Leishmaniasis

Updated: July 29, 2024
Reviewed: July 29, 2024

Epidemiology

Leishmaniasis is caused by protozoa that survive and replicate within macrophages and other mononuclear cells. There are over 20 species within the *Leishmania* (*L.*) genus that cause human disease, the main forms of which are visceral, cutaneous, and mucosal disease.[1] Leishmaniasis occurs in 99 countries or territories in the tropics and subtropics (including the southern United States, most of Central and South America, and southern Europe), with an estimated incidence of 1 million new cases annually. In 2022, 12,842 incident cases of visceral leishmaniasis and 205,986 new cases of cutaneous leishmaniasis were reported to the World Health Organization (WHO).[2]

Prevalence of the different *Leishmania* species varies geographically. The main *Leishmania* species that cause visceral leishmaniasis are *L. donovani, L. infantum* (syn. *L. chagasi*), and the more recently recognized *L. (Mundinia) martiniquensis*. The visceral leishmaniasis-causing species in the Americas are *L. infantum* and *L. martiniquensis*. Cutaneous leishmaniasis acquired outside the Americas is commonly caused by *L. tropica, L. major,* and *L. aethiopica*. In the Americas, the prevalent species that cause cutaneous leishmaniasis are of the *L.* (*Viannia)* subgenera (*braziliensis, guyanensis, panamensis, peruviana), L. mexicana* and *L. amazonensis*.[3] In the United States, there have been fewer than 100 recognized autochthonous cases in the past 100 years, mainly *L. mexicana* cutaneous leishmaniasis acquired in Texas.[3]

As of 2021, HIV-leishmaniasis coinfection has been reported in 45 countries,[4] predominantly as HIV-visceral leishmaniasis coinfection.[4,5] The first cases of HIV-leishmaniasis coinfection were described in Spain in the late 1980s.[6] After the introduction of combination antiretroviral therapy (ART), the incidence decreased substantially in developed countries,[7,8] but HIV-leishmaniasis coinfection poses a growing problem in parts of Asia, Africa, and Latin America.[9-12] New species *Leishmania (Mundinia) martiniquensis,* associated with visceral and disseminated cutaneous leishmaniasis, and *L. (Mundinia) orientalis*, which causes cutaneous leishmaniasis, have been reported from Thailand in people with HIV.[11-13]

In endemic areas, leishmaniasis is usually spread by infected sand flies of the genera *Phlebotomus* and *Lutzomyia*. However, in southern Europe, HIV and *L. infantum* visceral leishmaniasis coinfections have been reported in association with injection drug use, suggesting that *Leishmania* (which can infrequently be transmitted via blood[14,15]) also may be acquired by needle sharing; contaminated syringes have been shown to be an epidemiologically significant component of the transmission cycle of *Leishmania* amastigotes.[16,17]

Clinical Manifestations

The term leishmaniasis encompasses multiple syndromes—most notably, cutaneous leishmaniasis and visceral leishmaniasis, but also related syndromes such as mucosal (or mucocutaneous) leishmaniasis, disseminated cutaneous leishmaniasis, diffuse cutaneous leishmaniasis (an anergic form), and post-kala-azar dermal leishmaniasis.[18] The most reported clinical presentation of leishmaniasis in people with HIV is a systemic visceral disease syndrome. However, the predominant

parasite species varies geographically. In Europe, visceral disease has been reported in 95% of people with HIV-leishmaniasis coinfection (87% typical visceral, 8% atypical visceral).[6] In Brazil, mucosal, visceral, and cutaneous forms have accounted for 43%, 37%, and 20% of reported leishmaniasis cases in people with HIV, respectively.[19]

Most *Leishmania* infections in immunocompetent hosts are asymptomatic. In many disease-endemic areas, 30% or more of the population has evidence of latent infection, as demonstrated by a positive leishmanin skin test.[20-22] After primary infection, *Leishmania* remain viable in healthy individuals for long periods, creating a population at risk of reactivation if CD4 T lymphocyte (CD4) cell depletion occurs. In people with HIV without severe CD4 cell depletion, disease manifestations are similar to those in immunocompetent individuals. In those with advanced immunosuppression (i.e., CD4 count <200 cells/mm^3), manifestations of leishmaniasis can be both atypical and more severe. Dermotrophic species can disseminate both in skin and through the reticuloendothelial system to visceralize.[23,24] Relapse after treatment—especially of visceral leishmaniasis—is common.[25,26] Atypical disseminated leishmaniasis in people with HIV is considered a WHO clinical stage 4 HIV criterion.[27]

Visceral Leishmaniasis

In people with HIV and visceral disease, the most common clinical and laboratory findings are fever (65% to 100%), systemic malaise (70% to 90%), splenomegaly (usually moderate) (54% to 90%), hepatomegaly without splenomegaly (34% to 85%), hepatosplenomegaly (68% to 73%), lymphadenopathy (12% to 57%), and pancytopenia (50% to 80%).[6,26] Anemia is usually marked, with <10 g hemoglobin/dL (50% to 100%); leukopenia is moderate, with <2,400 leukocytes/μL (56% to 95%); and thrombocytopenia is usually present (52% to 93%). Splenomegaly is less pronounced in people with HIV than in immunocompetent patients with visceral leishmaniasis.[26] In people with HIV with more profound CD4 cell depletion, atypical manifestations have been described, including mucosal involvement, such as masses, ulcers, mucositis of the upper and lower gastrointestinal tract, serositis in pleural and peritoneal cavities, and lung and skin lesions.[6,7,26,28,29] Esophageal involvement can lead to dysphagia and odynophagia and must be distinguished from other causes of esophagitis in people with HIV, such as candidiasis.[6] Amastigote infiltration of the duodenum often presents as chronic diarrhea.[7] Nonulcerative cutaneous lesions that mimic Kaposi sarcoma (KS), nodular diffuse leishmaniasis, and post-kala-azar dermal leishmaniasis have been described in people with HIV and visceral leishmaniasis.[30-32] However, the presence of *Leishmania* amastigotes in skin can occur in the absence of lesions or in combination with other pathology, such as KS, and does not prove that the parasite is the cause of the lesions.[33,34]

Cutaneous Leishmaniasis

Cutaneous leishmaniasis in people with HIV varies depending on immune function. In people with HIV with well-controlled HIV and high CD4 counts, the presentation is not different than those without HIV except that there may be a higher rate of relapse.[35,36] In those with lower CD4 counts (e.g., <200 cells/mm^3), dermal leishmaniasis may disseminate in the skin, mucosa, and viscera.[37] Most have multiple skin lesions, often atypical (unusual morphology) for localized cutaneous leishmaniasis, and genital involvement seems more frequent.[37-39] Among people with HIV in Brazil, 68% had concomitant mucosal leishmaniasis, a rate much higher than those without HIV.[18] Additionally, as mentioned above, people with HIV and visceral leishmaniasis may present with cutaneous lesions.[40,41]

Mucosal Leishmaniasis

Mucosal leishmaniasis among people with HIV is most commonly associated with infections acquired in the New World, especially *L. braziliensis* and other species in the *L. (Viannia)* subgenera including *L. guyanensis* and *L. panamensis*.[19] Additionally, mucosal disease also has been reported with species that have geographic distribution beyond the Americas, including *L. infantum*, *L. aethiopica*, and *L. tropica*.[42] Presentation in people with HIV is similar to those without HIV and includes nasal septum destruction, obstructive masses in the nose, uvula erosion, ulcerated infiltrative lesions of the palate, and laryngeal involvement.[19,43-49] Mucosal leishmaniasis may occur concomitantly with cutaneous leishmaniasis or years after resolution of localized cutaneous leishmaniasis.[50]

Diagnosis

Demonstration of *Leishmania* parasites by histopathology, cultures, smears, and molecular methods in tissue specimens (such as scrapings, aspirates, and biopsies) is the standard for diagnosing cutaneous leishmaniasis in people with HIV. Coinfection of HIV and visceral leishmaniasis also can be diagnosed by demonstration of leishmanial parasites in the following: blood smears (approximately 50% sensitivity in expert hands); buffy-coat smear preparations; cultures from the peripheral blood; and smears, histopathology, and cultures from bone marrow (preferred) or splenic aspirates (significant procedural risk). Polymerase chain reaction (PCR) amplification can also be useful for detecting *Leishmania* nucleic acid in the blood or tissue of patients with HIV-leishmaniasis coinfection (>95% sensitivity).[51] Generally, PCR and *Leishmania* culture require specialty reference laboratory support. Assistance for conducting diagnostic tests for *Leishmania* is available by contacting the Centers for Disease Control and Prevention (CDC) at parasiteslab@cdc.gov.

Serologic tests that detect *Leishmania* antibodies have high sensitivity and can be used to support diagnosis of visceral leishmaniasis in immunocompetent patients.[51] They should be used only in those with a compatible clinical picture and an exposure history suggestive of visceral leishmaniasis. Serology has a lower sensitivity in people with HIV such that parasitological diagnosis should be sought when clinical suspicion has been raised.[6,52] The use of recombinant antigen in enzyme-linked immunosorbent assays (or ELISAs) may increase sensitivity for detection of *Leishmania* antibodies, but a proportion of people with HIV-leishmaniasis coinfection remain seronegative.[53] Immunoblotting with *L. infantum* soluble antigen has been successful in detecting specific antileishmanial antibodies in up to 70% of patients.[52]

Preventing Exposure

Prevention of exposure to leishmanial infection relies on reservoir host control in urban and periurban areas with zoonotic transmission (such as controlling visceral leishmaniasis in dogs) and vector control activities (such as indoor residual spraying, using insecticide-treated bed nets, and intervening in sand fly breeding sites).[54,55] Optimal control measures rely on local transmission characteristics, which vary by vector. For travelers to leishmaniasis-endemic areas, the best way to prevent infection is to protect themselves from sand fly bites. Personal protective measures include minimizing nocturnal outdoor activities, wearing protective clothing, and applying insect repellent to exposed skin.

People who inject drugs should undertake measures (such as the use of clean needles and injection equipment from syringe service programs) to decrease the risk of transmission of *Leishmania* parasites and other infectious agents.

Preventing Disease

Primary chemoprophylaxis to prevent leishmaniasis is not recommended. No screening or preemptive therapy is appropriate for people with HIV who may have been exposed to leishmanial infection. No vaccine against leishmaniasis is available.

Treating Disease

Recommendations for Treating Visceral and Cutaneous Leishmaniasis

Treating Visceral Leishmaniasis

- ART should be initiated as soon as possible (AIII). Initiation or optimization of ART may prevent reactivation of visceral leishmaniasis.

Leishmania infantum/chagasi

Preferred Therapy

- Liposomal amphotericin B*, achieving a total dose of 20–60 mg/kg (AII) via either
  - 3–5 mg/kg IV daily (AII), *or*
  - Interrupted schedule, such as 4 mg/kg IV on Days 1–5, 10, 17, 24, 31, and 38 (AII)

Alternative Therapy

- Amphotericin B deoxycholate* 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 grams (BII), *or*
- Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BII), currently available in the United States only by investigator-initiated investigational new drug application

Leishmania donovani

Preferred Therapy (Combination)

- Liposomal amphotericin B* 30 mg/kg IV total dose (5 mg/kg on Days 1, 3, 5, 7, 9, and 11), plus miltefosine 50 mg PO twice daily for 28 days (East Africa) or for 14 days (Southeast Asia) (BI)

Alternative Therapy

- Liposomal amphotericin B*, achieving a total dose of 20–60 mg/kg (AII) via either
  - 3–5 mg/kg IV daily (AII), *or*
  - Interrupted schedule, such as 4 mg/kg IV on Days 1–5, 10, 17, 24, 31, and 38 (AII)
- See Alternative Therapy for *L. infantum*, *or*
- For Indian *L. donovani*
  - Miltefosine (BII) (available in the United States via www.profounda.com), aiming for 2.5–3 mg/kg daily (maximum of 150 mg daily)
    - For patients who weigh 30–44 kg: 50 mg PO two times daily for 28 days
    - For patients who weigh ≥45 kg: 50 mg PO three times daily for 28 days

Chronic Maintenance Therapy for Visceral Leishmaniasis

Indication

- For patients with visceral leishmaniasis and CD4 count <200 cells/mm^3 (AII)

Preferred Therapy

- Liposomal amphotericin B* 4 mg/kg IV every 2–4 weeks (AII)

Alternative Therapy

- Amphotericin B lipid complex* 3 mg/kg every 21 days (BII), *or*
- Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM every 4 weeks (BII), *or*
- Pentamidine isethionate 4 mg/kg (maximum of 300 mg) IV every 2–4 weeks (BII)

Discontinuation of Chronic Maintenance Therapy

- Consider stopping secondary prophylaxis when the CD4 count is >350 cells/mm^3, HIV viral load has been undetectable for 6 months, and there are no symptoms of visceral leishmaniasis relapse (CIII).

Treating Cutaneous Leishmaniasis
• ART should be initiated as soon as possible (AIII). Initiation or optimization of ART may prevent reactivation of cutaneous leishmaniasis. *Preferred Therapy* • Liposomal amphotericin B* 4 mg/kg IV daily for 10 days or interrupted schedule (e.g., 4 mg/kg on days 1–5, 10, 17, 24, 31, 38) until a total dose of 20–60 mg/kg is achieved (BIII), *or* • Miltefosine 2.5 mg/kg/day PO in 2 or 3 divided doses for 28 days (*Viannia* subgenus); not well tolerated if more than 150 mg daily (BIII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BIII) *Alternative Therapy* • Other options for individual cases may include cryotherapy, topical paromomycin, intralesional pentavalent antimony (meglumine antimoniate) or pentamidine, fluconazole for *L. major* and *L. mexicana*, intravenous pentamidine or local heat therapy. Chronic Maintenance Therapy for Cutaneous Leishmaniasis • Indicated for immunocompromised patients with multiple relapses (CIII) • See drugs and doses for *Chronic Maintenance Therapy for Visceral Leishmaniasis*.
Pregnancy Considerations
• Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy (AIII). Amphotericin B deoxycholate can be given as alternative therapy (AIII). • In many uncomplicated cutaneous leishmaniasis cases, treatment can be delayed until postpartum (CIII). • In cases of severe cutaneous leishmaniasis with multiple and/or very large lesions, shared decision making with the patient is recommended to discuss the potential risks and benefits of deferring treatment until after pregnancy, treating with systemic therapy, or using local therapy as a temporizing approach (followed by systemic therapy to be given after pregnancy if the lesions do not resolve) (CIII). • Liposomal amphotericin B IV is the first choice for therapy of mucosal or severe cutaneous leishmaniasis in pregnancy (CIII).

* Patients treated with amphotericin B formulations should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions (AII). Infusion-related adverse events may be ameliorated by pre-treatment with acetaminophen or diphenhydramine (CIII). An infusion of 1 L of saline 1 hour prior to drug infusion is recommended to help reduce the risk of renal dysfunction during treatment (BIII).

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

Visceral Leishmaniasis

The following medications have been used to treat visceral leishmaniasis: amphotericin B deoxycholate, liposomal amphotericin B, pentavalent antimonial drugs (e.g., meglumine antimoniate), and miltefosine (for *L. donovani*). Lower cure rates, higher drug toxicity, more relapses, and higher mortality summarize the treatment outcomes for people with HIV with visceral leishmaniasis. Amphotericin deoxycholate and lipid formulations of amphotericin B appear to be at least as effective as pentavalent antimonials.[56-58] Liposomal and lipid complex preparations of amphotericin B are typically better tolerated than amphotericin B deoxycholate or pentavalent antimony (meglumine antimoniate).[59-61] The equivalent efficacy and better toxicity profile have led the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and

Adolescents With HIV (the Panel) to recommend liposomal amphotericin B as the preferred amphotericin formulation for treatment of visceral leishmaniasis in people with HIV **(AII).**[62] The optimal amphotericin B dosage has not been determined.[62,63]

Recommended regimens include liposomal preparations of 3 to 5 mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight **(AII).** An alternative regimen of amphotericin B deoxycholate, 0.5 to 1.0 mg/kg body weight/day intravenously (IV), to achieve a total dose of 1.5 to 2.0 g, can be administered **(BII).**[56,57,64-67] Pentavalent antimony (meglumine antimoniate) 20 mg/kg/day IV or intramuscular (IM) for 28 consecutive days, is an alternative **(BII).** Pentavalent antimonial drugs require an investigator-initiated investigational new drug application in the United States (see Instructions for Acquiring Glucantime [Meglumine antimoniate] for Treatment of Leishmaniasis). Due to toxicity concerns with pentavalent antimonial drugs, a pregnancy test (beta-human chorionic gonadotropin [β-hCG]) should be obtained by individuals of childbearing potential prior to start of therapy, and effective contraception during treatment is advised.

