm^3, there is in increased risk of HSV-2 shedding and genital ulcer disease in the first 6 months; suppressive ACV decreases the risk of GUD nearly 60% compared to placebo, and may be recommended for persons with CD4 cell counts <250 cells/mm^3 starting ART **(BI)**.

Suppressive anti-HSV therapy in persons with HIV infection not on ART also results in a decrease in plasma, anal, and genital secretion HIV RNA levels and in a lower risk of HIV progression.[27] However, antiviral regimens for herpes do not decrease the risk of HIV transmission to sexual partners, and should not be used to delay HIV progression in place of ART when ART is available.[28] In persons who are taking ART, suppressive HSV antivirals do not impact HIV progression, improve in CD4 T-cell recovery, or decrease markers of systemic inflammation[29,30] and should not be used for this purpose **(AI)**.

The use of daily suppressive therapy (when compared to episodic therapy) has been associated with a lower risk of development of acyclovir-resistant HSV in hematopoietic stem cell recipients;[31] there are no specific data for persons with HIV infection.

Special Considerations During Pregnancy

Diagnosis of 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 during HSV acquistion 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 **(AIII)**.[32] The use of valacyclovir and famciclovir during pregnancy has been described and they appear to be safe and well tolerated.[33] Valacyclovir use can be considered for treatment and suppressive therapy during pregnancy because of its simplified dosing schedule **(CIII)**.

An additional concern with HSV during pregnancy is the potential for HSV transmission to the fetus or neonate. The rate of HSV transmission to the newborn in HSV-2-seropositive pregnant women is low, except in those who acquire genital HSV late in pregnancy. The adverse sequelae for the neonate, however, can be very significant. The predominant risk for 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)**.[8] 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[34] and is likely to have similar efficacy in women with HIV infection. However, neonatal HSV disease has been reported in women treated with suppressive antiviral therapy.[35] 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)**.[36] Suppressive therapy for women who are only seropositive for HSV-2 without a history of genital lesions is not recommended. Maternal genital herpes was a risk factor for perinatal mother-to-child HIV transmission in the pre-highly active antiretroviral therapy era.[37] Whether HSV facilitates HIV transmission among pregnant women on ART is unknown.

Recommendations for Treating Herpes Simplex Virus (HSV) Infections (page 1 of 2)

Treating Orolabial Lesions (Duration: 5–10 days)

- Valacyclovir 1 g PO BID **(AIII)**, *or*
- Famciclovir 500 mg PO BID **(AIII)**, *or*
- Acyclovir 400 mg PO TID **(AIII)**

Treating Initial or Recurrent Genital Lesions (Duration: 5–10 Days)

- Valacyclovir 1 g PO BID **(AI)**, *or*
- Famciclovir 500 mg PO BID **(AI)**, *or*
- Acyclovir 400 mg PO TID **(AI)**

Treating Severe Mucocutaneous HSV Infections (AIII)

- Initial therapy acyclovir 5 mg/kg IV q8h
- 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)**, *or*
- To reduce the risk of GUD in patients with CD4 cell counts <250 cells/mm^3 who are starting ART **(BI)**

Treatment:

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

Recommendations for Treating Herpes Simplex Virus (HSV) Infections (page 2 of 2)

For Acyclovir-Resistant Mucocutaneous HSV infections

Preferred Therapy:

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

Alternative Therapy (Duration: 21–28 days or longer, based on clinical response) **(CIII)**:

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

Note:

- Topical formulations of trifluridine and cidofovir are not commercially available.
- Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir.

Key to Acronyms: BID = twice daily; GUD = genital ulcer disease; HSV = herpes simplex virus; IV = intraveneously; PO = orally; TID = three times daily

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Histoplasmosis (Last updated May 7, 2013; last reviewed March 13, 2019)

NOTE: Update in Progress

Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. Infection is endemic to the central and south-central United States and is especially common in the Ohio and Mississippi River Valleys. It is also endemic in Latin America, including Puerto Rico. In endemic areas, annual incidence approaches 5% in HIV-infected individuals. A CD4 T lymphocyte (CD4) count <150 cells/mm^3 is associated with an increased risk of symptomatic illness.[1,2]

Virtually all cases of primary histoplasmosis are acquired by inhalation of microconidia that form in the mycelial phase. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. When cellular immunity wanes, reactivation of a silent focus of infection that was acquired years earlier can occur, and it is the presumed mechanism for disease occurrence in nonendemic areas. Incidence of symptomatic histoplasmosis in HIV-infected patients appears to have declined with the advent of effective antiretroviral therapy (ART). When histoplasmosis does occur, however, it is reported as the AIDS-defining illness in 25% to 61% of patients.[3,4]

Clinical Manifestations

In HIV-infected patients, 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.[1,4] Central nervous system (CNS), gastrointestinal, and cutaneous manifestations occur in a smaller percentage, although in a series from Panama, diarrhea occurred in 50% of patients.[5] Approximately 10% of patients experience shock and multi-organ failure. Patients with CNS histoplasmosis typically experience fever and headache, and also (if brain involvement is present) seizures, focal neurological deficits, and changes in mental status.[6] Gastrointestinal disease usually manifests as diarrhea, fever, abdominal pain, and weight loss.[7] For patients whose CD4 counts are >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 histoplasmosis and acute pulmonary histoplasmosis[8] but is insensitive for chronic forms of pulmonary infection. Using a newer quantitative assay, antigen was detected in the urine of 100% and in the serum of 92% of AIDS patients with disseminated histoplasmosis.[9] Antigen detection in bronchoalveolar lavage fluid appears to be a useful method for diagnosis of pulmonary histoplasmosis.[10] In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by white blood cells. Histopathological examination of biopsy material from involved tissues demonstrates the characteristic 2 to 4 μm budding yeast and can provide a rapid diagnosis.

H. capsulatum can be cultured from blood, bone marrow, respiratory secretions, or other involved sites in >85% of patients with AIDS and disseminated histoplasmosis, but the organism requires several weeks to grow.[11] Serologic tests are less useful than antigen assays in AIDS patients with disseminated histoplasmosis but may be helpful in patients who have reasonably intact immune responses with pulmonary disease.[11,12]

The diagnosis of meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are a lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[6] However, *Histoplasma* antigen or antibodies against *H. capsulatum* can be detected in CSF in up to 70% of cases, and a positive result for either test is diagnostic. For some patients, none of these specific tests is positive, and a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not explained by another cause.

Preventing Exposure

HIV-infected individuals who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to it, but those with CD4 counts <150 cells/mm^3 should avoid activities known to be associated with increased risk **(BIII)**. These include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves.

Preventing Disease

When to Start Primary Prophylaxis

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 infection and who live in areas where histoplasmosis is highly endemic.[13] Prophylaxis with itraconazole at a dose of 200 mg daily can be considered for 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)**.

When to Stop Primary Prophylaxis

If used, primary prophylaxis can be discontinued in patients on potent ART once CD4 counts are ≥150 cells/mm^3 for 6 months **(BIII)**. Prophylaxis should be restarted if the 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), induced a more rapid and complete response, lowered mortality, 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 at least 2 weeks or until they clinically improve **(AI)**. Another lipid formulation of amphotericin B can be used at the same dosage if cost is a concern or in patients who cannot tolerate liposomal amphotericin B **(AIII)**. Step-down therapy to oral itraconazole, 200 mg 3 times daily for 3 days, and then 200 mg twice daily, should be given for a total of at least 12 months **(AII)**.[15] Because of potential drug interactions between itraconazole and both protease inhibitors and efavirenz, it is advisable to obtain serum levels of itraconazole after 2 weeks of therapy. A randomly obtained serum level of at least 1.0 µg/mL is recommended and levels >10 µg/mL are unnecessary.

In patients with less severe disseminated histoplasmosis, oral itraconazole, 200 mg 3 times daily for 3 days followed by 200 mg twice daily, is appropriate initial therapy **(AII)**.[15,16] 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, which should be given with food.

Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4 count >300 cells/mm^3, should be managed in a manner similar to that used for a nonimmunocompromised host **(AIII)**.[15]

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dosage of 5 mg/kg daily for 4 to 6 weeks **(AIII)**. This should be followed by maintenance therapy with itraconazole at a dose of 200 mg 2 or 3 times daily for at least 1 year and until resolution of abnormal CSF findings **(AIII)**.[15]

Oral posaconazole and voriconazole have been reported to be effective for histoplasmosis in a small number of patients who had AIDS or other immunosuppressive conditions[17-20] and may be reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**. Fluconazole is less effective

than itraconazole for histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily and may also be a reasonable alternative at this dose for those intolerant of itraconazole **(CII)**.[21] The echinocandins are not active against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis **(AIII)**.

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with histoplasmosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) is reportedly uncommon in HIV-infected patients with histoplasmosis.[22,23] ART should, therefore, **not** be withheld because of concern for the possible development of IRIS **(AIII)**.

All of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain ARV agents and other anti-infective agents. Table 5 lists these interactions and recommendations for dosage adjustments, where feasible.

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. Because absorption of itraconazole can be erratic, a random serum itraconazole level should be obtained after 2 weeks of therapy if there is concern about adherence or if medications with potentially adverse interactions are added to the drug regimen. The serum concentration should be >1 µg/mL.

As previously indicated, IRIS is uncommon in HIV-infected individuals with histoplasmosis.[22,23]

Managing Treatment Failure

Mortality rates remain high for patients with AIDS who develop disseminated histoplasmosis, many of whom had never received ART before diagnosis with histoplasmosis.[3-5,12] 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 voriconazole are reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII)**;[17-20] fluconazole also can be used at a dose of 800 mg daily **(CII)**.[21] Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir (Table 5). Posaconazole has fewer known drug interactions with ARV medications than voriconazole.

Preventing Recurrence

When to Start Secondary Prophylaxis

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered to patients with severe disseminated or CNS infection **(AIII)** and after re-induction therapy in those whose disease relapses despite initial receipt of appropriate therapy **(BIII)**. Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.[21,24] The role of voriconazole or posaconazole has not been evaluated.

When to Stop Secondary Prophylaxis

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that discontinuing itraconazole was safe for patients treated for histoplasmosis who have a good immunologic response to ART.[25] Subjects in that trial had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum antigen <2 units, and CD4 counts ≥150 cells/mm^3; and had been on effective ART for 6 months. No relapses were evident in 32 subjects who were followed for a median of 24 months.[25] Thus, discontinuing suppressive azole antifungal therapy appears to be safe for patients who meet the previously described criteria, noting that the detectable antigen level is now designated as 2 ng/mL **(AI)**. Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^3 **(BIII)**.

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 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 over 300 women with first trimester exposure did not show an increased risk of malformation.[26,27] 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 of 400 mg/day or more through or beyond the first trimester of pregnancy.[28] 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.[29,30] Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, low dose for treatment of vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 1 of 2)

Preventing 1st 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 living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) **(BI)**

Preferred Therapy:

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

Discontinue Primary Prophylaxis:

- If used, may discontinue if CD4 count ≥150 cells/mm^3 for 6 months on ART **(BIII)**

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 or amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily **(AIII)**

Duration:

- For at least 2 weeks or until clinically improved

Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months **(AII)**, with dosage adjustment based on interactions with ARV (see Table 5) and itraconazole serum concentration

Treating Less Severe Disseminated Disease

Induction and Maintenance Therapy

Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID for ≥12 months **(AII)**, with dosage adjustment based on interactions with ARV and itraconazole serum concentration

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

Alternative Therapy:

Note: These recommendations are based on limited clinical data (for patients intolerant to itraconazole who are only moderately ill).

- Posaconazole 400 mg PO BID **(BIII)**
- Voriconazole 400 mg PO BID for 1 day, then 200 mg PO BID **(BIII)**
- Fluconazole 800 mg PO 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 BID (TID for at least 12 months and until resolution of abnormal CSF findings) with dosage adjustment based on interactions with ARV and itraconazole serum concentration **(AIII)**

Long-Term Suppressive Therapy (Secondary Prophylaxis)

Indications:

- For patients with severe disseminated or CNS infection after completion of at least 12 months of treatment **(AIII)**, *and*
- In patients who relapsed despite appropriate initial therapy **(BIII)**

Preferred Therapy:

- Itraconazole 200 mg PO daily **(AIII)**

Alternative Therapy:

- Fluconazole 400 mg PO daily **(BIII)**

*Criteria for Discontinuing Long Term Suppressive Therapy **(AI)**:*

- Received azole treatment for >1 year, *and*
- Negative fungal blood cultures, *and*
- Serum Histoplasma antigen <2 ng/mL, *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 **(BIII)**

Other Considerations:

- Itraconazole serum concentrations should be performed in all patients to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions **(AIII)**. Random serum concentrations (itraconazole + hydroxyitraconazole) should be >1 µg/mL.
- Itraconazole oral solution is preferred over capsule because of improved absorption, but is less well tolerated. However, this formulation may not be necessary if itraconazole concentration is increased by concomitant use of a CYP3A4 inhibitor such as ritonavir-boosted PIs.
- Acute pulmonary histoplasmosis in HIV-infected patients with CD4 count >300 cells/mm^3 should be managed the same as for non-immunocompromised patients **(AIII)**
- 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. Table 5 lists these interactions and recommends dosage adjustments where feasible.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; IV = intravenous; PI = protease inhibitor; PO = orally; TID = three times daily

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Human Herpesvirus-8 Disease (Last updated May 29, 2018; last reviewed February 21, 2018)

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 (Last updated November 29, 2018; last reviewed November 29, 2018)

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 non-penetrative 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 are not considered oncogenic.[22-24]

In the United States and Western Europe, women with HIV/AIDS 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] In Africa, the data are more limited and inconsistent,[33] but a prospective registry-based study found increased risk of cervical cancer in women with HIV/AIDS.[34] HIV infection and low CD4 cell count also have been consistently and strongly associated with HPV infection itself and with precancerous cervical lesions, including low-grade cervical intraepithelial neoplasia (CIN), and the precursor to cervical cancer, CIN 3.[35-47] Higher rates of HPV infection and CIN are seen in adolescents with HIV, regardless of whether HIV was acquired vertically or horizontally.[36,48,49] 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 were also common in this group, with a cumulative rate of 12% by age 19 years.

Other cancers caused by HPV include most anal cancers and a subset of tumors of the vulva, vagina, penis, oral cavity, and oropharynx.[1,23,50-52] HPV16 is the type present in most HPV-positive non-cervical cancers.[1,23,50,53,54] Patients with HIV/AIDS also have a significantly elevated incidence of these tumors relative to the general population,[25,55,56] and CD4 cell count has been related to risk of anal cancer.[32] 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,[57-59] as are anal and genital warts, and in women, vulvar intraepithelial neoplasia (VIN) and vaginal intraepithelial neoplasia (VAIN).[60-62] In the U.S. general population, HPV also causes approximately 70% of oropharyngeal cancers (OPC)[63,64]; HPV16 causes 84% of HPV-associated OPC, and the HR HPV types contained in the nine-valent HPV vaccine cause approximately 94%.[65] HPV-associated OPC incidence is four- to five-fold higher in males than in females,[66] and two- to three-fold higher among individuals with HIV infection.[67]

Despite the associations between HIV and CD4 cell count and HPV-related cancers and precancers, the impact of antiretroviral therapy (ART) on the incidence of HPV-related tumors is uncertain, and it is possible that the impact differs by tumor type. Some studies found decreased persistence/progression of CIN with ART,[68] including a study that distinguished between adherent and non-adherent ART use.[69] Although several prior studies found the incidence of cervical cancer itself unchanged,[55] and reported that anal cancer incidence was increasing[55] more recent registry-based results have found significant decreases in cervical and

anal cancer risk in men and women with HIV infection.[70] Conversely, use of ART did not affect CIN rates in adolescents with perinatally or horizontally acquired HIV.[36,49] The incidence of high-grade VIN was not reduced with ART use, even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART,[60] and some[71,72] but not other[73,74] studies reported increased rates of oral warts following ART initiation.

Overall, whether the burden of HPV-related cancers will decrease or even increase over time is difficult to currently gauge, as the risk of these cancers in individuals with HIV infection remains high relative to the general population, even if these differences are moderately decreasing. Further, the successful prolongation of life with use of ART for HIV suppression can also lead to increasing cumulative incidence of tumors over time, as well as potentially longer duration of HPV persistence, and accumulation of somatic mutations and epigenetic changes that contribute to carcinogenesis. This clinical scenario may be of particular concern for HPV-related cancers, such as anal cancers, that are not currently subject to routine screening. However, increasing use of HPV vaccination in adolescents and young adults may begin to reduce the risk of HPV-associated cancers in persons with HIV infection in later life.

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.[75]

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 cm 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 may also 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 patients HIV infection.[76]

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.

Cervical Cancer Screening Recommendations

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.

Possible Pap test results include:

- 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)
- ASCUS (atypical squamous cells of undetermined significance)
- ASC-H (atypical squamous cells, cannot rule out a high-grade lesion)
- AGC (atypical glandular cells)

Women With HIV Infection Aged <30 years

Screening

The Pap test is the primary mode for cervical cancer screening for women with HIV infection <30 years of age. Screening for these women should commence within 1 year of the onset of sexual activity regardless of mode of HIV transmission (e.g., sexual activity, perinatal exposure) but no later than age 21 years. Women with HIV infection 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 infection is normal, the next Pap test should be in 12 months **(BII)**. Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**. If the results of the 3 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 women with HIV infection <30 years of age.

Abnormal Pap Test Results

For ASC-US Pap test, if reflex HPV testing is positive, a referral to colposcopy is recommended. If HPV testing is not available or not done, 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 (regardless of reflex HPV result, if done).

Rationale

These recommendations reflect evidence that women with HIV infection <21 years of age and sexually active may have a high rate of progression of abnormal cytology[36] **(BII)**. No similar prospective data are available for adolescents who acquired HIV during the perinatal period, but as noted earlier, Brogly and colleagues reported that 30% of such adolescents had ASC-US or greater on their first cervical Pap test.[49] The mean age at the time of the first Pap test was 16.7 years, with a range of 13 to 23 years.

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

Women With HIV Infection Aged ≥30 years

Cervical cancer screening in women with HIV infection 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, the woman with HIV infection should have a Pap test at the time of HIV diagnosis (baseline), then every 12 months **(BII)**. Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**. If the results of the 3 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 16 or 16/18 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, then referral to colposcopy is recommended. If the HPV testing is positive, but the genotype specific testing for HPV16 or HPV 16/18 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 ≥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 ≥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 for use of HPV co-testing with cytology. A negative HPV test predicts prolonged low risk of cancer. Cytology/HPV co-testing can allow for a prolonged cervical cancer screening interval in women with HIV infection 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 as women with HIV infection 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

There are three FDA-approved HPV vaccines: 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, and anal cancer and genital warts due to vaccine types based on randomized clinical trial (RCT) data.[77-79,80-83] Although there are no efficacy data with the 9-valent HPV vaccine in men, a clinical trial established the safety of the vaccine in young men aged 16 to 26 years and showed similar antibody concentrations as in the young women aged 16 to 26 years in whom efficacy was established.[84]

Although there are no clinical trials to demonstrate HPV vaccine efficacy in prevention of oropharyngeal cancers, there is some evidence that the prevalence of oral vaccine-type HPV infections are reduced with vaccination.[85,86] One prospective trial of the quadrivalent HPV vaccine in adults with HIV infection older than 27 years suggested efficacy for prevention of oral HPV infection.[87]

The Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with 9 valent HPV vaccine for all 11- or 12-year-old girls and boys. The vaccine series can be started at age 9 years. Catch-up vaccination is recommended for all 13- to 26-year-old females and all 13- to 21-year-old males who have not been vaccinated. Catch-up vaccination is also recommended for males aged 22 to 26 years who are men who have sex with men (MSM), or have HIV infection or are otherwise immunocompromised.[88,89]

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.[88,89] Although ACIP recommends a 2-dose schedule for adolescents initiating the vaccine series at ages 9 to 14 years,[90] three doses of HPV vaccine (0, 1–2, and 6 months) are recommended for females and males with HIV infection 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 adults with HIV infection older than 27 years.[87] 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[91,92] in a broad range of individuals with HIV infection.[93] Some studies have demonstrated lower antibody levels in individuals with HIV infection than in those who do not have are HIV infection; however, the clinical significance of this observation is unknown.[94-96] Studies have shown that HPV vaccination induces an anamnestic response in children and adults with HIV infection.[92,97,104] Immune responses appear stronger among those with higher CD4 counts and suppressed HIV viral loads.[93,98,96]

For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give additional full series of vaccination with recombinant 9-valent vaccine, but there are no data 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 depending on location in U.S. men and women.[65]

HPV vaccination prevents initial HPV infection and is ideally administered before sexual exposure to HPV. Because some individuals with HIV infection 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 infection aged 13 through 26 years **(AIII)**.

Current data do not support vaccination for those older than 26 years, and HPV vaccines are not approved for use in men or women older than 26 years. Women with HIV infection who have been vaccinated should also 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 women with HIV infection (especially those with low CD4 cell counts) than in women without HIV infection.

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 diseases (STDs) **(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.[99] 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 women with HIV infection, 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 STDs (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 STDs.

Male Circumcision

Evidence is growing that male circumcision reduces rates of oncogenic HPV infection of the penis, based on data from RCTs[100-103] 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 individuals with HIV infection 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 infection, 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 as for women with intact cervices as studies have shown that CIN is the most common indication for hysterectomy in women with HIV infection. Although vaginal Pap tests are often abnormal in women with HIV infection and more common than in women without HIV infection, VAIN 2+ and vaginal cancers are infrequent.[104] Another study by Smeltzer et al in women with HIV infection with previous hysterectomy and no previous abnormal Pap test, showed that among those with vaginal biopsies, 29% had VAIN 2 or VAIN 3. However, there were limitations to this study as 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 patients with HIV

infection may provide clinical benefits comparable to measures to prevent other opportunistic infection. AIN lesions are similar in many ways to CIN, but there may be differences 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 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 anal cancer with anal cytology should not be done without the availability of referral for high resolution anoscopy. If anal cytology is performed and indicates ASC-US, then ASC cannot rule out ASC-H, LSIL, or high-grade squamous intraepithelial lesion (HSIL), then it should be followed by high-resolution anoscopy **(BIII)**. Visible lesions should be biopsied to determine the level of histologic changes and to rule out invasive cancer **(BIII)** (see section on treatment for details on treating AIN).

Preventing Oropharyngeal Cancer

While HPV DNA detection and HPV serology might be useful in identifying individuals at high risk of oropharyngeal cancer, there are currently no adequate methods to determine the site of HPV-associated oropharyngeal pre-cancer or cancer to target biopsy or treatment, despite ongoing efforts. It should also be noted that rates of non-HPV associated oral cancer are also increased in individuals with HIV infection,[67] and oral potentially malignant disorders (OPMDs) can be diagnosed in some cases; albeit, the effectiveness of this approach has not been tested in RCTs.[105]

Treating Disease

Preferred and Alternative Approaches for Treatment, Including Duration of Therapy

Treating Genital and Oral Warts

Patients with HIV infection 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 patients with HIV, especially when immunity is relatively preserved. Treatments are available for genital warts, but none are uniformly effective or uniformly preferred. Lacking RCTs specific to individuals with HIV infection, guidelines for the treatment of STDs in patients with HIV infection should be followed. More than one treatment option may be required for refractory or recurrent lesions in patients with HIV infection. 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 generally recommended for uncomplicated external warts that can be easily identified and treated by the patient. Imiquimod (5% cream) is a topical cytokine inducer that should be applied at bedtime on three non-consecutive 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 completely cleared and not visible **(BIII)**.

No clinical trials of this latter treatment option have been conducted in individuals with HIV infection.

Provider-applied treatments such as cryotherapy, trichloroacetic acid (TCA), bichloroacetic acid (BCA), and surgery, are typically 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 side 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.

There is no consensus on optimal treatments of oral warts. 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

Women with HIV infection and CIN should be managed by a clinician with experience in colposcopy and treatment of cervical cancer precursors. In general, CIN in women with HIV infection should be managed according to ASCCP guidelines.

Women with satisfactory colposcopy and biopsy-confirmed high-grade CIN can be treated with either ablation (i.e., cryotherapy, laser vaporization, electrocautery, diathermy, and 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. For adolescents with HIV infection, the ASCCP guidelines for adolescents and young women 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, CIN2,3 not otherwise specified, and histologic HSIL in HIV-infected adolescents and women younger than 25 years **(BIII)**. If compliance is questionable, then it may be preferable to follow the treatment arm of management for CIN 2, CIN2,3, and HSIL **(BIII)**.

Management of invasive cervical, vaginal, and vulvar cancer should follow National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Although complication and failure rates may be higher in women with HIV infection, standard treatment appears safe and efficacious.

Treating VIN, Vulvar Cancer, VAIN, and Vaginal Cancer

Low-grade VIN/VAIN (VIN/VAIN1) can be observed or managed as for 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 imiquimod therapy. Treatment options for VAIN include topical 5-fluorouracil (5-FU), laser vaporization with CO2 laser, and excisional procedures with electrosurgical loops or a scalpel excision.

Management of vulvar and vaginal cancer must be individualized in consultation with a specialist, following NCCN guidelines (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp).

Treating AIN and Anal Cancer

For AIN2-3, no adequate RCTs have been reported, and data are insufficient to recommend a specific treatment approach. A RCT was recently initiated to determine if treatment of AIN2-3 reduces the incidence of anal cancer in patients with HIV infection. Definitive guidelines on anal screening and treatment in patients with HIV infection will likely follow from the results of this study. Until then, treatment decisions are based on assessment of the size and location of the lesion and its histologic grade. **All treatment modalities are associated with high rates of recurrence.** Topical treatment options including 5-FU, cidofovir, intra-anal imiquimod, and provider-applied TCA have demonstrated moderate efficacy for treatment of intra-anal AIN. Ablative therapies including infrared coagulation, cryotherapy, laser therapy, and electrocautery/hyfrecator are well tolerated. Repeated ablative treatment or a combination of treatment methods are often required for long-term clearance of AIN2-3.

In a retrospective analysis, infrared coagulation was proven to have moderate efficacy in treatment of AIN-2 or 3 in patients who are HIV seropositive,[106] and it was safe and well tolerated in this population in a prospective AIDS Malignancy Consortium study. No indications exist for systemic chemotherapy or radiation therapy for patients with AIN in the absence of evidence of invasive cancer.

The most commonly used treatment for anal cancer is combination radiation and chemotherapy.

Treating HPV-Associated Disease at Other Sites, Including the Penis and the Mouth

Penile and some oropharyngeal cancers are associated with HPV infection. Treatment options do not differ for men and women with and without HIV infection. 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 ART

Given the strong evidence that early ART initiation is clinically beneficial in reducing risk of AIDS and opportunistic infections (OIs), there is no reason to consider HPV-related oral, anal, or genital disease when deciding whether or when to initiate ART.

Monitoring Response to Therapy and Adverse Events (Including IRIS)

Monitoring by physical examination is required during and after treatment of genital warts to detect toxicity, persistence, or recurrence, all of which are common with each of the treatments.

Because recurrences of CIN and cervical cancer after conventional therapy are more common in patients who are HIV seropositive, they should be followed after treatment with frequent cytologic screening and colposcopic examination, according to published guidelines **(AII)** (see Preventing Disease and Treating 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.

There is no consensus on the treatment of biopsy-proven recurrent VIN and surgical excision can be considered.

Preventing Recurrence

Monitoring after therapy for cervical disease should follow ASCCP guidelines. In one study of women with HIV infection 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 living with HIV infection who have genital warts or anogenital HPV-related neoplasia are best managed by an interdisciplinary team of specialists (such as an obstetrician/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. There have been several case series describing 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 early-onset recurrent respiratory papillomatosis in children. This condition is rare but is more common among children of women who have genital warts at delivery. Cesarean delivery is not known to prevent this condition in infants and children.[107] 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 non-pregnant 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 can be managed the same as non-pregnant women, although deferral of colposcopy until at least 6 weeks postpartum is recommended **(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 cytology and colposcopy is recommended after 6 weeks postpartum. Women with CIN can deliver vaginally. An analysis of the Danish Medical Birth Register and National Patient Register found that among 1665 exposed pregnancies, quadrivalent HPV vaccination was not associated with a significantly increased risk of adverse pregnancy outcome.[108]

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.[109]

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 Infection

Women with HIV Infection Aged <30 Years:

- If younger than 21 years, known to have HIV infection or newly diagnosed HIV infection, and sexually active, screen within 1 year of onset of sexual activity regardless of mode of HIV infection.
- Women with HIV infection 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)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**
- If results of 3 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 Infection Aged ≥30 Years

Pap Testing Only:

- Pap test should be done at baseline and every 12 months **(BII)**.
- Some experts recommend a Pap test at 6 months after the baseline test **(CIII)**.
- If results of 3 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 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 test with Pap test and HPV co-testing should be performed 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 HPV-16 or HPV-18, colposcopy is recommended
  - If negative for HPV-16 and HPV-18, 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 HPV 16 or HPV 16/18 Specified in Co-Testing:

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

Recommendations for Preventing Human Papillomavirus Infections

Preventing First Episode of HPV Infection

Indications for HPV Vaccination:

- HIV-infected; aged 13 to 26 years **(AIII)**

Note: Please refer to Pediatric OI Guidelines for vaccination of boys and girls younger than age 13 years.