Oral miltefosine monotherapy (available in the United States via www.profounda.com) is recommended as an alternative treatment option for Indian *L. donovani* visceral leishmaniasis in people with HIV[63,68] at a dose of approximately 2.5 to 3 mg/kg daily (maximum of 150 mg daily) for 28 days **(BII).**[69-72] Combination therapy using miltefosine and liposomal amphotericin in the treatment of HIV-*L. donovani* visceral leishmaniasis has also shown promise. A randomized clinical trial of liposomal amphotericin 30 mg/kg total dose and miltefosine 100 mg/day for 28 days was compared to liposomal amphotericin 40 mg/kg total dose monotherapy among patients with *L. donovani* visceral leishmaniasis and HIV coinfection in Ethiopia. Parasite clearance persisting to 58 days was found in 88% of the combination treatment group versus 55% in the monotherapy group.[73] In India, 150 people with HIV with *L. donovani* visceral leishmaniasis received total doses of liposomal amphotericin 40 mg/kg IV versus liposomal amphotericin 30 mg/kg IV with oral miltefosine 50 mg twice daily for 14 days. At Day 210 follow-up, 7% of patients in the monotherapy arm died versus 1.3% in the combination arm.[74] These data have led the WHO to update their 2022 HIV and visceral leishmaniasis coinfection treatment guidelines to conditionally recommend combination liposomal amphotericin and miltefosine treatment; those with HIV-visceral leishmaniasis coinfection in Eastern Africa (*L. donovani*) should be administered miltefosine for 28 days, and those with HIV-visceral leishmaniasis coinfection (*L. donovani*) in South East Asia should be administered miltefosine for 14 days.[75] Since miltefosine is teratogenic and is contraindicated in pregnancy, β-hCG should be checked prior to initiation and effective contraception should be continued for 5 months.[63]

Data supporting the use of miltefosine monotherapy in people with HIV are relatively limited and restricted to Indian *L. donovani*. For visceral leishmaniasis caused by *L. infantum* (e.g., in the Americas, Europe), Pan American Health Organization guidelines recommend against miltefosine monotherapy due to lower efficacy and limited evidence.[76] Further research is also needed to confirm the efficacy of drug combinations in people with HIV to treat other *Leishmania* species and severe or refractory cases of visceral leishmaniasis in other geographic regions. Currently, there is no recommendation for combination therapy in visceral leishmaniasis due to *L. infantum*.

Cutaneous Leishmaniasis

Few systematic data are available on the efficacy of treatment for cutaneous leishmaniasis, mucosal leishmaniasis, or diffuse cutaneous leishmaniasis in people with HIV. Based on data from individuals

without HIV with cutaneous leishmaniasis and case reports in people with HIV-cutaneous leishmaniasis, patients with HIV-cutaneous leishmaniasis should be treated with some form of systemic therapy, depending on the type of cutaneous leishmaniasis and the clinical response. Liposomal amphotericin B **(BIII),**[67] miltefosine (*Viannia* subgenus infections) **(BIII),** or pentavalent antimony (meglumine antimoniate) **(BIII)** are options for treatment.[77,78] Pentavalent antimonial drugs require an investigator-initiated investigational new drug application in the United States (see Instructions for Acquiring Glucantime [Meglumine antimoniate] for Treatment of Leishmaniasis).

Potential alternatives for cutaneous leishmaniasis include cryotherapy, topical paromomycin, intralesional pentavalent antimony or pentamidine isoethionate, intravenous pentamidine isethionate,[79,80] fluconazole for *L. major* and *L. mexicana*, or local heat therapy. The effectiveness of these modalities is known to be dependent upon the infecting species of *Leishmania*.[66,81-83] However, these alternatives are based on data from people without HIV, not those with HIV-cutaneous leishmaniasis coinfection. For example, although the Pan American Health Organization 2022 guidelines recommend intralesional pentavalent antimonial treatment as first-line use in immunocompetent patients, this treatment has not been tested in people with HIV and New World cutaneous leishmaniasis; because of this, there are concerns about how effectively it will prevent dissemination like mucosal leishmaniasis in people with HIV, who may be at increased risk.[76,84] Therefore, these alternatives could be considered in individualized circumstances in patients with high CD4 counts and controlled viral load.

Special Considerations Regarding ART Initiation

Appropriate use of ART has substantially improved the survival of patients with coinfection and decreased the likelihood of relapse after antileishmanial therapy.[8,26,85] Therefore, ART should be started as soon as patients are able to tolerate it **(AIII).**

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

Patients treated with liposomal amphotericin B should be monitored for dose-dependent nephrotoxicity, electrolyte disturbances, and infusion-related adverse reactions **(AII).** Infusion-related adverse events may be ameliorated by pre-treatment with acetaminophen or diphenhydramine **(CIII).** An infusion of 1 L of saline 1 hour prior to drug infusion is recommended to help reduce the risk of glomerular function decline during treatment **(BIII).** The frequency of nephrotoxicity is lower for liposomal or lipid-associated preparations than for amphotericin B deoxycholate.[60]

Adverse events associated with miltefosine use include gastrointestinal symptoms (more commonly nausea or vomiting than diarrhea) that can result in prerenal azotemia, motion sickness-like symptoms, scrotal pain, thrombocytopenia, and hepatotoxicity. To decrease gastrointestinal symptoms, which are usually worse at the beginning of therapy, miltefosine should be administered in divided 50 mg doses during the day and taken with food containing some fat. Weekly assessment of renal and hepatic function and platelet counts is recommended.[67]

Patients receiving parenteral pentavalent antimony (meglumine antimoniate) should be monitored closely for adverse reactions.[77] Overall, at a dose of 20 mg/kg of body weight per day, more than 60% of patients have one or more of the following reactions: thrombophlebitis, anorexia, myalgia, arthralgia, abdominal pain, elevation of liver transaminases, amylase, or lipase, and clinical pancreatitis, in some patients. Weekly electrocardiograms are recommended during treatment, with careful monitoring for changes that may indicate early cardiotoxicity, such as prolonged QT intervals and T-wave inversion **(CIII).** Rarely, arrhythmias and sudden death have occurred.[58,66] Severe

adverse reactions to pentavalent antimony, including acute pancreatitis and leukopenia, appear to be more common in patients with coinfection than in those who do not have HIV.[86]

Cases of newly symptomatic visceral leishmaniasis, mucosal leishmaniasis, and cutaneous leishmaniasis have been reported in association with immune reconstitution inflammatory syndrome (IRIS) following initiation of ART.[87-90] Several of these cases have resembled post-kala-azar dermal leishmaniasis or disseminated cutaneous leishmaniasis.[91-95] Existing experience with IRIS-associated leishmaniasis, however, is insufficient to provide data for specific management guidelines.

People with HIV who respond to initial treatment should be clinically monitored for relapse (any recurrence or new consistent skin lesions) for at least 6 months to 1 year after treatment for cutaneous leishmaniasis; those with infection with *L. (Viannia)* subspecies also should be followed for 2 to 5 years for any signs or symptoms of inflammation of the nasal mucosa. People with HIV successfully treated for visceral leishmaniasis should be clinically monitored for symptoms or signs of recurrence such as fever, constitutional symptoms, hepatomegaly, splenomegaly, or cytopenia. Routine follow-up via parasitological testing with repeat biopsies or longitudinally tracking antibody levels is generally not recommended for people with HIV with treated leishmaniasis who do not demonstrate clinical signs or symptoms of recurrence. A positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse in people with HIV-visceral leishmaniasis coinfection.[96]

Managing Treatment Failure

For patients who fail to respond to initial therapy or who experience a relapse after initial treatment, a repeat course of the initial regimen, or one of the recommended alternatives for initial therapy, should be used as previously outlined **(AIII).** The response rate for retreatment appears to be similar to that for initial therapy, although some patients evolve to a chronic disease state with serial relapses despite aggressive acute and maintenance therapies.[97]

In a pharmacokinetic substudy of antileishmanial drugs for treatment of visceral leishmaniasis in people with HIV, blood concentrations of amphotericin were found to be twofold-lower than those measured in studies among those with visceral leishmaniasis without HIV. Additionally, lower observed miltefosine concentrations were likely due in part to lower weight-based dosing when compared to other studies, emphasizing the need to use a weight-based dosage approximating 2.5 mg/kg/day in adults. However, no relationship between amphotericin and miltefosine concentrations and treatment outcome was observed.[98]

Expert assistance to health care providers for clinical care for leishmaniasis is available at the CDC's Parasitic Diseases Hotline at (404) 718-4745 or parasites@cdc.gov.

Preventing Recurrence

Relapses, particularly of visceral leishmaniasis and disseminated cutaneous leishmaniasis, are common after cessation of antileishmanial therapy in people with HIV, and relapse is more frequent in those with lower CD4 count.[99] Reported associations with relapse are prior episode of visceral leishmaniasis, CD4 count <100 cells/mm^3 at time of primary visceral leishmaniasis, and no increase in CD4 count at follow-up.[99] In people with HIV-visceral leishmaniasis coinfection who were not receiving or responding to ART, the risk of relapse at 6 and 12 months was 60% and 90%, respectively, in the absence of secondary prophylaxis (chronic maintenance therapy).[6,100,101] In

Brazil, a relapse rate of 28.6% of patients with HIV-cutaneous leishmaniasis was reported, regardless of viral load and adherence to ART.[35] Therefore, secondary prophylaxis with an effective antileishmanial drug administered at least every 4 weeks is recommended, particularly for patients with visceral leishmaniasis and CD4 counts <200 cells/mm^3 **(AII).**[6,26,100,102]

The only published, randomized trial of secondary prophylaxis compared amphotericin B lipid complex (3 mg/kg every 21 days) in eight patients with no prophylaxis in nine patients; this trial reported relapse rates of 50% versus 78%, respectively, after 1 year of follow-up.[102] In retrospective observational studies, monthly pentavalent antimony or lipid formulations of amphotericin every 2 to 4 weeks were also associated with decreased relapse rates.[26,100] With a 2 year follow-up, 74 people with HIV-visceral leishmaniasis coinfection were given monthly intravenous pentamidine isethionate (4 mg/kg with a maximal dose 300 mg) and 71% were relapse-free after 12 months.[103] In 54 persons followed for 390 days stratified for CD4 above and below 200, there was a reported overall relapse-free survival of 50% and 53% if CD4 ≥200 cells/µL.[104]

Liposomal amphotericin B (4 mg/kg every 2–4 weeks) **(AII)** is the preferred regimen for secondary prophylaxis. Amphotericin B lipid complex (3 mg/kg every 21 days) **(BII)** and pentavalent antimony (meglumine antimoniate, 20 mg/kg IV or IM every 4 weeks) are alternatives **(BII).** Although pentamidine isethionate is no longer recommended to treat primary visceral leishmaniasis, a dosage of 4 mg/kg IV (300 mg for adult) every 2 to 4 weeks has been suggested as another alternative for secondary prophylaxis **(BII).**[105-107] Allopurinol, used for maintenance therapy, is less effective than monthly pentavalent antimony and **is not recommended (BII).**[100] Although no published data on efficacy are available, maintenance therapy may be indicated for immunocompromised patients with cutaneous leishmaniasis who have multiple relapses after adequate treatment **(CIII).**

When to Stop Secondary Prophylaxis

Some investigations suggest that secondary antileishmanial prophylaxis can be discontinued in patients whose CD4 count is >200 to 350 cells/mm^3 in response to ART.[105,108] Others, however, suggest that secondary prophylaxis should be maintained indefinitely. Among 74 patients in Ethiopia with HIV-visceral leishmaniasis coinfection, who received monthly intravenous pentamidine for 12 to 18 months, a 36.9% relapse rate was identified over a 2-year follow-up, mainly among those with a low baseline CD4 count of ≤100 cells/mm^3. All with CD4 count >200 cells/mm^3 at Month 12 were relapse-free.[105] In one study, a positive peripheral blood PCR for *Leishmania* correlated with a high risk of relapse.[96] Therefore, the Panel recommends considering cessation of secondary prophylaxis when CD4 count is >350 cell/mm^3 and HIV viral load has been undetectable for 6 months and there is no clinical evidence of visceral leishmaniasis relapse **(CIII).**

Special Considerations During Pregnancy

Diagnostic considerations in pregnant people are the same as in people who are not pregnant. Retrospective analyses suggest that rates of preterm birth and spontaneous abortion may be increased in women with visceral leishmaniasis during pregnancy, especially in the first trimester and when antimonial drugs are used.[109,110] Because visceral leishmaniasis is a potentially lethal disease, postponing treatment until after delivery is not an option. Several small published series of pregnant women treated with amphotericin B deoxycholate or liposomal amphotericin B have demonstrated good clinical outcomes.[111-115] Liposomal amphotericin B is the first choice for therapy of visceral leishmaniasis in pregnancy **(AIII).**[111] Amphotericin B deoxycholate, which has demonstrated positive

clinical and pregnancy outcomes in a small group of pregnant people, can be given as an alternative therapy **(AIII).**[111]

There are concerns about toxicity and lack of experience with use of pentavalent antimony compounds in human pregnancy; labels for pentavalent antimony compounds state that these drugs are contraindicated for use in pregnant people, although various antimonial compounds were found to not be teratogenic in chickens, rats, or sheep.[116-118] Therefore, pentavalent antimonial drugs are not recommended in individuals who are pregnant **(BIII).** Miltefosine is teratogenic and pentamidine is embryotoxic; therefore, both drugs **are not recommended** in pregnancy **(AII).**[63,119] In a systematic review including 346 pregnant people with visceral leishmaniasis, 176 pregnant individuals treated with liposomal amphotericin were reported to have 4 (2.3%) maternal deaths, 5 (2.8%) miscarriages, and 2 (1.1%) fetal deaths/stillbirths versus 88 pregnant people receiving pentavalent antimonial drugs, where reported outcomes included 4 (4.5%) maternal deaths, 24 (27.3%) spontaneous abortions, and 2 (2.3%) miscarriages.[115]

In contrast to visceral leishmaniasis, the Panel recommends deferring treatment of cutaneous leishmaniasis until the postpartum period for most individuals with HIV-cutaneous leishmaniasis **(CIII).** One study suggests that lesions of cutaneous leishmaniasis may be larger and are more likely to be exophytic in pregnancy, and that untreated cutaneous leishmaniasis may be associated with an increased risk of preterm delivery and stillbirth.[120] This is presumed to be related to transient modulation of maternal immune responses during pregnancy.[121] In cases of severe cutaneous leishmaniasis with multiple and/or very large lesions, the Panel recommends shared decision making with the patient to discuss the potential risks and benefits of deferring treatment until after pregnancy, treating with systemic therapy, or using local therapy as a temporizing approach (followed by systemic therapy to be given after pregnancy if the lesions do not resolve) **(CIII).** Systemic therapy is recommended in most cases of mucosal leishmaniasis in patients with HIV **(CIII).** When systemic therapy is chosen for mucosal leishmaniasis or cutaneous leishmaniasis in pregnant individuals with HIV, the treatment of choice is liposomal amphotericin B **(CIII).**

Perinatal transmission of *Leishmania spp*. is rare. In a systematic review of suspected cases of vertical transmission, 26 were reported after 6 months postbirth.[109,115,122-124] A case report described a woman with HIV who experienced visceral leishmaniasis relapse during pregnancy and was treated with 40 mg/kg liposomal amphotericin; the infant likely acquired leishmaniasis from amastigotes seen in the placenta.[125]

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis*. 2004;27(5):305-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15225981.

2. Ruiz-Postigo JA, Saurabh J, Madjou S, et al. Global leishmaniasis surveillance, 2022: assessing trends over the past 10 years. *Weekly Epidemiological Record*. 2023;98:471-487. Available at: https://www.who.int/publications/i/item/who-wer9840-471-487.

3. Curtin JM, Aronson NE. Leishmaniasis in the United States: emerging issues in a region of low endemicity. *Microorganisms*. 2021;9(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33799892.

4. World Health Organization. Leishmaniasis fact sheet. 2022. Available at: https://www.who.int/news-room/fact-sheets/detail/leishmaniasis.

5. Kantzanou M, Karalexi MA, Theodoridou K, et al. Prevalence of visceral leishmaniasis among people with HIV: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2023;42(1):1-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36427170.

6. Alvar J, Canavate C, Gutierrez-Solar B, et al. Leishmania and human immunodeficiency virus coinfection: the first 10 years. *Clin Microbiol Rev*. 1997;10(2):298-319. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9105756.

7. Rosenthal E, Marty P, del Giudice P, et al. HIV and *Leishmania* coinfection: a review of 91 cases with focus on atypical locations of *Leishmania*. *Clin Infect Dis*. 2000;31(4):1093-1095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11049794.

8. Tortajada C, Perez-Cuevas B, Moreno A, et al. Highly active antiretroviral therapy (HAART) modifies the incidence and outcome of visceral leishmaniasis in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2002;30(3):364-366. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12131576.

9. Wolday D, Berhe N, Akuffo H, Desjeux P, Britton S. Emerging leishmania/HIV co-infection in Africa. *Med Microbiol Immunol*. 2001;190(1-2):65-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11770113.

10. Mathur P, Samantaray JC, Vajpayee M, Samanta P. Visceral leishmaniasis/human immunodeficiency virus co-infection in India: the focus of two epidemics. *J Med Microbiol*. 2006;55(Pt 7):919-922. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16772420.

11. Charoensakulchai S, Bualert L, Manomat J, et al. Risk factors of *Leishmania* infection among HIV-infected patients in Trang Province, southern Thailand: a study on three prevalent species. *Am J Trop Med Hyg*. 2020;103(4):1502-1509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32700674.

12. Leelayoova S, Siripattanapipong S, Manomat J, et al. Leishmaniasis in Thailand: a review of causative agents and situations. *Am J Trop Med Hyg*. 2017;96(3):534-542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28093539.

13. Manomat J, Leelayoova S, Bualert L, et al. Prevalence and risk factors associated with *Leishmania* infection in Trang Province, southern Thailand. *PLoS Negl Trop Dis*. 2017;11(11):e0006095. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29155831.

14. Jimenez-Marco T, Fisa R, Girona-Llobera E, et al. Transfusion-transmitted leishmaniasis: a practical review. *Transfusion*. 2016;56 Suppl 1:S45-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27001361.

15. Rodrigues WF, Mendes NS, de Carvalho Ribeiro P, et al. A critical review of the applicability of serological screening for leishmaniasis in blood banks in Brazil. *J Parasit Dis*. 2021;45(1):109-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33746394.

16. Chicharro C, Morales MA, Serra T, Ares M, Salas A, Alvar J. Molecular epidemiology of *Leishmania infantum* on the island of Majorca: a comparison of phenotypic and genotypic tools. *Trans R Soc Trop Med Hyg*. 2002;96 Suppl 1:S93-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12055859.

17. Cruz I, Morales MA, Noguer I, Rodriguez A, Alvar J. *Leishmania* in discarded syringes from intravenous drug users. *Lancet*. 2002;359(9312):1124-1125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11943264.

18. Aronson N, Copeland, N. Leishmania species: visceral (kala-azar), cutaneous, and mucosal leishmaniasis. In: Blaser M, Cohen J, Holland S, eds. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases*. 10th ed. Elsevier; 2023.

19. Rabello A, Orsini M, Disch J. *Leishmania*/HIV co-infection in Brazil: an appraisal. *Ann Trop Med Parasitol*. 2003;97 Suppl 1:17-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14678630.

20. Marty P, Le Fichoux Y, Giordana D, Brugnetti A. Leishmanin reaction in the human population of a highly endemic focus of canine leishmaniasis in Alpes-Maritimes, France. *Trans R Soc Trop Med Hyg*. 1992;86(3):249-250. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1412644.

21. Moral L, Rubio EM, Moya M. A leishmanin skin test survey in the human population of l'Alacanti region (Spain): implications for the epidemiology of Leishmania infantum infection in southern Europe. *Trans R Soc Trop Med Hyg*. 2002;96(2):129-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12055798.

22. Werneck GL, Rodrigues L, Santos MV, et al. The burden of *Leishmania chagasi* infection during an urban outbreak of visceral leishmaniasis in Brazil. *Acta Trop*. 2002;83(1):13-18. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12062788.

23. Zijlstra EE. PKDL and other dermal lesions in HIV co-infected patients with leishmaniasis: review of clinical presentation in relation to immune responses. *PLoS Negl Trop Dis*. 2014;8(11):e3258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25412435.

24. Abdoli A, Maspi N, Ghaffarifar F, Nasiri V. Viscerotropic leishmaniasis: a systematic review of the case reports to highlight spectrum of the infection in endemic countries. *Parasitology Open*. 2018;4(E11):1-14. Available at:

https://www.cambridge.org/core/journals/parasitology-open/article/viscerotropic-leishmaniasis-a-systematic-review-of-the-case-reports-to-highlight-spectrum-of-the-infection-in-endemic-countries/096BDC88EEA424B04E4536C8CA423268.

25. Lopez-Velez R, Perez-Molina JA, Guerrero A, et al. Clinicoepidemiologic characteristics, prognostic factors, and survival analysis of patients coinfected with human immunodeficiency virus and *Leishmania* in an area of Madrid, Spain. *Am J Trop Med Hyg*. 1998;58(4):436-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9574788.

26. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in human immunodeficiency virus (HIV)-infected and non-HIV-infected patients. A comparative study. *Medicine (Baltimore)*. 2001;80(1):54-73. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11204503.

27. World Health Organization. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, Switzerland: 2007. Available at: https://apps.who.int/iris/bitstream/handle/10665/43699/9789241595629_eng.pdf?sequence=1&isAllowed=y.

28. Mota Sasaki M, Matsumo Carvalho M, Schmitz Ferreira ML, Machado MP. Cutaneous leishmaniasis coinfection in AIDS patients: case report and literature review. *Braz J Infect Dis*. 1997;1(3):142-144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11105130.

29. Diro E, van Griensven J, Mohammed R, et al. Atypical manifestations of visceral leishmaniasis in patients with HIV in north Ethiopia: a gap in guidelines for the management of opportunistic infections in resource poor settings. *Lancet Infect Dis*. 2015;15(1):122-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25300862.

30. Gonzalez-Beato MJ, Moyano B, Sanchez C, et al. Kaposi's sarcoma-like lesions and other nodules as cutaneous involvement in AIDS-related visceral leishmaniasis. *Br J Dermatol*. 2000;143(6):1316-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11122042.

31. Carnauba D, Jr., Konishi CT, Petri V, Martinez IC, Shimizu L, Pereira-Chioccola VL. Atypical disseminated leishmaniasis similar to post-kala-azar dermal leishmaniasis in a Brazilian AIDS patient infected with *Leishmania (Leishmania) infantum chagasi*: a case report. *Int J Infect Dis*. 2009;13(6):e504-507. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19447660.

32. Lindoso JA, Barbosa RN, Posada-Vergara MP, et al. Unusual manifestations of tegumentary leishmaniasis in AIDS patients from the New World. *Br J Dermatol*. 2009;160(2):311-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19187345.

33. Albrecht H, Stellbrink HJ, Gross G, Berg B, Helmchen U, Mensing H. Treatment of atypical leishmaniasis with interferon gamma resulting in progression of Kaposi's sarcoma in an AIDS patient. *Clin Investig*. 1994;72(12):1041-1047. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7711412.

34. Bosch RJ, Rodrigo AB, Sanchez P, de Galvez MV, Herrera E. Presence of *Leishmania* organisms in specific and non-specific skin lesions in HIV-infected individuals with visceral

leishmaniasis. *Int J Dermatol*. 2002;41(10):670-675. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12390190.

35. Araujo CF, Oliveira IBN, Silva MVT, et al. New world *Leishmania spp*. infection in people living with HIV: concerns about relapses and secondary prophylaxis. *Acta Trop*. 2021;224:106146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34562423.

36. Couppie P, Clyti E, Sobesky M, et al. Comparative study of cutaneous leishmaniasis in human immunodeficiency virus (HIV)-infected patients and non-HIV-infected patients in French Guiana. *Br J Dermatol*. 2004;151(6):1165-1171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15606511.

37. Alvar J, Aparicio P, Aseffa A, et al. The relationship between leishmaniasis and AIDS: the second 10 years. *Clin Microbiol Rev*. 2008;21(2):334-359, table of contents. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18400800.

38. Guerra JA, Coelho LI, Pereira FR, et al. American tegumentary leishmaniasis and HIV-AIDS association in a tertiary care center in the Brazilian Amazon. *Am J Trop Med Hyg*. 2011;85(3):524-527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21896816.

39. Choi CM, Lerner EA. Leishmaniasis: recognition and management with a focus on the immunocompromised patient. *Am J Clin Dermatol*. 2002;3(2):91-105. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11893221.

40. Puig L, Pradinaud R. Leishmania and HIV co-infection: dermatological manifestations. *Ann Trop Med Parasitol*. 2003;97 Suppl 1:107-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14678638.

41. Postigo C, Llamas R, Zarco C, et al. Cutaneous lesions in patients with visceral leishmaniasis and HIV infection. *J Infect*. 1997;35(3):265-268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9459400.

42. Aliaga L, Cobo F, Mediavilla JD, et al. Localized mucosal leishmaniasis due to *Leishmania (Leishmania) infantum*: clinical and microbiologic findings in 31 patients. *Medicine (Baltimore)*. 2003;82(3):147-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12792301.

43. Torrico F, Parrado R, Castro R, et al. Co-infection of *Leishmania (Viannia) braziliensis* and HIV: report of a case of mucosal leishmaniasis in Cochabamba, Bolivia. *Am J Trop Med Hyg*. 2009;81(4):555-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19815865.

44. De Godoy NS, Vera Demarchi A, Regina Maia S, Thelma O, Lucia Maria Almeida B. Unusual clinical manifestations of *Leishmania (L.) infantum chagasi* in an HIV-coinfected patient and the relevance of ITS1-PCR-RFLP: a case report. *Iran J Parasitol*. 2018;13(4):655-660. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30697322.

45. Bains A, Vedant D, Gupta P, Tegta GR. Unusual presentation of mucocutaneous leishmaniasis in HIV-infected patient. *Indian J Sex Transm Dis AIDS*. 2016;37(2):193-196. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27890957.

46. da Silva GA, Sugui D, Nunes RF, et al. Mucocutaneous leishmaniasis/HIV coinfection presented as a diffuse desquamative rash. *Case Rep Infect Dis*. 2014;2014:293761. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25548691.

47. Amato VS, Nicodemo AC, Amato JG, Boulos M, Neto VA. Mucocutaneous leishmaniasis associated with HIV infection treated successfully with liposomal amphotericin B (AmBisome). *J Antimicrob Chemother*. 2000;46(2):341-342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10933674.

48. Miralles ES, Nunez M, Hilara Y, Harto A, Moreno R, Ledo A. Mucocutaneous leishmaniasis and HIV. *Dermatology*. 1994;189(3):275-277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7949483.

49. Canovas DL, Carbonell J, Torres J, Altes J, Buades J. Laryngeal leishmaniasis as initial opportunistic disease in HIV infection. *J Laryngol Otol*. 1994;108(12):1089-1092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7861090.

50. Lindoso JA, Cunha MA, Queiroz IT, Moreira CH. Leishmaniasis-HIV coinfection: current challenges. *HIV AIDS (Auckl)*. 2016;8:147-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27785103.

51. Sundar S, Rai M. Laboratory diagnosis of visceral leishmaniasis. *Clin Diagn Lab Immunol*. 2002;9(5):951-958. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12204943.

52. Medrano FJ, Canavate C, Leal M, Rey C, Lissen E, Alvar J. The role of serology in the diagnosis and prognosis of visceral leishmaniasis in patients coinfected with human immunodeficiency virus type-1. *Am J Trop Med Hyg*. 1998;59(1):155-162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9684645.

53. Houghton RL, Petrescu M, Benson DR, et al. A cloned antigen (recombinant K39) of *Leishmania chagasi* diagnostic for visceral leishmaniasis in human immunodeficiency virus type 1 patients and a prognostic indicator for monitoring patients undergoing drug therapy. *J Infect Dis*. 1998;177(5):1339-1344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9593022.

54. Gonzalez U, Pinart M, Sinclair D, et al. Vector and reservoir control for preventing leishmaniasis. *Cochrane Database Syst Rev*. 2015;2015(8):CD008736. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26246011.

55. Stockdale L, Newton R. A review of preventative methods against human leishmaniasis infection. *PLoS Negl Trop Dis*. 2013;7(6):e2278. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23818997.

56. Davidson RN, Di Martino L, Gradoni L, et al. Liposomal amphotericin B (AmBisome) in Mediterranean visceral leishmaniasis: a multi-centre trial. *Q J Med*. 1994;87(2):75-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8153291.

57. Russo R, Nigro LC, Minniti S, et al. Visceral leishmaniasis in HIV infected patients: treatment with high dose liposomal amphotericin B (AmBisome). *J Infect*. 1996;32(2):133-137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8708370.

58. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. Spanish HIV-Leishmania Study Group. *AIDS*. 1999;13(9):1063-1069. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10397536.

59. Lazanas MC, Tsekes GA, Papandreou S, et al. Liposomal amphotericin B for leishmaniasis treatment of AIDS patients unresponsive to antimonium compounds. *AIDS*. 1993;7(7):1018-1019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8357549.

60. Sundar S, Mehta H, Suresh AV, Singh SP, Rai M, Murray HW. Amphotericin B treatment for Indian visceral leishmaniasis: conventional versus lipid formulations. *Clin Infect Dis*. 2004;38(3):377-383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14727208.

61. Torre-Cisneros J, Villanueva JL, Kindelan JM, Jurado R, Sanchez-Guijo P. Successful treatment of antimony-resistant visceral leishmaniasis with liposomal amphotericin B in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1993;17(4):625-627. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8268341.

62. Bern C, Adler-Moore J, Berenguer J, et al. Liposomal amphotericin B for the treatment of visceral leishmaniasis. *Clin Infect Dis*. 2006;43(7):917-924. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16941377.

63. Alvar J, Croft S, Olliaro P. Chemotherapy in the treatment and control of leishmaniasis. *Adv Parasitol*. 2006;61:223-274. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16735166.

64. Laguna F, Torre-Cisneros J, Moreno V, Villanueva JL, Valencia E. Efficacy of intermittent liposomal amphotericin B in the treatment of visceral leishmaniasis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1995;21(3):711-712. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8527591.

65. Meyerhoff A. U.S. Food and Drug Administration approval of AmBisome (liposomal amphotericin B) for treatment of visceral leishmaniasis. *Clin Infect Dis*. 1999;28(1):42-48; discussion 49-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10028069.

66. Laguna F, Videla S, Jimenez-Mejias ME, et al. Amphotericin B lipid complex versus meglumine antimoniate in the treatment of visceral leishmaniasis in patients infected with HIV: a randomized pilot study. *J Antimicrob Chemother*. 2003;52(3):464-468. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12888588.

67. Aronson N, Herwaldt BL, Libman M, et al. Diagnosis and treatment of leishmaniasis: clinical practice guidelines by the Infectious Diseases Society of America (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). *Clin Infect Dis*. 2016;63(12):e202-e264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27941151.

68. Sundar S, Jha TK, Thakur CP, Bhattacharya SK, Rai M. Oral miltefosine for the treatment of Indian visceral leishmaniasis. *Trans R Soc Trop Med Hyg*. 2006;100 Suppl 1:S26-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16730038.

69. Dorlo TP, Rijal S, Ostyn B, et al. Failure of miltefosine in visceral leishmaniasis is associated with low drug exposure. *J Infect Dis*. 2014;210(1):146-153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24443541.

70. Sindermann H, Engel KR, Fischer C, Bommer W, Miltefosine Compassionate Use Program. Oral miltefosine for leishmaniasis in immunocompromised patients: compassionate use in 39 patients with HIV infection. *Clin Infect Dis*. 2004;39(10):1520-1523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15546090.

71. Ramesh V, Dixit KK, Sharma N, Singh R, Salotra P. Assessing the efficacy and safety of liposomal amphotericin B and miltefosine in combination for treatment of post kala-azar dermal leishmaniasis. *J Infect Dis*. 2020;221(4):608-617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31854451.

72. Ritmeijer K, Dejenie A, Assefa Y, et al. A comparison of miltefosine and sodium stibogluconate for treatment of visceral leishmaniasis in an Ethiopian population with high prevalence of HIV infection. *Clin Infect Dis*. 2006;43(3):357-364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16804852.

73. Diro E, Blesson S, Edwards T, et al. A randomized trial of AmBisome monotherapy and AmBisome and miltefosine combination to treat visceral leishmaniasis in HIV co-infected patients in Ethiopia. *PLoS Negl Trop Dis*. 2019;13(1):e0006988. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30653490.

74. Burza S, Mahajan R, Kazmi S, et al. AmBisome monotherapy and combination AmBisome - miltefosine therapy for the treatment of visceral leishmaniasis in patients co-infected with HIV in India: a randomised open label, parallel arm, phase 3 trial. *Clin Infect Dis*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35147680.

75. World Health Organization. WHO guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. In: WHO guideline for the treatment of visceral leishmaniasis in HIV co-infected patients in East Africa and South-East Asia. Geneva: 2022. https://www.ncbi.nlm.nih.gov/pubmed/35763584.