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 **(AIII)**

- For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give additional full series of vaccination with recombinant 9-valent vaccine, but there are no data to define who might benefit or how cost effective this approach might be **(CIII)**

Treating Condyloma Acuminatum (Genital Warts)

Note: Patients with HIV infection 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 maybe required for refractory or recurrent lesions. Intra-anal, vaginal, or cervical warts should be 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 3 non-consecutive 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*
- Sinecatechins 15% ointment: Apply to area 3 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 to Acronyms: BCA = bichloroacetic acid; HPV = human papillomavirus; IM = intramuscular; OI = opportunistic infection; TCA = trichloroacetic acid

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Leishmaniasis (Last updated February 6, 2017; last reviewed March 13, 2019)

NOTE: Update in Progress

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 March 13, 2019)

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
  - The CDC malaria website: https://www.cdc.gov/malaria
  - The CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours.

Key to Acronyms: CDC = the Centers for Disease Control and Prevention; TMP-SMX = Trimethoprim-sulfamethoxazole

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Microsporidiosis (Last updated May 7, 2013; last reviewed March 13, 2019)

NOTE: Update in Progress

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. 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*, *Microsporidium* sp, *Nosema ocularum*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, and *Anncaliia* (syns *Brachiola/Nosema*) *algerae*.[1-7] In the pre-antiretroviral (ART) era, reported prevalence rates of microsporidiosis varied between 2% and 70% among HIV-infected patients with diarrhea, depending on the diagnostic techniques employed and the patient population described.[2-4,7] The incidence of microsporidiosis has declined with the widespread use of effective ART, but continues to occur among HIV-infected patients who are unable to obtain ART or to remain on it.[8] Microsporidiosis is increasingly recognized among HIV-uninfected persons, 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/μL.[2-4,7]

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.[2-4,7]

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* 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.[6]

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.[6] 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.[6,9] Assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

Patients with AIDS who have CD4 counts <200 cells/μL 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)**.[10] The precautions described in the section on cryptosporidiosis also are applicable to microsporidiosis (see also Appendix: Food and Water-Related Exposures).

Preventing Disease

Because chronic microsporidiosis occurs primarily in patients with advanced immunodeficiency, appropriate initiation of combination 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,[11,12] and administration of ART with immune restoration (an increase in CD4 count to >100 cells/μL) is associated with resolution of symptoms of enteric microsporidiosis, including that caused by *E. bieneusi*.[11-14] 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)**,[15,16] or to its synthetic analog, TNP-470 **(BIII)**.[17] However, fumagillin and TNP-470 are not available for systemic use in the United States. One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART;[18] however, the effect appeared to be minimal among patients with low CD4 cell counts. Therefore, this drug **cannot be recommended** with confidence **(CIII)**.

Albendazole, a benzimidazole that binds to β-tubulin, has activity against many species of microsporidia, but it is not effective against *Enterocytozoon* infections or *V. corneae*. The tubulin genes of both *E. bieneusi*[19] and *V corneae*[20] 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)**.[21-23]

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 HIV-infected patients with persistent diarrhea and *E. bieneusi* infection **(CIII)**;[24] 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)**.[21] Topical fumagillin is the only formulation available for treatment 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 also 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.[11,12]

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 an HIV-infected patient treated with ART in the setting of *E. bieneusi* infection;[25] 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/μL blood), treatment can probably be discontinued after ocular infection resolves **(CIII)**, but it should be continued indefinitely if CD4 counts fall below 200 cells/μL 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 levels >200 cells/μL for 6 months after ART **(BIII)**.[12]

Special Considerations During Pregnancy

Rehydration and initiation of ART should be the mainstays of initial treatment of cryptosporidiosis during pregnancy, as in nonpregnant women **(AII)**. In rats and rabbits, albendazole is embryotoxic and teratogenic at exposure levels less than that 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.[26]

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 exposed pregnancies.[27] Case reports exist of birth defects in infants exposed to itraconazole, but prospective cohort studies of

more than 300 women with first-trimester exposure did not show an increased risk of malformation.[28,29] 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.[30] 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 Gastrointestinal 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 have some effectiveness, but neither agent is available in the United States.
- Nitazoxanide may have some effect, but the efficacy is minimal in patients with low CD4 cell count, and cannot be recommended **(CIII)**.

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

- Albendazole 400 mg PO BID **(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 + albendazole 400 mg PO BID **(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 QID (investigational use only in United States) **(BII)**, plus albendazole 400 mg PO BID 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/uL for at least 6 months in response to ART **(BIII)**

Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; PO = orally, QID = four times daily

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

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 **is not recommended** for adults and adolescents who immediately initiate ART **(AII)**.

Indications for Initiating Primary Prophylaxis:

- Not on fully suppressive ART, *and*
- CD4 count <50 cells/mm^3 after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some people with HIV) **(AI)**

Preferred Therapy:

- Azithromycin 1200 mg PO once weekly **(AI)**, *or*
- Clarithromycin 500 mg PO BID **(AI)**, *or*
- Azithromycin 600 mg PO twice weekly **(BIII)**

Alternative Therapy:

- Rifabutin 300 mg PO daily **(BI)** (dose adjustment may be necessary based on drug-drug interactions, please refer to Table 5 for dosing recommendation when used with ARV drugs).
- **Note:** Active TB should be ruled out before starting rifabutin.

Indication for Discontinuing Primary Prophylaxis:

- Initiation of effective ART **(AI)**

Indication for Restarting Primary Prophylaxis:

- CD4 count <50 cells/mm^3 (only if not on fully suppressive ART) **(AIII)**

Treating Disseminated MAC Disease

Preferred Therapy:

- At least 2 drugs as initial therapy to prevent or delay emergence of resistance **(AI)**
  - Clarithromycin 500 mg PO twice daily **(AI)** plus ethambutol 15 mg/kg PO daily **(AI)**, *or*
  - Azithromycin 500–600 mg **(AII)** plus ethambutol 15 mg/kg PO daily **(AI)** when drug interactions or intolerance precludes the use of clarithromycin
  - **Note:** Testing of susceptibility to clarithromycin or azithromycin is recommended.

Alternative Therapy:

- Some experts would recommend addition of a third or fourth drug for people with HIV with high mycobacterial loads (i.e., >2 log CFU/mL of blood), or in the absence of effective ART **(CIII)**.

The Third or Fourth Drug Options May Include:

- Rifabutin 300 mg PO daily **(CI)** (dose adjustment may be necessary based on drug-drug interactions), *or*
- A fluoroquinolone **(CIII)** (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), *or*
- An injectable aminoglycoside **(CIII)** (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 gm IV or IM daily)

Chronic Maintenance Therapy (Secondary Prophylaxis):

- Same as treatment regimens

*Criteria for Discontinuing Chronic Maintenance Therapy **(AII)**:*

- Completed **at least** 12 months therapy, *and*
- No signs and symptoms of MAC disease, *and*
- Have sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART

Indication for Restarting Secondary Prophylaxis:

- CD4 <100 cells/mm^3 **(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 22, 2017; last reviewed March 13, 2019)

NOTE: Update in Progress

Epidemiology

Despite being preventable and curable, tuberculosis (TB) is the leading cause of death from infectious disease globally, with nearly 10 million people developing TB and 1.5 million people dying from TB in 2014.[1] TB is the leading cause of morbidity and mortality among people living with HIV worldwide, with 1.2 million new HIV-infected persons reported with TB and 390,000 deaths in 2014.

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.

It is estimated that the annual risk of reactivation with TB disease among persons with untreated HIV infection is 3 to 16% per year, which approximates the lifetime risk among HIV-negative persons with LTBI (~5%).[2] TB incidence doubles in the first year following HIV infection[3] and can occur at any CD4 cell count, though the risk increases with progressive immunodeficiency.[3,4]

Antiretroviral therapy (ART) results in a prompt and marked decrease in the incidence of TB disease, and this effect has been documented in settings with low case rates, such as the United States,[5] and in settings with very high case rates.[6,7] 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.[8]

Rates of TB in the United States are declining, with 3.0 new cases of TB disease per 100,000 population (a total of 9,412 cases) reported in 2014, a decline of 2.2% from 2013.[9] The prevalence of LTBI in the general population of the United States is 4.7%,[10] 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 in the general population,[11] in part due to the widespread use of ART. In 2014, there were 506 reported cases of HIV/TB co-infection in the United States (6.3% of individuals with TB who were tested for HIV).[12] Like TB disease in the general population of the United States, HIV-related TB is increasingly a disease of persons born outside of the United States.[11] Notably, TB disease has not decreased significantly in recent years among foreign-born persons with HIV disease in the United States.[11,13]

Despite these favorable epidemiological trends, TB remains an important opportunistic illness in the United States. Unlike most opportunistic infections, TB is transmissible, particularly to other 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.[10] Therefore, patients with HIV infection who travel 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 return. While there are risks for TB exposure in some healthcare and correctional settings in the United States, there is no need for precautions for persons with HIV infection beyond those taken for all persons in those settings.

Preventing Disease—Diagnosis and Treatment of Latent TB Infection

The estimated annual risk for active TB among HIV-infected persons with LTBI is 3 to 12 times the risk in the general population.[14,15] Furthermore, development of HIV-related TB increases viral load,16 and the risk of HIV disease progression[16] and death,[17] compared to CD4-matched HIV-seropositive controls without TB. Risk of progression from LTBI to TB disease in HIV-infected persons is reduced both by antiretroviral treatment and by treatment of LTBI. Treatment of LTBI (as defined by a positive tuberculin skin test [TST]) decreases the risk of TB disease by 62% and the risk of death by 26% among persons with HIV infection.[18-20] Isoniazid preventive therapy and ART independently decrease the risk of death and severe HIV-related illness.[21] Among persons receiving ART, isoniazid preventive therapy further decreased the risk of TB by 37% when compared to placebo.[22] In Brazil, a country with medium TB burden, the protective effect of isoniazid against TB in HIV-infected persons with a positive TST lasted throughout 7 years of follow-up.[23] Therefore, prevention of TB disease by screening and appropriate treatment for LTBI are key components of HIV care.

Diagnosis of LTBI

All persons should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure **(AII)**. Among HIV-infected persons, the benefit of isoniazid preventive therapy has been seen primarily in persons with evidence of LTBI (e.g., a positive TST).[24,25] However, in one study in South Africa, a setting with a high TB burden, isoniazid decreased the TB risk among all persons receiving ART regardless of TST or interferon gamma release assay result.[22] Persons with negative diagnostic tests for LTBI, advanced HIV infection (CD4 cell count <200 cells/μL), 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/μL to ensure the initial test was a true negative result.[26,27] Annual testing for LTBI using TST is recommended for HIV-infected persons who are at high risk for repeated or ongoing exposure to persons with active TB **(AIII)**.

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48 to 72 hours in HIV-infected persons) in persons with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among persons with HIV infection, 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.[28] These limitations of the TST have led to interest in interferon-gamma release assays (IGRA) for detection of LTBI.

Current evidence suggests that, compared to the TST, IGRAs have higher specificity (92%–97% vs. 56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*,[29] and less cross-reactivity with BCG vaccination and nontuberculous mycobacteria.[30,31] Three IGRAs are FDA-approved and available in the United States. Progressive immunodeficiency is associated with decreased sensitivity of IGRAs, though the effect of immunodeficiency on the sensitivity of IGRAs may be less than its effect on the sensitivity of the TST.[32] Like the TST, the reproducibility of positive results of IGRAs is limited.[33] Among 46 HIV-infected patients having 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.[34]

Among persons with HIV infection, the correlation between the TST and IGRAs is poor to moderate.[35,36] In prospective studies, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease;[37,38] 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.[39,40] For all of its limitations, a positive TST result remains strongly predictive of decreased risk of TB progression in response to isoniazid preventive therapy among persons with HIV infection.[18] Whether the same is true of the IGRAs remains to be demonstrated.

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.[41-43] The use of an IGRA for TB screening may increase the proportion of patients who complete TB screening.

There have been no definitive comparisons of the TST and IGRAs for screening persons with HIV infection in low-burden settings like the United States. Both the TST and the approved IGRAs are appropriate for TB screening among HIV-infected persons in the United States.[44] Some experts have suggested using both the TST and an IGRA to screen for LTBI, but the predictive value of this approach is not clear, and its adoption would be more expensive and more difficult to implement. The routine use of both TST and IGRAs to screen for LTBI **is not recommended** in the United States.[44]

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, HIV-infected persons with TB disease have symptoms (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.[45] 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 this is not cost-effective in screening asymptomatic HIV-infected persons, particularly in the United States where the prevalence of TB is very low. Therefore, symptom screening (asking for cough of *any* duration) coupled with chest radiography is recommended to exclude TB disease in a patient with a positive screening test.

Treatment of LTBI

Once it is established that there is no evidence of TB disease, HIV-infected persons with a positive screening test should receive prophylaxis **(AI)**. Additionally, HIV-infected close contacts of an infectious case of TB should receive prophylaxis, regardless of screening tests for LTBI. HIV-infected persons who have a negative TST and are not recent contacts of a case of infectious TB may not benefit from treatment of LTBI **(AI)**,[24,46-48] though at least one study from a high-burden setting in South Africa showed isoniazid decreased TB risk regardless of TST or IGRA result.[22]

Preferred and Alternative Drugs for LTBI Treatment, Including Duration of Therapy

Isoniazid prophylaxis for 9 months remains the preferred therapy, with proven efficacy, good tolerability, and infrequent severe toxicity **(AII)**. Although peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or various antiretroviral 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 **(BII)**.[22] 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.[49] Shorter regimens are more likely to be completed.[49-52] Alternative regimens for chemoprophylaxis are shown in Table 1. Rifapentine plus isoniazid given by directly observed therapy (DOT) once weekly for 12 weeks is as effective and well-tolerated as 6 to 9 months of daily LTBI treatment with isoniazid, including in persons with HIV infection whose CD4 lymphocyte counts are generally >350 cells/mm^3 and who are not yet on ART.[53-55] 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 is favorable.[56] In a PK study of 12 HIV-infected adults without TB receiving once-weekly 900 mg rifapentine with efavirenz, there was minimal effect on efavirenz exposure.[57] Raltegravir concentrations were modestly increased, not decreased, when it was given with once-weekly rifapentine.[58] Thus, despite the lack of clinical trial outcome data, once-weekly rifapentine/isoniazid can be used with efavirenz or raltegravir without dose adjustment based on available PK data. Increased clinical monitoring is not recommended, but should be based on clinical judgment. When using rifampin-containing regimens, either dose adjustment or substitution of key ART drugs may be needed. The regimen of two months rifampin plus pyrazinamide is not recommended due to the risk of severe and sometimes fatal hepatotoxicity **(AII)**.

LTBI treatment and ART act independently to decrease the risk of TB disease.[19,22,59,60] Therefore, use of both interventions is recommended for those persons with LTBI and an indication for ART **(AI)**.

Monitoring of Response to Treatment of LTBI

Individuals receiving self-administered daily chemoprophylaxis should be seen by the prescribing clinician on a monthly basis to assess adherence and evaluate for possible drug toxicity; generally, a clinician should not prescribe more than one month's supply of a drugs. Although HIV-infected persons may not have a higher risk of hepatitis from isoniazid prophylaxis than HIV-uninfected persons, it is recommended that baseline serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin be measured and repeated if abnormal at baseline.[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.[61] With isoniazid, liver enzymes typically increase in the first 3 months but then, through the process of hepatic adaptation, liver enzymes return to normal despite continued therapy. If the serum aminotransferase level increases 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. Patients should be reminded at each visit about potential adverse effects (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 isoniazid and return to the clinic for an assessment should any of these occur.

The ultimate decision regarding resumption of therapy with the same or a different agent for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease[62] and in consultation with an expert in treating LTBI in persons with HIV infection.

Clinical Manifestations of TB Disease

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.[45] The sensitivity of classic TB symptoms is lower in people on ART.[63] Culture-positive TB disease can be subclinical or oligo-symptomatic.[64] The duration of symptoms is shorter in HIV-infected patients,[65] and in patients who are markedly immune suppressed TB can be a severe systemic disease with high fevers, rapid progression, and sepsis syndrome.[66] After initiation of ART, immune reconstitution can unmask subclinical active TB, resulting in pronounced inflammatory reactions at the sites of infection (see section below on "Unmasking TB-IRIS").

The presentation of active TB disease is influenced by the degree of immunodeficiency.[67,68] In HIV-infected patients with CD4 counts >200 cells/μL, HIV-related TB generally resembles TB among HIV-uninfected persons. The majority of patients have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.[69]

In patients with CD4 counts <200 cells/μL, the chest radiographic findings of pulmonary TB are markedly different with infiltrates showing no predilection for the upper lobes, and cavitation is uncommon.[67,69,70] Normal chest radiographs are not uncommon in patients with respiratory symptoms and positive sputum cultures.[71]

With increasing degrees of immunodeficiency, extrapulmonary or disseminated TB (e.g., lymphadenitis, genitourinary TB, osteal TB, pleuritis, pericarditis, and meningitis), with or without pulmonary involvement, are more common. Clinical manifestations of extrapulmonary TB are not substantially different from those described in HIV-uninfected persons. TB must be considered in disease processes involving any site in the body,[72] but especially those related to central nervous system (CNS) or meningeal symptoms in which early TB treatment is essential to improve outcomes.[73-75]

Diagnosis

Initial diagnostic testing 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, even in the absence of pulmonary symptoms or signs; pulmonary involvement is common at all CD4 counts.[64,76] 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.[77,78] Therefore, sputum smear and culture should be considered 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.

Sputum smear-negative TB is common among persons with HIV infection, particularly those with advanced immunodeficiency and non-cavitary disease.[79] However, the yield of sputum mycobacterial culture is not affected by HIV or the degree of immunodeficiency. If a sensitive broth culture technique is used, the sensitivity of sputum culture is quite high.[80] Smear and culture of three sputum specimens is recommended in that there was a 10% incremental yield for broth culture between the second and third specimens in a recent large study of patients with HIV.[81]

Extrapulmonary and disseminated TB are more common in persons with HIV infection, particularly with advanced immunosuppression.[82,83] 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.[84] 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.[68]

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 compared to sputum but nonetheless 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[68,72] 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 needed in patients with HIV infection 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, these assays are highly predictive of TB among specimens that are AFB smear-positive. Non-tuberculous 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 among 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[85,86] and up to 90% when three NAA tests are performed. Therefore, use of an NAA test is recommended on at least one specimen from all patients with suspected pulmonary TB.[87] NAA tests can also be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than in sputum specimens.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations 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 HIV-infected patients.[88] 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[89] and as an aid in decisions regarding respiratory isolation in 2015.[90] 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 83%–92%) and 98% (95% confidence interval 97%–99%), respectively. The assay is somewhat less sensitive among HIV-infected patients (pooled sensitivity of 80%, 95% confidence interval 67%–88%) than among HIV-uninfected patients (pooled sensitivity of 89%, 95% confidence interval 81%–94%);[91] however, this may be in part attributed to a higher prevalence of smear negative disease in HIV-infected individuals.[92] In some studies, the sensitivity of Xpert MTB/RIF has been related to CD4 cell count, with higher sensitivity among patients with more advanced immunodeficiency.[93]

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.[94] 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%).

Lipoarabinomannan (LAM): LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of TB patients. LAM can be detected using an ELISA or a lateral flow point of care test. The diagnostic utility of LAM is limited by a low sensitivity but has the advantages of being available as a true point of care test that can be performed on urine. LAM has demonstrated the best performance in HIV-infected patients with low CD4 cell counts (<100 cells/mm^3) with a sensitivity of 37 to 56% and specificity of up to 95%.[95-97] In addition, LAM has higher sensitivity in patients with worse prognoses,[98] who are therefore a high priority to identify. Combining LAM with other diagnostic strategies such as Xpert MTB/RIF testing or smear may improve the diagnostic utility.[99,100]

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; 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, 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 up to 11 to 30% of patients with active TB.[44]

Drug susceptibility testing: Drug-susceptibility testing should be performed on the initial isolates for 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.[101] 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.[102] Thus, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on 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. Drug-susceptibility tests (DST) 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. DST 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.

Phenotypic 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,[103] 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 HIV-infected individuals.[102]

NAA testing 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.[104] Commercial NAA tests such as Xpert MTB/RIF identify resistance mutations associated with rifampin and commercially available line probe assays identify genotypic resistance for rifampin and isoniazid.[92,105] Next generation commercial line probe assays such as GenoType MTBDR*sl* identify genotypic resistance to other TB medications, but results should be confirmed with standard culture-based DST.[106] 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 assay. In a 2014 meta-analysis, the sensitivity for detection of rifampin resistance was 95% (95% confidence interval 90%–97%) and specificity was 98% (95% confidence interval 97%–99%).[91] False-positive results for rifampin resistance with the Xpert MTB/RIF assay can occur, although this appears to be less common with the current version of the assay.[107] However, the comparator for most studies—phenotypic drug-susceptibility testing—should not be considered an absolute gold standard.[108,109] 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 *rpoB* gene compared to patients whose isolates had normal *rpoB* gene sequences.[110,111]

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, phenotypic drug susceptibility testing), and additional specimens should be obtained from such patients. Consultation with an expert in the diagnosis and treatment of MDR TB should be strongly considered.

Clinicians who suspect drug-resistant TB in an HIV-infected patient should make every effort to expedite their diagnosis. In the United States, the Centers for Disease Control and Prevention (CDC), Division of TB Elimination, has a Molecular Detection of Drug Resistance (MDDR) service to make rapid molecular testing for first-and second-line TB medications available for persons suspected of having drug-resistant TB (http://www.cdc.gov/tb/topic/laboratory/rapidmoleculartesting/moldstreport.pdf).

Drug resistance should be considered in any patient with:

- known exposure to a drug-resistant TB case
- residence in a setting with high rates of primary drug-resistant TB (e.g., a country or area with high rates of drug-resistant TB in new patients)
- 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

Treatment of Disease

Preferred and Alternative Drugs for Treatment, Including Duration of Therapy

TB among persons with advanced immunodeficiency can be a rapidly progressive and fatal illness if treatment is delayed. Furthermore, such patients often have smear-negative sputum specimens.[80] 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 HIV-infected individuals is the same as for HIV-uninfected persons, 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 once complete DST results are available. 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 assistance in establishing or re-engaging with HIV care, if needed (enhanced DOT).

Drug-susceptible TB should be treated with a 2-month intensive phase of the four drugs listed above. 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 phase have been associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in HIV co-infected persons.[112-117] Therefore, daily therapy (5–7 days per week) given as DOT is recommended during the intensive treatment phase **(AII)**. Regimens that included once- or twice-weekly dosing during the continuation phase of therapy were also associated with increased risks of treatment failure or relapse with acquired rifamycin resistance.[118,119] Therefore, daily (5–7 days per week) dosing is also recommended during the continuation phase of therapy **(AII)**. Although drug-drug interaction studies suggest that thrice-weekly and daily rifampin dosing is associated with similar levels of cytochrome P450 enzyme induction when dosed with raltegravir,[120] whether there is a difference between daily and thrice-weekly dosing during the continuation phase of therapy has not been adequately studied in randomized trials. 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).[115] Although earlier recommendations for TB treatment in HIV-uninfected persons 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 HIV-infected individuals. Every effort should be made to assure that patients receive daily therapy as previously described, allowing up to 28 weeks to complete at least 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 infection 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 co-infection have been good.[1,12] 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.[121] Two trials in high-burden settings showed higher risks of recurrent TB among patients treated with 6 months of therapy, compared to those assigned to 9-[112] or 12-month regimens.[122] However, the applicability of these two trials is uncertain in low-burden settings in which ART is used, such as the United States.

Three randomized clinical trials have evaluated strategies to reduce the duration of anti-TB treatment from 6 to 4 months in persons with drug-susceptible TB by substituting moxifloxacin or gatifloxacin for either ethambutol or isoniazid in the intensive phase of treatment and adding one of these to a 2-month continuation phase.[123-125] A fourth study evaluated the substitution of moxifloxacin for ethambutol and the substitution of rifapentine for rifampin in a 4-month regimen.[126] In each of these trials, despite evidence of more rapid sputum culture conversion, overall 2-month culture conversion rates were not significantly different than with the standard 6-month control regimen, and rates of unfavorable outcomes (as defined by treatment failure or relapse after 18 months of follow-up) were higher. The number of HIV-infected participants in these studies was small, but when analyzed by HIV status the results were similar. These findings reinforce the current recommendation to treat drug-susceptible TB in HIV-infected individuals for at least 6 months **(BII)**. Extension of therapy to 9 months is recommended for those with a positive 2-month sputum culture **(BII)**.

Intensified therapy for CNS TB may be beneficial, but there are limited data to support this. A recent randomized trial that compared 9 months of standard therapy that included rifampicin 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 both HIV-uninfected

and HIV co-infected individuals with tuberculous meningitis.[127] A PK study of 60 participants in Indonesia suggested that rifampicin administered in doses equivalent to 13 mg/kg or higher given intravenously (similar to 26 mg/kg delivered orally) reduced mortality,[128] but this finding requires confirmation in a larger trial. Addition of a fluoroquinolone may improve outcomes in patients with isoniazid-monoresistant tuberculous meningitis.[127]

Adjunctive corticosteroid therapy should be considered in HIV-infected individuals with TB involving the CNS or pericardium **(AI)**.[129] Adjunctive corticosteroid therapy increases survival overall for patients with TB and CNS involvement, although studies were underpowered for detecting a statistically significant survival benefit for those with HIV infection.[75] Adjunctive corticosteroid therapy reduces the incidence of constrictive pericarditis, although in a randomized trial of adjunctive prednisolone compared with placebo administered for 6 weeks in HIV-uninfected and co-infected individuals 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.[129] There have been no trials comparing different doses and treatment durations of adjunctive corticosteroids. Dexamethasone was used in trials of adjunctive corticosteroids for CNS disease (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); prednisone or prednisolone was used in trials of pericardial disease (60 mg/day and taper 10 mg per week; total duration of 6 weeks).[75,129]

Special Considerations with Regard to Starting ART

Optimal management of HIV-related TB requires that both infections be addressed. Although data are conflicting with regard to whether sequential treatment of TB followed by initiation of ART is acceptable for those with CD4 cell counts >220 to 250 cells/mm^3,[130,131] recently published results from large, international, randomized trials of immediate versus delayed initiation of ART indicate that substantial personal health benefits accrue at all CD4 cell counts in persons without active TB. When coupled with the preponderance of data from randomized trials in persons with HIV and active TB, these results support the recommendation that ART should not be withheld until completion of TB treatment **(AI)**.[21,132,133] Co-treatment of HIV and TB is complex because of the adherence demands of multidrug therapy for two infections, drug-drug interactions between the rifamycins and many antiretroviral drugs, overlapping side effect profiles of anti-TB and antiretroviral drugs, and the development of immune reconstitution inflammatory syndrome (IRIS), although the rates of IRIS are higher primarily in those with lower CD4 cell counts. Despite these substantial clinical challenges, co-treatment of HIV-related TB improves survival[130] (particularly for persons with CD4 cell counts <50 cells/μL), decreases the risk of additional opportunistic illnesses,[134] can achieve high rates of viral suppression,[135] may improve TB treatment outcomes,[136] and, despite higher rates of IRIS at low CD4 cell counts, is not associated with higher rates of other treatment-related adverse events.[131]

The SAPIT trial randomized 642 South African adults with CD4 cell counts <500 cells/mm^3 and AFB smear + TB to start ART at TB treatment initiation, after the intensive phase of TB therapy but before TB treatment completion, or after TB treatment completion.[130] The study was stopped early when the mortality of the two integrated treatment arms was 56% lower than the sequential treatment arm, demonstrating that ART should be started before TB completion. Notably, there was a survival benefit across the range of CD4 cell counts among patients enrolled, including within the stratum of baseline CD4 cell 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 the course of TB treatment. In CAMELIA, 661 adults in Cambodia with confirmed pulmonary TB and a median CD4 cell count of 25 cells/mm^3 (IQR, 10, 56) were randomized to receive ART at 2 or 8 weeks after starting TB treatment. The mortality rate was decreased from 13.77 per 100 person-years in the 2-week arm to 8.28 per 100 person-years in the 8-week arm,[137] and viral suppression rates were very high among those who survived (>95%).

The ACTG A5221 STRIDE study randomized 809 patients from North America, South America, Africa, and Asia with confirmed or suspected TB and a median CD4 cell count of 77 cells/mm^3 (IQR, 33,146)

to immediate ART (within 2 weeks) or early ART (8–12 weeks).[138] A new OI or death occurred among 12.9% of patients in the immediate arm and 16.1% in the early arm by week 48 ($P = 0.45$). In patients with screening CD4 lymphocytes <50 cells/mm^3, 15.5% of patients on the immediate arm versus 26.6% on early ART experienced AIDS or death, ($P = 0.02$). Tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) was more common in the immediate ART arm (11%) compared to the early arm (5%), $P = 0.002$. Viral suppression rates were similar between the arms.

The TB-HAART trial included 1,538 HIV-infected patients in South Africa, Uganda, Zambia, and Tanzania who had culture-confirmed pulmonary TB and CD4 cell counts ≥220 cells/mm^3 and who had tolerated 2 weeks of TB treatment. Subjects were randomized to early (after 2 weeks of TB treatment initiation) versus delayed (until 6 months after initiation of TB treatment) ART.[131] The median CD4 cell count overall was 367 cells/mm^3 (IQR 289, 456). The composite primary endpoint of TB treatment failure, recurrence and death within 12 months of starting TB treatment occurred in 8.5% of patients in the early ART group and 9.2% in the delayed group (RR 0.91, 95% CI 0.64-1.30; $P = 0.9$). Mortality, grade 3 and 4 adverse events and IRIS did not differ among the treatment groups. Patients in the early ART group had higher CD4 cell 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 cell 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 2 months after starting TB treatment among 253 patients with HIV-related TB meningitis.[139] This study did not show a survival benefit to early ART initiation. On the contrary, early ART was associated with similar mortality and more frequent and severe adverse events (86%) compared to the deferred ART arm (75%). The overall mortality rates in this study were very high (58%), likely at least in part because the majority of participants had advanced AIDS (median baseline CD4 cell count 41 cells/mm^3); it is unclear if these findings would generalize to other settings. Nonetheless, caution in the timing of ART initiation with specific monitoring for drug-related toxicities is warranted in patients with TB disease affecting the CNS.

In conclusion, ART is recommended in all HIV-infected persons with TB **(AI)**. For ART-naive patients, ART should be started within 2 weeks after TB treatment initiation when the CD4 cell count is <50 cells/mm^3 and, based on the preponderance of data, within 8 weeks of starting anti-TB treatment in those with higher CD4 cell counts **(AI)**. Given the need for the initiation of five to seven new medications in a short time, adherence support should be offered. In patients with TB meningitis and low CD4 cell 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, 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 a number of antiretroviral drugs (Table 3 [TB Drug Dosing] and the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents). 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 antiretroviral agents.

The preferred co-treatment regimen for HIV-related TB disease is rifampin-based TB therapy with an

antiretroviral 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.[140] Data on the magnitude of the change in efavirenz concentrations when co-administered with rifampin are conflicting. Early studies reported a 26% reduction in efavirenz plasma concentrations,[141] but more recent and larger studies in HIV-infected patients with 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.[142-144] Previous recommendations to increase the dose of efavirenz, especially in patients weighing >60 kg, are thus not supported by good 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). Given the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[140,145] the 600 mg daily dose of efavirenz is recommended **(BII)**.

Rifampin has a more significant effect on the concentration of nevirapine. Earlier studies suggested that clinical outcomes were reasonably good among patients on a co-treatment regimen of rifampin-based TB treatment with an antiretroviral regimen of nevirapine plus two nucleoside analogues when nevirapine once-daily lead-in dosing was avoided.[140,146-148] However, more recent data and a meta-analysis indicate that 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 in patients on TB treatment.[149-151] Nevirapine should generally be avoided unless there are no other options **(AI)**. For patients unable to take efavirenz due to intolerance, nevirapine-based ART is a reasonable alternative, but the lead-in dose of nevirapine should be omitted for patients who are established on rifampin.[140]

Alternatives to efavirenz-based antiretroviral treatment for HIV/TB co-infected patients include regimens with integrase inhibitors or protease inhibitors (PIs). One preferred alternative co-treatment regimen is the combination of raltegravir-based antiretroviral treatment, using 400 or 800 mg twice daily, with standard rifampin dosing **(BI)**.[152] Another alternative co-treatment regimen is rifabutin-based TB therapy with an antiretroviral 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 co-infection taking ART, in general, rifabutin is thought to be a reasonable substitute for rifampin for treatment of TB.[153,154] Although the dramatic effects of rifampin on serum concentrations of lopinavir may be overcome by doubling the dose of lopinavir/ritonavir,[155,156] the safety of this strategy has yet to be firmly established. High rates of hepatotoxicity were reported when adjusted ritonavir-boosted PIs were given with rifampin to healthy volunteers.[157-159] In patients with HIV and TB co-infection, double doses of lopinavir/ritonavir are reasonably well tolerated in those on rifampicin-based TB treatment, but the strategy of increasing ritonavir dosing to 400 mg twice daily leads to high rates of hepatotoxicity.[156,160,161] Thus, a strategy of first increasing the dose 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 stable on full dose).

Use of rifabutin with boosted PI is thus preferred to use of rifampin with double-dose PI in settings where rifabutin is readily available. Rifabutin has little effect on ritonavir-boosted lopinavir[162] or atazanavir,[163] and its co-administration results in moderate increases in darunavir[164] and fosamprenavir concentrations.[165] However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal metabolites, desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased to avoid dose-related toxicity, such as uveitis and neutropenia.[166] In studies of HIV-infected people, rifabutin exposures were significantly lower when rifabutin was dosed 150 mg thrice-weekly with lopinavir/ritonavir compared with rifabutin concentrations when given 300 mg daily in the absence of a protease inhibitor, but concentrations of the active desacetyl metabolite were high.[167,168] Among individuals co-infected with HIV and TB, there have been case reports of acquired rifamycin resistance with 150 mg thrice-weekly doses of rifabutin in the presence of a boosted PI-based antiretroviral regimen.[169,170] A recent study conducted in South Africa in 16 HIV-infected patients on a lopinavir/ritonavir-based ART regimen demonstrated that rifabutin administered in 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).[168] A randomized clinical trial evaluating rifabutin PK and TB and ART outcomes using this dose with lopinavir/ritonavir-based ART is in progress. Based on available PK data, it is recommended that rifabutin should be dosed 150 mg daily (at least during the first 2 months of TB treatment) 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.

Raltegravir concentrations are significantly decreased when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[171] However, it is unclear whether or not an increase in dose is needed. In a Phase 2 randomized trial in HIV-infected people with TB, virologic responses appeared to be similar in non-comparative analyses of the raltegravir 400 and 800 mg twice daily arms.[152] Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without dose adjustment of either drug.[172] Dolutegravir may be another reasonable treatment option. A pharmacokinetic 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.[173] Dolutegravir has not yet been studied in a significant number of HIV-infected individuals with TB. Due to the potential for significant drug interactions as detailed above, the following drugs **should not be used** with rifampin: rilpivirine, etravirine, and elvitegravir co-formulated with cobicistat **(AIII)**. Their use with rifabutin has not been evaluated. Tenofovir alafenamide **should not be used** with any of the rifamycins.

The breadth and magnitude of drug-drug interactions between the rifamycins and many antiretroviral 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 antiretroviral drugs should be managed, not avoided. Rifamycins remain the most potent drug class for TB treatment, and regimens that included just 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among patients with HIV-related TB.[174,175] If a rifamycin cannot be used, TB treatment duration must be extended substantially, as there is currently no drug substitute with the curative power of rifampin. 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 to be 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). Patients with susceptible TB typically convert sputum cultures to negative by 2 months of first-line TB therapy, although patients with advanced disease (i.e., cavitary TB disease) may take longer to convert sputum cultures to negative.[176] Patients who have not had sputum culture conversion at or after 4 months of therapy have failed treatment and should have sputum sent for resistance testing.

Management of 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 his/her cultures have not converted. The initial culture results and drug-resistance tests, treatment regimen, and adherence should also be reviewed. Samples from all available sites (e.g., sputum, blood, urine, etc.) should be taken

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, empiric TB treatment should be broadened using second-line TB drugs, in consultation with an expert in the field **(BIII)**.

Adverse Drug Reactions in TB Patients on ART

HIV-infected patients not on ART are more likely to experience adverse events thought to be drug-related during the course of anti-TB therapy than HIV-uninfected patients.[177,178] Many adverse drug reactions are shared between antiretrovirals and anti-TB therapy, including the potentially life-threatening drug-induced liver injury (DILI) and cutaneous adverse drug reactions (CADRs). Retrospective observational studies had reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy,[177] but two recent randomized controlled trials of ART commencement during or after anti-TB therapy reported similar rates of adverse events during anti-TB therapy with and without ART.[130,131] Therefore, there does not seem to be significant additive toxicity when ART is given together with anti-TB therapy. 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 cotrimoxazole is very difficult.

Because alternative drugs are less efficacious and have more toxicities than first-line anti-TB drugs, the first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently without strong evidence that the specific anti-TB drug was the cause of the reaction. In such situations, decisions regarding re-challenge 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 infection.

DILI can be caused by isoniazid, rifamycins, pyrazinamide, many antiretroviral drugs, and cotrimoxazole. Anti-TB DILI is defined as an ALT elevation to ≥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,[62,179] but many of these patients only have transient, mild elevations of ALT.[62] If these criteria 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 (ethambutol, an aminoglycoside, and moxifloxacin or levofloxacin[180]) as a "bridging regimen" until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed **(BIII)**. A re-challenge with the hepatotoxic first-line anti-TB medications can be started by adding them one at a time at intervals of 7 days to the "bridging regimen" after the ALT level returns to <2.5 times the ULN (or to near baseline for patients with pre-existing abnormalities) with frequent monitoring of ALT. Re-challenge was successful in almost 90% of HIV-uninfected patients in one randomized controlled trial of different re-challenge regimens.[180] Because the rifamycins are a critical part of the TB regimen, they should be restarted first. Re-challenge with pyrazinamide is controversial, because some studies have reported high rates of recurrent ALT elevations, but this may be considered in severe forms of TB (e.g., meningitis or disseminated TB).[181] Depending on the outcome of the re-challenge, the anti-TB therapy regimen and duration may need to be altered—expert consultation is advised. After anti-TB drug re-challenge, if appropriate, relevant antiretroviral drugs and cotrimoxazole may be restarted.

CADRs may occur with all of the first-line anti-TB drugs, notably rifampin and isoniazid,[182] many antiretroviral drugs, notably the non-nucleoside reverse transcriptase inhibitors, and cotrimoxazole. If 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 antiretrovirals, 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 antiretroviral drugs and cotrimoxazole may be recommenced.

Management of Drug-Resistant TB

Although drug-resistant TB represents a small fraction of TB cases seen 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. There is a need for clinical trials to determine the optimal management of patients with drug-resistant TB. The most active and effective TB drugs are those used in first-line TB treatment regimens (isoniazid and rifampin, in particular). When resistance develops to these medications, alternative combinations of first- and second-line TB medications must be used, but their optimal use has not been tested using rigorous clinical trials.

Growing evidence demonstrates that there is an increased risk of treatment failure associated with baseline isoniazid monoresistance,[183] particularly in patients with HIV co-infection.[112] Substitution of a fluoroquinolone (levofloxacin or moxifloxacin) for isoniazid is suggested for at least the first 2 months of therapy **(BIII)** and considered during the continuation phase with rifampin and ethambutol as well **(CIII)**, for a total duration of treatment of 9 months **(BII)**.

Resistance to rifampin alone, or to rifampin and other drugs, substantially increases the complexity and duration of treatment. Treatment of these drug-resistant TB cases 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 (ATS/CDC/IDSA 2003).[184] Treatment outcomes for MDR TB are considerably worse than those for drug-susceptible TB—especially in patients with HIV co-infection.[102] Consensus treatment guidelines for MDR TB[184] are based on a review of published observational studies[185] and recommend use of at least five drugs with known or likely activity against the patient's isolate **(BIII)**. In general, such regimens will include a later-generation fluoroquinolone, a second-line injectable agent (i.e., kanamycin, amikacin, or capreomycin), ethionamide, pyrazinamide and at least one other second-line drug, such as cycloserine or para-aminosalicylic acid **(BIII)**. Additional resistance to one or more of these drugs (e.g., extensively drug-resistant [XDR] TB), however, may necessitate use of alternate or third-line agents with uncertain anti-TB activity. Whenever possible, treatment should be individualized to the patient's specific drug-susceptibility testing results or based upon his or her treatment history. An intensive phase of 8 months is then followed by a continuation phase without the injectable agent for an additional 12 to 18 months. Surgery (removal of the TB lesion) should be considered as an adjunctive measure in those with localized disease.[186]

The World Health Organization (WHO) recently 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.[187] The regimen composition is based on combinations evaluated as the Bangladesh regimen,[188] 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. This approach has not been evaluated in randomized clinical trials among HIV-infected persons on ART or in higher resourced settings with consistent access to DST such as the United States. Based on promising observational data, an additional clinical trial is examining the efficacy of an intensive, shortened, 9-month treatment regimen for MDR TB (NCT02409290) using currently available medications, but at present there are insufficient data to support this approach in HIV-infected individuals.

Current 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 educated regarding 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, and audiometry. Sputum cultures should be sent monthly, even after culture-conversion, so that any relapse and amplified resistance are detected early.

The treatment of MDR TB is evolving as new drugs for TB treatment are introduced. Bedaquiline, a novel drug in an entirely new class, was recently approved in the United States for treatment of MDR TB. However, late, unexplained higher mortality among the relatively small number of patients who received bedaquiline in randomized trials[189] suggests that this drug should be used with caution and only in patients without other MDR TB treatment options while awaiting additional studies.[190] Although clinical experience with bedaquiline is still very limited, early studies have revealed several important drug-drug interactions with common antiretroviral agents. Specifically, efavirenz decreases bedaquiline levels and should not be used concurrently.[173] Lopinavir/ritonavir, by contrast, increases bedaquiline plasma concentrations approximately 2-fold when given at steady-state, but the clinical significance of this increase is not yet known.[191,192]

Delamanid, an additional new agent with a mechanism of action distinct from bedaquiline's, has also shown promise in early phase clinical trials.[193] Delamanid has been approved in Europe and Japan but is not yet available in the United States. A Phase 3 trial is currently underway (NCT01424670).

Given these complexities, treatment of MDR TB should involve an expert with experience in treating drug-resistant TB cases (one option is to contact a CDC Regional Training and Medical Consultation Center at http://www.cdc.gov/tb/education/rtmc/default.htm, if a local expert is not available).

Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome

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.[194-196] 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.[197]

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 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,[195,198] 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.[195,199,200] 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.[201,202] A liver biopsy reveals a granulomatous hepatitis.[203] 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%–54%). A recent meta-analysis provided a pooled incidence of 18%, with death attributable to TB-IRIS occurring in 2% of TB-IRIS cases.[204] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[205-210] The syndrome lasts for 2 to 3 months on average,[199,211] but some cases may have symptoms for months and rarely local manifestations may persist or recur over a year after onset.[197,211,212] Such prolonged TB-IRIS cases usually manifest with suppurative lymphadenitis and abscess formation.

The most consistently identified risk factors for paradoxical TB-IRIS are a low CD4 cell count at start of ART, especially those patients with a CD4 cell count <100 cells/mm^3,[208,213] high HIV viral load prior to

ART,[214,215] disseminated or extrapulmonary TB,[199,207,209,213] and a short interval between starting TB treatment and ART, particularly if ART is started within the first 1 to 2 months of TB treatment.[199,206,208] Even though early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in those with CD4 cell counts <50 cells/μL, given that this reduces risk of AIDS progression and death.[204]

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 prior to ART, deterioration with inflammatory features of TB soon after starting ART, demonstration of a response to ART (CD4 rise and/or HIV viral load reduction) and, very importantly, investigations to exclude alternative causes for deterioration, particularly undetected TB drug resistance.[202]

Management of Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many patients require symptomatic therapy (analgesia, anti-emetics), and if symptoms are significant, anti-inflammatory therapy should be considered. 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.[216] Those 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,[216] observational data,[200] and clinical trials of patients treated with corticosteroids at the time of TB meningitis presentation where corticosteroids reduced mortality[75] 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). Among all patients developing TB-IRIS, 4 weeks of prednisone treatment was insufficient in a subset, and they may require more gradual tapering of steroids over a few months **(BIII)**.[216] Tapering of corticosteroids should be guided by repeated clinical assessment of symptoms **(BIII)**. Corticosteroids should be avoided in patients with Kaposi's sarcoma, as life-threatening exacerbations can occur,[217] and also where the diagnosis of paradoxical TB-IRIS is not certain. There are case reports of patients with steroid-refractory and prolonged IRIS responding to TNF-blockers or thalidomide.[218-220]

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 provide symptom relief **(CIII)**. Repeated aspirations may be required as abscesses and effusions often re-accumulate.[199]

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in patients who have unrecognized TB at the start of ART (because it is oligo-symptomatic or because the diagnosis has been missed). These patients may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[197] 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.[197,216,221-223] Focal inflammatory manifestations such as abscesses and lymphadenitis may also develop.[224] The treatment should be standard TB treatment and corticosteroids, if the manifestations are life-threatening, although there is no clinical trial evidence to support steroid use **(BIII)**.

Prevention of Recurrent TB

The risk of recurrent TB among patients with HIV co-infection appears to be somewhat higher than in HIV-uninfected patients treated with the same TB treatment regimen in the same setting.[225] 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.[226,227] In settings with low rates of TB (such as the United States), recurrent TB due to re-infection is uncommon, even among HIV-infected patients.[228]

Several interventions have been suggested to decrease the risk of recurrent TB among patients with HIV co-infection: longer TB treatment regimens, more frequent dosing of TB therapy, 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,[229,230] 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 its beneficial effects on the risk of initially developing TB disease, it is very likely that ART decreases the risk of re-infection with TB disease.

Special Considerations During Pregnancy

HIV-infected pregnant women 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 should be tested during pregnancy **(AIII)**. The frequency of anergy is not increased during pregnancy, and routine anergy testing for HIV-infected pregnant women is not recommended.[231-234] There are several studies examining the performance of the IGRAs for diagnosis of LTBI in pregnant women. In a study in HIV-infected pregnant women 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/μL, a positive IGRA result was associated with a 5-fold increased risk of maternal mortality or active TB and a 3-fold increased risk of either active TB or mortality in infants.[235] Antenatal IGRA testing has also been demonstrated to correlate with postpartum IGRA test positivity (i.e., TB infection) in HIV-infected women.[236] In women without HIV infection, the test appears to perform well but cost issues for routine screening are an area of debate.[237] If LTBI is diagnosed during pregnancy and active TB has been ruled out, preventive treatment should be considered during pregnancy **(BIII)**. The potential risk of isoniazid toxicity must be weighed against the consequences of active TB developing during pregnancy and postpartum. Studies in HIV/TB co-infected individuals who are not receiving ART have found a high risk of progression from LTBI to active TB (10% per year) and there is a high risk of maternal and infant mortality in HIV-infected pregnant women with active TB.[238,239] However, the risk of progression from LTBI to active TB in individuals on ART is significantly decreased.[240] Given that HIV-infected pregnant women should be receiving ART for prevention of mother-to-child transmission, the risks and benefits of isoniazid therapy should be discussed. The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy and frequent monitoring is needed for women receiving therapy.[241] Pregnant women receiving isoniazid should receive daily pyridoxine supplementation as they are at risk of isoniazid-associated peripheral neuropathy.[242]

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 treatment is not begun until late in pregnancy.[231-234,243-246] Congenital TB infection of the infant has been reported, although it appears relatively uncommon.[247] However, in one study of 107 women with active TB during pregnancy in South Africa, *M. tuberculosis* was detected in 16% of neonates (12 by culture and 4 by smear microscopy) sampled within the first 3 weeks of life.[248]

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

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently in pregnancy and the postpartum period.[249] 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 born after exposure *in utero*.

- Pyrazinamide is not teratogenic in animals. Experience is limited with use in human pregnancy. Although WHO and the International Union Against Tuberculosis and Lung Diseases[250,251] have made recommendations for the routine use of pyrazinamide in pregnant women, it has not been recommended for general use during pregnancy in the United States because data characterizing its effects in this setting are limited.[252] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy should be 9 months **(CIII)**. The decision regarding whether to include pyrazinamide for treatment should be made after consultation among obstetricians, TB specialists, and patients, taking into account gestational age and likely susceptibility pattern of the infecting strain.

Considering the information above, the preferred first-line treatment for TB in pregnancy is isoniazid, rifampin, and ethambutol.[253] Experience with using the majority of the second-line drugs for TB during pregnancy is limited.[254-257] MDR TB in pregnancy should be managed in consultation with a specialist. 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 *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 musculoskeletal abnormalities.[258,259] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(CIII)**.[260]
- Para-aminosalicylic acid is not teratogenic in rats or rabbits.[252] In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed during the first trimester.[261] No specific pattern of defects and no increase in rate of defects have been detected in subjects 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 mice and rabbits.[262-264] Case reports have documented cases of CNS defects in humans but overall experience is limited with use during human pregnancy.[265] 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

Treating LTBI (to prevent TB disease)

Indications:

- (+) screening test[a] for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB **(AI)**;
- Close contact with a person with infectious TB, regardless of screening test result **(AII)**

Preferred Therapy (Duration of Therapy = 9 Months):

- INH 300 mg PO daily + pyridoxine 25-50 mg PO daily **(AII)** *or*
- INH 900 mg PO twice weekly (by DOT) + pyridoxine 25-50 mg PO daily **(BII)**

Alternative Therapies:

- RIF 600 mg PO daily x 4 months **(BIII)** *or*
- RFB (dose adjusted based on concomitant ART) x 4 months **(BIII)** *or*
- RPT (weight-based, 900 mg max) PO weekly + INH 15 mg/kg weekly (900 mg max) + pyridoxine 50 mg weekly x 12 weeks – in patients receiving an EFV- or RAL-based ART regimen **(BIII)**
  - 32.1–49.9 kg 750 mg
  - ≥50.0 kg 900 mg
- For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts or with public health authorities **(AII)**

Treating Active TB Disease

- After collecting specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in HIV-infected persons with clinical and radiographic presentation suggestive of HIV-related TB **(AIII)**.
- DOT is recommended for all patients requiring treatment for HIV-related TB **(AII)**.
- Please refer to the table below for TB drug dosing recommendations and to the Adult and Adolescent ARV Guidelines for dosing recommendations of ARV drugs when used with RIF or RFB.

For Drug-Sensitive TB

Intensive Phase (2 Months)

- INH + (RIF or RFB) + PZA + EMB **(AI)**; if drug susceptibility report shows sensitivity to INH & RIF, then EMB may be discontinued.

Continuation Phase (For Drug-Susceptible TB)

- INH + (RIF or RFB) daily (5–7 days per week) **(AII)**

Total Duration of Therapy:

- Pulmonary, drug-susceptible TB—6 months **(BII)**
- Pulmonary TB & positive culture at 2 months of TB treatment—9 months **(BII)**
- Extrapulmonary TB w/CNS involvement—9 to 12 months **(BII)**
- Extrapulmonary TB w/bone or joint involvement—6 to 9 months **(BII)**
- Extrapulmonary TB in other sites—6 months **(BII)**

For Drug-Resistant TB

Empiric Therapy for Suspected Resistance to Rifamycin +/- Resistance to Other Drugs:

- INH + (RIF or RFB) + PZA + EMB + (moxifloxacin or levofloxacin) + (an aminoglycoside or capreomycin)
- Therapy should be modified based on drug susceptibility results
- A TB expert should be consulted

Resistant to INH

- (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months (BIII); followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months **(BII)**

Resistant to Rifamycins +/- Other Antimycobacterial Agents:

- Therapy and duration of treatment should be individualized based on drug susceptibility, clinical and microbiological responses, and with close consultation with experienced specialists **(AIII)**.

Other Considerations in TB Management

- Adjunctive corticosteroid improves survival for patients with HIV-related TB involving the CNS and pericardium **(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.
- Prednisone or prednisolone may be used in pericardial disease (e.g., 60 mg PO daily and taper by 10 mg per day weekly; total duration 6 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 there is rifamycin-resistant isolate or the patient has a severe adverse effect that is likely to be due to the rifamycin (please refer to the table below and to the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents for dosing recommendations involving concomitant use of RIF or RFB and different antiretroviral drugs).
- If NVP is to be added to a patient who is receiving RIF, the lead-in dose for NVP should be omitted.
- RFB is a less potent CYP 3A4 inducer than RIF and is preferred in patients receiving HIV PIs **(BIII)**.
- Rifamycins administered once or twice weekly can result in development of resistance in HIV-infected patients and is not recommended for patients with TB disease **(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

- In patients on a RIF-based regimen: prednisone 1.5 mg/kg/day x 2 weeks, then 0.75 mg/kg x 2 weeks
- In patients on a RFB + boosted PI based regimen: prednisone 1.0 mg/kg/day x 2 weeks, then 0.5 mg/kg/day x 2 weeks
- A more gradual tapering schedule over a few months may be necessary in some patients.

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

Key to Abbreviations: ART = antiretroviral therapy; ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; EFV = efavirenz; EMB = ethambutol; INH = isoniazid; LTBI = latent tuberculosis infection; NVP = nevirapine; PI = protease inhibitor; PO = per os (oral); PZA = pyrazinamide; RAL = raltegravir; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; TB = tuberculosis; TIW = thrice weekly; TST = tuberculin skin test; IGRA = interferon-gamma release assays

Dosing Recommendations for Anti-Tuberculosis Drugs for Treatment of Active TB

Drug	Daily
Isoniazid	5 mg/kg (usual dose 300 mg)
Rifampin[a] **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, EVG/COBI, or TAF	10 mg/kg (usual dose 600 mg)
Rifabutin[a]	5 mg/kg (usual dose 300 mg)
without HIV PIs, EFV, RPV	
with HIV PIs	150 mg[b]
with EFV	450–600 mg
with TAF or EVG/COBI containing regimens	not recommended
Pyrazinamide (weight-based dosing)	1000 mg (18.2–25.0 mg/kg)
40–55 kg	
56–75 kg	1500 mg (20.0–26.8 mg/kg)
76-90 kg	2000 mg (22.2–26.3 mg/kg)
>90 kg	2000 mg[c]
Ethambutol	800 mg (14.5–20.0 mg/kg)
40–55 kg	
56–75 kg	1200 mg (16.0–21.4 mg/kg)
76-90 kg	1600 mg (17.8–21.1 mg/kg)
>90 kg	1600 mg[c]

[a] For more detailed guidelines on use of different antiretroviral drugs with rifamycin, clinicians should refer to the Drug Interactions section of the Adult and Adolescent ARV Guidelines

[b] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

[c] Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide

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

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/mm^3 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/mm^3 to ≤250 cells/mm^3 **(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 June 14, 2017)

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 (Formerly Penicilliosis) (Last updated May 7, 2013; last reviewed March 13, 2019)

NOTE: Update in Progress

Epidemiology

Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.[1-3] More recently, indigenous cases of penicilliosis have been seen in several states of India, particularly Manipur, which is a new endemic area for this fungus.[4-6]

Before the era of antiretroviral therapy (ART), penicilliosis was the presenting AIDS-defining illness in 6.8% of HIV-infected patients from the northern provinces of Thailand and less common elsewhere.[7] Most cases of penicilliosis are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm^3.[8] The infection is associated with a high mortality rate if timely treatment with appropriate antifungal drugs is not administered.[9]

No data are available on acquisition and transmission of penicilliosis. However, like histoplasmosis, it is believed to be acquired by inhalation of microconidia from the mycelial phase of the organism. Reactivation of a silent focus of infection that was acquired years earlier can occur when cellular immunity wanes and it is the presumed mechanism for disease occurrence in nonendemic areas. Evidence exists for seasonality in penicilliosis infections; increased cases have been noted during the rainy months.[10,11]

Clinical Manifestations

The common clinical manifestations include fever, anemia, weight loss, and generalized skin papules with central umbilication resembling molluscum contagiosum.[1,5] Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia. Involvement of other organs, such as the central nervous system, bone marrow, lymph node, lung, liver, and intestine, has been reported. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly, and a marked increase in serum alkaline phosphatase levels.[3]

Diagnosis

The definitive diagnosis of penicilliosis is based on isolation of organisms from cultures of blood or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. *P. marneffei* exibits dimorphic growth in culture. At 25°C, the fungus grows as a mold, demonstrating characteristic colonies that include a flat green surface and underlying deep red coloring. At 37°C the fungus grows as white colonies of yeast.[12]

An early presumptive diagnosis can be made several days before the results of fungal cultures are available by microscopic examination of Wright-stained samples of skin scrapings, bone marrow aspirate, or lymph node biopsy specimens. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffei*.[1,5] In some patients, the fungus can be identified by microscopic examination of a Wright's-stained peripheral blood smear.[13]

Preventing Exposure

Available information does not support specific recommendations regarding exposure avoidance. However, patients with advanced HIV disease should avoid visiting endemic areas, and particularly rural areas in those regions **(BIII)**.