76. Pan American Health Organization. Guideline for the treatment of leishmaniasis in the Americas. 2nd ed. 2022. Available at: https://iris.paho.org/handle/10665.2/56120.

77. Herwaldt BL, Berman JD. Recommendations for treating leishmaniasis with sodium stibogluconate (Pentostam) and review of pertinent clinical studies. *Am J Trop Med Hyg*. 1992;46(3):296-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1313656.

78. Reithinger R, Dujardin JC, Louzir H, Pirmez C, Alexander B, Brooker S. Cutaneous leishmaniasis. *Lancet Infect Dis*. 2007;7(9):581-596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17714672.

79. Christen JR, Bourreau E, Demar M, et al. Use of the intramuscular route to administer pentamidine isethionate in *Leishmania guyanensis* cutaneous leishmaniasis increases the risk of treatment failure. *Travel Med Infect Dis*. 2018;24:31-36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29482012.

80. Piccica M, Lagi F, Bartoloni A, Zammarchi L. Efficacy and safety of pentamidine isethionate for tegumentary and visceral human leishmaniasis: a systematic review. *J Travel Med*. 2021;28(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33890115.

81. Belay AD, Asafa Y, Mesure J, Davidson RN. Successful miltefosine treatment of post-kala-azar dermal leishmaniasis occurring during antiretroviral therapy. *Ann Trop Med Parasitol*. 2006;100(3):223-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16630379.

82. Reithinger R, Mohsen M, Wahid M, et al. Efficacy of thermotherapy to treat cutaneous leishmaniasis caused by *Leishmania tropica* in Kabul, Afghanistan: a randomized, controlled trial. *Clin Infect Dis*. 2005;40(8):1148-1155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15791515.

83. Soto J, Arana BA, Toledo J, et al. Miltefosine for new world cutaneous leishmaniasis. *Clin Infect Dis*. 2004;38(9):1266-1272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15127339.

84. Aronson NE, Billick K. Intralesional antimonial drug treatment for *Leishmania braziliensis* cutaneous leishmaniasis: the knowns and the unknowns. *Clin Infect Dis*. 2023;77(4):583-588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37185765.

85. de la Rosa R, Pineda JA, Delgado J, et al. Influence of highly active antiretroviral therapy on the outcome of subclinical visceral leishmaniasis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 2001;32(4):633-635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11181128.

86. Delgado J, Macias J, Pineda JA, et al. High frequency of serious side effects from meglumine antimoniate given without an upper limit dose for the treatment of visceral leishmaniasis in human immunodeficiency virus type-1-infected patients. *Am J Trop Med Hyg*. 1999;61(5):766-769. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10586909.

87. Berry A, Abraham B, Dereure J, Pinzani V, Bastien P, Reynes J. Two case reports of symptomatic visceral leishmaniasis in AIDS patients concomitant with immune reconstitution due to antiretroviral therapy. *Scand J Infect Dis*. 2004;36(3):225-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15119371.

88. Posada-Vergara MP, Lindoso JA, Tolezano JE, Pereira-Chioccola VL, Silva MV, Goto H. Tegumentary leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome in 2 patients with AIDS. *J Infect Dis*. 2005;192(10):1819-1822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16235183.

89. Lee GL, Woods KL, Clark L, Peters S, Wong HK, McGwire BS. Short communication: mucocutaneous leishmaniasis in HIV-related immune reconstitution syndrome. *AIDS Res Hum Retroviruses*. 2015;31(9):889-892. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26154873.

90. Gois L, Badaro R, Schooley R, Grassi MF. Immune response to *Leishmania* antigens in an AIDS patient with mucocutaneous leishmaniasis as a manifestation of immune reconstitution inflammatory syndrome (IRIS): a case report. *BMC Infect Dis*. 2015;15:38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25645330.

91. Chrusciak-Talhari A, Ribeiro-Rodrigues R, Talhari C, et al. Tegumentary leishmaniasis as the cause of immune reconstitution inflammatory syndrome in a patient co-infected with human immunodeficiency virus and Leishmania guyanensis. *Am J Trop Med Hyg*. 2009;81(4):559-564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19815866.

92. Sinha S, Fernandez G, Kapila R, Lambert WC, Schwartz RA. Diffuse cutaneous leishmaniasis associated with the immune reconstitution inflammatory syndrome. *Int J Dermatol*. 2008;47(12):1263-1270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19126013.

93. Tadesse A, Hurissa Z. Leishmaniasis (PKDL) as a case of immune reconstitution inflammatory syndrome (IRIS) in HIV-positive patient after initiation of anti-retroviral therapy (ART). *Ethiop Med J*. 2009;47(1):77-79. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19743785.

94. Antinori S, Longhi E, Bestetti G, et al. Post-kala-azar dermal leishmaniasis as an immune reconstitution inflammatory syndrome in a patient with acquired immune deficiency syndrome. *Br J Dermatol*. 2007;157(5):1032-1036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17854365.

95. Rousset S, Zenou M, Saunier A, et al. Immune recovery-related patterns of post kala-azar dermal and ocular leishmaniasis in people living with HIV. *AIDS*. 2022;36(13):1819-1827. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35848585.

96. Bourgeois N, Bastien P, Reynes J, Makinson A, Rouanet I, Lachaud L. 'Active chronic visceral leishmaniasis' in HIV-1-infected patients demonstrated by biological and clinical long-term follow-up of 10 patients. *HIV Med*. 2010;11(10):670-673. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20500233.

97. Monge-Maillo B, Lopez-Velez R. Treatment options for visceral leishmaniasis and HIV coinfection. *AIDS Rev*. 2016;18(1):32-43. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26936761.

98. Kip AE, Blesson S, Alves F, et al. Low antileishmanial drug exposure in HIV-positive visceral leishmaniasis patients on antiretrovirals: an Ethiopian cohort study. *J Antimicrob Chemother*. 2021;76(5):1258-1268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33677546.

99. Cota GF, de Sousa MR, Rabello A. Predictors of visceral leishmaniasis relapse in HIV-infected patients: a systematic review. *PLoS Negl Trop Dis*. 2011;5(6):e1153. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21666786.

100. Ribera E, Ocana I, de Otero J, Cortes E, Gasser I, Pahissa A. Prophylaxis of visceral leishmaniasis in human immunodeficiency virus-infected patients. *Am J Med*. 1996;100(5):496-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8644760.

101. ter Horst R, Collin SM, Ritmeijer K, Bogale A, Davidson RN. Concordant HIV infection and visceral leishmaniasis in Ethiopia: the influence of antiretroviral treatment and other factors on outcome. *Clin Infect Dis*. 2008;46(11):1702-1709. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18419422.

102. Lopez-Velez R, Videla S, Marquez M, et al. Amphotericin B lipid complex versus no treatment in the secondary prophylaxis of visceral leishmaniasis in HIV-infected patients. *J Antimicrob Chemother*. 2004;53(3):540-543. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14739148.

103. Diro E, Ritmeijer K, Boelaert M, et al. Use of pentamidine as secondary prophylaxis to prevent visceral leishmaniasis relapse in HIV infected patients, the first twelve months of a prospective cohort study. *PLoS Negl Trop Dis*. 2015;9(10):e0004087. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26431253.

104. Diro E, Edwards T, Ritmeijer K, et al. Long term outcomes and prognostics of visceral leishmaniasis in HIV infected patients with use of pentamidine as secondary prophylaxis based on CD4 level: a prospective cohort study in Ethiopia. *PLoS Negl Trop Dis*. 2019;13(2):e0007132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30789910.

105. Diro E, Ritmeijer K, Boelaert M, et al. Long-term clinical outcomes in visceral leishmaniasis/human immunodeficiency virus-coinfected patients during and after pentamidine secondary prophylaxis in Ethiopia: a single-arm clinical trial. *Clin Infect Dis*. 2018;66(3):444-451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29020217.

106. Patel TA, Lockwood DN. Pentamidine as secondary prophylaxis for visceral leishmaniasis in the immunocompromised host: report of four cases. *Trop Med Int Health*. 2009;14(9):1064-1070. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19552658.

107. Dorlo TP, Kager PA. Pentamidine dosage: a base/salt confusion. *PLoS Negl Trop Dis*. 2008;2(5):e225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18509543.

108. Berenguer J, Cosin J, Miralles P, Lopez JC, Padilla B. Discontinuation of secondary anti-leishmania prophylaxis in HIV-infected patients who have responded to highly active antiretroviral therapy. *AIDS*. 2000;14(18):2946-2948. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11153679.

109. Adam GK, Abdulla MA, Ahmed AA, Adam I. Maternal and perinatal outcomes of visceral leishmaniasis (kala-azar) treated with sodium stibogluconate in eastern Sudan. *Int J Gynaecol Obstet*. 2009;107(3):208-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19766208.

110. Mueller M, Balasegaram M, Koummuki Y, Ritmeijer K, Santana MR, Davidson R. A comparison of liposomal amphotericin B with sodium stibogluconate for the treatment of visceral leishmaniasis in pregnancy in Sudan. *J Antimicrob Chemother*. 2006;58(4):811-815. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16916865.

111. Pagliano P, Carannante N, Rossi M, et al. Visceral leishmaniasis in pregnancy: a case series and a systematic review of the literature. *J Antimicrob Chemother*. 2005;55(2):229-233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15649998.

112. Gradoni L, Gaeta GB, Pellizzer G, Maisto A, Scalone A. Mediterranean visceral leishmaniasis in pregnancy. *Scand J Infect Dis*. 1994;26(5):627-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7855563.

113. Topno RK, Pandey K, Das VN, et al. Visceral leishmaniasis in pregnancy - the role of amphotericin B. *Ann Trop Med Parasitol*. 2008;102(3):267-270. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18348781.

114. Pekelharing JE, Gatluak F, Harrison T, Maldonado F, Siddiqui MR, Ritmeijer K. Outcomes of visceral leishmaniasis in pregnancy: a retrospective cohort study from South Sudan. *PLoS Negl Trop Dis*. 2020;14(1):e0007992. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31978116.

115. Dahal P, Singh-Phulgenda S, Maguire BJ, et al. Visceral leishmaniasis in pregnancy and vertical transmission: a systematic literature review on the therapeutic orphans. *PLoS Negl Trop Dis*. 2021;15(8):e0009650. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34375339.

116. James LF, Lazar VA, Binns W. Effects of sublethal doses of certain minerals on pregnant ewes and fetal development. *Am J Vet Res*. 1966;27(116):132-135. Available at: https://www.ncbi.nlm.nih.gov/pubmed/5913019.

117. Ridgway LP, Karnofsky DA. The effects of metals on the chick embryo: toxicity and production of abnormalities in development. *Ann N Y Acad Sci*. 1952;55(2):203-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12977037.

118. Rossi F, Acampora R, Vacca C, et al. Prenatal and postnatal antimony exposure in rats: effect on vasomotor reactivity development of pups. *Teratog Carcinog Mutagen*. 1987;7(5):491-496. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2893463.

119. Ito S, Koren G. Estimation of fetal risk from aerosolized pentamidine in pregnant healthcare workers. *Chest*. 1994;106(5):1460-1462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7956402.

120. Morgan DJ, Guimaraes LH, Machado PR, et al. Cutaneous leishmaniasis during pregnancy: exuberant lesions and potential fetal complications. *Clin Infect Dis*. 2007;45(4):478-482. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17638198.

121. Conceicao-Silva F, Morgado FN, Pimentel MI, et al. Two women presenting worsening cutaneous ulcers during pregnancy: diagnosis, immune response, and follow-up. *PLoS Negl Trop Dis*. 2013;7(12):e2472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24349585.

122. Boehme CC, Hain U, Novosel A, Eichenlaub S, Fleischmann E, Loscher T. Congenital visceral leishmaniasis. *Emerg Infect Dis*. 2006;12(2):359-360. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17080586.

123. Meinecke CK, Schottelius J, Oskam L, Fleischer B. Congenital transmission of visceral leishmaniasis (Kala Azar) from an asymptomatic mother to her child. *Pediatrics*. 1999;104(5):e65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10545591.

124. Zinchuk A, Nadraga A. Congenital visceral leishmaniasis in Ukraine: case report. *Ann Trop Paediatr*. 2010;30(2):161-164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20522305.

125. Argy N, Lariven S, Rideau A, et al. Congenital leishmaniasis in a newborn infant whose mother was coinfected with leishmaniasis and HIV. *J Pediatric Infect Dis Soc*. 2020;9(2):277-280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31589299.

Malaria

Updated: March 28, 2017
Reviewed: January 10, 2024

Epidemiology

Malaria continues to contribute disproportionately to the global burden of infectious diseases, especially in sub-Saharan Africa and Southeast Asia. In 2015, the World Health Organization estimated that 97 countries had ongoing malaria transmission, and almost half the world's population, approximately 3.2 billion people, lived in areas with some risk of malaria transmission.[1] Of the nearly 214 million cases of malaria worldwide in 2015 (based on reports and models), approximately 88% (188 million) occurred in Africa, the area of the world with the highest HIV prevalence.[1] Approximately 438,000 deaths were attributable to malaria in 2015, with ~90% occurring in Africa and 74% of those deaths in children younger than 5 years of age. Fifteen countries, mainly in sub-Saharan Africa, account for 80% of malaria cases and 78% of deaths worldwide.[1] Current attributable morbidity and mortality are likely underestimated, given our limited understanding, surveillance, and reporting of non-falciparum infections.

Malaria typically is transmitted by the bite of an infected female *Anopheles sp*. mosquito. Reports of vertical transmission and infection after blood transfusion do exist, but these routes of transmission are uncommon in non-endemic areas.[2-5]

Malaria in humans can be caused by any one of five species: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi* (a zoonotic species that also infects macaques in Southeast Asia).[4] Although *P. vivax* infections are more common and occur in a far wider geographic distribution,[6] *P. falciparum* malaria represents the most serious public health problem because of its tendency toward severe or fatal infections. *P. vivax*, however, should not be discounted as a risk for travelers in many parts of the world.

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

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

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

Clinical Manifestations

The clinical syndromes caused by *Plasmodium* species depend on prior exposure.[22] While many native U.S. travelers have no prior immunity, clinical manifestations in those who have resided in malarious areas depend

on whether they lived in an area with stable endemic malaria transmission (year round) or unstable (seasonal, infrequent or very low) transmission.[23]

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

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

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

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

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

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

Effect of HIV on Parasitemia and Clinical Severity

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

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

Effects of Malaria on Mother-to-Child HIV Transmission

Placental malaria also has been associated with increased expression of CCR5 receptors in placental macrophages[38] and increased viral load,[39] raising the possibility of placental malaria leading to increased mother-to-child transmission (MTCT) of HIV. In addition, fetal immune activation by malaria antigens may increase susceptibility to HIV infection.[40] Data are conflicting concerning the effect of malaria during pregnancy on risk of MTCT in the pre-ART era and are limited since the widespread use of ART for prevention of MTCT.[41-43]

Diagnosis

A malaria diagnosis must be considered in all febrile patients who have traveled to or lived in malaria-endemic areas or who have received blood products, tissues, or organs from individuals who have been to such areas.

Several diagnostic methods are available, including microscopic diagnosis, antigen detection tests, polymerase chain reaction-based assays, and serologic tests, though serologic tests which detect host antibody are inappropriate for the diagnosis of acute malaria.

Direct microscopic examination of intracellular parasites on stained blood films is the standard for definitive diagnosis in nearly all settings because it allows for identification of the species and provides a measure of parasite density. Microscopic diagnosis of *P. knowlesi* is difficult because it is commonly misidentified as *P. malariae,* which tends to follow a more benign course. Providers should have a high index of suspicion for *P. knowlesi* in travelers returning from Southeast Asia.[31]

In non-immune patients with all types of malaria, symptoms may develop before detectable levels of parasitemia are evident. For this reason, several blood smear examinations taken at 12- to 24-hour intervals may be needed to positively rule out a diagnosis of malaria in symptomatic patients. Guidelines for laboratory diagnosis are summarized elsewhere and are available at the Centers for Disease Control and Prevention

(CDC)'s malaria website (https://www.cdc.gov/malaria). Rapid diagnostic tests, particularly for the diagnosis of *P. falciparum,* can be used depending on the local expertise and practice and can facilitate prompt diagnosis and treatment of infected patients, but must be followed by microscopy.

Preventing Exposure

Pre-travel evaluation by a travel medicine specialist can provide specific education about risk of exposure in various geographic locales, the utility of insecticide-impregnated bed nets in the setting where the individual will be traveling or residing, and the use of DEET (N,N-diethyl-3-methyl-benzamide)-containing repellants.