Preventing Disease

A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole,

200 mg daily for primary prophylaxis, significantly reduced occurrence of systemic fungal infections (cryptococcosis and penicilliosis) in HIV-infected patients with CD4 counts <200 cells/mm^3.[8] Fluconazole may also be effective prophylaxis.[14] For most patients from the United States, such primary prophylaxis would only be indicated in unusual situations in which those who are highly immunosuppressed have to travel to high-risk areas.

Indication for Primary Prophylaxis

All HIV-infected patients with CD4 counts <100 cells/mm^3 who reside or stay for a long period in northern Thailand, Vietnam, and southern China, and particularly in rural areas, should be administered primary prophylaxis **(BI)**. The preferred drug for prophylaxis is oral itraconazole, 200 mg/day **(BI)**. An alternative drug is oral fluconazole 400 mg once weekly **(BII)**. Primary prophylaxis is not indicated in other geographic areas.[15]

Discontinuation of Primary Prophylaxis

No randomized, controlled study has demonstrated the safety of discontinuation of primary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse in penicilliosis and invasive fungal infections after discontinuation of itraconazole in patients receiving ART who had CD4 counts >100 cells/mm^3.[16] Therefore, primary prophylaxis for penicilliosis can logically be discontinued in AIDS patients who receive combination ART and have CD4 counts >100 cells/mm^3 for ≥6 months but there are no convincing data addressing this issue **(CII)**. Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(BIII)**.

Treating Disease

The recommended treatment is liposomal amphotericin B, 3 to 5 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks **(AII)**, followed by secondary prophylaxis.[17] Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks **(BII)**,[18] followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when taken with or immediately after a meal. Itraconazole oral solution can be taken on an empty stomach.

The alternative drug for primary treatment in the hospital is IV voriconazole, 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day 1, and then 200 mg twice daily for 12 weeks **(BII)**.[19] The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.

Special Considerations with Regard to Starting ART

No studies exist regarding the optimal time to start ART in HIV-infected patients with acute penicilliosis, but anecdotal experience and information from clinical trials on other HIV associated opportunistic infections suggests that in those with active penicilliosis who have CD4 counts ≤50 cells/mm^3, ART should be started as soon as possible after the initiation of antifungal therapy **(BIII)**. In patients with CD4 counts >50 cells/mm^3, it may be prudent to delay initiation of ART until after completion of the first 2 weeks of induction therapy for penicilliosis **(CIII)**.

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

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline reduces the risk of nephrotoxicity during treatment **(BII)**. Infusion-related adverse reactions can be ameliorated by pretreatment with acetaminophen and diphenhydramine.

Because absorption of itraconazole can be erratic and because itraconazole can interact with some antiretroviral drugs, serum itraconazole levels should be obtained in all patients to ensure adequate drug exposure **(AIII)**. The serum concentration should be >1 µg/mL. Itraconazole solution is recommended over the capsule formulation

because of better bioavailability, but this has not been studied specifically in AIDS patients.

Azoles and antiretroviral drugs such as protease ihibitors (PIs) and non-nucleoside reverse transciptase inhibitors (NNRTIs) do interact (see Table 5). Through the CYP3A4 mechanism, itraconazole and voriconazole can increase blood levels and effects of PIs and NNRTIs. On the other hand, NNRTIs can slightly decrease blood levels of itraconazole and voriconazole. Close monitoring should be done when using these drugs together.

The unmasking type of immune reconstitution inflammatory syndrome (IRIS) has been reported in several patients with penicilliosis.[20,21] No paradoxical IRIS responses have been reported when ART is initiated in patients with established penicilliosis. ART should not be withheld because of concern for possible development of IRIS **(AIII)**.

Managing Treatment Failure

Voriconazole has been reported to have good outcomes and can be used in patients whose infections fail to respond to initial therapy with amphotericin B followed by itraconazole **(BII)**.[19]

Preventing Recurrence

When To Start Secondary Prophylaxis

A study showed that more than 50% of patients not treated with ART had relapse of *P. marneffei* within 6 months after discontinuation of antifungal therapy.[18,22] A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients, reduced the relapse rate for *P. marneffei* from 57% to 0% ($P < 0.001$).[22] All patients who successfully complete treatment for penicilliosis should receive secondary prophylaxis (chronic maintenance therapy) with oral itraconazole 200 mg/day **(AI)** and should be started on ART if that was not done during acute disease **(AIII)**.

When To Stop Secondary Prophylaxis

No randomized, controlled study has demonstrated the safety of discontinuation of secondary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse of penicilliosis after discontinuation of itraconazole in patients receiving ART whose CD4 cell counts were >100 cells/mm^3.[16] Therefore, secondary prophylaxis for penicilliosis can be discontinued in AIDS patients who receive combination ART and have CD4 cell counts >100 cells/mm^3 for at least 6 months **(BII)**. Secondary prophylaxis should be reintroduced if the CD4 cell count decreases to <100 cells/mm^3 **(AIII)**

Special Considerations During Pregnancy

Diagnosis and treatment of penicilliosis during pregnancy are similar to those 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 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 has been shown to be teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so the data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole, but experience is very limited. Voriconazole is Food and Drug Administration category D because of 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. No evidence of birth defects has been seen after episodic exposure to single, 150-mg doses of fluconazole. With chronic use of doses ≥400 mg in pregnancy, however, 5 cases of a syndrome of craniosynostosis, characteristic facies, digital synostosis, and limb contractures have been reported (fluconazole embryopathy).[23]

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 cell

Preventing 1st Episode of Penicilliosis (Primary Prophylaxis)

Indication for Primary Prophylaxis:

- Patients with CD4 count <100 cells/mm^3 who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas **(BI)**

Preferred Therapy:

- Itraconazole[a] 200 mg PO once daily **(BI)**

Alternative Therapy:

- Fluconazole 400 mg PO once weekly **(BII)**

Indication for Discontinuing Primary Prophylaxis:

- CD4 count >100 cells/mm^3 for ≥6 months in response to ART **(CII)**

Indication for Restarting Primary Prophylaxis:

- CD4 count decreases to <100 cells/mm^3 **(BIII)**g/mL.

Treating Acute Infection in Severely Ill Patients

Preferred Therapy:

- Liposomal amphotericin B, 3 to 5 mg/kg/day IV for 2 weeks; followed by itraconazole[a] 200 mg PO BID for 10 weeks **(AII)**, followed by chronic maintenance therapy **(AII)**

Alternative Therapy:

- Voriconazole[a] 6 mg/kg IV q12h for 1 day, then 4 mg/kg q12h for at least 3 days, followed by voriconazole[a] 200 mg PO BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy **(BII)**

Treating Mild Disease

Preferred Therapy:

- Itraconazole[a] 200 mg PO BID for 8 weeks **(BII)**, followed by chronic maintenance therapy. **(BII**)

Alternative Therapy:

- Voriconazole[a] 400 mg PO BID for 1 day, then 200 mg BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy. **(BII)**

Chronic Maintenance Therapy (Secondary Prophylaxis)

- Itraconazole[a] 200 mg PO daily **(AI)**

Criteria for Discontinuing Chronic Maintenance Therapy:

- CD4 count >100 cells/mm^3 for ≥6 months in response to ART **(BII)**

Criteria for Restarting Chronic Maintenance Therapy:

- CD4 count <100 cells/mm^3 **(AIII)**, *or*
- If penicilliosis recurs at CD4 count >100 cells/mm^3 **(CIII)**

Other Considerations:

- ART should be administered simultaneously with treatment for penicilliosis to improve outcome. **(CIII)**
- Because of the erratic absorption and potential for drug interactions with ARV therapy, itraconazole concentration should be monitored, and serum concentration should be > 1 mc

[a] Both itraconazole and voriconazole can have significant drug-drug interactions with various ARV drugs, dosage adjustment may be necessary, consider therapeutic drug monitoring to guide therapy. See Table 5 for drug interaction information

Key to Acronyms: CD4 = CD4 T lymphocyte; PO = orally; IV = intravenous; q(n)h = every "n" hours; BID = twice daily; ART = antiretroviral therapy, ARV = antriretroviral

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Toxoplasma gondii Encephalitis (Last updated July 25, 2017; last reviewed March 13, 2019)

NOTE: Update in Progress

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 (Last updated July 8, 2013; last reviewed March 13, 2019)

NOTE: Update in Progress

Epidemiology

More than 95% of adults (aged >20 years) born in the United States have immunity to varicella, the vast majority due to primary VZV infection, known as varicella (or chickenpox). Reactivation of latent VZV results in herpes zoster (or shingles). A person's lifetime risk for herpes zoster is 15% to 20%, with the highest incidence occurring in the elderly and immunocompromised individuals. The incidence of herpes zoster is >15-fold higher for HIV-infected adults than for age-matched controls.[1] Herpes zoster can occur in HIV-infected adults at any CD4 T lymphocyte (CD4) cell count, but frequency of disease is highest with CD4 counts of <200 cells/μL.[2-4] Antiretroviral therapy (ART) has not been shown to reduce the incidence of herpes zoster in adult populations: in fact, rates appear to be higher in the period immediately after initiation of ART. Lower frequency of herpes zoster in pediatric patients treated with ART has been observed, but it is difficult to separate ART effect from the impact of varicella vaccine.[5,6]

Clinical Manifestations

Varicella rash tends to have a central distribution with lesions first appearing on the head, then 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 and by successive crops of new lesions and by the presence of lesions in different stages of development at the same time. New vesicle formation continues for 2 to 4 days, accompanied by pruritus, fever, headache, malaise, and anorexia.[7] Primary varicella can cause substantial morbidity in HIV-seropositive adolescents and adults. Visceral dissemination, especially VZV pneumonitis, is well documented.[7] Because most HIV-infected adults 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%–50% of cases), followed by cranial nerve (20%–25%), cervical (15%–20%), lumbar (15%), and sacral (5%) dermatomes. 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 HIV-infected patients 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%.[3,8] Approximately 10% to 15% of HIV-seropositive patients report post-herpetic neuralgia as a complication following herpes zoster.[3,9]

Most herpes zoster-related complications in HIV-seropositive patients, including disseminated herpes zoster, occur in patients with CD4 counts of <200 cells/μL.[10] The CNS is the primary target organ for herpes zoster dissemination in patients coinfected with HIV. Various VZV-related neurologic syndromes occur in HIV-infected patients, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.

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 in AIDS patients with CD4 counts <100 cells/μL.[11] In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of retinal vasculitis, and multiple discrete peripheral lesions in the outer retinal layer.[12] PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.[13] Both ARN and PORN are associated with high rates of visual loss.

Diagnosis

Varicella and herpes zoster are distinctive in appearance and diagnosis can usually be made clinically. Varicella can also be diagnosed retrospectively by documenting seroconversion. Immunocompromised persons can have atypical presentations and varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); history of varicella or VZV exposure, a rash that began with a dermatomal pattern, and VZV serologic testing to assess prior VZV infection may be helpful. When lesions are atypical or the diagnosis of VZV from other exanthems is uncertain, swabs from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase chain reaction (PCR). Additionally, scabs are very good 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).[14] Routine serologic testing to determine the VZV serologic status of HIV-infected adults is not recommended.

Preventing Exposure

HIV-infected persons who are susceptible to VZV (i.e., persons who have no history of varicella 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 **(AII)**.

If household contacts of HIV-infected persons without evidence of immunity to varicella are themselves without evidence of immunity, then these household contacts should be vaccinated to prevent acquisition of varicella and potential transmission of wild-type VZV to their susceptible HIV-infected contacts **(BIII)**.

Preventing Disease

Long-term prophylaxis with antiviral drugs to prevent varicella is not recommended **(AIII)**. Rather, for HIV-infected persons who are susceptible to VZV, post-exposure prophylaxis following known or suspected VZV exposure is recommended.

Vaccination To Prevent Primary Infection

The live attenuated varicella vaccine has been documented to be safe and immunogenic in HIV-infected children with relatively preserved immune systems (CD4 lymphocyte percentage ≥15%)[15-18] and is recommended for them **(AI)**.[19] Varicella vaccination of HIV-seropositive children also reduces the risk of subsequent herpes zoster.[6,18] No studies have evaluated the vaccine in HIV-infected adolescents or adults, but varicella vaccination (2 doses, administered 3 months apart) may be considered in HIV-seropositive/VZV-seronegative persons ≥8 years old with CD4 counts ≥200 cells/μL **(CIII)**.[20] If 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 HIV-infected patients (CD4 counts <200 cells/μL) is not recommended **(AIII)**. Because of the high prevalence of VZV seropositivity in adults, use of varicella vaccine in this population 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)**.[21] If post-exposure acyclovir has been administered, an interval of at least 3 days is recommended before varicella vaccination **(CIII)**.

Post-Exposure Prophylaxis To Prevent Primary Infection

After close contact with a person who has active varicella or herpes zoster, HIV-infected adolescents and adults who are susceptible to VZV should receive VariZIG as soon as possible, but within 10 days after exposure **(AIII)**.[22] Risk for VZV transmission is higher following exposure to a person with varicella than after exposure to localized herpes zoster. In the United States, VariZIG can be obtained only under a treatment investigational new drugs application (IND) by contacting FFF Enterprises (Temecula, CA), at (800) 843-7477. The duration of protection is at least 3 weeks. Patients receiving monthly high-dose

intravenous immune globulin (IVIG >400 mg/kg) are likely to be protected and probably do not require VariZIG if the last dose of IVIG was administered <3 weeks before exposure. Short-term post-exposure administration of acyclovir or valacyclovir beginning 7 to 10 days after exposure[23] may be considered for preventing varicella among susceptible HIV-infected adolescents or adults but this intervention has not been studied in these populations **(BIII)**. 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 adolescents and adults has also not been established.

Treating Disease

Varicella

No controlled prospective studies of antiviral therapy for varicella in HIV-infected adults have been reported. For uncomplicated varicella, the preferred treatment options are valacyclovir (1 g PO 3 times daily), or famciclovir (500 mg PO 3 times daily) for 5 to 7 days **(AII)**. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg 5 times daily) can be an alternative **(BII)**. Intravenous (IV) acyclovir for 7 to 10 days is the recommended initial treatment for HIV-infected patients with severe varicella **(AIII)**.[7,24,25] If no evidence of visceral involvement with VZV is apparent, switching to oral antiviral therapy after the patient has defervesced may be permissible **(BIII)**.[26]

Herpes Zoster

Prompt antiviral therapy should be instituted in all HIV-seropositive patients whose herpes zoster is diagnosed within 1 week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in HIV-infected cpatients 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)**.[27] 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)**. Because of the absence of data to support benefit in this population, adjunctive corticosteroid therapy for herpes zoster is not recommended **(AIII)**. Optimization of ART is recommended for all patients with VZV infections that are difficult to treat (e.g., retinitis, encephalitis) **(AIII)**.

Optimal antiviral therapy for PORN remains undefined.[28-30] Outcomes with intravenous acyclovir or ganciclovir monotherapy were poor. Better results were obtained with intravenous ganciclovir (or the combination of ganciclovir plus foscarnet), along with intravitreal antiviral drug injections.[29] Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet) **(AIII)**.[31,32] Treatment regimens for PORN recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet ***plus*** intravitreal injections of ganciclovir and/or foscarnet **(AIII)**. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

Optimization of ART in HIV-infected patients with PORN is also recommended **(AIII)**.[32] Anecdotal reports have described success with IV cidofovir for PORN. 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.

ARN appears to be more responsive than PORN to antiviral therapy. One recommended treatment is high-dose IV acyclovir (10–15 mg/kg every 8 hours for 10–14 days), followed by prolonged oral valacyclovir (1 gram 3 times daily for 6 weeks) **(AIII)**. Many experts would also include 1 or 2 doses of intravitreal ganciclovir as part of the initial induction therapy **(BIII)**. Involvement of an experienced ophthalmologist in

management of patients with VZV retinitis is strongly recommended **(AIII)**.

When to Start ART

A single uncomplicated episode of herpes zoster in an HIV-infected individual is not an indication to initiate ART nor is it an indication to defer ART. Initiation of ART should be strongly considered in a patient who has multiple recurrences of herpes zoster or who has a complication of VZV disease (e.g., PORN, encephalitis) **(AIII)**.

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

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding sections on herpes simplex virus and cytomegalovirus.

Immune reconstitution following initiation of ART appears to be associated with an increased frequency of VZV reactivation.[33-36] Observational studies have shown the risk of zoster to increase 2- to 4-fold between 4 and 16 weeks after initiating ART. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution do not differ from those observed in other HIV-infected patients and such episodes should be managed in the same manner.

Managing Treatment Failure

Treatment failure caused by resistance of VZV to acyclovir (and related drugs) is rare, but should be suspected if clinical findings do not improve within 10 days of initiation of therapy or if 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 or resistance 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)**.[37] IV cidofovir is a potential alternative **(AIII)**.

Preventing Recurrence

The efficacy of long-term antiviral prophylaxis to prevent herpes zoster recurrences in HIV-seropositive persons has not been evaluated and is not routinely recommended.

An attenuated virus vaccine for prevention of herpes zoster is FDA-approved for use in immunocompetent persons aged ≥50 years, but is recommended for use beginning at age 60 years by the Advisory Committee on Immunization Practices (ACIP). The zoster vaccine is contraindicated in persons with CD4 cell counts <200 cells/μL.

Special Considerations During Pregnancy

HIV-infected pregnant women 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)[22] 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)**.

Specific risks among HIV-infected women with varicella during pregnancy have not been reported. For HIV-seronegative women with varicella, the risk of transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when infection occurs at or before 12 weeks' gestation, 2.2% with infection at 13 to 20 weeks, and is negligible after 20 weeks.[38] Women with varicella during the first half of pregnancy should be counseled about the risks and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome.[38] Administration of varicella-zoster immune globulin is recommended primarily to prevent complications in the mother; whether it has any benefit in prevention of congenital varicella syndrome is unknown. Infants born to women who have varicella from 5 days before until 2 days after delivery should receive VariZIG 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 HIV-infected pregnant women who have uncomplicated varicella during pregnancy **(BIII)**. Pregnant women 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 shingles in pregnant HIV-infected women is oral acyclovir or valacyclovir **(BIII)**. Pregnant women should not receive the herpes zoster vaccine **(AIII)**.

Recommendations for Preventing and Treating Varicella Zoster Virus (VZV) Infections (page 1 of 2)

Pre-Exposure Prevention of VZV Primary Infection

Indications:

- Adult and adolescent patients with CD4 count ≥200 cells/mm^3 without documentation of vaccination, health-care provider diagnosis or verification of a history of varicella or herpes zoster, laboratory confirmation of disease, or persons who are seronegative for VZV **(CIII)**

Note: Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended.

Vaccination:

- Primary varicella vaccination (Varivax™), 2 doses (0.5 mL SQ) administered 3 months apart **(CIII)**
- If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended **(AIII)**.
- VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts **(BIII)**.
- If post-exposure VariZIG has been administered, wait at least 5 months before varicella vaccination **(CIII)**.
- If post-exposure acyclovir has been administered, wait at least 3 days before varicella vaccine **(CIII)**.

Post-Exposure Prophylaxis:

*Indication **(AIII)**:*

- Close contact with a person who has active varicella or herpes zoster, *and*
- Is susceptible to VZV (i.e., has no history of vaccination or of either condition, or is known to be VZV seronegative)

Preferred Prophylaxis:

- VariZIG 125 international units per 10 kg (maximum of 625 international units) IM, administered as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster **(AIII)**
- VariZIG can be obtained only through an expanded access program under a treatment IND by contacting FFF Enterprise at (800) 843-7477.
- If post-exposure VariZIG has been administered, wait at least 5 months before varicella vaccination **(CIII)**.

Note: Patients receiving monthly high dose IVIG (i.e., > 400 mg/kg) are likely to be protected against VZV and probably do not require VariZIG if the last dose of IVIG was administered <3 weeks before VZV exposure.

Alternative Prophylaxis (Begin 7–10 Days After Exposure):

- Acyclovir 800 mg PO 5 times/day for 5–7 days **(BIII)**, *or*
- Valacyclovir 1 g PO TID for 5–7 days **(BIII)**

Note:

- Neither these pre-emptive interventions nor post-exposure varicella vaccination have been studied in HIV-infected adults and adolescents.
- If acyclovir or valacyclovir is used, varicella vaccines should not be given until at least 72 hours after the last dose of the antiviral drug.

Treatment of Varicella Infections

Primary Varicella Infection (Chickenpox)

Uncomplicated Cases

Preferred Therapy:

- Valacyclovir 1 g PO TID **(AII)**, *or*
- Famciclovir 500 mg PO TID **(AII)**

Alternative Therapy:

- Acyclovir 800 mg PO 5 times daily **(BII)**

Duration:

- 5–7 days

Severe or Complicated Cases:

- Acyclovir 10–15 mg/kg IV q8h for 7–10 days **(AIII)**
- May switch to oral famciclovir, valacyclovir, or acyclovir after defervescence if no evidence of visceral involvement is evident **(BIII)**

Herpes Zoster (Shingles)

Acute Localized Dermatomal

Preferred Therapy:

- Valacyclovir 1000 mg PO TID **(AII)**, *or*
- Famciclovir 500 mg PO TID **(AII)**

Alternative Therapy:

- Acyclovir 800 mg PO 5 times daily **(BII)**

Duration:

- 7–10 days, longer duration should be considered if lesions resolve slowly

Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10–15 mg/kg IV q8h until clinical improvement is evident **(AII)**
- Switch to oral therapy (valacyclovir 1 g TID, famciclovir 500 mg TID, or acyclovir 800 mg PO 5 times daily)—to complete a 10–14 day course, when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving **(BIII)**

PORN

- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**
- Ganciclovir 5 mg/kg and/or foscarnet 90 mg/kg IV q12h ***plus*** ganciclovir 2 mg/0.05mL and/or foscarnet 1.2 mg/0.05mL intravitreal twice weekly **(AIII)**
- Optimize ART regimen **(AIII)**
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with ophthalmologist.

Note: ganciclovir ocular implants are no longer commercially available

ARN

- Acyclovir 10 - 15 mg/kg IV q8h for 10–14 days, followed by valacyclovir 1 g PO TID for 6 weeks PLUS ganciclovir 2 mg/0.05mL intravitreal twice weekly X 1-2 doses **(AIII)**
- Involvement of an experienced ophthalmologist is strongly recommended **(AIII)**
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with ophthalmologist.

Key to Acronyms: ARN = acute retinal necrosis; CD4 = CD4 T lymphocyte cell; IND = investigational new drug application; IV = intraveneously; IVIG = intraveneous immunoglobulin; PO = orally; PORN = progressive outer retinal necrosis; q(n)h = every "n" hours; SQ = subcutaneously; TID = three times a day; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus

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Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 1 of 6)
(Last updated March 28, 2019; last reviewed March 28, 2019)

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)**	
Hepatitis A Virus (HAV) Infection	HAV-susceptible patients with chronic liver disease, or who are injection-drug users, or MSM **(AII)**.	Hepatitis A vaccine 1 mL IM x 2 doses at 0 and 6–12 months **(AII)**. IgG antibody response should be assessed 1 month after vaccination; non-responders should be revaccinated when CD4 count >200 cells/μL. **(BIII)**.	For patients susceptible to both HAV and hepatitis B virus (HBV) infection (see below): Combined HAV and HBV vaccine (Twinrix®), 1 mL IM as a 3-dose (0, 1, and 6 months) or 4-dose series (days 0, 7, 21 to 30, and 12 months) **(AII)**

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 2 of 6)
(Last updated March 28, 2019; last reviewed March 28, 2019)

Opportunistic Infections	Indication	Preferred	Alternative
Hepatitis B Virus (HBV) Infection	• Patients without chronic HBV or without immunity to HBV (i.e., anti-HBs <10 international units/mL) **(AII)** • Vaccination is recommended before CD4 count falls below 350 cells/μL **(AII)**. • In patients with CD4 counts 350 cells/μL, vaccination should not be deferred until CD4 count reaches >350 cells/μL, because some patients with CD4 counts <200 cells/μL do respond to vaccination **(AII)**.	• HBV vaccine IM (Engerix-B 20 μg/mL or Recombivax HB 10 μg/mL), 0, 1, and 6 months **(AII)**, *or* • HBV vaccine IM (Engerix-B 40 μg/mL or Recombivax HB 20 μg/mL), 0, 1, 2 and 6 months **(BI)**, • 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®. • Combined HAV and HBV vaccine (Twinrix®), 1 mL IM as a 3-dose (0, 1, and 6 months) or 4-dose series (days 0, 7, 21 to 30, and 12 months) **(AII)** Anti-HBs should be obtained 1 month after completion of the vaccine series. Patients with anti-HBs <10 international units/mL at 1 month are considered non-responders **(BIII)**. <u>For patients with isolated anti-HBc</u> • One standard dose of HBV vaccine followed by anti-HBs at 1-2 months. If the titer is >100 IU/mL, no further vaccination is needed, but if it is <100 IU/mL, a complete series of HBV vaccine should be completed followed by anti-HBs testing **(BII)**.	Some experts recommend vaccinating with 40-μg doses of either HBV vaccine **(CIII)**.
	<u>Vaccine Non-Responders</u>: • Anti-HBs <10 international units/mL 1 month after vaccination series • For patients with low CD4 counts at time of first vaccine series, some experts might delay revaccination until after a sustained increase in CD4 count with ART **(CIII)**.	Re-vaccinate with a second vaccine series **(BIII)**	• HBV vaccine IM (Engerix-B 40 μg/mL or Recombivax HB 20 μg/mL), 0, 1, 2 and 6 months **(BI)**.

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 3 of 6)

Opportunistic Infections	Indication	Preferred	Alternative
Histoplasmosis	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)**	
Human Papillomavirus (HPV) Infection	Females and males aged 13–26 years **(AIII)**	• HPV recombinant vaccine 9 valent (Types 6, 11, 16, 18, 31, 33, 45, 52, 58) 0.5 mL IM at 0, 1–2, and 6 months **(AIII)**	For patients who have completed a vaccination series with the recombinant bivalent or quadrivalent vaccine, many experts would give an additional full series of recombinant 9-valent vaccine, but there are no data to define who might benefit or how cost effective this approach might be **(CIII)**.
Influenza A and B Virus Infection	All HIV-infected patients **(AIII)**	Inactivated influenza vaccine annually (per recommendation for the season) **(AIII)** Live-attenuated influenza vaccine is **contraindicated** in HIV-infected patients **(AIII)**.	
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and HIV-uninfected patients. Recommendations are based on region of travel, malaria risks, and drug susceptibility in the region. Refer to the following website for the most recent recommendations based on region and drug susceptibility: http://www.cdc.gov/malaria/.	
***Mycobacterium avium* Complex (MAC) Disease**	For CD4 Count <50 cells/mm^3 • **Not recommended** for those who immediately initiate ART **(AII)**. • Recommended for those who are not on fully suppressive ART, after ruling out active disseminated MAC disease **(AI)**.	• Azithromycin 1200 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.

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 4 of 6)

Opportunistic Infections	Indication	Preferred	Alternative
***Mycobacterium tuberculosis* (TB) Infection** (i.e., treatment of latent TB infection [LTBI])	• (+) 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 **(AII)**.	• (INH 300 mg + pyridoxine 25–50 mg) PO daily x 9 months **(AII)**, *or* • INH 900 mg PO BIW (by DOT) + pyridoxine 25–50 mg PO daily x 9 months **(BII)**.	• Rifampin 600 mg PO daily x 4 months **(BIII)**, *or* • Rifabutin (dose adjusted based on concomitant ART)[a] x 4 months **(BIII)**, *or* • [Rifapentine (see dose below) PO + INH 900 mg PO + pyridoxine 50 mg PO] once weekly x 12 weeks *rifapentine dose:* • 32.1 to 49.9 kg: 750 mg • >50 mg: 900 mg Rifapentine only recommended for patients receiving raltegravir or efavirenz-based ART regimen 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, 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 1500 mg PO daily **(BI)**, *or* • (Atovaquone 1500 mg plus pyrimethamine[e] 25 mg plus leucovorin 10 mg) PO daily **(CIII)**

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 5 of 6)

Opportunistic Infections	Indication	Preferred	Alternative
***Streptococcus pneumoniae* Infection**	For individuals who have not received any pneumococcal vaccine, regardless of CD4 count, followed by: • if CD4 count ≥200 cells/μL • if CD4 count <200 cells/μL	PCV13 0.5 mL IM x 1 (AI). PPV23 0.5 mL IM at least 8 weeks after the PCV13 vaccine **(AII)**. PPV23 can be offered at least 8 weeks after receiving PCV13 **(CIII)** or can wait until CD4 count increased to ≥200 cells/μL **(BIII)**.	PPV23 0.5 mL IM x 1 **(BII)**
	For individuals who have previously received PPV23	One dose of PCV13 should be given at least 1 year after the last receipt of PPV23 **(AII)**.	
	Re-vaccination • 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	• PPV23 0.5 mL IM or SQ x 1 **(BIII)** • PPV23 0.5 mL IM or SQ x 1 **(BIII)**	
Syphilis	• For individuals exposed to a sex partner with a diagnosis of primary, secondary, or early latent syphilis within 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 MSM or pregnant women **(AII)**
Talaromycosis (Formerly Penicilliosis)	Patients with CD4 cell counts <100 cells/μL who live or stay for a long period in rural areas in northern Thailand, Vietnam, or Southern China **(BI)**	Itraconazole 200 mg once daily **(BI)**	Fluconazole 400 mg PO once weekly **(BII)**
***Toxoplasma gondii* Encephalitis**	• Toxoplasma IgG-positive patients with CD4 count <100 cells/μL **(AII)** **Note:** All regimens recommended for primary prophylaxis against toxoplasmosis are also effective as PCP prophylaxis.	TMP-SMX[c] 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 + (pyrimethamine[e] 50 mg + leucovorin 25 mg) PO weekly **(BI)**, *or* • (Dapsone[d] 200 mg + pyrimethamine[e] 75 mg + leucovorin 25 mg) PO weekly **(BI)**; *or* • Atovaquone 1500 mg PO daily **(CIII)**; *or* • (Atovaquone 1500 mg + pyrimethamine[e] 25 mg + leucovorin 10 mg) PO daily **(CIII)**

Table 1. Prophylaxis to Prevent First Episode of Opportunistic Disease (page 6 of 6)

Opportunistic Infections	Indication	Preferred	Alternative
Varicella-Zoster Virus (VZV) Infection	Pre-exposure prevention: Patients with CD4 counts ≥200 cells/μL who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV **(CIII)** **Note:** Routine VZV serologic testing in HIV-infected adults and adolescents is not recommended. Post-exposure prevention: **(AIII)** Close contact with a person with chickenpox or herpes zoster; and is susceptible (i.e., no history of vaccination or of either condition, or known to be VZV seronegative)	Pre-exposure prevention: Primary varicella vaccination (Varivax™), 2 doses (0.5 mL SQ each) administered 3 months apart **(CIII)**. If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended **(AIII)**. Post-exposure prevention: Varicella-zoster immune globulin (VariZIG™) 125 international units per 10 kg (maximum 625 international units) IM, administered as soon as possible and within 10 days after exposure **(AIII)** **Note:** VariZIG is exclusively distributed by FFF Enterprises at 800-843-7477. Individuals receiving monthly high-dose IVIG (>400 mg/kg) are likely to be protected if the last dose of IVIG was administered <3 weeks before exposure.	Pre-exposure prevention: VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts **(BIII)**. Alternative post-exposure prevention: • Acyclovir 800 mg PO 5 x/day for 5–7 days **(BIII)**, *or* • Valacyclovir 1 g PO TID for 5–7 days **(BIII)** These alternatives have not been studied in the HIV population. If antiviral therapy is used, varicella vaccines should not be given until at least 72 hours after the last dose of the antiviral drug.

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

[b] Screening tests for LTBI include TST or IGRA.

[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. Alternative agent should be used in patients found to have G6PD deficiency.

[e] Refer to Daraprim Direct for information regarding how to access pyrimethamine.

Key to Acronyms: anti-HBc = hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; ART = antiretroviral therapy; BID = twice daily; BIW = twice a week; CD4 = CD4 T lymphocyte cell; DOT = directly observed therapy; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; HAV = hepatitis A virus; HBV = hepatitis B virus; HPV = human papillomavirus; IgG = immunoglobulin G; IgM = immunoglobulin M; IGRA = interferon-gamma release assays; IM = intramuscular; INH = isoniazid; IV= intravenously; IVIG = intravenous immunoglobulin; LTBI = latent tuberculosis infection; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; PCV13 = 13-valent pneumococcal conjugate vaccine; PO = orally; PPV23 = 23-valent pneumococcal polysaccharides vaccine; SQ = subcutaneous; SS = single strength; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole; TST = tuberculin skin test; VZV = varicella zoster virus

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 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 1 of 23) (Last updated March 28, 2019; last reviewed March 28, 2019)

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) (page 2 of 23)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections, continued	***Clostridium difficile* Infection (CDI)**	Vancomycin 125 mg (PO) QID for 10–14 days **(AI)** For severe, life-threatening CDI, see text and references for additional information.	For mild, outpatient disease: metronidazole 500 mg (PO) TID for 10–14 days **(CII)**.	*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.
	Salmonellosis	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)**.		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.
		• Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h, if susceptible **(AIII)** Duration of Therapy: *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/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)** Secondary Prophylaxis Should Be Considered For: • Patients with recurrent *Salmonella* gastroenteritis +/- bacteremia **(CIII)**, *or* • Patients with CD4 <200 cells/μL with severe diarrhea **(CIII)**	• 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)**	

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 3 of 23)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections, continued	**Shigellosis**	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) q12h **(AIII)** Duration of Therapy: • *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.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 4 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Respiratory Diseases *(with focus on pneumonia)*	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)**.		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 **(BIII)**. Patients receiving a macrolide for MAC prophylaxis should not receive macrolide monotherapy for empiric treatment of bacterial pneumonia. For patients begun on IV antibiotic therapy, switching to PO should be considered when they are clinically improved and able to tolerate oral medications. Chemoprophylaxis can be considered for patients with frequent recurrences of serious bacterial pneumonia **(CIII)**. Clinicians should be cautious about using antibiotics to prevent recurrences because of the potential for developing drug resistance and drug toxicities.

	Empiric Outpatient Therapy:
	• A PO beta-lactam + a PO macrolide (azithromycin or clarithromycin) **(AII)**
	  • *Preferred beta-lactams:* high-dose amoxicillin or amoxicillin/clavulanate
	  • *Alternative beta-lactams:* cefpodoxime or cefuroxime, *or*
	• *For penicillin-allergic patients:* Levofloxacin 750 mg PO once daily **(AII)**, or moxifloxacin 400 mg PO once daily **(AII)**
	
	Duration: 7–10 days (a minimum of 5 days). Patients should be afebrile for 48–72 hours and clinically stable before stopping antibiotics.
	
	Empiric Therapy for Non-ICU Hospitalized Patients:
	• An IV beta-lactam + a macrolide (azithromycin or clarithromycin) **(AII)**
	  • *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
	• *For penicillin-allergic patients:* Levofloxacin, 750 mg IV once daily **(AII)**, or moxifloxacin, 400 mg IV once daily **(AII)**
	
	Empiric Therapy for ICU Patients:
	• An IV beta-lactam + IV azithromycin **(AII)**, *or*
	• An IV beta-lactam + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(AII)**
	  • *Preferred beta-lactams:* ceftriaxone, cefotaxime, or ampicillin-sulbactam
	
	Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia:
	• An IV antipneumococcal, antipseudomonal beta-lactam + (ciprofloxacin 400 mg IV q8–12h or levofloxacin 750 mg IV once daily) **(BIII)**
		Empiric Outpatient Therapy:
		• A PO beta-lactam + PO doxycycline **(CIII)**
		  • *Preferred beta-lactams:* high-dose amoxicillin or amoxicillin/clavulanate
		  • *Alternative beta-lactams:* cefpodoxime or cefuroxime
		
		Empiric Therapy for Non-ICU Hospitalized Patients:
		• An IV beta-lactam + doxycycline **(CIII)**
		
		Empiric Therapy For ICU Patients:
		• *For penicillin-allergic patients:* Aztreonam IV + (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 + an aminoglycoside + azithromycin **(BIII)**, *or*
		• Above beta-lactam + an aminoglycoside + (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) **(BIII)**, *or*
		• *For penicillin-allergic patients:* Replace the beta-lactam with aztreonam **(BIII)**.	

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 5 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Respiratory Diseases *(with focus on pneumonia)*, continued	• *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 **(BIII)**. • Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production **(CIII)**.		
Bartonellosis	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis: • Doxycycline 100 mg PO or IV q12h **(AII)**, *or* • Erythromycin 500 mg PO or IV q6h **(AII)** CNS Infections: • (Doxycycline 100 mg +/- RIF 300 mg) PO or IV q12h **(AIII)** Confirmed *Bartonella* Endocarditis: • (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)** Other Severe Infections: • (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)** Duration of Therapy: • At least 3 months **(AII)**	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, And Osteomyelitis: • Azithromycin 500 mg PO daily **(BIII)** • Clarithromycin 500 mg PO BID **(BIII)** Confirmed *Bartonella* Endocarditis but with Renal Insufficiency: • (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 6 of 23)

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 1 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 BID for 1 day, then 400 mg daily **(BI)** *Topical Therapy* • Clotrimazole troches, 10 mg PO 5 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) **(BI)**, *or* • Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily **(BII)** For Esophageal Candidiasis (For 14–21 Days): • Voriconazole 200 mg PO or IV BID **(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)**	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 BID **(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 7 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Chagas Disease	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 **(AII)**, *or* • Itraconazole 200 mg* PO BID **(BII)** Bone or Joint Infections: • Itraconazole 200 mg* PO BID **(AI)** Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): • Lipid formulation amphotericin B 3-5 mg/kg IV daily **(AIII)**, *or* • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)** • Duration of therapy: continue until clinical improvement, then switch to a triazole **(BIII)** Meningeal Infections: • Fluconazole 400–800 mg* IV or PO daily **(AII)**	Mild Infections (Focal Pneumonia) *For Patients Who Failed to Respond to Fluconazole or Itraconazole:* • Posaconazole 300 mg delayed-release tablet* PO BID x 1 day, then once daily **(BIII)**, *or* • Posaconazole 400 mg oral suspension* PO BID **(BII)**, *or* • Voriconazole 200 mg* PO BID **(BIII)** Bone or Joint Infection: • Fluconazole 400 mg* PO daily **(BI)** Severe, Non-Meningeal Infection (Diffuse Pulmonary Infection or Severely Ill Patients with Extrathoracic, Disseminated Disease): • Some specialists will add a triazole (fluconazole* or itraconazole*) 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* • Voriconazole 200–400 mg* PO BID **(BIII)**, *or* • Posaconazole 300 mg delayed-release tablet* PO BID x 1 day, then once daily **(CIII)**, *or* • Posaconazole 400 mg oral suspension* PO BID **(CIII)**, *or* • Intrathecal amphotericin B deoxycholate, when triazole antifungals are ineffective **(AIII)**	Relapse can occur in 25%–33% of HIV-negative patients with diffuse pulmonary or disseminated diseases. Therapy should be given for 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)**. Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of HIV-infected patients after discontinuation of triazole therapy **(AII)**. *Fluconazole, itraconazole, posaconazole, and voriconazole may have significant interactions with other medications including ARV drugs. These interactions are complex and can be bi-directional. Refer to Table 5 or Antiretroviral guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and reduce concentration-related toxicities. Intrathecal amphotericin B should only be given in consultation with a specialist and administered by an individual with experience with the technique.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 8 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptococcosis	Cryptococcal Meningitis *Induction Therapy (for at least 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.) *Consolidation Therapy (for at least 8 weeks **(AI)**, followed by maintenance therapy):* • Fluconazole 400 mg PO (or IV) daily **(AI)** *Maintenance Therapy:* • Fluconazole 200 mg PO daily for at least 12 months **(AI)** For Non-CNS, Extrapulmonary Cryptococcosis and Diffuse Pulmonary Disease: • Treatment same as for cryptococcal meningitis **(BIII)** Non-CNS Cryptococcosis with Mild-to-Moderate Symptoms and Focal Pulmonary Infiltrates: • Fluconazole, 400 mg PO daily for 12 months **(BIII)**	Cryptococcal meningitis *Induction Therapy (for at least 2 weeks, followed by consolidation therapy):* • Amphotericin B deoxycholate 0.7 mg/kg IV daily + flucytosine 25 mg/kg PO QID **(AI)**, *or* • 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 mg PO or IV daily **(BIII)**, *or* • Amphotericin B deoxycholate 0.7 mg/kg IV daily + fluconazole 800 mg PO or IV daily **(BI)**, *or* • Fluconazole 400–800 mg PO or IV daily + flucytosine 25 mg/kg PO QID **(BII)**, *or* • Fluconazole 1200 mg PO or IV daily **(CII)** *Consolidation Therapy (for at least 8 weeks **(AI)**, followed by maintenance therapy):* • Itraconazole 200 mg PO BID for 8 weeks—less effective than fluconazole **(CI)** *Maintenance Therapy:* • No alternative therapy recommendation	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 30–80 mcg/mL) or close monitoring of blood counts for development of cytopenia. Dosage should be adjusted in patients with renal insufficiency **(BII)**. 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 **(BIII)**. Corticosteroids and mannitol are ineffective in reducing ICP and are NOT recommended **(BII)**. Corticosteroid should not be routinely used during induction therapy unless it is used for management of IRIS **(AI)**.
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 500–1000 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).**
Cystoisosporiasis (Formerly Isosporiasis)	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.	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/1600 mg) three times weekly **(BIII)**	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)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 9 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cystoisosporiasis (Formerly Isosporiasis), continued	Chronic Maintenance Therapy (Secondary Prophylaxis): • In patients with CD4 count <200/µL, TMP-SMX (160 mg/800 mg) PO TIW **(AI)**	• Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily **(BIII)** • Ciprofloxacin 500 mg three times weekly **(CI)** as a second-line alternative	
Cytomegalovirus (CMV) Disease	CMV Retinitis Induction Therapy (followed by Chronic Maintenance Therapy): *For Immediate Sight-Threatening Lesions (within 1500 microns of the fovea):* • Intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) for 1-4 doses over a period of 7-10 days to achieve high intraocular concentration faster **(AIII)**; plus • Valganciclovir 900 mg PO BID for 14– 21 days, then 900mg once daily **(AI)**: *For Peripheral Lesions:* • Valganciclovir 900 mg PO BID for 14– 21 days, then 900 mg once daily **(AI)** Chronic Maintenance: • Valganciclovir 900 mg PO daily **(AI)** for 3-6 months until ART induced immune recovery (see Table 4) 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)** • 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.***	CMV Retinitis *For Immediate Sight-Threatening Lesions (within 1500 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):* • Ganciclovir 5 mg/kg IV q12h for 14–21 days **(AI)**, *or* • Foscarnet 90 mg/kg IV q12h or 60 mg/kg q8h for 14–21 days **(AI)**, *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) **(BI)**. (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 (see Table 4):* • Ganciclovir 5 mg/kg IV 5–7 times weekly **(AI)**, *or* • 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)**	The choice of therapy for CMV retinitis should be individualized, based on location and severity of the lesions, level of immunosuppression, and other factors (e.g., concomitant medications and ability to adhere to treatment) **(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. For sight threatening retinitis, intravitreal injections of ganciclovir or foscarnet can be given to achieve higher ocular concentration faster. 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 corticosteroid 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)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 10 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cytomegalovirus (CMV) Disease, continued	• 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. • Optimize ART to achieve viral suppression and immune reconstitution **(BIII)**.	• For mild disease, if ART can be initiated without delay, consider withholding CMV therapy **(CIII)**.	
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, with [(tenofovir DF 300 mg or tenofovir alafenamide* 10 or 25mg) + (emtricitabine 200 mg or lamivudine 300 mg)] PO once daily (+ additional drug (s) for HIV) **(AIII)**. Please refer to Table 7 for dosing recommendations in patients with renal impairment. Duration: Continue treatment indefinitely **(CIII)** * Tenofovir alafenamide (TAF) 10 mg dose is in the fixed dose combination tablets of elvitegravir/cobicistat/TAF/emricitabine and darunavir/cobicistat/TAF/emtricitabine; when TAF is used with other ARVs, the dose is 25 mg.	For Patients Who Refuse or Are Unable to Take ART or Who Are HIV Long-Term Non-Progressors: HBV treatment is indicated for all those who meet criteria for treatment according to the AASLD 2018 guidelines. • 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)**	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)**. 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)**.
Hepatitis C Virus (HCV) Disease	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 updated recommendations.		

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	Orolabial Lesions (For 5–10 Days): • Valacyclovir 1 g PO BID **(AIII)**, *or* • Famciclovir 500 mg PO BID **(AIII)**, *or* • Acyclovir 400 mg PO TID **(AIII)** Initial or Recurrent Genital HSV (For 5–14 Days): • Valacyclovir 1 g PO BID **(AI)**, *or* • Famciclovir 500 mg PO BID **(AI)**, *or* • Acyclovir 400 mg PO TID **(AI)** Severe Mucocutaneous HSV: • Initial therapy acyclovir 5 mg/kg IV q8h **(AIII)** • After lesions begin to regress, change to PO therapy as above. Continue until lesions are completely healed. 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 BID **(AI)** • Famciclovir 500 mg PO BID **(AI)** • Acyclovir 400 mg PO BID **(AI)** • Continue indefinitely regardless of CD4 cell count.	For Acyclovir-Resistant HSV *Preferred Therapy:* • Foscarnet 80–120 mg/kg/day IV in 2–3 divided doses until clinical response **(AI)** *Alternative Therapy **(CIII)**:* • IV cidofovir (dosage as in CMV retinitis), *or* • Topical trifluridine, *or* • Topical cidofovir, *or* • Topical imiquimod Duration of Therapy: • 21–28 days or longer	Patients with HSV infections can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences. Topical formulations of trifluridine and cidofovir are not commercially available. Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 12 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
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 TID for 3 days, then 200 mg PO BID **(AII)** Less Severe Disseminated Disease *Induction and Maintenance Therapy:* • Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID **(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 BID to TID for ≥1 year 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 those 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 3 mg/kg IV daily **(AIII)**, *or* • Amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily **(AIII)** Alternatives to Itraconazole for Maintenance Therapy or Treatment of Less Severe Disease: • Voriconazole 400 mg PO BID for 1 day, then 200 mg BID **(BIII)**, *or* • Posaconazole 400 mg PO BID **(BIII)** • Fluconazole 800 mg PO daily **(CII)** Meningitis: • No alternative therapy recommendation Long-Term Suppression Therapy: • Fluconazole 400 mg PO daily **(BIII)**	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 ARV efficacy and reduce concentration-related toxicities. Random serum concentration of itraconazole + hydroitraconazole should be >1 µg/mL. Clinical experience with voriconazole or posaconazole in the treatment of histoplasmosis is limited. Acute pulmonary histoplasmosis in HIV-infected patients with CD4 counts >300 cells/µL should be managed as non-immunocompromised host **(AIII)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 13 of 23)

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 doxorubin 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.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 14 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
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 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.
	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 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)**.	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 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)**.	

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 15 of 23)

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Leishmaniasis	**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. *Another Option:* • Miltefosine 100 mg PO daily for 4 weeks (available in the United States under a treatment IND) **(CIII)** 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.
	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)** Chronic Maintenance Therapy: May be indicated in immunocompromised patients with multiple relapses **(CIII)**	Possible Options Include: • 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)**.	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

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 16 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Malaria, continued	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.		
Microsporidiosis	For GI Infections Caused by *Enterocytozoon bienuesi*: • Initiate or optimize ART as immune restoration to CD4 count >100 cells/µL **(AII)**; *plus* • Manage severe dehydration, malnutrition, and wasting by fluid support **(AII)** and nutritional supplement **(AIII)** For Intestinal and Disseminated (Not Ocular) Infections Caused by Microsporidia Other Than *E. bienuesi* and *Vittaforma corneae*: • Albendazole 400 mg PO BID **(AII)**, continue until CD4 count >200 cells/µL for >6 months after initiation of ART **(BIII)** For Ocular Infection: • Topical fumagillin bicylohexylammonium (Fumidil B) eye drops: 3 mg/mL in saline (fumagillin 70 µg/mL)—2 drops q2h for 4 days, then 2 drops QID (investigational use only in United States) **(BII)** + albendazole 400 mg PO BID, for management of systemic infection **(BIII)** • Therapy should be continued until resolution of ocular symptoms and CD4 count increase to >200 cells/µL for >6 months in response to ART **(CIII)**.	For GI Infections Caused by *E. bienuesi:* • Fumagillin 60 mg/day **(BII)** and TNP-470 (a synthetic analog of fumagillin) **(BIII)** may be effective, but neither is available in the United States. • Nitazoxanide (1000 mg BID) may have some effect but response may be minimal in patients with low CD4 cell counts **(CIII)**. For Disseminated Disease Attributed to *Trachipleistophora* or *Anncaliia*: • Itraconazole 400 mg PO daily + albendazole 400 mg PO BID **(CIII)**	Anti-motility agents can be used for diarrhea control if required **(BIII).**

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 17 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
***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/mm^3 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)**.
***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, 5–7 Times/Week by DOT) **(AI)**: • INH + [RIF or RFB] + PZA + EMB **(AI)**, Continuation Phase: • INH + (RIF or RFB) daily (5–7 times/week) **(AIII)** Total Duration of Therapy (For Drug-Susceptible TB): • Pulmonary drug-susceptible TB: 6 months **(BII)** • Pulmonary TB and culture-positive after 2 months of TB treatment: 9 months **(BII)** • Extra-pulmonary TB w/CNS infection: 9–12 months **(BII)**; • Extra-pulmonary TB w/bone or joint involvement: 6 to 9 months **(BII)**; • Extra-pulmonary TB in other sites: 6 months **(BII)** Total duration of therapy should be based on number of doses received, not on calendar time.	**Treatment for Drug-Resistant TB** Resistant to INH: • (RIF or RFB) + EMB + PZA + (moxifloxacin or levofloxacin) for 2 months **(BII)**; followed by (RIF or RFB) + EMB + (moxifloxacin or levofloxacin) for 7 months **(BII)** Resistant to Rifamycins +/- Other Drugs: • Regimen and duration of treatment should be individualized based on resistance pattern, clinical and microbiological responses, and in close consultation with experienced specialists **(AIII)**.	Adjunctive corticosteroid improves survival for TB meningitis and pericarditis **(AI)**. See text for drug, dose, and duration recommendations. All rifamycins may have significant pharmacokinetic interactions with antiretroviral drugs, please refer to the Drug Interactions section in the Adult and Adolescent ARV Guidelines for dosing recommendations. Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART. Paradoxical IRIS that is not severe can be treated with NSAIDs without a change in TB or HIV therapy **(BIII)**. For severe IRIS reaction, consider prednisone and taper over 4 weeks based on clinical symptoms **(BIII)**. For example: • If receiving RIF: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks • If receiving RFB: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 18 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
***Mycobacterium tuberculosis* (TB) Disease**, continued			A more gradual tapering schedule over a few months may be necessary for some patients.
***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 1500 mg PO daily **(BI)**, *or* • (Atovaquone 1500 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)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 19 of 23)

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	Early Stage (Primary, Secondary, and Early-Latent Syphilis): • Benzathine penicillin G 2.4 million units IM for 1 dose **(AII)** Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): • Benzathine penicillin G 2.4 million units IM weekly for 3 doses **(AII)** Late-Stage (Tertiary–Cardiovascular or Gummatous Disease): • 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) Neurosyphilis (Including Otic or Ocular Disease): • 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)**	Early Stage (Primary, Secondary, and Early-Latent Syphilis): *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)**) Late-Latent Disease (>1 year or of Unknown Duration, and No Signs of Neurosyphilis): *For penicillin-allergic patients* • Doxycycline 100 mg PO BID for 28 days **(BIII)** Neurosyphilis: • 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 **is not recommended** 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 20 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Talaromycosis (Formerly Penicilliosis)	For Acute Infection in Severely Ill Patients: • Liposomal amphotericin B 3–5 mg/kg/day IV for 2 weeks, followed by itraconazole 200 mg PO BID for 10 weeks **(AII)**, followed by chronic maintenance therapy (as below) For Mild Disease: • Itraconazole 200 mg PO BID for 8 weeks **(BII)**; followed by chronic maintenance therapy (as below) Chronic Maintenance Therapy (Secondary Prophylaxis): • Itraconazole 200 mg PO daily **(AI)**	For Acute Infection in Severely Ill Patients: • Voriconazole 6 mg/kg IV q12h for 1 day, then 4 mg/kg IV q12h for at least 3 days, followed by 200 mg PO BID for a maximum of 12 weeks **(BII)**, followed by maintenance therapy For Mild Disease: • Voriconazole 400 mg PO BID for 1 day, then 200 mg BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy	ART should be initiated simultaneously with treatment for penicilliosis to improve treatment outcome **(CIII)**. Itraconazole 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 ARV efficacy and reduce concentration-related toxicities.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 21 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments

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 1000 mg PO q6h + leucovorin 10–25 mg PO once daily
	  • If ≥60 kg, pyrimethamine[a] 75 mg PO once daily + sulfadiazine 1500 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 initated on chronic maintenance therapy
	
	Chronic Maintenance Therapy:
	• Pyrimethamine[a] 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses) + leucovorin 10–25 mg PO daily **(AI)**
		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 1500 mg PO BID with food + pyrimethamine[a] (leucovorin)* **(BII)**, *or*
		• Atovaquone 1500 mg PO BID with food + sulfadiazine 1000–1500 mg PO q6h (weight-based dosing, as in preferred therapy) **(BII)**, *or*
		• Atovaquone 1500 mg PO BID with food **(BII)**
		
		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*
		• TMP-SMX DS 1 tablet once daily **(BII)**; *or*
		• Atovaquone 750–1500 mg PO BID + (pyrimethamine[a] 25 mg + leucovorin 10 mg) PO daily **(BII)**, *or*
		• Atovaquone 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2–4 divided doses) **(BII)**, *or*
		• Atovaquone 750–1500 mg PO BID with food **(BII)**
		
		* Pyrimethamine[a] and leucovorin doses are the same as for preferred therapy.
			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.
			
			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)**.

Table 2. Treatment of AIDS-Associated Opportunistic Infections (Includes Recommendations for Acute Treatment and Secondary Prophylaxis/Chronic Suppressive/Maintenance Therapy) (page 22 of 23)

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Varicella-Zoster Virus (VZV) Disease	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases (For 5–7 Days):* • Valacyclovir 1 g PO TID **(AII)**, *or* • Famciclovir 500 mg PO TID **(AII)** *Severe or Complicated Cases:* • Acyclovir 10–15 mg/kg IV q8h 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 TID **(AII)**, *or* • Famciclovir 500 mg TID **(AII)** *Extensive Cutaneous Lesion or Visceral Involvement:* • Acyclovir 10–15 mg/kg IV q8h 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)**. Progressive Outer Retinal Necrosis (PORN): • (Ganciclovir 5 mg/kg +/- foscarnet 90 mg/kg) IV q12h + (ganciclovir 2 mg/0.05mL +/- foscarnet 1.2 mg/0.05 ml) intravitreal injection BIW **(AIII)** • Initiate or optimize ART **(AIII)** Acute Retinal Necrosis (ARN): • (Acyclovir 10-15 mg/kg IV q8h) + (ganciclovir 2 mg/0.05mL intravitreal injection BIW X 1-2 doses) for 10-14 days, followed by valacyclovir 1g PO TID for 6 weeks **(AIII)**	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases (For 5-7 Days):* • Acyclovir 800 mg PO 5 times/ 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/ day **(BII)**	In managing VZV retinitis - Consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended **(AIII)**. Duration of therapy for VZV retinitis is not well defined, and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses. Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) **(AIII)**.