Infection with *P. falciparum* can be more severe in HIV-infected patients with low CD4 cell counts and in pregnant women regardless of HIV infection than in other individuals. Because no chemoprophylactic regimen is completely effective, HIV-infected patients with low CD4 cell counts and women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible **(AIII).** If travel to an endemic area cannot be deferred, use of an effective chemoprophylaxis regimen is essential, along with careful attention to personal protective measures to prevent mosquito bites.

Preventing Disease

For United States travelers (including HIV-infected patients) to endemic areas, a combination of chemoprophylaxis and personal protective measures can be highly effective in preventing malaria. Recommendations for prophylaxis are the same for HIV-infected patients as for those who are not HIV-infected and are available at CDC's malaria website **(AIII)** (https://www.cdc.gov/malaria).

Malaria incidence has been markedly reduced in African adults with HIV who receive cotrimoxazole (trimethoprim-sulfamethoxazole) prophylaxis.[44] A recent study of HIV-infected patients in Uganda demonstrated that malaria burden was reduced by 70% with cotrimoxazole, and then reduced another 50% when antiretroviral (ARV) drugs were provided, and finally reduced another 50% with provision of insecticide-treated nets.[45] However, cotrimoxazole is not as effective an antimalarial prophylactic regimen as the recommended antimalarials. Therefore, HIV-infected travelers should not rely on prophylaxis with cotrimoxazole for chemoprophylaxis against malaria **(AIII).**

Treating Disease

Because *P. falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infections should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to treatment **(AIII).** Diagnosis prior to treatment should always be pursued; however, treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed **(AIII).**

Choice of treatment is guided by the degree of parasitemia, the species of *Plasmodium,* a patient's clinical status, and the likely drug susceptibility of the infecting species (as determined by where the infection was acquired).

For HIV-infected patients who do acquire *Plasmodium* infection, treatment recommendations are the same as for HIV-uninfected patients **(AIII).** CDC posts current treatment recommendations on its website (https://www.cdc.gov/malaria) and has clinicians on call 24 hours to provide advice to clinicians on diagnosing and treating malaria (CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours).

Special Considerations with Regard to Starting Antiretroviral Therapy (ART)

There is no reason to defer ART initiation after patients have recovered from acute malaria.

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

Careful monitoring of patients (especially those with *P. falciparum* malaria) is necessary, including measurement of peripheral parasitemia and hemoglobin and blood glucose levels, as well as assessment of cerebral, pulmonary, and renal function. Frequency of monitoring depends on severity of disease, a patient's immune status, and the species of *Plasmodium*.

Chemoprophylaxis or treatment for malaria in patients receiving ARV agents requires attention to potential drug interactions. Several potential drug interactions can occur between antimalarial and HIV drugs as well as other medications used to treat HIV-associated opportunistic infections (see Table 4).[46] Providers are also encouraged to check for drug-drug interactions by using an interactive web-based resource from the University of Liverpool at https://www.hiv-druginteractions.org. Mefloquine in repeated doses has been observed to reduce area under the concentration-time curve and maximal plasma concentrations of ritonavir by 31% and 36%, respectively. Insufficient data are available to suggest that dose adjustments are needed.

Quinine levels may be increased by ritonavir-containing regimens or cobicistat; conversely, nevirapine and efavirenz can reduce plasma quinine levels. Potential interactions can occur between ritonavir or cobicistat and chloroquine, but their clinical significance is unclear, and until further data are available, no dose adjustments are recommended.

Artemether-lumefantrine is now approved in the United States for treatment of uncomplicated *P. falciparum* infection. Data in children suggest that this combination is well tolerated and safe in HIV-infected children,[47] however, efficacy data are conflicting in HIV-infected adults. An open-label trial in Tanzania demonstrated excellent efficacy (97.6%) of artemether-lumefantrine for treating uncomplicated *P. falciparum* malaria in HIV-infected adults on nevirapine-based ART.[48] Conversely, 28-day clinical and parasitologic response was sub-optimal in the efavirenz-based ART group, with efficacy of 82.5%, and a 19-fold increased risk of recurrent parasitemia compared to the control group of HIV-infected adults not on ART.[48] Artesunate is available for treatment of severe malaria through a compassionate use Investigational New Drug application. A trial in Uganda demonstrated the effectiveness of artesunate plus amodiaquine in HIV-infected children, but treatment was associated with increased risk of neutropenia in those on ART, particularly zidovudine, which was attributed to the amodiaquine component of therapy.[49]

Ritonavir or cobicistat-boosted ARV regimens and non-nucleoside reverse transcriptase inhibitors have the potential to affect metabolism of artemisinin-containing drugs,[50] but the overall effect and clinical significance remain unclear. No dose alterations currently are recommended.

No immune reconstitution inflammatory syndrome (IRIS) has been described in association with malaria.

Managing Treatment Failure

HIV-infected individuals are at increased risk of malaria treatment failure.[51] Management of treatment failure is the same in HIV-infected and HIV-uninfected patients, except for considerations about drug interactions between ART and antimalarial drugs. Drug-resistant malaria and possible concomitant infections should be considered in HIV-infected patients whose malaria fails to respond to therapy.

Preventing Recurrence

If the species of malaria identified is *P. vivax* or *P. ovale*, which can cause recurrence due to hepatic phase of infection, then treatment with primaquine in addition to standard treatment is recommended to prevent recurrence **(AI).** Guidelines for primaquine treatment do not differ in HIV-infected individuals.

Special Considerations During Pregnancy

Malaria in pregnancy affects both mother and fetus. Infection with *P. falciparum* during pregnancy can increase maternal risk of severe disease and anemia and risk for stillbirth, preterm birth, and low birth weight.[52] The diagnosis of malaria in pregnant women is the same as in women who are not pregnant.

For pregnant women with a diagnosis of uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, and chloroquine-sensitive *P. falciparum*, prompt treatment with chloroquine is recommended.[53] For pregnant women with a diagnosis of chloroquine-resistant *P. vivax*, treatment with mefloquine for 7 days is recommended. For pregnant women with a diagnosis of uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with mefloquine or quinine and clindamycin is recommended as per CDC guidelines.[54]

On the basis of extensive experience with its use, chloroquine is considered the drug of choice for prophylaxis and treatment of sensitive strains of malaria in pregnancy. Although quinine at high doses has been associated with an increased risk of birth defects (especially deafness) in some animal species and humans (usually during attempted abortion), use of therapeutic doses in pregnancy is considered safe.[53,55] Because of the potential for hypoglycemia, glucose levels should be monitored in pregnant women treated with quinine and their neonates. Clindamycin use has not been associated with birth defects. Animal and human data on use of prophylactic and treatment doses of mefloquine do not suggest teratogenicity and the drug can be used safely during all trimesters.[56] One randomized trial of mefloquine used in addition to daily cotrimoxazole for malaria prophylaxis in pregnant women living with HIV demonstrated an increased risk of transmission of HIV to the infant in the mefloquine arm, potentially because of drug interactions.[57] Although experience is limited, available data on artemether-lumefantrine during pregnancy suggest that use is not associated with increased adverse events or birth defects.[58] A pharmacokinetic study in HIV-uninfected persons found no difference in levels between pregnant and non-pregnant subjects except for small differences in elimination half-life of lumefantrine.[59] Data on pharmacokinetics in HIV-infected pregnant women were not included. Because of limited data, atovaquone-proguanil is not recommended for treatment in pregnancy and should be used only if quinine plus clindamycin, quinine monotherapy, or mefloquine are unavailable or not tolerated.[55] Tetracyclines are not recommended in pregnancy because of increased risk of maternal hepatotoxicity and staining of fetal teeth and bones. Primaquine use during pregnancy is not recommended because of limited experience with its use and the potential for fetal glucose-6-phosphate dehydrogenase (G6PD) deficiency. After treatment, all pregnant women with *P. vivax* and *P. ovale* should receive chloroquine prophylaxis for the duration of pregnancy to avoid relapses. Once-weekly mefloquine can be used for prophylaxis in pregnant women with *P. vivax* acquired in an area with chloroquine-resistant strains. Women who have normal G6PD screening tests can be treated with primaquine after delivery.

Recommendations for Preventing and Treating Malaria

Preventing Malaria in Patients Traveling to Endemic Areas:

- Recommendations are the same for HIV-infected and HIV-uninfected patients.
- Specific recommendations are based on region of travel, malaria risks, and drug susceptibility in the region.
- Clinicians should refer to the following website for the most up-to-date recommendations: https://www.cdc.gov/malaria
- TMP-SMX has been shown to reduce malaria in HIV-infected adults in Africa. However, it is not as effective as antimalarial prophylactic regimens. Therefore, HIV-infected travelers should not rely on TMP-SMX for prophylaxis against malaria (AIII).

Treating Malaria

- Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all HIV-infected patients with confirmed or suspected *P. falciparum* infection should be admitted to the hospital for evaluation, initiation of treatment, and observation of response to therapy (AIII).
- When suspicion of malaria is low, antimalarial treatment should not be initiated until the diagnosis has been confirmed by laboratory investigations.
- Treatment should not be delayed when malaria is strongly suspected but laboratory services are unavailable or results will be delayed (AIII).
- When malaria is strongly suspected, but not yet confirmed, clinicians are advised to consider and initiate treatment for other possible diagnoses in addition to malaria.
- Treatment recommendations for HIV-infected patients are the same as HIV-uninfected patients (AIII).
- Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, and the likely drug susceptibility of the infected species.
- For treatment recommendations for specific region, clinicians should refer to
  - The CDC malaria website: https://www.cdc.gov/malaria
  - The CDC Malaria Hotline: (770) 488-7788; Monday through Friday. 8 a.m. to 4:30 p.m. EST. (770) 488-7100 after hours.

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

References

1. World Health Organization. World Malaria Report 2015. 2015.Available at: https://www.who.int/publications/i/item/9789241565158. Accessed: April 5, 2016.

2. Mungai M, Tegtmeier G, Chamberland M, Parise M. Transfusion-transmitted malaria in the United States from 1963 through 1999. *N Engl J Med*. 2001;344(26):1973-1978. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11430326.

3. Austin SC, Stolley PD, Lasky T. The history of malariotherapy for neurosyphilis. Modern parallels. *JAMA*. 1992;268(4):516-519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1619744.

4. Mali S, Steele S, Slutsker L, Arguin PM, Centers for Disease Control and Prevention. Malaria surveillance - United States, 2008. *MMWR Surveill Summ*. 2010;59(7):1-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20577158.

5. Centers for Disease Control and Prevention. Update: self-induced malaria associated with malariotherapy for Lyme disease--Texas. *MMWR Morb Mortal Wkly Rep*. 1991;40(39):665-666. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1896006.

6. Guerra CA, Howes RE, Patil AP, et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. *PLoS Negl Trop Dis*. 2010;4(8):e774. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20689816.

7. Korenromp EL, Williams BG, de Vlas SJ, et al. Malaria attributable to the HIV-1 epidemic, sub-Saharan Africa. *Emerg Infect Dis*. 2005;11(9):1410-1419. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16229771.

8. Van Geertruyden JP, Menten J, Colebunders R, Korenromp E, D'Alessandro U. The impact of HIV-1 on the malaria parasite biomass in adults in sub-Saharan Africa contributes to the emergence of antimalarial drug resistance. *Malar J*. 2008;7:134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18647387.

9. Slutsker L, Marston BJ. HIV and malaria: interactions and implications. *Curr Opin Infect Dis*. 2007;20(1):3-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17197875.

10. Kemper CA, Linett A, Kane C, Deresinski SC. Frequency of Travel of Adults Infected with HIV. *J Travel Med*. 1995;2(2):85-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9815367.

11. Simons FM, Cobelens FG, Danner SA. Common health problems in HIV-infected travelers to the (sub)tropics. *J Travel Med*. 1999;6(2):71-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10381957.

12. Castelli F, Patroni A. The human immunodeficiency virus-infected traveler. *Clin Infect Dis*. 2000;31(6):1403-1408. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11096010.

13. Bhadelia N, Klotman M, Caplivski D. The HIV-positive traveler. *Am J Med*. 2007;120(7):574-580. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17602926.

14. Smego RA, Jr. Effectiveness of antimalarial drugs. *N Engl J Med*. 2005;353(4):420-422; author reply 420-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16050053.

15. Suh KN, Mileno MD. Challenging scenarios in a travel clinic: advising the complex traveler. *Infect Dis Clin North Am*. 2005;19(1):15-47. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15701545.

16. Sherrard AW, McCarthy AE. Travel patterns and health risks for patients infected with HIV. *Travel Med Infect Dis*. 2009;7(5):291-295. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19747664.

17. Ryan ET, Wilson ME, Kain KC. Illness after international travel. *N Engl J Med*. 2002;347(7):505-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12181406.

18. Spira AM. Assessment of travellers who return home ill. *Lancet*. 2003;361(9367):1459-1469. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12727414.

19. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis*. 1987;156(1):84-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3598228.

20. Winer L, Alkan M. Incidence and precipitating factors of morbidity among Israeli travelers abroad. *J Travel Med*. 2002;9(5):227-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12962594.

21. Wilson ME, Weld LH, Boggild A, et al. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis*. 2007;44(12):1560-1568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17516399.

22. Mackinnon MJ, Marsh K. The selection landscape of malaria parasites. *Science*. 2010;328(5980):866-871. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20466925.

23. Snow RW, Marsh K. The consequences of reducing transmission of Plasmodium falciparum in Africa. *Adv Parasitol*. 2002;52:235-264. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12521262.

24. Matteelli A, Casalini C, Bussi G, et al. Imported malaria in an HIV-positive traveler: a case report with a fatal outcome. *J Travel Med*. 2005;12(4):222-224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16086898.

25. Daneshvar C, Davis TM, Cox-Singh J, et al. Clinical and laboratory features of human Plasmodium knowlesi infection. *Clin Infect Dis*. 2009;49(6):852-860. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19635025.

26. Severe and complicated malaria. World Health Organization, Division of Control of Tropical Diseases. *Trans R Soc Trop Med Hyg*. 1990;84 Suppl 2(Suppl 2):1-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2219249.

27. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. *Bull World Health Organ*. 1989;67(2):189-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2743538.

28. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med*. 1989;71(265):441-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2690177.

29. English M, Sauerwein R, Waruiru C, et al. Acidosis in severe childhood malaria. *QJM*. 1997;90(4):263-270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9307760.

30. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med*. 1995;332(21):1399-1404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7723795.

31. Cox-Singh J, Davis TM, Lee KS, et al. Plasmodium knowlesi malaria in humans is widely distributed and potentially life threatening. *Clin Infect Dis*. 2008;46(2):165-171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18171245.

32. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. *Lancet*. 2000;356(9235):1051-1056. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11009139.

33. Patnaik P, Jere CS, Miller WC, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. *J Infect Dis*. 2005;192(6):984-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16107950.

34. Mouala C, Guiguet M, Houze S, et al. Impact of HIV infection on severity of imported malaria is restricted to patients with CD4 cell counts < 350 cells/microl. *AIDS*. 2009;23(15):1997-2004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19654499.

35. Laufer MK, van Oosterhout JJ, Thesing PC, et al. Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi. *J Infect Dis*. 2006;193(6):872-878. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16479522.

36. Cohen C, Karstaedt A, Frean J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis*. 2005;41(11):1631-1637. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16267737.

37. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS*. 2004;18(3):547-554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15090809.

38. Tkachuk AN, Moormann AM, Poore JA, et al. Malaria enhances expression of CC chemokine receptor 5 on placental macrophages. *J Infect Dis*. 2001;183(6):967-972. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11237815.

39. Mwapasa V, Rogerson SJ, Molyneux ME, et al. The effect of Plasmodium falciparum malaria on peripheral and placental HIV-1 RNA concentrations in pregnant Malawian women. *AIDS*. 2004;18(7):1051-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15096809.

40. Steiner K, Myrie L, Malhotra I, et al. Fetal immune activation to malaria antigens enhances susceptibility to in vitro HIV infection in cord blood mononuclear cells. *J Infect Dis*. 2010;202(6):899-907. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20687848.

41. Msamanga GI, Taha TE, Young AM, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1. *Am J Trop Med Hyg*. 2009;80(4):508-515. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19346367.

42. Bulterys PL, Chao A, Dalai SC, et al. Placental malaria and mother-to-child transmission of human immunodeficiency virus-1 in rural Rwanda. *Am J Trop Med Hyg*. 2011;85(2):202-206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21813835.

43. Ezeamama AE, Duggan C, Manji KP, et al. Clinical malaria diagnosis in pregnancy in relation to early perinatal mother-to-child transmission of HIV: a prospective cohort study. *HIV Med*. 2014;15(5):276-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24215465.

44. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. *Lancet*. 1999;353(9163):1463-1468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10232311.