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

Key to Acronyms: ACTG = AIDS Clinical Trials Group; 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; 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

[a] Refer to http://www.daraprimdirect.com for information regarding how to access pyrimethamine

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. Recommended Doses of First-Line Drugs for Treatment of Tuberculosis in Adults and Adolescents (Last updated May 18, 2017; last reviewed May 18, 2017)

Drug	Daily
Isoniazid	5 mg/kg (usual dose 300 mg)
Rifampin[a] **Note:** Rifampin is not recommended in patients receiving HIV PIs, ETR, RPV, EVG/COBI, or TAF	10 mg/kg (usual dose 600 mg)
Rifabutin[a] without HIV PIs, EFV, RPV	5 mg/kg (usual dose 300 mg)
with HIV PIs	150 mg[b]
with EFV	450–600 mg
with TAF or EVG/COBI containing regimens	not recommended
Pyrazinamide (weight-based dosing) 40–55 kg	1000 mg (18.2–25.0 mg/kg)
56–75 kg	1500 mg (20.0–26.8 mg/kg)
76-90 kg	2000 mg (22.2–26.3 mg/kg)
>90 kg	2000 mg[c]
Ethambutol 40–55 kg	800 mg (14.5–20.0 mg/kg)
56–75 kg	1200 mg (16.0–21.4 mg/kg)
76-90 kg	1600 mg (17.8–21.1 mg/kg)
>90 kg	1600 mg[c]

[a] For more detailed guidelines on use of different antiretroviral drugs with rifamycin, clinicians should refer to the Drug Interactions section of the Adult and Adolescent ARV Guidelines

[b] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg twice weekly dosing together with ritonavir-boosted PIs. May consider therapeutic drug monitoring when rifabutin is used with a ritonavir-boosted PI and adjust dose accordingly.

[c] Monitor for therapeutic response and consider therapeutic drug monitoring to assure dosage adequacy in patients who weigh >90 kg.

Key to Acronyms: COBI = cobicistat; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; TAF = tenofovir alafenamide

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 March 28, 2019; last reviewed March 28, 2019)

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 and with viral suppression while on ART **(CIII)**	Restart at CD4 count <250 cells/ μL **(BIII)**	Only for patients with focal coccidioidal pneumonia **(AII)**: • Clinically responded to ≥ 6 months antifungal therapy, with CD4 count ≥250 cells/mm^3, and with viral suppression while on ART. • Should continue monitoring for recurrence with serial chest radiographs and coccidioidal serology every 6-12 months. For patients with diffuse pulmonary **(BIII)**, disseminated non-meningeal **(BIII)**: • Therapy 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 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 maintenance therapy, *and* • Remain asymptomatic of cryptococcal infection, *and* • CD4 count ≥100 cells/μL for >3 months, 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
Cystoisosporiasis (Formerly Isosporiasis)	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
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)**
Histoplasmosis	CD4 count >150 cells/μL for 6 months while on ART **(BIII)**	For patients at high risk of acquiring histoplasmosis, restart at CD4 count <150 cells/μL **(CIII)**	If the following criteria **(AI)** are fulfilled: • Received itraconazole for >1 year, *and* • Negative fungal blood cultures, *and* • CD4 count ≥150 cells/μL for ≥6 months in response to ART, *and* • Serum *Histoplasma* antigen <2 ng/mL	CD4 count <150 cells/mm^3 **(BIII)**
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 (Formerly Penicilliosis)	CD4 count >100 cells/μL for >6 months in response to ART **(BII)**	CD4 count <100 cells/μL **(BIII)**	CD4 count >100 cells/μL for ≥6 months in response to ART **(BII)**	• CD4 count <100 cells/μL (AIII), *or* • If penicilliosis recurs at CD4 count >100 cells/μL **(CIII)**
***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, 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 for Drugs Used to Treat or Prevent Opportunistic Infections (page 1 of 15) (Last updated September 22, 2017; last reviewed September 22, 2017)

This table lists the known or suspected/predicted pharmacokinetic interactions between drugs used for the treatment or prevention of HIV-associated opportunistic infections (OIs). Many of the drugs listed in this table may also interact with antiretroviral drugs. Clinicians should refer to the drug interaction tables in the most current Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents to assess interaction potentials between OI drugs and antiretroviral therapy (ART).

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 co-administer"

Indicates 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/may result in either:

1) Increase in concentrations of one or both drugs, which may lead to excessive risk of toxicity; *or*
2) Decrease in concentrations of one or both drugs, which may render one or both drugs ineffective.

"Co-administration should be avoided, if possible"

There is a potential for significant pharmacokinetic interactions. However, co-administration of the drugs may be necessary if there are no other acceptable therapeutic options that provide a more favorable benefit-to-risk ratio. If other more favorable options exist, clinicians are advised to consider changing components of the regimen to accommodate a safer or more effective regimen.

"Use with caution"

Drug combinations are recommended to be used with caution when:

1. Pharmacokinetic studies have shown a moderate degree of interaction of unknown clinical significance; *or*
2. Based on the known metabolic pathway of the two drugs, there is a potential for pharmacokinetic interaction of unknown clinical significance.

Rifamycin-Related Interactions

Rifamycins are potent inducers of Phase I and Phase II drug metabolizing reactions. Daily doses of rifampin are well studied, and induction increases over a week or more. Based on limited data, larger doses of rifampin (e.g., 1200 mg) appear to produce the same maximum induction, 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 tuberculosis [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, but may result in reduction of exposure of drugs that are CYP3A4 substrates. When a rifamycin is used with a potential interacting drug, close monitoring for clinical efficacy of the other agent is advised.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether/ Lumefantrine	Clarithromycin	↑ Lumefantrine expected	Co-administration 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-associated toxicities.
	Erythromycin	↑ Lumefantrine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Lumefantrine possible	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Itraconazole	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Posaconazole	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.
	Rifampin[a]	↓ Artemether, DHA, and lumefantrine AUC by 89%, 85%, and 68%, respectively	Do not co-administer.
	Rifapentine[a]	↓ Artemether, DHA, and lumefantrine expected	Do not co-administer.
	Voriconazole	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
Atovaquone	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↔ Atovaquone (based on data from atovaquone and atazanavir/ritonavir interaction)	No dosage adjustment necessary.
	Doxycycline	Atovaquone conc. ↓ by approximately 40% with tetracycline. No interaction study with doxycycline.	Dose adjustment not established; if co-administered, 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 co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifampin[a]	Atovaquone C_{SS} ↓ 52%; rifampin C_{SS}↑ 37%	Do not co-administer.
	Rifapentine[a]	↓ Atovaquone expected	Do not co-administer.
Bedaquiline	Clarithromycin	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider alternative HCV regimen.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Erythromycin	↑ Bedaquiline possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Bedaquiline possible	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Itraconazole	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Posaconazole	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Bedaquiline possible	If co-administered, monitor for bedaquiline efficacy.
	Rifampin[a]	Bedaquiline AUC ↓ 53%	Do not co-administer.
	Rifapentine[a]	Bedaquiline AUC ↓ 55% (with daily rifapentine)	Do not co-administer.
	Voriconazole	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
Caspofungin	Rifabutin[a]	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
	Rifampin[a]	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be increased to 70 mg/day.
	Rifapentine[a]	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
Chloroquine	Clarithromycin	↑ Chloroquine expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ Chloroquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Chloroquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Itraconazole	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Posaconazole	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	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	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
Clarithromycin	Artemether/Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided if possible. Consider azithromycin in place of clarithromycin.
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Daclatasvir	↑ Daclatasvir expected	↓ Daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Clarithromycin and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Elbasvir/ Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity. Consider azithromycin in place of clarithromycin.
	Fluconazole	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Itraconazole	↑ Itraconazole and clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If co-administered, monitor for toxicities of both itraconazole and clarithromycin (e.g., QT prolongation), consider monitoring itraconazole conc. and adjust dose accordingly.
	Mefloquine	↑ Mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for mefloquine toxicity (e.g., QT prolongation).
	Posaconazole	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Quinine	↑ Quinine expected; ↑ clarithromycin possible	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Rifabutin[a]	Clarithromycin AUC ↓ by 44%; 14-OH AUC ↑ 57%; rifabutin AUC ↑ 76% to 99%; des-Rbt AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, consider reducing rifabutin dose, monitoring clarithromycin and rifabutin concentrations, and monitoring for rifabutin-associated toxicities (e.g., uveitis).
	Rifampin[a]	Mean clarithromycin conc. ↓ 87%; rifampin AUC ↑ 60%	Do not co-administer. 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 co-administered, monitor for rifapentine-associated toxicities, consider monitoring clarithromycin and rifapentine concentrations and adjusting doses accordingly.
	Simeprevir	↑ Simeprevir expected	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Voriconazole	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
Daclatasvir	Clarithromycin	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Erythromycin	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Fluconazole	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Itraconazole	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Posaconazole	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	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 co-administer.
	Rifapentine[a]	↓ Daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitor for therapeutic efficacy.
	Simeprevir	Simeprevir AUC ↑ 44%; daclatasvir AUC ↑ 96%	No dosage adjustment. Monitor for simeprevir and daclatasvir-associated toxicities.
	Voriconazole	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
Dapsone	Rifabutin[a]	Dapsone AUC ↓ 27% to 40%	Co-administration should be avoided if possible. Consider alternatives for dapsone.
	Rifampin[a]	Dapsone conc. ↓ 7- to 10-fold and $t_{1/2}$ ↓ from 24 to 11 hours	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Rifapentine[a]	↓ Dapsone expected	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
Dasabuvir Ombitasvir Paritaprevir Ritonavir	Artemether/ Lumefantrine	↑ Artemether and lumefantrine possible	Use with caution. Monitor for artemether- and lumefantrine-associated toxicities.
	Atovaquone	↔ Atovaquone (based on data from atovaquone and ritonavir/ atazanavir interaction)	No dosage adjustment necessary.
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. Consider alternative HCV regimen.
	Clarithromycin	↑ Clarithromycin and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ Erythromycin expected and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Itraconazole	↑ Itraconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Itraconazole doses >200 mg/day are not recommended unless dosing is guided by itraconazole levels. Monitor for itraconazole and HCV regimen-associated toxicities.
	Posaconazole	↑ Posaconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Monitor for posaconazole and HCV regimen-associated toxicities. Monitor posaconazole conc. and adjust dose if necessary.
	Rifabutin[a]	↑ Rifabutin expected; ↓ paritaprevir possible	Co-administration should be avoided if possible. With co-administration, decrease rifabutin dose to 150 mg/ day and monitor rifabutin conc. Monitor HCV regimen for efficacy.
	Rifampin[a]	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	Do not co-administer.
	Rifapentine[a]	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	Do not co-administer.
	Voriconazole	Voriconazole AUC ↓ 39% (with ritonavir); ↑ paritaprevir expected	Co-administer only if the benefits outweigh the risk. Monitor voriconazole conc. to guide dosage adjustments.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Doxycycline	Atovaquone	Atovaquone concentration ↓ by approximately 40% with tetracycline. No interaction study with doxycycline.	Dose adjustment not established; if co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifabutin[a]	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Rifampin[a]	Doxycycline AUC ↓ by 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	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity. Consider azithromycin in place of clarithromycin.
	Itraconazole	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Posaconazole	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Rifabutin[a]	↓ Elbasvir and grazoprevir possible	Co-administration should be avoided if possible. Consider alternative HCV regimen.
	Rifampin[a]	Grazoprevir AUC ↓ 7%, C_{24} ↓ 90%; ↓ elbasvir expected	Do not co-administer.
	Rifapentine[a]	↓ Elbasvir and grazoprevir possible	Do not co-administer.
	Voriconazole	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided if possible. If co-administered, monitor closely for hepatotoxicity.
Erythromycin	Artemether/ Lumefantrine	↑ Lumefantrine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Bedaquiline	↑ Bedaquiline possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Chloroquine	↑ Chloroquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Daclatasvir	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Erythromycin and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Co-administration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Itraconazole	Itraconazole AUC ↑ 36%; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Posaconazole	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Quinine	↑ Quinine expected; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Rifabutin[a]	↓ Erythromycin possible; ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy or rifabutin toxicities (e.g., uveitis).
	Rifampin[a]	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Rifapentine[a]	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Simeprevir	Simeprevir AUC ↑ 647%, C_{min} ↑ 1,174%; erythromycin AUC ↑ 90%, C_{min} ↑ 208%	Do not co-administer. Consider azithromycin in place of erythromycin.
	Voriconazole	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.
Fluconazole	Artemether/ Lumefantrine	↑ Lumefantrine possible	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Bedaquiline	↑ Bedaquiline possible	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	Clarithromycin AUC ↑ 18%, C_{min} ↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Daclatasvir	↑ Daclatasvir possible	No dosage adjustment. Monitor for daclatasvir-associated toxicities.
	Erythromycin	↑ Erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected; ↑ fluconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine and fluconazole toxicity (e.g., QT prolongation).
	Rifabutin[a]	Rifabutin AUC ↑ 80%; ↔ fluconazole	Use with caution. Monitor for rifabutin-associated toxicities (e.g., uveitis). Consider monitoring rifabutin conc.; may need to lower rifabutin dose to 150 mg/day.
	Rifampin[a]	Fluconazole AUC ↓ 23% to 56%	Monitor for antifungal efficacy; may need to raise fluconazole dose.
	Rifapentine[a]	↓ Fluconazole expected	Monitor for antifungal efficacy; may need to raise fluconazole dose.
	Simeprevir	↑ Simeprevir possible	Do not co-administer.
Itraconazole	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	↑ Itraconazole and clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If co-administered, monitor for toxicities of both itraconazole and clarithromycin (e.g., QT prolongation), consider monitoring itraconazole conc. and adjusting dose accordingly.
	Daclatasvir	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Itraconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Itraconazole doses >200 mg/day are not recommended unless dosing is guided by itraconazole levels. Monitor for itraconazole and HCV regimen-associated toxicities.
	Elbasvir/ Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	Itraconazole AUC ↑ 36%; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected; ↑ itraconazole possible	Co-administration should be avoided, if possible. If used concomitantly, monitor for quinine and itraconazole toxicity (e.g, QT prolongation), monitor itraconazole conc. and adjust dose accordingly.
	Rifabutin[a]	Itraconazole AUC ↓ 70%; ↑ rifabutin expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifampin[a]	Itraconazole AUC ↓ 64% to 88%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	↓ Itraconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Simeprevir	↑ Simeprevir expected	Do not co-administer.
Ledipasvir/ Sofosbuvir	Rifabutin[a]	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Rifampin[a]	Ledipasvir AUC ↓ 59%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Rifapentine[a]	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Simeprevir	Ledipasvir AUC ↑ 92%; simeprevir AUC ↑ 116%	Do not co-administer.
	TAF	Ledipasvir AUC ↑ 79%	No dosage adjustment.
	TDF	TDF AUC ↑ 98% (when given with EFV/FTC) TDF AUC ↑ 40% (when given with RPV/FTC) When used with EVG/c/TDF/FTC, ↑ TDF and ledipasvir expected	Monitor for TDF-associated toxicities when coadministered with PI/r, PI/c, or EFV. Consider an alternative to PI/r plus TDF/FTC or alternative HCV therapy if possible. Do not co-administer with EVG/c/TDF/FTC. Consider TAF in place of TDF.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Linezolid	Rifabutin[a]	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
	Rifampin[a]	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy.
	Rifapentine[a]	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
Mefloquine	Clarithromycin	↑ Mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for mefloquine toxicity (e.g., QT prolongation).
	Erythromycin	↑ Mefloquine possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Mefloquine possible	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Itraconazole	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Posaconazole	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Mefloquine possible	Monitor for mefloquine efficacy.
	Rifampin[a]	Mefloquine AUC ↓ 68%	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Rifapentine[a]	↓ Mefloquine expected	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Voriconazole	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
Posaconazole	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Daclatasvir	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Posaconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Monitor for posaconazole and HCV regimen-associated toxicities. Monitor posaconazole conc. and adjust dose if necessary.
	Elbasvir/ Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Posaconazole and paritaprevir expected; ↑ ombitasvir and dasabuvir possible	Monitor for posaconazole and HCV regimen-associated toxicities. Monitor posaconazole conc. and adjust dose if necessary.
	Elbasvir/grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected; ↑ posaconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
	Rifabutin[a]	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole and rifabutin conc. and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities (e.g., uveitis).
	Rifampin[a]	↓ Posaconazole expected	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole conc. and adjust dose accordingly; monitor for clinical response.
	Rifapentine[a]	↓ Posaconazole expected	Co-administration should be avoided, if possible, or monitor posaconazole conc. and adjust dose accordingly; monitor clinical response.
	Simeprevir	↑ Simeprevir expected	Do not co-administer.
Quinine	Clarithromycin	↑ Quinine expected; ↑ clarithromycin possible	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ Quinine expected; ↑ erythromycin possible	Do not co-administer. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ Quinine expected; ↑ fluconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine and fluconazole toxicity (e.g., QT prolongation).
	Itraconazole	↑ Quinine expected; ↑ itraconazole possible	Co-administration should be avoided, if possible. If used concomitantly, monitor for quinine and itraconazole toxicity (e.g., QT prolongation), monitor itraconazole conc. and adjust dose accordingly.
	Posaconazole	↑ Quinine expected; ↑ posaconazole possible	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
	Rifabutin[a]	↓ Quinine possible; ↑ rifabutin possible	Monitor for quinine efficacy. Monitor rifabutin conc. and toxicity (e.g., uveitis).
	Rifampin[a]	Quinine AUC ↓ 75% to 85%	Do not co-administer.
	Rifapentine[a]	↓ Quinine expected	Do not co-administer.
	Voriconazole	↑ Quinine expected	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
Rifabutin[a]	Artemether/ Lumefantrine	↓ Artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Atovaquone	Atovaquone C_{SS} ↓ 34%; rifabutin C_{SS} ↓ 19%	Dose adjustment not established; if co-administered, take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Bedaquiline	↓ Bedaquiline possible	If co-administered, monitor for bedaquiline efficacy.
	Caspofungin	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
	Chloroquine	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Clarithromycin	Clarithromycin AUC ↓ by 44%; 14-OH AUC ↑ 57%; rifabutin AUC ↑ 76% to 99%; des-Rbt AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, consider reducing rifabutin dose, monitoring clarithromycin and rifabutin conc., and monitoring for rifabutin-associated toxicities (e.g., uveitis).
	Daclatasvir	↓ Daclatasvir expected	Dose not established. Consider increase daclatasvir dose to 90 mg once daily and monitoring for therapeutic efficacy.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↑ Rifabutin expected; ↓ paritaprevir possible	Co-administration should be avoided if possible. With co-administration, decrease rifabutin dose to 150 mg/day and monitor rifabutin conc. Monitor HCV regimen for efficacy.
	Dapsone	Dapsone AUC ↓ 27% to 40%	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Doxycycline	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Elbasvir/ Grazoprevir	↓ Elbasvir and grazoprevir possible	Co-administration should be avoided, if possible. Consider alternative HCV regimen.
	Erythromycin	↓ Erythromycin possible; ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy or rifabutin toxicities (e.g., uveitis).
	Fluconazole	Rifabutin AUC ↑ 80%; ↔ fluconazole	Use with caution. Monitor for rifabutin-associated toxicities (e.g., uveitis). Consider monitoring rifabutin conc.; may need to lower rifabutin dose to 150 mg/day.
	Itraconazole	Itraconazole AUC ↓ 70%; ↑ rifabutin expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Ledipasvir/ Sofosbuvir	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Linezolid	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
	Mefloquine	↓ Mefloquine possible	Monitor for mefloquine efficacy.
	Posaconazole	Posaconazole AUC ↓ 49%; rifabutin AUC ↑ 72%	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole and rifabutin conc. and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities (e.g., uveitis).
	Quinine	↓ Quinine possible; ↑ rifabutin possible	Monitor for quinine efficacy. Monitor rifabutin conc. and toxicity (e.g., uveitis).
	Simeprevir	↓ Simeprevir expected	Do not co-administer.
	Sofosbuvir	↓ Sofosbuvir expected	Do not co-administer.
	TAF	↓ TAF expected	Do not co-administer
	Velpatasvir/ Sofosbuvir	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	Voriconazole AUC ↓ 79%; rifabutin AUC ↑4-fold	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s). If coadministration is absolutely necessary, monitor voriconazole and rifabutin conc. to guide therapy.
Rifampin[a]	Artemether/ Lumefantrine	↓ Artemether, DHA, and lumefantrine AUC by 89%, 85%, and 68%, respectively	Do not co-administer.
	Atovaquone	Atovaquone C_{ss} ↓ 52% and $t_{1/2}$ ↓ 40%; rifampin C_{ss} ↑ 37%	Do not co-administer.
	Bedaquiline	Bedaquiline AUC ↓ 53%	Do not co-administer.
	Caspofungin	Caspofungin C_{min} ↓ 30%	Caspofungin dose should be ↑ to 70 mg/day.
	Chloroquine	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Clarithromycin	Mean clarithromycin conc. ↓ 87%; rifampin AUC ↑ 60%	Do not co-administer. Use azithromycin in place of clarithromycin.
	Daclatasvir	Daclatasvir AUC ↓ 79%	Do not co-administer.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected	Do not co-administer.
	Dapsone	Dapsone conc. ↓ 7- to 10-fold and $t_{1/2}$ ↓ from 24 to 11 hours	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Doxycycline	Doxycycline AUC ↓ by 59%	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
	Elbasvir/ Grazoprevir	Grazoprevir AUC ↓ 7%, C_{24} ↓ 90%; ↓ elbasvir expected	Do not co-administer.
	Erythromycin	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Fluconazole	Fluconazole AUC ↓ by 23% to 56%	Monitor for antifungal efficacy. May need to increase fluconazole dose.
	Itraconazole	Itraconazole AUC ↓ 64% to 88%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Ledipasvir/ Sofosbuvir	Ledipasvir AUC ↓ 59%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Linezolid	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy.
	Mefloquine	Mefloquine AUC ↓ 68%	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Posaconazole	↓ Posaconazole expected	Co-administration should be avoided, if possible. If co-administered, monitor posaconazole conc. and adjust dose accordingly; monitor for clinical response.
	Quinine	Quinine AUC ↓ 75% to 85%	Do not co-administer.
	Simeprevir	Simeprevir C_{min} ↓92%, AUC ↓ 48%	Do not co-administer.
	Sofosbuvir	Sofosbuvir AUC ↓ 72%	Do not co-administer.
	TAF	↓ TAF expected	Do not co-administer
	Velpatasvir/ Sofosbuvir	Velpatasvir AUC ↓ 82%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Voriconazole	Voriconazole AUC ↓ 96%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Rifapentine[a]	Artemether/ Lumefantrine	↓ Artemether, DHA, lumefantrine expected	Do not co-administer.
	Atovaquone	↓ Atovaquone expected	Do not co-administer.
	Bedaquiline	Bedaquiline AUC ↓ 55% (with daily rifapentine)	Do not co-administer.
	Caspofungin	No data. ↓ Caspofungin possible.	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day.
	Chloroquine	↓ Chloroquine expected	Monitor for chloroquine efficacy.
	Clarithromycin	↓ Clarithromycin expected; ↑ 14-OH and rifapentine expected	Use with caution. Consider azithromycin in place of clarithromycin. If co-administered, monitor for rifapentine-associated toxicities, consider monitoring clarithromycin and rifapentine conc. and adjusting doses accordingly.
	Daclatasvir	↓ Daclatasvir expected	Dose not established. Consider increasing daclatasvir dose to 90 mg once daily and monitoring for therapeutic efficacy
	Dapsone	↓ Dapsone expected	Co-administration should be avoided, if possible. Consider alternatives for dapsone.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	↓ Paritaprevir, ritonavir, ombitasvir, and dasabuvir expected.	Do not co-administer.
	Elbasvir/ Grazoprevir	↓ Elbasvir and grazoprevir possible	Do not co-administer.
	Doxycycline	No data. ↓ Doxycycline possible.	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Erythromycin	↓ Erythromycin expected	Consider azithromycin in place of erythromycin. If co-administered, monitor for erythromycin efficacy.
	Fluconazole	↓ Fluconazole expected	Monitor for antifungal efficacy; may need to ↑ fluconazole dose.
	Itraconazole	↓ Itraconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Ledipasvir/ Sofosbuvir	↓ Ledipasvir and sofosbuvir expected	Do not co-administer.
	Linezolid	No data. ↓ Linezolid possible.	Monitor for linezolid efficacy.
	Mefloquine	↓ Mefloquine expected	Do not co-administer. Use alternative antimalarial drug or rifabutin.
	Posaconazole	↓ Posaconazole expected	Co-administration should be avoided, if possible, or monitor posaconazole conc. and adjust dose accordingly; monitor for clinical response.
	Quinine	↓ Quinine expected	Do not co-administer.
	Simprevir	↓ Simeprevir expected	Do not co-administer.
	Sofosbuvir	↓ Sofosbuvir expected	Do not co-administer.
	TAF	↓ TAF expected	Do not co-administer
	Velpatasvir/ Sofosbuvir	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	↓ Voriconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
Simeprevir	Clarithromycin	↑ Simeprevir expected	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Daclatasvir	Simeprevir AUC ↑ 44%; daclatasvir AUC ↑ 96%	No dosage adjustment. Monitor for simeprevir- and daclatasvir-associated toxicities.
	Erythromycin	Simeprevir AUC ↑ 647%, C_{min} ↑ 1,174%; erythromycin AUC ↑ 90%, C_{min} ↑ 208%	Do not co-administer. Consider azithromycin in place of clarithromycin.
	Fluconazole	↑ Simeprevir possible	Do not co-administer.
	Itraconazole	↑ Simeprevir expected	Do not co-administer.
	Ledipasvir/Sofosbuvir	Ledipasvir AUC ↑ 92%; simeprevir AUC ↑ 116%	Do not co-administer.
	Posaconazole	↑ Simeprevir expected	Do not co-administer.
	Rifabutin[a]	↓ Simeprevir expected	Do not co-administer.
	Rifampin[a]	Simeprevir C_{min} ↓ 92%, AUC ↓ 48%	Do not co-administer.
	Rifapentine[a]	↓ Simeprevir expected	Do not co-administer.
	Voriconazole	↑ Simeprevir expected	Do not co-administer.
Sofosbuvir	Rifabutin[a]	↓ Sofosbuvir expected	Do not co-administer.
	Rifampin[a]	Sofosbuvir AUC ↓ 72%	Do not co-administer.
	Rifapentine[a]	↓ Sofosbuvir expected	Do not co-administer.
TAF	Ledipasvir/Sofosbuvir	Ledipasvir AUC ↑79%	No dosage adjustment.
	Rifabutin[a]	↓ TAF expected	Do not co-administer
	Rifampin[a]	↓ TAF expected	Do not co-administer
	Rifapentine[a]	↓ TAF expected	Do not co-adminster
	Velpatasvir/Sofosbuvir	TAF AUC ↓ 13%	No dosage adjustment.
TDF	Ledipasvir/ Sofosbuvir	TDF AUC ↑ 98% (when given with EFV/FTC) TDF AUC ↑ 40% (when given with RPV/FTC) When used with EVG/c/TDF/FTC, ↑ TDF and ledipasvir expected	Monitor for TDF-associated toxicities when coadministered with PI/r, PI/c, or EFV. Consider an alternative to PI/r plus TDF/FTC or alternative HCV therapy if possible. Do not co-administer with EVG/c/TDF/FTC. Consider TAF in place of TDF.
	Velpatasvir/ Sofosbuvir	TDF AUC ↑35% to 40% when given with EVG/c/FTC or RPV/FTC TDF AUC ↑ 81% when given with EFV/FTC	Monitor for TDF-associated toxicities with PI/r or EFV co-administration. Consider TAF in place of TDF.
Velpatasvir/ Sofosbuvir	Rifabutin[a]	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.
	Rifampin[a]	Velpatasvir AUC ↓ 82%; sofosbuvir AUC ↓ 72%	Do not co-administer.
	Rifapentine[a]	↓ Velpatasvir and sofosbuvir expected	Do not co-administer.
	TAF	TAF AUC ↓ 13%	No dosage adjustment.
	TDF	TDF AUC ↑35% to 40% when given with EVG/c/FTC or RPV/FTC TDF AUC ↑ 81% when given with EFV/FTC	Monitor for TDF-associated toxicities with PI/r or EFV co-administration. Consider TAF in place of TDF.

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

Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Voriconazole	Artemether/ Lumefantrine	↑ Lumefantrine expected	Co-administration should be avoided, if possible. If co-administered, monitor for lumefantrine toxicities (e.g., QT prolongation).
	Bedaquiline	↑ Bedaquiline expected	Co-administration should be avoided, if possible. If co-administered, monitor for bedaquiline toxicities (e.g., QT prolongation).
	Chloroquine	↑ Chloroquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for chloroquine toxicities (e.g., QT prolongation).
	Clarithromycin	↑ Clarithromycin expected	Co-administration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Daclatasvir	↑ Daclatasvir expected	Reduce daclatasvir dose to 30 mg once daily.
	Dasabuvir Ombitasvir Paritaprevir Ritonavir	Voriconazole AUC ↓ 39% (with ritonavir); ↑ paritaprevir expected	Co-administer only if the benefits outweigh the risks. Monitor voriconazole conc. to guide dosage adjustments.
	Elbasvir/Grazoprevir	↑ Elbasvir and grazoprevir expected	Co-administration should be avoided, if possible. If co-administered, monitor closely for hepatotoxicity.
	Erythromycin	↑ Erythromycin expected	Do not co-administer. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ Mefloquine expected	Co-administration should be avoided, if possible. If co-administered, monitor for mefloquine toxicities (e.g., QT prolongation).
	Quinine	↑ Quinine expected	Co-administration should be avoided, if possible. If co-administered, monitor for quinine toxicities (e.g., QT prolongation).
	Rifabutin[a]	Voriconazole AUC ↓ 79%; rifabutin AUC ↑ 4-fold	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s). If coadministration is absolutely necessary, monitor voriconazole and rifabutin conc. to guide therapy.
	Rifampin[a]	Voriconazole AUC ↓ 96%	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	↓ Voriconazole expected	Do not co-administer. Consider alternative antifungal and/or antimycobacterial agent(s).
	Simeprevir	↑ Simeprevir expected	Do not co-administer.

Key to Acronyms: 14-OH = active metabolite of clarithromycin; AUC = area under the curve; C_{24} = concentration at 24h post dose; C_{min} = minimum concentration; C_{ss} = concentration at steady state; CYP3A4 = Cytochrome P450 3A4; des-Rbt = desacetyl rifabutin; DHA = dihydroartemisinin; EFV = efavirenz; EVG = elvitegravir; FTC = emtricitabine; HCV = hepatitis C virus; PI/c = cobicistat-boosted protease inhibitor; PI/r = ritonavir-boosted protease inhibitor; RPV = rilpivirine; $T_{1/2}$ = half-life; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate

[a] Rifamycins are potent inducers of Phase I and Phase II drug-metabolizing reactions. Daily doses of rifampin are well studied, and induction increases over a week or more. Based on limited data, larger doses of rifampin (for example, 1200 mg) appear to produce the same maximum induction, 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, but may result in reduction of exposure of drugs that are CYP3A4 substrates. When a rifamycin is used with a potential interacting drug, close monitoring for clinical efficacy of the other agent is advised.

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 1 of 6) (Last updated March 13, 2017; last reviewed March 13, 2017)

Drugs	Common or Serious Adverse Reactions
Acyclovir	Crystalluria (associated with high dose, dehydration, or pre-existing renal impairment), neurotoxicity (high doses, especially in patients with renal impairment and/or older adults; agitation, confusion, hallucination, seizure, coma), nephrotoxicity secondary to obstructive urolithiasis (particularly after rapid IV infusion), 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 at high doses (especially in patients with renal dysfunction)
Amphotericin B Deoxycholate and Lipid Formulations	Nephrotoxicity, infusion-related reactions (fever, chills, rigors, back pain, hypotension), hypokalemia, hypomagnesemia, anemia, thrombophlebitis, nausea, vomiting Liposomal formulations have lower incidence of nephrotoxicity and infusion-related reactions.
Anidulafungin	Generally well-tolerated. Hepatotoxicity, histamine-related infusion reactions (flushing, rash, pruritus, hypotension, and dyspnea are rare if 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, hemolytic anemia (rare), QTc prolongation
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, torsades de pointes (risk is greatest in patients with underlying QTc prolongation)
Aztreonam	Diarrhea, hypersensitivity reaction (rare), thrombophlebitis, neutropenia, increased liver enzymes, *C. difficile*-associated diarrhea
Benznidazole	Photosensitivity, allergic dermatitis, paresthesia, peripheral neuropathy, nausea, vomiting, abdominal pain, anorexia, weight loss
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
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, pain

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 2 of 6)

Drugs	Common or Serious Adverse Reactions
Cephalosporins (for Ceftriaxone, see above)	Hypersensitivity reaction, rash, nausea, vomiting, diarrhea, C. difficile-associated diarrhea and colitis, bone marrow suppression, CNS toxicities such as seizure and confusion (rare, mostly seen with high doses used in patients with renal insufficiency or elderly patients without dosage adjustment), hemolytic anemia
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, neuromyopathy (rare, but may occur with long-term use), 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 (may require adjustment of antidiabetic medications)
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 of probenecid: 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, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures, peripheral neuropathy
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, increase in serum transaminases (rare)
Cycloserine	Neuropsychiatric toxicities (headache, somnolence, lethargy, vertigo, tremor, dysarthria, irritability, confusion, paranoia, psychosis), seizures (particularly in patients with history of chronic alcoholism), allergic dermatitis, rash, elevated transaminases, congestive heart failure (in patients receiving cycloserine 1-1.5 g daily)
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 erythmatosus, 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), hepatotoxicity (rare), intracranial hypertension, *C. difficile*-associated diarrhea and colitis, tissue hyperpigmentation
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, 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)

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 3 of 6)

Drugs	Common or Serious Adverse Reactions
Ethambutol	Optic neuritis (dose dependent), peripheral neuropathy, headache, nausea, vomiting, anorexia, hepatotoxicity, hyperuricemia, hypersensitivity reaction, disorientation, hallucinations
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/d for >2 months), QTc prolongation
Foscarnet	Nephrotoxicity, electrolyte imbalances (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
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 such as 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 (fever, headache, fatigue, and myalgia), neuropsychiatric disorders (depression and suicidal ideation), neutropenia, anemia, thrombocytopenia, thyroid dysfunction, injection-site reactions, alopecia, nausea, anorexia, diarrhea, weight loss, development or exacerbation of autoimmune disorders, ocular effects (retinal hemorrhage, retinal artery or vein obstructions, and cotton wool spots)
Isoniazid	Hepatotoxicity, peripheral neuropathy, optic neuritis, psychosis (rare), diarrhea, nausea
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
Levofloxacin	Nausea, vomiting, abdominal pain, diarrhea, *C. difficile*-associated diarrhea and colitis, headache, dizziness, sleep disturbances, tendonitis and tendon rupture (associated with >60 years of age and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures (rare), peripheral neuropathy
Linezolid	Anemia, neutropenia, thrombocytopenia (especially with treatment lasting for longer than 2- to 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), lactic acidosis (rare), diarrhea, headache, nausea, vomiting
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

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 4 of 6)

Drugs	Common or Serious Adverse Reactions
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 (such as 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, hemolysis (rare)
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), hypersensitivity reaction (rare—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 >60 years of age and concomitant steroid use), photosensitivity, hypoglycemia, hepatotoxicity, QTc prolongation, neurotoxicity (especially with high doses, use in elderly patients, or use in patients with renal dysfunction), seizures (rare), peripheral neuropathy
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, hypersensitivity reaction (rare)
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 (high dose), neurovascular damage (as a result of 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, pancreatitis (rare)
Pentavalent Antimony (Sodium Stibogluconate)	Nausea, vomiting, abdominal pain, anorexia, pancreatitis (rare), headache, hepatotoxicity, arthralgia, myalgia, cardiac toxicity with higher than 20 mg/kg dose, rash, thrombophlebitis, leukopenia, anemia, thrombocytopenia
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, which may lead to renal toxicities)
Piperacillin-Tazobactam	Generally well-tolerated. Hypersensitivity reaction, rash, diarrhea, nausea, vomiting, *C. difficile*-associated diarrhea and colitis, thrombophlebitis, thrombocytopenia (rare), impaired platelet aggregation, seizure (with high doses used in patients with renal insufficiency)
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

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 5 of 6)

Drugs	Common or Serious Adverse Reactions
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, 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
Simeprevir	Rash and pruritus (generally mild in severity, but severe rashes have been reported), photosensitivity reaction, direct and indirect asymptomatic hyperbilirubinemia without elevation in AST/ALT, mild dyspnea, headache, fatigue, insomnia, dizziness, nausea
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), other severe neurotoxic reactions (mostly in patients with impaired renal function), pain upon IM injection, eosinophilia, *C. difficile*-associated diarrhea and colitis
Sulfadiazine	Rash (including SJS, EM, TEN), anemia, neutropenia, thrombocytopenia, crystalluria (with or without urolithiasis), renal insufficiency, nausea, vomiting, drug fever, hepatotoxicity, headache, peripheral neuritis, tinnitus, vertigo, insomnia
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	Less renal or bone toxicities compared to tenofovir DF
Tetracycline	Photosensitivity, tooth discoloration if taken by infants and children, 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, 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 renal impairment), neurotoxicity (with high doses, especially in patients with renal impairment; agitation, confusion, hallucination, seizure, coma), 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, thrombocytopenia (rare), ototoxicity (associated with excessive concentration), nephrotoxicity (associated with high daily dose and high trough concentrations)

Table 6. Common or Serious Adverse Reactions Associated With Drugs Used for Preventing or Treating Opportunistic Infections (page 6 of 6)

Drugs	Common or Serious Adverse Reactions
Velpatasvir/Sofosbuvir	Headache, fatigue
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), peripheral neuropathy (rare), fluorosis and periotitis with high dose and/or prolonged use, cyclodextrin accumulation (associated with use of IV formulation in patients with CrCl <50 mL/min, which may lead to renal toxicities)

Key to Acronyms: 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; SJS = Stevens-Johnson syndrome; SLE = systemic lupus erythematosus; TEN = toxic epidermal necrolysis; TMP = trimethoprim

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 1 of 7)
(Last updated May 7, 2013; last reviewed May 7, 2013) **NOTE: Update in Progress**

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		Creatinine Clearance (mL/min)*	Dose
Acyclovir	IV dose for: • serious HSV - 5 mg/kg IV q8h, *or* • VZV infections - 10 mg/kg IV q8h	25-50	100% of dose IV q12h
		10-25	100% of dose IV q24h
		<10	50% of dose IV q24h
		hemodialysis	50% of dose q24h; administer after dialysis on day of dialysis
	PO Dose for Herpes Zoster: 800 mg PO 5 times/day	10-25	800 mg PO q8h
		<10	800 mg PO q12h
		hemodialysis	800 mg PO q12h; administer dose after dialysis
Adefovir	10 mg PO q24h	30-49	10 mg PO q48h
		10-29	10 mg PO q72h
		hemodialysis	10 mg PO weekly (dose after dialysis)
Amikacin (for mycobacterial infections)	IV 15 mg/kg/day or 25 mg/kg TIW	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.
Amphotericin B	• 0.7–1.0 mg/kg/day IV (amphotericin B deoxycholate), *or* • 3–6 mg/kg/day IV (lipid formulation)		No dosage adjustment necessary; alternative antifungals should be considered if renal insufficiency occurs during therapy despite adequate hydration.
Capreomycin	15 mg/kg (maximum dose 1000 mg) IV or IM per day	Use with caution in patients with renal insufficiency.	Refer to product label for dosing guidelines based on CrCl. Consider monitoring capreomycin serum concentrations.
Chloroquine (base)	For Treatment of Acute Malaria: • 600 mg PO for 1 dose, followed by 300 mg PO at 6, 24, and 48 hours (for a total dose of 1500 mg)	<10	50% of dose
Cidofovir	• 5 mg/kg IV on day 0, repeat 5 mg/kg IV dose at day 7, then 5 mg/kg IV every 2 weeks (days 21, 35, 49, 63, etc.) Each dose should be given with probenecid and saline hydration (see Table 2).	• Pretreatment SCr >1.5 mg/dL, *or* • CrCl < 55 mL/min, *or* • >100 mg/dL (>2+) protein in urinalysis	Cidofovir is not recommended
		If SCr increases by 0.3–0.4 mg/dL from baseline	3 mg/kg IV per dose
		• If SCr increases >0.5 mg/dL >baseline, or • ≥3+ proteinuria	Discontinue therapy

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 2 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		Creatinine Clearance (mL/min)*	Dose	
Ciprofloxacin	• 500–750 mg PO q12h, *or* • 400 mg IV q8–12h	<30	250–500 mg PO q24h *or* 400 mg IV q24h	
		hemodialysis or peritoneal dialysis	250–500 mg PO q24hr *or* 200–400 mg IV q24h (administered after dialysis)	
Clarithromycin	500 mg PO BID	<30	250 mg PO BID or 500 mg PO once daily	
Cycloserine	10 mg/kg/day PO in 2 divided doses (maximum 1000 mg/day)	50-80	Normal dose, consider monitoring serum concentration and toxicities	
		<50 (not on hemodialysis)	Not recommended because of accumulation and toxicities.	
		hemodialysis	250 mg PO once daily or 500 mg PO TIW—consider monitoring serum cycloserine concentration	
Emtricitabine	• 200–mg tablet PO once daily, *or* • 240–mg solution PO once daily		<u>Oral Tablets</u>	<u>Oral Solution</u>
		30-49	200 mg q48h	120 mg q24h
		15-29	200 mg q72h	80 mg q24h
		<15 or hemodialysis (dose after dialysis)	200 mg q96h	60 mg q24h
Emtricitabine/ Tenofovir (co-formulation as Truvada) Please refer to product information for dosing recommendations for other ARV fixed dose combination product containing tenofovir/ emtricitabine.	200 mg/300 mg - 1 tablet PO daily	30-49	1 tablet PO q48h (monitor for worsening renal function; consider alternative to TDF)	
		<30 or hemodialysis	Co-formulated tablet should not be used for CrCl <30 mL/min. Use individual formulation and adjust dose according to recommendations for individual drugs.	
Entecavir	<u>Usual Dose</u>: • 0.5 mg PO once daily <u>For Treatment of 3TC-Refractory HBV or for Patients with Decompensated Liver Disease</u>: • 1 mg PO once daily		<u>Usual Dose</u>	<u>3TC-Refractory or Decompensated Liver Disease</u>
		30 to <50	• 0.25 mg q24h, *or* • 0.5 mg q48h	• 0.5 mg q24h, *or* • 1 mg q48h
		10 to <30	• 0.15 mg q24h, *or* • 0.5 mg q72h	• 0.3 mg q24h, *or* • 1 mg q72h
		<10 or hemodialysis or CAPD (administer after dialysis on dialysis day)	• 0.05 mg q24h, *or* • 0.5 mg q7 days	• 0.1 mg q24h, *or* • 1 mg q7 days
Ethambutol	• 15–25 mg/kg PO daily • (15 mg/kg PO daily for MAI; 15–25 mg/kg PO daily for MTB)	10-50	15–25 mg/kg q24–36h	
		<10	15–25 mg/kg q48h	
		hemodialysis	15–25 mg/kg TIW after hemodialysis Can consider TDM to guide optimal dosing	

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 3 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		Creatinine Clearance (mL/min)*	Dose	
Famciclovir	For Herpes Zoster: • 500 mg PO q8h	40-59	500 mg PO q12h	
		20-39	500 mg PO q24h	
		<20	250 mg PO q24h	
		hemodialysis	250 mg PO after each dialysis	
Fluconazole	200–1200 mg PO or IV q24h	≤50	50% of dose q24h	
		hemodialysis	Full dose after each dialysis	
Flucytosine	25 mg/kg PO q6h If available, TDM is recommended for all patients to guide optimal dosing (goal peak 30–80 mcg/mL 2 hour post dose)	20-40	25 mg/kg q12h	
		10-20	25 mg/kg q24h	
		<10	25 mg/kg q48h	
		hemodialysis	25–50 mg/kg q48–72h (after hemodialysis)	
Foscarnet	180 mg/kg/day IV in 2 divided doses for induction therapy for CMV infection 90–120 mg/kg IV once daily for maintenance therapy for CMV infection or for treatment of HSV infections	Dosage adjustment needed according to calculated CrCl/kg; consult product label for dosing table.		
Ganciclovir	Induction Therapy: • 5 mg/kg IV q12h	50-69	2.5 mg/kg IV q12h	
		25-49	2.5 mg/kg IV q24h	
		10-24	1.25 mg/kg IV q24h	
		<10 or on hemodialysis	1.25 mg/kg IV TIW after dialysis	
	Maintenance Therapy: • 5 mg/kg IV q24h	50-69	2.5 mg/kg IV q24h	
		25–49	1.25 mg/kg IV q24h	
		10–24	0.625 mg/kg IV q24h	
		<10 or on hemodialysis	0.625 mg/kg IV TIW after dialysis	
Lamivudine	300 mg PO q24h	30-49	150 mg PO q24h	
		15-29	150 mg PO once, then 100 mg PO q24h	
		5-14	150 mg PO once, then 50 mg PO q24h	
		<5 or on hemodialysis	50 mg PO once, then 25 mg PO q24h (give the dose after dialysis on dialysis day)	
Levofloxacin	500 mg (low dose) or 750 mg (high dose) IV or PO daily Nosocomial Pneumonia/ Osteomyelitis: • 750 mg daily		Lower Dose	High Dose
		20-49	500 mg once, then 250 mg q24h	750 mg q48h
		<20 or on CAPD or hemodialysis (dose after dialysis)	500 mg once, then 250 mg q48h	750 mg once, then 500 mg q48h
Peginterferon Alfa-2a	180 mcg SQ once weekly	<30 or on hemodialysis	135 mcg SQ once weekly	
Peginterferon Alfa-2b	1.5 mcg/kg SQ once weekly	30–50	Reduce dose by 25%	
		10–29 and hemodialysis	Reduce dose by 50%	

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 4 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		Creatinine Clearance (mL/min)*	Dose
Penicillin G Potassium (or sodium)	Neurosyphilis or Ocular/Otic Syphilis: • 3–4 million units IV q4h, *or* • 18–24 million units IV daily as continuous infusion	10-50	2–3 million units q4h or 12–18 million units as continuous infusion
		<10	2 million units q4–6h or 8–12 million units as continuous infusion
		hemodialysis or CAPD	2 million units q6h or 8 million units as continuous infusion
Pentamidine	4 mg/kg IV q24h	10-50	3 mg/kg IV q24h
		<10	4 mg/kg IV q48h
Pyrazinamide	See Table 3 for weight-based dosing guidelines	<10	50% of usual dose
		hemodialysis	Usual dose given after dialysis
Quinidine Gluconate (salt) (10 mg quinidine gluconate salt = 6.25 mg quinidine base)	10 mg/kg (salt) IV over 1–2 hours, then 0.02 mg/kg/min (salt) IV for up to 72 hours or until able to take PO meds Consider TDM for all patients to optimize dosing.	<10	75% of normal dose
		hemodialysis	75% of normal dose; some clinicians recommend supplementation with 100 mg–200 mg after dialysis.
Quinine Sulfate	650 mg salt (524 mg base) PO q8h	<10 or hemodialysis	650 mg once, then 325 mg PO q12h
Ribavirin	For genotypes 1 and 4: • 1000–1200 mg PO per day in 2 divided doses (based on weight, see Table 2 for full dosing recommendation) For genotypex 2 and 3: • 400 mg PO BID for genotypes 2 and 3	30-50	Alternate dosing 200 mg PO and 400 mg PO every other day
		<30 or hemodialysis	200 mg PO daily
Rifabutin	300 mg PO daily (see Table 5 for dosage adjustment based on drug-drug interaction)	<30	50% of dose once daily. Consider TDM
Streptomycin	• 15 mg/kg IM or IV q24h, *or* • 25 mg/kg IM or IV TIW	Use with caution in patients with renal insufficiency.	Adjust dose based on serum concentrations.
Sulfadiazine	1000–1500 mg PO q6h (1500 mg q6h for >60kg)	10-50	1000–1500 mg PO q12h (ensure adequate hydration)
		<10 or hemodialysis	1000–1500 mg PO q24h (dose after HD on days of dialysis)
Telbivudine	600 mg PO daily	30-49	Oral tablets: 600 mg PO q48h Oral solution: 400 mg PO q24h
		<30	Oral tablets: 600 mg PO q72h Oral solution: 200 mg PO q24h
		hemodialysis	Oral tablets: 600 mg PO q96h (dose after dialysis) Oral solution: 120 mg PO q24h (dose after dialysis on dialysis day)

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 5 of 7)

Drugs	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		Creatinine Clearance (mL/min)*	Dose	
Tenofovir	300 mg PO daily	30-49	300 mg PO q48h	
		10-29	300 mg PO q72–96h	
		<10 and not on dialysis	Not recommended	
		hemodialysis	300 mg PO once weekly (dose after dialysis) Can consider alternative agent for treatment of HBV and/or HIV if TDF-associated renal toxicity occurs.	
Tetracycline	250 mg PO q6h Consider using doxycycline in patients with renal dysfunction.	10-49	250 mg PO q12–24h	
		<10	250 mg PO q24h	
		hemodialysis	250 mg PO q24h; dose after dialysis	
Trimethoprim/ Sulfamethoxazole	For PCP Treatment: • 5 mg/kg (of TMP component) IV q8h, *or* • 2 DS tablets PO q8h	10-30	5 mg/kg (TMP) IV q12h or TMP-SMX 2 DS tablets PO q12h	
		<10	5 mg/kg (TMP) IV q24h, or TMP-SMX DS tablet PO q12h (or 2 TMP-SMX DS tablets q24h)	
		hemodialysis	5 mg/kg/day (TMP) IV or 2 TMP-SMX DS tablets PO; dose after dialysis on dialysis day Can consider TDM to optimize therapy (target TMP concentrations: 5–8 mcg/mL)	
Valacyclovir	For Herpes Zoster: • 1 g PO TID	30-49	1 g PO q12h	
		10-29	1 g PO q24h	
		<10	500 mg PO q24h	
		hemodialysis	500 mg PO q24h; dose after dialysis on dialysis days	
Valganciclovir	Induction Therapy: • 900 mg PO BID Maintenance Therapy: • 900 mg PO daily		Induction	Maintenance
		40-59	450 mg PO BID	450 mg PO daily
		25-39	450 mg PO daily	450 mg PO q48h
		10-25	450 mg PO q48h	450 mg PO BIW
		<10 not on dialysis	not recommended	not recommended
		hemodialysis (clinical efficacy of this dosage has not been established)	200 mg PO TIW after dialysis (oral powder formulation)	100 mg PO TIW after dialysis (oral powder formulation)
Voriconazole	• 6 mg/kg IV q12h 2 times, then 4 mg/kg q12h, *or* • 200–300 mg PO q12h	<50	IV voriconazole is not recommended because of potential toxicity due to accumulation of sulfobutylether cyclodexrin (vehicle of IV product). Should switch to PO voriconazole in these patients. No need for dosage adjustment when PO dose is used.	

Table 7. Dosing Recommendations for Drugs Used in Treating or Preventing Opportunistic Infections Where Dosage Adjustment is Needed in Patients with Renal Insufficiency (page 6 of 6)

Key to Acronyms: 3TC = lamivudine; BID = twice daily; BIW = twice weekly; CAPD = continuous ambulatory peritoneal dialysis; CMV = cytomegalovirus; CrCl = creatinine clearance; DS = double strength, HBV = hepatitis B virus; HSV = herpes simplex virus; IM = intramuscular; IV = intravenous; MAI = *Mycobacterium avium intracellulare*; MTB = *Mycobacterium tuberculosis*; PCP = *Pneumocystis* pneumonia; PO = orally; q(n)h = every "n" hours; SQ = subcutaneous; SCr = ; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TID = three times daily; TIW = three times weekly; TMP = trimethoprim; SMX = sulfamethoxazole; VZV = varicella zoster virus

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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 1 of 9) (Last updated October 28, 2014; last reviewed July 25, 2017)

NOTE: Update in Progress

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Acyclovir	B	No teratogenicity in mice, rats, rabbits at human levels. Large experience in 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 human use in pregnancy.	Not recommended because of limited data in pregnancy. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com
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, amox./ clavulanate, ampicillin/ sulbactam	B	Not teratogenic in animals. Large experience in human pregnancy does not suggest an increase in adverse events.	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.	Therapy of visceral leishmaniasis not responsive to amphotericin B or pentamidine
Artesunate, artemether, 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 adverse events.	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 not available or have failed. Report cases of exposure to 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 adverse events.	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 can not 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 9)

Drug	FDA Category	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. Large experience in human pregnancy has not suggested increase in adverse outcomes.	Bacterial infections; alternate treatment for MAC
Chloroquine	C	Associated with anophthalmia, microophthalmia 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, other quinolones	C	Arthropathy in immature animals; not embryotoxic or teratogenic in mice, rats, rabbits, or monkeys. More than 1100 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 chloroquineresistant malaria; alternate agent for secondary prophylaxis of *Toxoplasma* encephalitis
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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 3 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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.	Alternate choice for primary or secondary PCP prophylaxis
Diphenoxylate	C	Limited animal and human data do not indicate teratogenicity.	Symptomatic treatment of diarrhea
Doxycycline, other tetracyclines	D	Risk of hepatic toxicity increased with tetracyclines in pregnancy; staining of fetal bones and teeth contraindicates use in pregnancy.	No indications
Emtricitabine	B	No concerns in pregnancy from limited animal and human data.	As part of fully suppressive combination antiretroviral regimen for treatment of HIV, HBV. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Entecavir	C	Animal data do not suggest teratogenicity at human doses; 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 Antiretroviral Pregnancy Registry: http://www.APRegistry.com
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.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 4 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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 lifethreatening fungal infections.
Foscarnet	C	Skeletal variants in rats, rabbits and hypoplastic dental enamel in rats. Single case report of use in human pregnancy in third trimester.	Iternate agent for treatment or secondary prophylaxis of life-threatening or sightthreatening 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, 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 lifethreatening or sight-threatening CMV infection. Preferred agent for therapy in children.
Imipenem, meropenem	C/B	Not teratogenic in animals; limited human experience.	Serious bacterial infections
Imiquimod	B	Not teratogenic in rats and rabbits; 8 case reports of human use, only 2 in first trimester.	Because of limited experience, other treatment modalities such as cryotherapy or trichloracetic 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, 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.
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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 5 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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 over 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
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 >3700 first-trimester exposures reported to Antiretroviral Pregnancy Registry.	HIV and HBV therapy, only as part of a fully suppressive combination ARV regimen. Report exposures to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Ledipasvir/sofusbuvir	B	No evidence of teratogenicity in rats or rabbits. No experience in human pregnancy	Treatment of hepatitis C 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 if use of pyrimethamine cannot be avoided.
Linezolid	C	Not teratogenic in animals. Decreased fetal weight and neonatal survival at ~ 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**	
Metronidazole	B	Multiple studies do not indicate teratogenicity. Studies on several hundred women with firsttrimester 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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 6 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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
Para-amino salicylic acid (PAS)	C	Occipital bone defects in one study in rats; not teratogenic in rabbits. Possible increase in limb, ear anomalies in one study with 143 first-trimester exposures; no specific pattern of defects noted, several studies did not find increased risk.	Drug-resistant TB
Paromomycin	C	Not teratogenic in mice and rabbits. Limited human experience, but poor oral absorption makes toxicity, teratogenicity unlikely.	Amebic intestinal infections, possibly cryptosporidiosis
Penicillin	B	Not teratogenic in multiple animal species. Vast experience with use in human pregnancy does not suggest teratogenicity, other adverse outcomes.	Syphilis, other susceptible bacterial infections
Pentamidine	C	Embryocidal but not teratogenic in rats, rabbits with systemic use. Limited experience with systemic use in 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. HIVinfected pregnant women should be on ART before vaccination to limit potential increases in HIV RNA levels with immunization.
Podophyllin, 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 not recommended; 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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 7 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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 8th nerve damage reported.	Alternate treatment of malaria, control of fetal arrhythmias
Quinine sulfate	C	High doses, often taken as an abortifacient, have been associated with birth defects, especially deafness, in humans and animals. Therapeutic doses have not been associated with an increased risk of defects in humans or animals. Monitor for hypoglycemia.	Treatment of chloroquine-resistant malaria
Ribavirin	X	Dose-dependent risk of multiple defects (craniofacial, central nervous system, skeletal, anophthalmia) in rats, mice, hamsters starting at below human doses. Reports of treatment during second half of pregnancy in nine women without incident; first 49 cases in registry did not suggest increased risk, but limited data.	Contraindicated in early pregnancy; no clear indications in pregnancy. Report exposures during pregnancy to Ribavirin Pregnancy Registry at (800) 593-2214 or www.ribavirinpregnancyregistry.com
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
Simeprevir	C	Decreased fetal weights and increased skeletal variants in mice at 4x 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.
Sofobusvir	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.