45. Mermin J, Ekwaru JP, Liechty CA, et al. Effect of co-trimoxazole prophylaxis, antiretroviral therapy, and insecticide-treated bednets on the frequency of malaria in HIV-1-infected adults in Uganda: a prospective cohort study. *Lancet*. 2006;367(9518):1256-1261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16631881.

46. Khoo S, Back D, Winstanley P. The potential for interactions between antimalarial and antiretroviral drugs. *AIDS*. 2005;19(10):995-1005. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15958830.

47. Katrak S, Gasasira A, Arinaitwe E, et al. Safety and tolerability of artemether-lumefantrine versus dihydroartemisinin-piperaquine for malaria in young HIV-infected and uninfected children. *Malar J*. 2009;8:272. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19948038.

48. Maganda BA, Minzi OM, Kamuhabwa AA, Ngasala B, Sasi PG. Outcome of artemether-lumefantrine treatment for uncomplicated malaria in HIV-infected adult patients on anti-retroviral therapy. *Malar J*. 2014;13:205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24885714.

49. Gasasira AF, Kamya MR, Achan J, et al. High risk of neutropenia in HIV-infected children following treatment with artesunate plus amodiaquine for uncomplicated malaria in Uganda. *Clin Infect Dis*. 2008;46(7):985-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18444813.

50. Parikh S, Gut J, Istvan E, Goldberg DE, Havlir DV, Rosenthal PJ. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. *Antimicrob Agents Chemother*. 2005;49(7):2983-2985. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15980379.

51. Van Geertruyden JP, Mulenga M, Mwananyanda L, et al. HIV-1 immune suppression and antimalarial treatment outcome in Zambian adults with uncomplicated malaria. *J Infect Dis*. 2006;194(7):917-925. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16960779.

52. Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis*. 2007;7(2):93-104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17251080.

53. Griffith KS, Lewis LS, Mali S, Parise ME. Treatment of malaria in the United States: a systematic review. *JAMA*. 2007;297(20):2264-2277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17519416.

54. Centers for Disease Control and Prevention. Part 3: Alternatives for Pregnant Women and Treatment of Severe Malaria. In: Secondary Centers for Disease Control and Prevention, ed^eds. Subsidiary Centers for Disease Control and Prevention, trans. Secondary Part 3: Alternatives for Pregnant Women and Treatment of Severe Malaria. Vol. ed.: 2013.

55. McGready R, Thwai KL, Cho T, et al. The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy. *Trans R Soc Trop Med Hyg*. 2002;96(2):180-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12055810.

56. Centers for Disease Control and Prevention. Update: New Recommendations for Mefloquine Use in Pregnancy. 2011. Available at: http://www.cdc.gov/malaria/new_info/2011/mefloquine_pregnancy.html.

57. Gonzalez R, Desai M, Macete E, et al. Intermittent preventive treatment of malaria in pregnancy with mefloquine in HIV-infected women receiving cotrimoxazole prophylaxis: a multicenter randomized placebo-controlled trial. *PLoS Med*. 2014;11(9):e1001735. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25247995.

58. Manyando C, Kayentao K, D'Alessandro U, Okafor HU, Juma E, Hamed K. A systematic review of the safety and efficacy of artemether-lumefantrine against uncomplicated Plasmodium falciparum malaria during pregnancy. *Malar J*. 2012;11:141. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22548983.

59. Nyunt MM, Nguyen VK, Kajubi R, et al. Artemether-Lumefantrine Pharmacokinetics and Clinical Response Are Minimally Altered in Pregnant Ugandan Women Treated for Uncomplicated Falciparum Malaria. *Antimicrob Agents Chemother*. 2015;60(3):1274-1282. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26666942.

Microsporidiosis

Updated: November 14, 2023
Reviewed: January 10, 2024

Epidemiology

Microsporidia are protists related to fungi, defined by the presence of a unique invasive organelle consisting of a single polar tube that coils around the interior of the spore. They are ubiquitous organisms and are likely zoonotic and/or waterborne in origin. Phylogenetic studies now place microsporidia with the Cryptomycota as the basal branch of the fungal kingdom (or alternatively as a sister phylum).[1] The microsporidia reported as pathogens in humans include *Encephalitozoon cuniculi*, *Encephalitozoon hellem*, *Encephalitozoon* (syn *Septata*) *intestinalis*, *Enterocytozoon bieneusi*, *Trachipleistophora hominis*, *Trachipleistophora anthropophthera*, *Pleistophora* species, *Pleistophora ronneafiei*, *Vittaforma* (syn *Nosema*) *corneae*, *Tubulonosema acridophagus*, *Endoreticulatus* sp., *Nosema ocularum*, *Anncaliia* (syns *Brachiola/Nosema*) *connori*, *Anncaliia* (syn *Brachiola*) *vesicularum*, *Anncaliia* (syns *Brachiola/Nosema*) *algerae*, and *Microsporidium* sp.[2-8] In the pre-antiretroviral therapy (ART) era, reported prevalence rates of microsporidiosis varied between 2% and 70% among people with HIV/AIDS with diarrhea, depending on the diagnostic techniques employed and the population described.[3-5,8] The incidence of microsporidiosis has declined with the widespread use of effective ART, but it continues to occur among people with HIV who are unable to obtain ART or to remain on it.[9] Microsporidiosis is increasingly recognized among people without HIV, including children, travelers, organ transplant recipients, contact lens wearers, and the elderly. In people with immune suppression, clinical signs related to microsporidiosis[3-5,8] are most commonly observed when CD4 T lymphocyte (CD4) cell counts are <100 cells/mm^3.

Clinical Manifestations

The most common manifestation of microsporidiosis is gastrointestinal tract infection with diarrhea; however, encephalitis, ocular infection, sinusitis, myositis, and disseminated infection have also been described.[3-5,8]

Clinical syndromes can vary by infecting species. *E. bieneusi* is associated with malabsorption, diarrhea, and cholangitis. *E. cuniculi* is associated with hepatitis, encephalitis, and disseminated disease. *E. intestinalis* is associated with diarrhea, disseminated infection, and superficial keratoconjunctivitis. *E. hellem* is associated with superficial keratoconjunctivitis, sinusitis, respiratory disease, prostatic abscesses, and disseminated infection. *Anncaliia*, *Vittaforma*, and *Trachipleistophora* are associated with keratoconjunctivitis. *Nosema*, *Vittaforma*, and *Microsporidium* are associated with stromal keratitis following trauma in immunocompetent hosts. *Pleistophora*, *Anncaliia*, and *Trachipleistophora* are associated with myositis. *Trachipleistophora* is associated with encephalitis and disseminated disease.

Diagnosis

Effective morphologic demonstration of microsporidia by light microscopy can be accomplished with staining methods that produce differential contrast between the spores of the microsporidia and the cells and debris in clinical samples, such as stool. In addition, because of the small size of the spores (1–5 mm), magnification up to 1,000 times is required for visualization. Chromotrope 2R and

the fluorescent brighteners calcofluor white and Uvitex 2B are useful as selective stains for microsporidia in stool and other body fluids.[7]

In biopsy specimens, microsporidia can be visualized with Giemsa, tissue Gram stains (Brown-Hopps Gram stain), calcofluor white or Uvitex 2B (fluorescent brighteners) staining, Warthin-Starry silver staining, or Chromotrope 2A.[7] In gastrointestinal disease, examination of three stools with chromotrope and chemofluorescent stains is often sufficient for diagnosis. If stool examination is negative and microsporidiosis is suspected, a small bowel biopsy may be useful. If the etiologic agent is *Encephalitozoon* or *Trachipleistophora* sp., examination of urine often also reveals the organism. Determination of the species of microsporidia causing disease can be made by the morphology of the organism demonstrated by transmission electron microscopy, by staining with species-specific antibodies, or by polymerase chain reaction using species- or genus-specific primers.[7,10] The assistance of specialists familiar with the species differentiation of microsporidia should be sought.

Preventing Exposure

People with HIV who have CD4 counts <200 cells/mm^3 should avoid untreated water sources **(AIII).** Additional recommendations include increasing attention to hand washing and personal hygiene, avoiding eating undercooked meat or seafood, and limiting exposure to animals known to be infected with microsporidia **(BIII).**[11] The precautions described in the section on cryptosporidiosis also are applicable to microsporidiosis.

Preventing Disease

Preventing Chronic Microsporidiosis
• Because chronic microsporidiosis occurs primarily in people with advanced immunodeficiency, initiate ART before severe immunosuppression occurs (AII).

Key: ART = antiretroviral therapy

Because chronic microsporidiosis occurs primarily in people with advanced immunodeficiency, appropriate initiation of ART before severe immunosuppression should prevent this disease **(AII).** No specific chemoprophylactic regimens are known to be effective in preventing microsporidiosis.

Treating Disease

Managing Microsporidiosis
• Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 (AII).
• Manage severe dehydration, malnutrition, and wasting with fluid support (AII) and nutritional supplements (AIII).
• Antimotility agents can be used for diarrhea control, if required (BIII).
GI Infections Caused by Enterocytozoon bieneusi
• The best treatment option is ART and fluid support (AII).
• No specific therapeutic agent is available for this infection.
• Fumagillin 60 mg PO daily (BII) and TNP-470 (BIII) (unavailable in the United States)

- Nitazoxanide 500 mg twice daily for at least 14 days may resolve chronic diarrhea and is a reasonable alternative if fumagillin is not available (CIII), but the effect appeared to be minimal in people with low CD4 counts.

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

- Albendazole is recommended only for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* (AII). Albendazole 400 mg PO twice daily (AII) for at least 14 days; continue therapy until the CD4 count is >200 cells/mm^3 after initiation of ART (BIII).

Disseminated Disease Caused by Trachipleistophora or Anncaliia

- Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily (CIII)

Ocular Infection

- Topical fumagillin bicylohexylammonium (Fumidil B) 3 mg/mL in saline (fumagillin 70 µg/mL) eye drops: 2 drops every 2 hours for 4 days, then 2 drops four times daily (investigational use only in the United States; needs to be prepared by a compounding pharmacy) (BII), *and*
- Albendazole 400 mg PO twice daily for management of systemic infection (BIII)
- For people with CD4 count >200 cells/mm^3, therapy can be discontinued after ocular infection resolves (CIII).
- For people with CD4 count ≤200 cells/mm^3, therapy should be continued indefinitely as recurrence or relapse may occur when therapy is discontinued (BIII).

Discontinuation of Chronic Maintenance Therapy for Non-Ocular Manifestations (BIII)

- No longer have signs and symptoms of microsporidiosis, *and*
- Sustained increase in CD4 count >200 cells/mm^3 for ≥3 months after ART

Pregnancy Considerations

- Albendazole is not recommended for use during the first trimester (BIII); use in later pregnancy should be considered only if benefits outweigh potential risks (CIII).
- Fumagillin has an antiangiogenic effect and should not be used systemically in pregnant people (AIII). Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate (CIII).
- Nitazoxanide has not been associated with adverse outcomes in pregnancy; however, data are very limited on its use during pregnancy (CIII).
- Azole antifungals should be avoided during the first trimester (BIII).
- Loperamide should be avoided in the first trimester unless benefits outweigh potential risks of congenital malformations (CIII). Loperamide is the preferred antimotility agent in late pregnancy (CIII).
- Opiate exposure in late pregnancy has been associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium is not recommended in late pregnancy (AIII).

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

Data suggest that treatment with ART enables a person's own defenses to eradicate microsporidia,[12,13] and administration of ART with immune restoration (an increase in CD4 count to >100 cells/mm^3) is associated with resolution of symptoms of enteric microsporidiosis, including illness caused by *E. bieneusi*.[12-15] Everyone, therefore, should be offered ART as part of the initial management of microsporidial infection **(AII),** and they should be given fluid support if they have signs of diarrhea and dehydration **(AII).** People with malnutrition and wasting should be treated with

nutritional supplementation **(AIII).** Antimotility agents can be used if required for diarrhea control **(BIII).**

No specific therapeutic agent is available for *E. bieneusi* infection. Based on results from a controlled clinical trial, oral fumagillin (60 mg/day), a water-insoluble antibiotic made from *Aspergillus fumigatus* **(BII),**[16,17] or to its synthetic analog, TNP-470 can be administered **(BIII).**[18] Fumagillin and TNP-470 are not commercially available for systemic use in the United States, and Sanofi in France no longer produces FLISINT (fumagillin). One report indicated that treatment with nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi* in the absence of ART;[19] however, the effect appeared to be minimal among people with low CD4 counts. Based on the professional experience of several experts who have treated diarrhea caused by *E. bieneusi* with nitazoxanide in organ transplant recipients, nitazoxanide is a reasonable alternative for the treatment of diarrhea due to *E. bieneusi* if fumagillin is not available **(CIII).**[20]

Albendazole, a benzimidazole that binds to β-tubulin, has activity against many species of microsporidia, but it is not effective against *E. bieneusi* or *V. corneae* infections. The tubulin genes of both *E. bieneusi*[21] and *V. corneae*[22] have amino acid residues associated with albendazole resistance. Albendazole is recommended only for initial therapy of intestinal and disseminated microsporidiosis caused by microsporidia other than *E. bieneusi* and *V. corneae* **(AII).**[23-25]

Itraconazole may be useful in disseminated disease when combined with albendazole, especially in infections caused by *Trachipleistophora* or *Anncaliia* **(CIII).** Treatment with furazolidone (an agent that is not currently available in the United States) combined with albendazole was reported to improve clinical signs in four people with HIV with persistent diarrhea and *E. bieneusi* infection **(CIII)**[26]; however, furazolidone has not been demonstrated to be active in other case reports. Metronidazole and atovaquone are not active *in vitro* or in animal models and **should not be used** to treat microsporidiosis **(AII).**

People with ocular infections caused by microsporidia should be administered topical Fumidil B (fumagillin bicylohexylammonium) in saline (to achieve a concentration of 70 µg/mL of fumagillin) **(BII).**[23] Topical fumagillin solution needs to be made by a compounding pharmacy because it is not commercially available in the United States and is investigational. Although clearance of microsporidia from the eye can be demonstrated, the organism often is still present systemically and can be detected in urine or in nasal smears; therefore, the use of albendazole as a companion systemic agent to fumagillin is recommended in ocular infections **(BIII).**

Special Considerations with Regard to Starting ART

As noted above, people with HIV should be offered ART as part of the initial management of microsporidial infection, as well as fluid support if they have signs of diarrhea and dehydration **(AII).** Data suggest that treatment with ART, which results in immune reconstitution, enables a person's own defenses to eradicate microsporidia.[12,13]

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

Although side effects with albendazole are rare, hepatic enzymes should be monitored because elevations have been reported. Albendazole is not known to be carcinogenic or mutagenic. Topical fumagillin has not been associated with substantial side effects. Oral fumagillin has been associated with thrombocytopenia, which is reversible after stopping the drug.

One report of immune reconstitution inflammatory syndrome (IRIS) has been described in a person with HIV treated with ART in the setting of *E. bieneusi* infection;[27] however, no IRIS reactions have been reported with other species of microsporidia or with other cases of *E. bieneusi*. Concerns about IRIS should not alter therapy or the use of ART **(AIII).**

Managing Treatment Failure

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

Preventing Recurrence

In individuals with relatively competent immune systems (>200 CD4 cells/mm^3), treatment should be discontinued after ocular infection resolves **(CIII);** treatment should be continued indefinitely if CD4 counts fall below 200 cells/mm^3 because recurrence or relapse may occur after treatment discontinuation **(BIII).** Whether it is safe to discontinue treatment for other manifestations after immune restoration with ART is unknown. Based on experience with discontinuation of secondary prophylaxis for other opportunistic infections, it is reasonable to discontinue chronic maintenance therapy in those who no longer have signs and symptoms of microsporidiosis and have a sustained increase in their CD4 counts to >200 cells/mm^3 for 3 to 6 months after ART **(BIII).**[13]

Special Considerations During Pregnancy

Rehydration and initiation of ART are the preferred initial treatment of microsporidiosis during pregnancy, as in nonpregnant people **(AII).** In rats and rabbits, albendazole is embryotoxic and teratogenic at exposure levels less than those estimated with therapeutic human dosing. There are no adequate and well-controlled studies of albendazole exposure in early human pregnancy. A recent randomized trial in which albendazole was used for second-trimester treatment of soil-transmitted helminth infections found no evidence of teratogenicity or other adverse pregnancy effects.[28]

Based on these data, albendazole **is not recommended** for use during the first trimester **(BIII);** use in later pregnancy should be considered only if benefits outweigh potential risks **(CIII).** Systemic fumagillin has been associated with increased resorption and growth retardation in rats. No data on use in human pregnancy are available. However, because of the antiangiogenic effect of fumagillin, this drug **should not be used** systemically in pregnant people **(AIII).** Topical fumagillin has not been associated with embryotoxic or teratogenic effects and can be considered when therapy with this agent is appropriate **(CIII).** Furazolidone is not teratogenic in animal studies, but human data are limited to a case series that found no association between first-trimester use of furazolidone and birth defects in 132 furazolidone-exposed pregnancies.[29] Nitazoxanide has not been associated with adverse outcomes in pregnancy; however, data are very limited on its use during pregnancy **(CIII).** Case reports exist of birth defects in infants exposed to itraconazole, but prospective cohort studies of >300 women with first-trimester exposure did not show an increased risk of malformation.[30,31] In general, however, azole antifungals should be avoided during the first trimester **(BIII).** Loperamide is poorly absorbed and has not been associated with birth defects in animal studies; however, a recent study identified an increased risk of congenital malformations, specifically hypospadias, among 683 women with exposure to loperamide in early pregnancy.[32] Therefore, loperamide should be avoided in the first trimester unless benefits outweigh potential risks **(CIII).** Loperamide is the preferred antimotility agent in late pregnancy **(CIII).** Opiate exposure in late pregnancy has been

associated with neonatal respiratory depression, and chronic exposure may result in neonatal withdrawal; therefore, tincture of opium **is not recommended** in late pregnancy **(AIII).**

References

1. James TY, Pelin A, Bonen L, et al. Shared signatures of parasitism and phylogenomics unite Cryptomycota and microsporidia. *Curr Biol*. 2013;23(16):1548-1553. Available at: https://www.pubmed.ncbi.nlm.nih.gov/23932404.