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 8 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
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 antiretroviral regimen with antiretroviral agents active against both HIV and hepatitis B. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
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 2000 first-trimester exposures in women.	Component of fully suppressive antiretroviral regimen in pregnant women. Report exposures during pregnancy to Antiretroviral Pregnancy Registry: http://www.APRegistry.com.
Trichloracetic acid, bichloracetic 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 firsttrimester 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

Table 8. Summary of Pre-Clinical and Human Data on, and Indications for, Opportunistic Infection Drugs During Pregnancy (page 9 of 9)

Drug	FDA Category	Pertinent Animal Reproductive and Human Pregnancy Data	Recommended Use During Pregnancy
Voriconazole	D	Embryotoxic in rats, rabbits. Teratogenic in rats (cleft palate, hydronephrosis, and ossification defects). No experience with human use.	Not recommended

Key to Acronyms: 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 1 (Last updated September 13, 2017; last reviewed September 13, 2017)

Figure. Recommended immunization schedule for adults and adolescents with HIV infection, United States, 2017

Adapted from the Advisory Committee on Immunization Practices (ACIP) recommended immunization schedules for adults and adolescents. 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.

VACCINE	Age					CD4 Cell Count (cells/µL)	
	13–18 years	19–26 years	27–59 years	60–64 years	≥65 years	<200	≥200
Influenza[1]	1 dose annually					1 dose annually	
Tdap/Td[2]	1 dose Tdap, then Td booster every 10 yrs					1 dose Tdap, then Td booster every 10 yrs	
MMR[3]	2 doses if CD4 cell count ≥200					Contraindicated	2 doses if born in 1957 or later
VAR[4]	2 doses if CD4 cell count ≥200					Contraindicated	2 doses
HZV[5]						Contraindicated	
HPV[6]	3 doses					3 doses through age 26 yrs	
PCV13[7]	1 dose					1 dose	
PPSV23[7]	2 doses				1 dose	Up to 3 doses depending on age	
HepA[8]	2 or 3 doses depending on vaccine					2 or 3 doses depending on vaccine	
HepB[9]	3 doses					3 doses	
MenACWY[10]	2 doses, then booster every 5 yrs					2 doses, then booster every 5 yrs	
MenB[10]	2 or 3 doses depending on vaccine					2 or 3 doses depending on vaccine	
Hib[11]	1 or 3 doses depending on indication					1 or 3 doses depending on indication	

Recommended for adults and adolescents with HIV infection

Recommended for adults and adolescents with HIV infection and other indications

Contraindicated

No recommendation

Abbreviations used for vaccines

HepA	hepatitis A vaccine	IIV	inactivated influenza vaccine	RIV	recombinant influenza vaccine
HepA-HepB	hepatitis A and hepatitis B vaccine	MenACWY	serogroups A, C, W, and Y meningococcal vaccine	Td	tetanus and diphtheria toxoids
HepB	hepatitis B vaccine	MenB	serogroup B meningococcal vaccine	Tdap	tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine
Hib	*Haemophilus Influenzae* type b vaccine	MMR	measles, mumps, and rubella vaccine (live)		
HPV vaccine	human papillomavirus vaccine	PCV13	13-valent pneumococcal conjugate vaccine	VAR	varicella vaccine (live)
HZV	herpes zoster vaccine (live)	PPSV23	23-valent pneumococcal polysaccharide vaccine		

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Report clinically significant postvaccination events to the Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or by telephone, 800-822-7967.

All vaccines listed on this immunization schedule except herpes zoster and 23-valent pneumococcal polysaccharide vaccines are covered by the Vaccine Injury Compensation Program. Information on how to file a claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382.

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

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

Leadership (Last Reviewed: May 14, 2019; Last Updated: May 14, 2019)

Member		Financial Disclosure	
		Company	Relationship
Benson, Constance	*University of California, San Diego*	Dr. Benson has served on an advisory and a data monitoring board for GlaxoSmithKline/ViiV Healthcare and received research grants awarded to her institution from Gilead Sciences, Inc. Her spouse has served as a consultant to CytoDyn, Gilead Sciences, Inc, Pfizer, and Vir Biotechnology; has received grant support from Gilead Sciences, Inc; and holds stock or stock options in Antiva Biosciences and CytoDyn.	
Brooks, John T.	*Centers for Disease Control and Prevention*	None	N/A
Holmes, King	*University of Washington School of Medicine*	Merck	Honoraria
Masur, Henry	*National Institutes of Health*	None	N/A
Pau, Alice	*National Institutes of Health*	None	N/A

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from May 1, 2017, through May 1, 2019.

Pneumocystis Pneumonia (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Crothers, Kristina	*Yale University School of Medicine*	• NIH	• Research
Furrer, Hansjakob	*Universitatsspital Bern, Switzerland*	None	N/A
Helweg-Larsen, Jannik	*Rigshospitalet, Copenhagen University, Denmark*	None	N/A
Huang, Laurence	*University of California, San Francisco*	• NIH	• Research
Kovacs, Joe*	*National Institutes of Health*	None	N/A
Miller, Robert	*University College London, England*	• Gilead	• Honoraria, Speaker's Bureau
		• Janssen-Cilag	• Honoraria, Speaker's Bureau
		• Mark Allen Healthcare	• Honoraria
		• Merck	• Honoraria, Speaker's Bureau
Morris, Alison	*University of Pittsburgh Medical School*	• Associates of Cape Cod	• Research Support
		• Gilead	• Research Support
		• NIH	• Research Support
		• Roche	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Toxoplasma gondii Encephalitis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Boyd, Sarita	*Food and Drug Administration*	None	N/A
Chow, Felicia	*University of California, San Francisco*	• Gilead	• Stock Holder†
Kovacs, Joe*	*National Institutes of Health*	None	N/A
Lai, Leon	*Washington Hospital Center*	• Advanced Medical	• Stock Holder
		• Amgen	• Stock Holder
		• Bristol-Myers Squibb	• Stock Holder
		• DuPont	• Stock Holder
		• Eli Lilly & Co.	• Stock Holder
		• Merck	• Stock Holder
		• Pfizer	• Stock Holder
		• Schering-Plough	• Stock Holder
Miro, Jose M.	*Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain*	• Abbvie	• Consultant, Honoraria, Speaker's Bureau
		• Astellas	• Consultant
		• Bristol-Myers Squibb	• Consultant, Honoraria, Research Support, Speaker's Bureau
		• Cubist	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Fundacion Maximo Soriano Jimenez, Barcelona, Spain	• Research Support
		• Gilead	• Consultant, Honoraria, Speaker's Bureau
		• GlaxoSmithKline	• Honoraria, Speaker's Bureau
		• Instituto de Salud Carlos III, Spanish Ministry of Health, Madrid, Spain	• Research Support
		• Janssen-Cilag	• Speaker's Bureau
		• Merck	• Consultant, Speaker's Bureau
		• National Institutes of Health	• Research Support
		• Novartis	• Advisory Board, Consultant, Honoraria,Research Support, Speaker's Bureau
		• Pfizer	• Consultant, Speaker's Bureau
		• ViiV Healthcare	• Honoraria, Speaker's Bureau, Research Support
Montoya, Jose	Stanford University	None	N/A

Toxoplasma gondii Encephalitis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Podzamczer, Daniel	*Hospital Universitari de Bellvitge, Spain*	• Abbott	• Advisory Board, Speaker's Bureau
		• Boehringer Ingelheim	• Advisory Board, Research Support, Speaker's Bureau, Travel Support
		• Bristol-Myers Squibb	• Advisory Board, Speaker's Bureau
		• Gilead	• Advisory Board, Research Support, Speaker's Bureau
		• GlaxoSmithKline	• Advisory Board, Research Support, Speaker's Bureau
		• Janssen-Cilag	• Advisory Board, Speaker's Bureau
		• Merck	• Advisory Board, Speaker's Bureau
		• Pfizer	• Advisory Board, Research Support, Speaker's Bureau
		• ViiV	• Advisory Board, Research Support, Speaker's Bureau

* Group lead; † Divested

Note: Members were asked to disclose all relationships from 24 months prior to the update date. The period of reporting was from September 1, 2012, through September 1, 2014.

Cryptosporidiosis and Microsporidiosis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Desruisseaux, Mahalia	*Albert Einstein College of Medicine*	None	N/A
Didier, Elizabeth	*Tulane University*	None	N/A
Ward, Honorine	*Tufts University Medical School*	None	N/A
Weiss, Louis*	*Albert Einstein College of Medicine*	• NIH	• Research Support
White, A. Clinton	*University of Texas Medical Branch*	None	N/A
Xiao, Lihua	*Centers for Disease Control and Prevention*	• Water Research Foundation	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the update date. The period of reporting was from September 1, 2012, through September 1, 2014.

Mycobacterium tuberculosis Infection and Disease (Last Reviewed: March 1, 2018; Last Updated: March 1, 2018)

Member		Financial Disclosure	
		Company	Relationship
Brust, James*	*Albert Einstein College of Medicine*	None	N/A
Dooley, Kelly	*Johns Hopkins University*	• Viiv Health Care	• Research Support
Maartens, Gary	*University of Cape Town, South Africa*	• Janssen	• Consultant
Meintjes, Graeme	*University of Cape Town, South Africa*	• Gilead	• Research Support
Shah, Sarita	*Centers for Disease Control and Prevention*	None	N/A
Sterling, Timothy	*Vanderbilt University*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 12 months prior to the updated date. The period of reporting was from March 1, 2017, through March 1, 2018.

Disseminated *Mycobacterium avium* Complex Disease (Last Reviewed: November 1, 2012; Last Updated: November 1, 2012)

Member		Financial Disclosure	
		Company	Relationship
Cohn, David	*University of Colorado School of Medicine*	None	N/A
Currier, Judith	*University of California, Los Angeles*	• Achillion	• DSMB Member
		• EMD Seronon	• Advisory Board
		• Gilead	• Consultant
		• GlaxoSmithKline	• Honoraria
		• Janssen-Cilag	• Honoraria, Travel Support
		• Koronis	• DSMB Member
		• Merck	• Advisory Board, Research Support
		• Pfizer	• Advisory Board
		• Schering-Plough	• Research Support
		• Tibotec	• Advisory Support, Research Support, Travel Support
Dorman, Susan	*Johns Hopkins University*	• Bill and Melinda Gates Foundation	• Research Support
		• FDA	• Research Support
		• NIH	• Research Support
Gordin, Fred*	*Veterans Affairs Medical Center; Washington, DC*	None	N/A
Horsburgh, C. Robert	*Boston University*	• Bill and Melinda Gates Foundation	• Travel Support
		• CDC	• Research Support
		• Medical Research Council (UK)	• Travel Support
		• NIH	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months before the writing panel convened. The period of reporting was from June 1, 2008, through November 1, 2012.

Bacterial Respiratory Disease (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Crothers, Kristina*	*University of Washington*	None	N/A
Miller, Robert	*University College London, England*	• Gilead	• Honoraria, Speaker's Bureau
		• Mark Allen Healthcare	• Honoraria
		• Merck	• Honoraria, Speaker's Bureau
Moore, Matthew	*Centers for Disease Control and Prevention*	None	N/A
Morris, Alison	*University of Pittsburgh Medical School*	• Cape Cod Association	• Research Support
		• Gilead	• Research Support
		• NIH	• Research Support
		• Roche	• Research Support
Niederman, Michael	*Winthrop University Hospital*	• Bayer	• Advisory Board, Honoraria, Research Support
		• Cubist	• Research Support
		• Merck	• Advisory Board
		• Pfizer	• Advis
		• Thermo-Fisher	• Honoraria

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012 through September 1, 2014.

Bacterial Enteric Infections (Last Reviewed: April 1, 2016; Last Updated: April 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Bowen, Anna	*Centers for Disease Control and Prevention*	• Procter and Gamble	• Research Support
Pham, Paul	*University of Maryland & Westview Urgent Care Medi Center*	None	• N/A
Sears, Cynthia*	*Johns Hopkins University*	• Clinical Infectious Diseases	• Other
		• Merieux Institute	• Research Support
		• NIH	• Research Support
		• Up-To-Date	• Other
Wanke, Christine	*Tufts University Medical School*	• GlaxoSmithKline	• Research Support
		• Optimer Pharmaceutical	• DS
		• Pfizer	• Clinical Trial Even Adjucation

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from April 1, 2014, through April 1, 2016.

Bartonellosis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Basgoz, Nesli	*Harvard Medical School*	• Forest Labs	• Other
Chomel, Bruno	*University of California Davis*	None	N/A
Kirby, James	*Harvard Medical School*	None	N/A
Koehler, Jane*	*Univer*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Syphilis (Last Reviewed: February 1, 2016; Last Updated: February 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Bolan, Gail	*Centers for Disease Control and Prevention*	None	N/A
Ghanem, Khalil	*Johns Hopkins University*	None	N/A
Hollier, Lisa	*Baylor College of Medicine*	None	N/A
Hook, Edward W.	*University of Alabama at Birmingham*	• Becton-Dickinson	• Honoraria, Research Support
		• Gen Probe	• Research Support
		• GlaxoSmithKline	• Research Support
		• Merck	• Honoraria
		• Siemens	• Research Support
Sena, Arlene	*University of North Carolina*	None	N/A
Stoner, Brad	*Washington University School of Medicine*	None	N/A
Workowski, Kim*	*Emory University*	• Bristol-Myers Squibb	• Research Support
		• CDC	• Consultant
		• Gilead	• Consultant
		• Vertex	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from February 1, 2014, through February 1, 2016.

Mucocutaneous Candidiasis (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Lionakis, Michail*	*National Institutes of Health*	None	N/A
Ostrosky-Zeichner, Luis	*University of Texas Houston*	• Astellas	• Advisory Board, Consultant, Research Support
		• Cape Cod Assoc.	• Research Support
		• Merck	• Advisory Board, Consultant, Research Support, Speaker's Bureau
		• Pfizer	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• T2 Biosystems	• Research Support
Revankar, Sanjay	*Wayne State University School of Medicine*	• Astellas	• Research Support
		• Merck	• Research Support
		• Optimer	• Consultant
		• T2 Biosystems	• Research Support
Sobel, Jack	*Wayne State University School of Medicine*	• Astellas	• Honoraria, Speaker's Bureau
Vazquez, Jose	*Henry Ford Hospital*	• Astellas	• Honoraria, Research Support, Speaker's Bureau
		• Forest	• Advisory Board, Honoraria, Speaker's Bureau
		• Merck	• Honoraria, Research Support, Speaker's Bureau
		• Pfizer	• Honoraria,
		• Strativa	• Honoraria, Speaker's Bureau

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Invasive Mycoses (Last Reviewed: November 10, 2016; Last Updated: November 10, 2016)

Member		Financial Disclosure	
		Company	Relationship
Ampel, Neil*	*University of Arizona*	• Nielsen BioSciences	• Research Support
Blair, Janis	*Mayo Clinic Arizona*	None	N/A
Hage, Chadi	*Indiana University*	None	N/A
Hamill, Richard	*Baylor College of Medicine*	None	N/A
Kauffman, Carol	*University of Michigan and VA Ann* Arbor Healthcare System	None	N/A
Pappas, Peter	*University of Alabama at Birmingham*	• Astellas	• Advisory Board, Consulting, Honoraria, Research Support
		• Merck	• Advisory Board, Research Support, Speaker's Bureau
		• Pfizer	• Advisory Board, Research Support
		• T-2 Diagnostics	• Advisory Board
Perfect, John	*Duke University*	• Amplyx	• Consultant, Research Support
		• Astellas	• Advisory Board, Consultant, Honoraria, Research Support
		• Cidara	• Consultant
		• F2G	• Consultant
		• Merck	• Advisory Board, Consultant, Honoraria, Research Support
		• Minnetronix	• Consultant, Research Support
		• Pfizer	• Consultant, Research Support
		• Scynexis	• Consultant
		• TEVA	• Honoraria
		• *Viamet*	• Consultant
		• Vical	• Consultant

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from November 1, 2014, through November 1, 2016.

Herpes (Last Reviewed: February 2018; Last Updated: February 2018)

Member		Financial Disclosure	
		Company	Relationship
Durand, Christine	*Johns Hopkins*	Gilead	Advisory Board
		GlaxoSmithKline	Research Support
		Merck	Research Support
		ViiV Healthcare	Research Support
Gnann, John	*Medical University of South Carolina*	BioCryst	DSMB Member
		GlaxoSmithKline	DSMB Member
		Merck	DSMB Member, Consultant
Gary Holland	*University of California, Los Angeles*	None	N/A
Johnston, Christine*	*University of Washington*	Aicuris	DSMB Member
		Genocea	Research Support
		Novavax	Advisory Board
		Sanofi	Research Support
		Vical	Research Support
Parsons, Christopher	*Pardee Hospital, University of North Carolina Health Systems*	None	N/A
Phipps, Warren	*University of Washington School of Medicine*	None	N/A
Ross, Shannon	*University of Alabama at Birmingham*	Merck	Advisory Board
Van Wagonar, Nicholas	*University of Alabama at Birmingham*	Genocea	Research Support
		Vical	Research Support
Wohl, David	*University of North Carolina at Chapel Hill*	Clinical Research Management	Research Support
		Gilead	Research Support, Scientific Advisory Board
		Janssen	Scientific Advisory Board
		ViiV	Research Support

* Group lead

Note: Members were asked to disclose all relationships from 12 months prior to the updated date. The period of reporting was from February 1, 2017, through February 1, 2018.

Human Papillomavirus Disease (Last Reviewed: March 1, 2018; Last Updated: March 1, 2018)

Member		Financial Disclosure	
		Company	Relationship
Brown, Darron	*Indiana University School of Medicine*	• Merck	• Advisory Board, Honoraria, Patent, Speaker's Bureau
		• PDS, Inc.	• Advisory Board
Cu-Uvin, Susan*	*Brown University*	• Gilead	• Advisory Board
Dunne, Eileen	Centers for Disease Control and Prevention	None	N/A
Einstein, Mark	*Rutgers New Jersey Medical School*	• Baxalta	• Research Support
		• Becton-Dickinson	• Research Support
		• Eli Lilly	• Research Support
		• Inovio	• Advisory Board, Research Support, Travel Support
		• Natera	• Consultant
		• Papivax	• Consultant
		• PDS, Inc.	• Consultant, Research Support, Travel Support
		• Photocure	• Consultant, Research Support, Travel Support
		• Roche Molecular Diagnostics	• Advisory Board, Travel Support
Massad, L. Stewart	*Washington University School of Medicine*	None	N/A
Moscicki, Anna Barbara	*University of California, Los Angeles*	• Inovio	• Advisory Board
		• Merck	• Advisory Board, Honoraria
Palefsky, Joel	*University of California, San Francisco*	• Aura Biosciences	• Advisory Board, Travel Support
		• Hologic	• Research Support
		• Merck	• Advisory Board, Consultant, Research Support, Travel Support
		• Pharmajet	• Advisory Board
		• Qiagen	• Consultant
Stier, Elizabeth	*Boston University Medical Center*	None	N/A
Strickler, Howard	*Albert Einstein College of Medicine*	• BD Sciences, Arbor Vita, MTM/Roche, Norchip AS	• These companies providing free testing in a study of molecular methods for cervical cancer screening in HIV+ women.
Wilkin, Timothy	*Weill Cornell Medical College*	• GlaxoSmithKline/ViiV	• Consultant, Research Support
		• Johnson & Johnson	• Spouse owns stock.

* Group lead

Note: Members were asked to disclose all relationships from 12 months prior to the updated date. The period of reporting was from March 1, 2017, through March 1, 2018.

Hepatitis B Virus Infection (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Bhattacharya, Debika	*University of California, Los Angeles*	• International Antiviral Society – USA	• Honoraria
		• Vertex	• Research Support
Jain, Mamta	*University of Texas Southwestern Medical Center*	• AbbVie	• Advisory Board, Research Support
		• Actelion	• Research Support
		• Boehringer Ingelheim	• Advisory Board, Research Support
		• Gilead Sciences	• Advisory Board, Research Support, Speaker's Bureau
		• GlaskoSmithKline	• Research Support
		• Theratechnologies	• Research Support
		• Viiv	• Research Support
Nunez, Marina	*Wake Forest University Health Sciences*	• Bristol Myers Squibb	• Consultant
		• Gilead	• Advisory Board
Peters, Marion*	*University of California, San Francisco*	• Biotron	• Advisory Board
		• Genentech	• Other
		• GReD	• Spouse has relationship
		• International Antiviral Society (IAS-USA)	• Advisory Board
		• Johnson and Johnson	• Honoraria
Thio, Chloe	*Johns Hopkins University*	None	• N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Hepatitis C Virus Infection (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Bansal, Nina	*Mount Sinai Hospital*	None	N/A
Kim, Arthur	*Harvard Medical School*	• Abbvie Pharmaceuticals	• Advisory Board, Consultant, Research Support
		• Bristol-Myers Squibb	• Advisory Board, Consultant
		• Gilead	• Consultant, Research Support
Kim, Nina	*University of Washington*	None	N/A
Naggie, Susanna	*Duke University*	• Abbvie	• Advisory Board, Research Support
		• Achillion	• Consultant, Research Support
		• BMS	• Advisory Board, Research Support
		• Gilead Sciences	• Advisory Board, Research Support
		• Janssen	• Research Support
		• Merck	• Advisory Board, Research Support
		• Vertex Pharmaceuticals	• Research Support
Sulkowski, Mark*	*Johns Hopkins University*	• AbbVie	• Advisory Board, Research Support
		• Bristol-Myers Squibb	• Advisory Board, Research Support
		• Gilead	• Advisory Board, Research Support
		• Janssen	• Advisory Board, Research Support
		• Merck	• Advisory Board, Research Support
Wyles, David	*University of California, San Diego*	• AbbVie	• Consultant, Research Support
		• Bristol-Myers Squibb	• Consultant, Research Support
		• Gilead	• Consultant, Research Support
		• Janssen Pharmaceuticals	• Advisory Board
		• Merck	• Consulant, Research Support
		• Tacere	• Research Support
		• Vertex	• Research Support

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the reviewed date. The period of reporting was from September 1, 2012, through September 1, 2014.

Progressive Multifocal Leukoencephalopathy (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014) (page 1 of 2)

Member		Financial Disclosure	
		Company	Relationship
Cinque, Paola	*San Raffaele Scientific Institute, Milan, Italy*	• Abbott	• Advisory Board, Speaker's Bureau
		• AbbVie	• Advisory Board, Speaker's Bureau
		• Biogen	• Advisory Board, Consultant, Research Support
		• Boehringer Ingelheim	• Advisory Board, Speaker's Bureau
		• Bristol-Myers Squibb	• Speaker's Bureau
		• Gilead	• Speaker's Bureau
		• Janssen-Cilag	• Advisory Board, Speaker's Bureau
		• Johnson & Johnson	• Consultant
		• Merck	• Speaker's Bureau
		• Millenium Pharmaceuticals	• Consultant
		• Pfizer	• Consultant, DSMB Member
		• ViiV Healthcare	• Advisory Board
Clifford, David*	*Washington University School of Medicine*	• Amgen	• Consultant
		• Biogen	• Consultant, Honoraria
		• Bristol-Myers Squibb	• Advisory Board, Consultant
		• Drinker Biddle, Reath LLC	• Advisory Board
		• Genentech	• Advisory Board, DSMB Member
		• Genzyme	• DSMB Member
		• GlaxoSmithKline	• Honoraria
		• Merck Serono	• DSMB Member
		• Millennium	• Consultant, DSMB Member, Honoraria
		• Novartis	• Consultant, Research Support
		• Pfizer	• Consultant, DSMB Member
Marra, Christina	*Washington University School of Medicine*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Member		Financial Disclosure	
		Company	Relationship
Miro, Jose M.	*Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain*	• Abbvie	• Consultant, Honoraria, Speaker's Bureau
		• Astellas	• Consultant
		• Bristol-Myers Squibb	• Consultant, Honoraria, Research Support, Speaker's Bureau
		• Cubist	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Fundacion Maximo Soriano Jimenez, Barcelona, Spain	• Research Support
		• Gilead	• Consultant, Honoraria, Speaker's Bureau
		• GlaxoSmithKline	• Honoraria, Speaker's Bureau
		• Instituto de Salud Carlos III, Spanish Ministry of Health, Madrid, Spain	• Research Support
		• Janssen-Cilag	• Speaker's Bureau
		• Merck	• Consultant, Speaker's Bureau
		• NIH	• Research Support
		• Novartis	• Advisory Board, Consultant, Honoraria, Research Support, Speaker's Bureau
		• Pfizer	• Consultant, Speaker's Bureau
		• ViiV Healthcare	• Honoraria, Research Support, Speaker's Bureau
Nath, Avi	*National Institutes of Health*	None	N/A
Weber, Thomas	*Marienkrankenhaus Hamburg*	• Bayer	• Honoraria, Travel Support
		• Biogen Idec	• Advisory Board, Consultant, Honoraria, Research Support
		• Genzyme	• Honoraria
		• Merck	• Honoraria, Travel Support
		• Novartis	• Honoraria

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.

Geographic (Last Reviewed: August 1, 2014; Last Updated: August 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Boggild, Andrea	*University of Toronto Department of Medicine*	None	N/A
Dhanireddy, Shireesha*	*University of Washington School of Medicine*	None	N/A
Herwaldt, Barbara	*Centers for Disease Control and Prevention*	None	N/A
Kantipong, Pacharee	*Chiangrai Regional Hospital, Thailand*	None	N/A
Lynch, John	*University of Washington School of Medicine*	None	N/A
Montgomery, Susan	*Centers for Disease Control and Prevention*	None	N/A
Supparatpinyo, Khuanchai	*Chiang Mai University, Thailand*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from August 1, 2012, through August 1, 2014.

Pharmacology (Last Reviewed: November 1, 2016; Last Updated: November 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Dooley, Kelly	*Johns Hopkins University School of Medicine*	• Viiv Healthcare	• Research Support
George, Jomy	*National Institutes of Health*	None	N/A
Kuriakose, Safia	*National Institutes of Health*	None	N/A
Pau, Alice*	*National Institutes of Health*	None	N/A
Peloquin, Charles	*University of Florida*	• Astra Zeneca	• Research Support
		• Jacobus Pharmaceuticals	• Research Support
		• Otsuka	• Advisory Board
Pham, Paul	*Westview Urgent Care*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from November 1, 2014, through November 1, 2016.

Pregnancy (Last Reviewed: March 1, 2016; Last Updated: March 1, 2016)

Member		Financial Disclosure	
		Company	Relationship
Anderson, Jean	*Johns Hopkins University*	• Gilead	• Scientific Advisory Board
Cohan, Deborah	*University of California San Francisco*	None	N/A
Hughes, Brenna	*Women & Infants Hospital of Rhode Island*	None	N/A
Watts, Heather*	*Office of the Global AIDS Coordinator*	None	N/A
Wright, Rodney	*Albert Einstein College of Medicine*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from March 1, 2014, through March 1, 2016.

Immunizations (Last Reviewed: September 1, 2014; Last Updated: September 1, 2014)

Member		Financial Disclosure	
		Company	Relationship
Kim, David*	*Centers for Disease Control and Prevention*	None	N/A
Peters, Philip	*Centers for Disease Control and Prevention*	None	N/A

* Group lead

Note: Members were asked to disclose all relationships from 24 months prior to the updated date. The period of reporting was from September 1, 2012, through September 1, 2014.