2. Beauvais B, Sarfati C, Molina JM, Lesourd A, Lariviere M, Derouin F. Comparative evaluation of five diagnostic methods for demonstrating microsporidia in stool and intestinal biopsy specimens. *Ann Trop Med Parasitol*. 1993;87(1):99-102. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8346996.

3. Deplazes P, Mathis A, Weber R. Epidemiology and zoonotic aspects of microsporidia of mammals and birds. *Contrib Microbiol*. 2000;6:236-260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10943515.

4. Kotler DP, Orenstein JM. Clinical syndromes associated with microsporidiosis. *Adv Parasitol*. 1998;40:321-349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9554078.

5. Mathis A. Microsporidia: emerging advances in understanding the basic biology of these unique organisms. *Int J Parasitol*. 2000;30(7):795-804. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10899524.

6. Weber R, Bryan RT, Owen RL, Wilcox CM, Gorelkin L, Visvesvara GS. Improved light-microscopical detection of microsporidia spores in stool and duodenal aspirates. The Enteric Opportunistic Infections Working Group. *N Engl J Med*. 1992;326(3):161-166. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1370122.

7. Weiss LM, Vossbrinck CR. Microsporidiosis: molecular and diagnostic aspects. *Adv Parasitol*. 1998;40:351-395. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9554079.

8. Wittner M, Weiss L. The microsporidia and microsporidiosis. Washington D.C.: ASM Press; 1999.

9. Stark D, Barratt JL, van Hal S, Marriott D, Harkness J, Ellis JT. Clinical significance of enteric protozoa in the immunosuppressed human population. *Clin Microbiol Rev*. 2009;22(4):634-650. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19822892.

10. Sheoran AS, Feng X, Singh I, et al. Monoclonal antibodies against Enterocytozoon bieneusi of human origin. *Clin Diagn Lab Immunol*. 2005;12(9):1109-1113. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16148179.

11. Didier ES, Weiss LM. Microsporidiosis: current status. *Curr Opin Infect Dis*. 2006;19(5):485-492. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16940873.

12. Goguel J, Katlama C, Sarfati C, Maslo C, Leport C, Molina JM. Remission of AIDS-associated intestinal microsporidiosis with highly active antiretroviral therapy. *AIDS*. 1997;11(13):1658-1659. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9365777.

13. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2000;25(2):124-129. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11103042.

14. Conteas CN, Berlin OG, Speck CE, Pandhumas SS, Lariviere MJ, Fu C. Modification of the clinical course of intestinal microsporidiosis in acquired immunodeficiency syndrome patients by immune status and anti-human immunodeficiency virus therapy. *Am J Trop Med Hyg*. 1998;58(5):555-558. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9598440.

15. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with human immunodeficiency virus type 1. *Eur J Clin Microbiol Infect Dis*. 2000;19(3):213-217. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10795595.

16. Molina JM, Goguel J, Sarfati C, et al. Trial of oral fumagillin for the treatment of intestinal microsporidiosis in patients with HIV infection. ANRS 054 Study Group. Agence Nationale de Recherche sur le SIDA. *AIDS*. 2000;14(10):1341-1348. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10930148.

17. Molina JM, Tourneur M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med*. 2002;346(25):1963-1969. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12075057.

18. Didier PJ, Phillips JN, Kuebler DJ, et al. Antimicrosporidial activities of fumagillin, TNP-470, ovalicin, and ovalicin derivatives in vitro and in vivo. *Antimicrob Agents Chemother*. 2006;50(6):2146-2155. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16723577.

19. Bicart-See A, Massip P, Linas MD, Datry A. Successful treatment with nitazoxanide of Enterocytozoon bieneusi microsporidiosis in a patient with AIDS. *Antimicrob Agents Chemother*. 2000;44(1):167-168. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10602740.

20. Saffo Z, Mirza N. Successful treatment of Enterocytozoon bieneusi gastrointestinal infection with nitazoxanide in a immunocompetent patient. *IDCases*. 2019;18:e00586. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31388488.

21. Akiyoshi DE, Weiss LM, Feng X, et al. Analysis of the beta-tubulin genes from Enterocytozoon bieneusi isolates from a human and rhesus macaque. *J Eukaryot Microbiol*. 2007;54(1):38-41. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17300517.

22. Franzen C, Salzberger B. Analysis of the beta-tubulin gene from Vittaforma corneae suggests benzimidazole resistance. *Antimicrob Agents Chemother*. 2008;52(2):790-793. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18056284.

23. Diesenhouse MC, Wilson LA, Corrent GF, Visvesvara GS, Grossniklaus HE, Bryan RT. Treatment of microsporidial keratoconjunctivitis with topical fumagillin. *Am J Ophthalmol*. 1993;115(3):293-298. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8117342.

24. Dieterich DT, Lew EA, Kotler DP, Poles MA, Orenstein JM. Treatment with albendazole for intestinal disease due to Enterocytozoon bieneusi in patients with AIDS. *J Infect Dis*. 1994;169(1):178-183. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8277179.

25. Molina JM, Chastang C, Goguel J, et al. Albendazole for treatment and prophylaxis of microsporidiosis due to Encephalitozoon intestinalis in patients with AIDS: a randomized double-blind controlled trial. *J Infect Dis*. 1998;177(5):1373-1377. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9593027.

26. Dionisio D, Manneschi LI, Di Lollo S, et al. Persistent damage to Enterocytozoon bieneusi, with persistent symptomatic relief, after combined furazolidone and albendazole in AIDS patients. *J Clin Pathol*. 1998;51(10):731-736. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10023334.

27. Sriaroon C, Mayer CA, Chen L, Accurso C, Greene JN, Vincent AL. Diffuse intra-abdominal granulomatous seeding as a manifestation of immune reconstitution inflammatory syndrome associated with microsporidiosis in a patient with HIV. *AIDS Patient Care STDS*. 2008;22(8):611-612. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18627278.

28. Ndyomugyenyi R, Kabatereine N, Olsen A, Magnussen P. Efficacy of ivermectin and albendazole alone and in combination for treatment of soil-transmitted helminths in pregnancy and adverse events: a randomized open label controlled intervention trial in Masindi district, western Uganda. *Am J Trop Med Hyg*. 2008;79(6):856-863. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19052293.

29. Heinonen OP, Slone D, Shapiro S. Birth defects and drugs in pregnancy. Littleton: Publishing Sciences Group; 1977.

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

31. Bar-Oz B, Moretti ME, Bishai R, et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol*. 2000;183(3):617-620. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10992182.

32. Kallen B, Nilsson E, Otterblad Olausson P. Maternal use of loperamide in early pregnancy and delivery outcome. *Acta Paediatr*. 2008;97(5):541-545. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18394096.

Mpox

Updated: July 24, 2023
Reviewed: July 24, 2023

Epidemiology

Mpox is a zoonotic viral disease caused by mpox virus, an enveloped double-stranded DNA virus that belongs to the same *Orthopoxvirus* genus of the *Poxviridae* family as the causative agent of smallpox. Mpox virus circulates among certain small mammals found in the forested regions of some parts of Africa, creating a reservoir of disease in the animal population. This reservoir is believed to have been the source of the sporadic human outbreaks that have occurred in certain African countries since the first cases were identified in the 1970s until the recent 2022 multinational mpox outbreak.[1] Two distinct clades of mpox virus have been described in different geographic regions of Africa; Clade I (previously called Congo Basin clade) was classically associated with more severe disease and more human-to-human transmission than Clade II (previously called West African clade).[2,3] Historically, risk for serious infection and death has been greatest for children <8 years of age as well as developing fetuses infected perinatally.[4]

The epidemiology of Clade II mpox has evolved as human cases of mpox outside of Africa have been identified.[5] The first notable mpox outbreak occurred in the United States in 2003 and was associated with the importation of small African mammals; transmission occurred through direct contact or contaminated fomites.[6] Mpox also re-emerged in countries like Nigeria, which saw a large outbreak in 2017 and 2018 after decades without human cases.[7,8] However, from 2018 until May 2022, all cases involved persons traveling from endemic areas to other nations, including the United Kingdom (4 cases), Singapore (1 case), Israel (1 case), and the United States (2 cases).[9-14]

In May 2022, a large multinational outbreak of Clade II mpox was recognized. Multiple lineages of mpox virus were detected in the United States during the early months of the outbreak, suggesting multiple introductions of mpox worldwide and raising concerns for future outbreaks.[15] The majority of infections in 2022 were transmitted sexually through intimate contact with one or more mpox lesions on the skin or mucosal surfaces of people with mpox infection.[16] Infections have disproportionately affected gay, bisexual, same-gender-loving, and other men who have sex with men (MSM). Notably, infections in women and children and occupational infections transmitted to health care personnel through injury with contaminated sharps also have been reported.[17-25] Among MSM, coinfection with HIV and other sexually transmitted infections (STIs) has been common.[17] Across reports, around 40% to 50% of cases have been in people with HIV, and around 15% to 30% of cases have been diagnosed concomitantly with gonorrhea, syphilis, chlamydia, or other STIs.[17,18,26,27] Severe and fatal cases have disproportionately been reported in people with HIV, especially among people with advanced or uncontrolled HIV.[28-39] Although the overall mortality rate for Clade II infection is low (<1%), mortality among people with advanced HIV has been higher.[8,36-39]

Clinical Manifestations

In outbreaks prior to 2022, mpox cases had been characterized by prodromal symptoms of fever, headache, lymphadenopathy, myalgias, or fatigue followed by a distinctive rash that progresses synchronously from macules to papules, vesicles, pustules, and, ultimately, crusted lesions. In prior

outbreaks, some cases among people with HIV were identified; these cases involved longer duration of illness, larger size of lesions, more frequent secondary bacterial infections, and presence of genital ulcers.[8,38]

In the 2022 multinational mpox outbreak, the clinical manifestations associated with Clade II infection were distinct in several respects.[18,40] Prodromal symptoms have been mild or absent and have not always preceded the rash.[40] Rash commonly occurs as anogenital or oropharyngeal/perioral lesions, with rash involving the limbs, face, and trunk also occurring.[18,40] Lesions can be single or multiple and limited to a single body site and also can progress in varying stages.[18,40] Inguinal, cervical, and/or axillary lymphadenopathy may be present, similar to historic outbreaks, but not as reliably as with classic presentations.[40]

Most patients, including those with well-controlled HIV, experience self-limiting disease and recover with supportive care alone.[41] For a subset of patients, infection can be more severe.[41] Pharyngeal involvement can result in tonsillitis or pharyngitis associated with odynophagia or dysphagia.[18] Anorectal involvement has caused tenesmus, proctitis, and rectal bleeding, which can be severe.[18,42] Inflammation from genital lesions can produce dysuria occasionally complicated by significant paraphimosis/phimosis or urethritis that limits the ability to urinate.[39,43,44] Severe gastrointestinal manifestations, such as enteritis or colitis, and anogenital involvement can necessitate hospitalization for enhanced symptom control, including pain management.[18,39,44] Lesions have led to stricture and scar formation, causing urethral or bowel obstruction.[39,44] Ocular involvement from autoinoculation can result in conjunctivitis, blepharitis, keratitis, corneal ulcer with possible scarring, and, in rare cases, loss of vision.[45-47] Bacterial superinfections (e.g., staphylococcal skin and soft tissue infections) can also occur.[39] Other reported manifestations have included nodular pulmonary disease, encephalitis and transverse myelitis, myocarditis and pericarditis, septic arthritis, viral "cold abscesses," and genital necrosis.[39,48,49]

During the current outbreak, cases among pediatric patients and pregnant people have been less common and have not yet been associated with severe disease.[50,51] People who are significantly immunocompromised, most commonly from poorly controlled HIV (CD4 T lymphocyte [CD4] cell count <350 cells/mm^3 and especially <50 cells/mm^3), have experienced more severe infections, including increased likelihood of hospitalization and disseminated disease, likely because their weakened immune systems are unable to clear the virus.[28-39] These more severe manifestations can include coalescing or necrotic lesions involving areas of skin (including genitalia) that require surgical debridement and that can continue to progress despite initiation of medical treatment for mpox (see Treating Disease below).[52] Patients' illness can continue to worsen if immune function is not restored, resulting in death.[39]

Diagnosis

Clinical presentation with symptoms such as a characteristic rash associated with mpox lesions is strongly suggestive of mpox.[53] However, diagnosis of mpox based solely on clinical presentation can be challenging due to the protean appearance of mpox lesions. Mpox lesions can mimic lesions seen in other infections such as herpes zoster, as well as STIs such as syphilis, herpes simplex, and molluscum contagiosum. For this reason, and due to the high frequency of coinfection with STIs seen during the multinational 2022 Clade II mpox outbreak, a broad differential diagnosis is encouraged for all people undergoing evaluation for mpox, and screening for STIs, including HIV, is recommended.[17]

Mpox is typically confirmed by the presence of mpox virus DNA in a clinical specimen using the polymerase chain reaction (PCR).[16,53] The recommended specimen is skin lesion material, which can include swabs of a lesion's surface, lesion exudate, or lesion crusts. In the absence of a lesion on epithelialized skin, specimens from mucosal (e.g., oropharynx, saliva, anorectum) lesions or tissues can support diagnosis of mpox. Unroofing or aspiration of lesions is neither required nor recommended and has led to occupational infections from injuries with contaminated sharps; vigorous swabbing of lesion surfaces alone is sufficient.[22,23,54] Testing is available through state public health laboratories and multiple commercial laboratories.

The diagnosis of mpox can also be established by serologic testing demonstrating detectable levels of anti-*Orthopoxvirus* immune globulin M antibody during the period of 4 to 56 days after rash onset in the absence of recent mpox vaccination.[53] If there is high clinical suspicion for mpox and inconclusive or negative testing via PCR or antibody testing, additional testing—such as next-generation sequencing, viral culture to demonstrate the presence of replication-competent virus, biopsy with immunohistochemical staining to demonstrate the presence of viral antigen, or electron microscopy to demonstrate the presence of characteristic viral particles—can be used to confirm the diagnosis, but these diagnostic technologies have varying availability.[53]

Preventing Exposure

Strategies to prevent mpox exposure are similar for people with and without HIV.[55] Regardless of vaccination, people with HIV at risk for mpox should avoid skin-to-skin or other close intimate contact (including sex) with people who may have constitutional symptoms or a rash suspicious for mpox, avoid contact with contaminated surfaces or objects (including linens) used by a person with mpox, and perform frequent hand hygiene after touching rash material or surfaces that may have had contact with rash material **(AIII).** Condoms or other barrier methods may provide additional protection during sex or other intimate activity. During active mpox outbreaks when rates of community transmission may be high, it is recommended that people (including people with HIV) be counseled about the value of reducing their number of sexual partners and limiting visits to venues where group sex or other prolonged skin-to-skin contact is possible **(CIII).**

Recommendations regarding the use of personal protective equipment and other infection control practices when clinically managing patients with mpox can be found at the CDC web page on Infection Prevention and Control of Mpox in Healthcare Settings. Of particular note, sharps should not be used to unroof lesions when collecting diagnostic samples. Self-inoculation with sharps contaminated with mpox via penetrating wound injuries has been the leading cause of health care-associated infections.[22-25]

Preventing Disease

Recommendations for Preventing Mpox Infection
Vaccination Before Mpox Exposure • Indications o Mpox vaccination should be offered to all people with HIV who have potential for mpox exposure or anticipate potential exposure to mpox per CDC interim clinical considerations (BII). o Mpox vaccination should be provided to any other people with HIV who request vaccination (CII).

- Vaccination
  - MVA-BN vaccine, sold in the United States as JYNNEOS, is the preferred vaccine before mpox exposure and is safe to use in people with HIV; administer JYNNEOS in two doses (0.1 mL ID or 0.5 mL SQ) 28 days apart (AII).
  - Administration of live, replicating vaccinia vaccines (i.e., ACAM2000) to pregnant or immunocompromised people, including people with HIV, is contraindicated (AII).

Vaccination Following Mpox Exposure

- Indications
  - For unvaccinated people with HIV who experience a known or presumed exposure, post-exposure vaccination is recommended as soon as possible, ideally within 4 days after exposure; however, administration 4 to 14 days after exposure may still provide some protection against mpox and should be offered (BII).
- Vaccination
  - JYNNEOS is the preferred vaccine following mpox exposure and is safe to use in people with HIV; administer JYNNEOS in two doses (0.1 mL ID or 0.5 mL SQ) 28 days apart as soon as possible and within 14 days after exposure to mpox (AII).
  - Administration of live, replicating vaccinia vaccines (i.e., ACAM2000) to pregnant, breastfeeding, or immunocompromised individuals, including people with HIV, is contraindicated (AII).

Alternative Post-Exposure Prophylaxis

- On a case-by-case basis and in consultation with an infectious disease expert, people with HIV who have advanced immunosuppression or a contraindication to vaccination can consider—
  - Tecovirimat 600 mg PO every 12 hours (people weighing 40 kg to <120 kg) or every 8 hours (patients weighing ≥120 kg) for 14 days (CIII), *or*
  - VIGIV 6,000–9,000 units/kg IV single dose (CIII)
- NOTE: There are no clinical data regarding the effectiveness of mpox post-exposure prophylaxis with these agents.

Key: CDC = Centers for Disease Control and Prevention; ID = intradermal; MVA-BN = modified vaccinia Ankara-Bavarian Nordic; IV = intravenous; PO = orally; SQ = subcutaneous; VIGIV = vaccinia immune globulin intravenous

Vaccination is the principal biomedical means of preventing mpox. Mpox vaccination should be offered to all people with HIV who have potential for mpox exposure or anticipate potential exposure to mpox per Centers for Disease Control and Prevention (CDC) interim clinical considerations **(BII).** Additionally, mpox vaccination should be provided to any other people with HIV who request vaccination **(CII).** For unvaccinated people with HIV who experience a known or presumed exposure, post-exposure vaccination is recommended as soon as possible, ideally within 4 days after exposure; however, administration 4 to 14 days after exposure may still provide some protection against mpox and should be offered **(BII).** At this time, vaccination recommendations are in the context of a rapidly evolving multinational mpox outbreak. For current mpox vaccination recommendations, please see CDC's interim clinical considerations.

People with HIV who are eligible for vaccination against mpox should receive modified vaccinia Ankara (MVA) vaccines **(AII),** a live, non-replicating viral vaccine sold as JYNNEOS in the United States and as IMVANEX or IMVAMUNE elsewhere**.** JYNNEOS consists of two doses given 4 weeks (28 days) apart. CDC's interim clinical considerations for mpox vaccination recommend vaccine administration either subcutaneously or intradermally—both have been found to be effective.[56] For JYNNEOS, if the second dose is not administered during the recommended interval, it should be administered as soon as possible **(CIII).** There is no need to restart or add doses to the

series if there is an extended interval between doses **(CIII).** People who have received smallpox vaccination more than 10 years ago should still receive two doses of JYNNEOS **(CIII).**

Use of live, replicating vaccinia vaccines, such as ACAM2000, is **contraindicated** in immunocompromised individuals, including people with HIV, due to the risk of serious complications from the enhanced replication and dissemination of vaccinia virus **(AII).**[57]

JYNNEOS has been demonstrated to be both safe for people with HIV and equally immunogenic in people with HIV as in people without HIV.[58-60] However, these studies were limited to people who were virologically suppressed and had CD4 counts ≥100 cells/mm^3. Immunogenicity among people with HIV who are not virologically suppressed or have lower CD4 counts remains unknown.

Several studies indicate that JYNNEOS is effective against mpox.[61-67] Matched case control study data indicate that vaccine effectiveness against symptomatic infection ranges from 36-75% after one dose to 66-89% after two doses.[65-67] However, all studies to date have had insufficient data to assess the effectiveness of JYNNEOS against mpox by HIV status or CD4 count, and immunologic correlates of protection have not yet been established.

For people with HIV who have advanced immunosuppression or a contraindication to vaccination, tecovirimat or vaccinia immune globulin intravenous (VIGIV) can be used for mpox post-exposure prophylaxis on a case-by-case basis in consultation with an infectious diseases expert and CDC **(CIII);** however, there are no clinical data regarding the effectiveness of mpox post-exposure prophylaxis with these agents. Per U.S. Food and Drug Administration (FDA) labeling, VIGIV might theoretically impair the efficacy of live attenuated virus vaccines; however, the extent to which it might affect live but non-replicating vaccines, such as JYNNEOS, is unclear.[68] Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration **(CIII).**[68] People who received VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin **(CIII).**[68]

Treating Disease

Recommendations for Treating Mpox
• People not presently taking ART should initiate treatment as soon as possible (AIII).
*Preferred Therapy for Severe Disease or at Risk for Severe Disease**
• Tecovirimat 600 mg PO every 12 hours (<120 kg) or every 8 hours (≥120 kg) for 14 days (BIII) within 30 minutes of a fatty meal; *or*
• Tecovirimat 200 mg IV every 12 hours for 14 days (<120 kg) or 300 mg IV every 12 hours (≥ 120 kg), if concern exists regarding altered gastrointestinal absorption capacity, the inability to take PO, or the extent of organ systems affected by mpox (BIII).
• NOTE: Patients with severe immunocompromise might benefit from extended treatment (i.e., >14 days) of preferred or adjunctive therapies if new confirmed mpox lesions occur or existing lesions worsen despite treatment.
• NOTE: For severe disease, the Panel recommends early intervention with combination therapy at the time of the first medical encounter, in consultation with CDC or an expert in mpox treatment (CIII).
*Adjunctive Therapy for Severe Disease or at Risk for Severe Disease**

- Cidofovir 5 mg/kg/week IV for two doses with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) (BIII), *or*
  - Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/dL, a calculated creatinine clearance ≤55 mL/min, or a urine protein ≥100 mg/dL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised. This regimen should be avoided in patients with sulfa allergy because of cross-hypersensitivity with probenecid.
- Brincidofovir 200 mg PO once weekly for two doses (BIII), *or*
- VIGIV 6,000–9,000 units/kg IV single dose (BIII)
  - NOTE: Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration (CIII). People who received VIGIV shortly after a live virus vaccination should be revaccinated 3 months after administration of the immune globulin (CIII).
- NOTE: Consultation with local health department and/or CDC should be obtained prior to initiating the above therapies.

Preferred Therapy for Ocular Mpox

- Tecovirimat 600 mg PO every 12 hours (<120 kg) or every 8 hours (≥120 kg) for 14 days (CIII) within 30 minutes of a fatty meal, *and*
- Trifluridine (Viroptic) 1 drop into affected eye(s) every 2 hours when awake (max: 9 drops/day) until reepithelialization, then every 4 hours (min: 5 drops/day) for 7 days or until all periocular lesions have healed (CIII)
  - Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided (AII).
- NOTE: Trifluridine should be used in consultation with an ophthalmologist.

Other Considerations

- CDC offers a clinical consultation service (email eocevent482@cdc.gov), or health care providers may contact the CDC Emergency Operations Center (EOC) at 770-488-7100, where CDC can provide additional guidance to clinicians with patient management questions.
- Patients with mpox benefit from supportive care and pain control that is implemented early in the illness (BIII).

Pregnancy Considerations

- Tecovirimat can be used as a first-line antiviral for people who are pregnant, recently pregnant, or breastfeeding (BIII).
- In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are not recommended for use in pregnancy (AIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; IV = intravenous; the Panel = Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV; PO = orally; VIGIV = vaccinia immune globulin intravenous

* People with HIV who are not virologically suppressed or who have CD4 counts <350 cells/mm^3 are considered at high risk for severe mpox. Severe mpox might manifest as hemorrhagic disease; a large number of lesions such that they are confluent; sepsis; encephalitis; ocular or periorbital infections; or other conditions requiring hospitalization.

For people with well-controlled HIV, mpox is typically a self-limiting illness that resolves spontaneously without antiviral treatment. However, people with HIV who are not virologically suppressed, who have CD4 counts <350 cells/mm^3, or who are otherwise severely immunocompromised can experience prolonged severe illness with serious sequelae and are therefore candidates for antiviral treatment.[41] See the CDC's Mpox Clinical Considerations for more information.

If therapy is considered, oral tecovirimat should be administered as first-line treatment **(BIII).** Tecovirimat, which inhibits the *Orthopoxvirus* VP37 envelope-wrapping protein, is available as an oral capsule or intravenous (IV) injection. The decision to use oral or IV tecovirimat should be based on the severity of illness (e.g., extent of other organ systems affected by mpox, presence of coalescing non-healing lesions), other comorbidities that could contribute to greater severity of illness, expected adherence to the oral formulation, and gastrointestinal absorption capacity.[41] Oral tecovirimat requires intact gastrointestinal absorption and the ability to consume a high-fat meal (600 calories and 25 g fat) to support absorption, which may pose a challenge.[69]

Tecovirimat should be administered early in the course of illness for patients with advanced HIV, along with supportive care and pain control **(BIII).** Studies using a variety of animal models have shown that tecovirimat is effective in treating *Orthopoxvirus* disease.[70-72] Human clinical trials have demonstrated the drug had an acceptable safety profile.[71,73,74] A case report from the United Kingdom has suggested that tecovirimat may shorten the duration of mpox illness and mpox viral shedding.[75] There are ongoing clinical trials to assess the efficacy of tecovirimat to treat mpox.[76-78] Tecovirimat can be provided under an expanded access investigational new drug (IND) protocol or through clinical trials.

IV cidofovir or oral brincidofovir can be used as adjunctive therapy in people with severe manifestations of mpox or at risk of severe manifestations **(BIII).** Cidofovir, which acts via competitive inhibition of DNA polymerase to block DNA synthesis of many DNA viruses, is an FDA-approved antiviral medication for the treatment of cytomegalovirus (CMV) retinitis in people with advanced HIV. Brincidofovir, available orally as a tablet or suspension, is a prodrug of cidofovir that acts similarly and is thought to have less toxicity. Human data are not available on the effectiveness of cidofovir or brincidofovir to treat mpox in people with HIV. However, *in vitro* and animal studies have demonstrated that these drugs are effective against other *Orthopoxviruses*.[79-84] Data from animal models suggest that the combination of tecovirimat and brincidofovir may act synergistically to improve outcomes and could be considered for patients with disseminated infection **(CIII).**[85]

Cidofovir or brincidofovir can be used for people with or at risk for severe disease or people who experience clinically significant progression while receiving tecovirimat, develop recrudescence of disease after an initial period of improvement while receiving tecovirimat, or are otherwise ineligible to receive oral or IV tecovirimat **(BIII).** Brincidofovir is available from federal partners to clinicians who request and obtain a single-patient emergency use IND authorization for treatment of mpox. Clinicians should consider the side effect profiles of both medications when deciding on their use.

VIGIV can be used in severe cases where the development of a robust antibody response may be impaired **(BIII).** Data are not available on the effectiveness of VIGIV to treat mpox in people with HIV. In animal models using non-human primates, vaccine-induced vaccinia antibodies were protective against lethal challenge with mpox virus. The benefit of VIGIV for treatment of severe mpox is unknown. VIGIV is administered under an expanded access IND. Subsequent dosing (i.e., redosing) decisions should be made on a case-by-case basis in consultation with CDC and can be considered when: mpox lesions affect a large percentage of a patient's body surface at the time of diagnosis; new lesions (or expanding borders on existing lesions) emerge several days after VIGIV; lesions affect mobility or are concerning for long-term sequelae, such as sexual dysfunction; or adverse events or contraindications preclude maximal use of other medical countermeasures.[41]

Depending on the severity of immunocompromise and uncontrolled viral replication, these additional therapies to tecovirimat (i.e., VIGIV and brincidofovir or cidofovir) can be considered after balancing the benefits and harms. In severe cases, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommends early intervention with combination therapy at the time of the first medical encounter, in consultation with CDC or an expert in mpox treatment **(CIII)**.

The role of topical therapy in the treatment of mpox remains unknown. Topical cidofovir has been used for skin lesions with mixed success.[86,87] For ocular involvement, trifluridine, in addition to systemic therapy, can be used in cases of mpox virus conjunctivitis and is recommended in cases of mpox virus keratitis, in consultation with an ophthalmologist **(CIII).**[45,88,89] Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided **(AII).**[90]

Treatments for mpox have the potential for complex and possibly bidirectional interactions with certain antiretroviral agents. Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines describe such interactions and recommendations for therapeutic drug monitoring and dosage adjustments, where feasible.

Special Considerations with Regard to Starting Antiretroviral Therapy

People with HIV not presently taking antiretroviral therapy (ART) should initiate treatment as soon as possible to improve T and B cell function, which have key roles in modulating mpox disease severity and preventing mortality **(AIII).**[41,91-93] In people with advanced HIV (e.g., CD4 count <350 cells/mm^3), those whose HIV viral load is unsuppressed, or those who otherwise merit treatment for mpox, ART should ideally be started at the same time as mpox therapy **(AIII).**

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

As with other opportunistic infections in people with advanced HIV, dysregulated immune responses, such as immune reconstitution inflammatory syndrome (IRIS), following initiation of ART have been raised as a potential concern.[35] IRIS could lead to paradoxical worsening or a protracted course of mpox disease. Data are insufficient to inform recommendations on identification and management of dysregulated immune responses in the setting of mpox infection in people with advanced HIV. Providing passive immunity with the use of VIGIV and extending the duration of antivirals such as tecovirimat should be considered pending immune recovery **(CIII).** VIGIV has an estimated half-life of up to 3 weeks. If immune reconstitution is slow, repeat dosing should be considered on a case-by-case basis, as noted above **(BIII).**

Monitoring is recommended during and after treatment of mpox to detect toxicity, as well as persistence or recurrence of mpox.

The most common adverse effects of tecovirimat are headache and nausea.[69] After the treating clinician has assessed the risks and benefits and determined that IV tecovirimat is clinically necessary, the IV formulation should be used with caution in patients with severe renal impairment (creatinine clearance [CrCl] <30 mL/min) due to accumulation of an excipient in the IV formulation (hydroxypropyl-beta-cyclodextrin) that has shown potential for nephrotoxicity at very high exposure levels. If the IV formulation is used, closely monitor renal function; if renal toxicity is suspected,

switching to oral tecovirimat, if possible, or an alternative agent can be considered in consultation with CDC.

Adverse effects of cidofovir include dose-related nephrotoxicity, neutropenia, uveitis, and hypotony (low intraocular pressure).[94] The risk of severe renal injury from IV cidofovir can be reduced by prehydration and oral probenecid before and after cidofovir administration. In patients receiving IV cidofovir, analysis of blood urea nitrogen and creatinine levels and urinalysis should be performed before each infusion.[94] Drug administration is **contraindicated** if renal dysfunction or substantial proteinuria is detected (a serum creatinine >1.5 mg/dL, creatinine clearance ≤55 mL/min, or a urine protein ≥100 mg/dL [equivalent to ≥2+ proteinuria]).[94] Particular attention is needed for patients receiving other potentially nephrotoxic medications, including tenofovir disoproxil fumarate.[94] Periodic ophthalmologic examinations are needed to monitor for cidofovir-associated uveitis or hypotony.[94]

Adverse effects of brincidofovir include diarrhea, nausea, and other gastrointestinal adverse events and elevations in hepatic enzymes (e.g., alanine transaminase, aspartate aminotransferase) and bilirubin.[95] Brincidofovir-induced diarrhea may impair absorption of oral tecovirimat. Screening for liver test abnormalities should be performed before starting therapy and repeat testing for follow-up as clinically indicated.[95] Since brincidofovir is usually given only in two doses 1 week apart, monitoring of liver function parameters is generally done before the second dose (Day 8).[95] If serum aminotransferases are elevated and persist above 10 times the upper limit of normal, consider not giving the second dose of brincidofovir.[95] The second and final dose of brincidofovir should not be given on Day 8 if elevation of serum aminotransferases is accompanied by clinical signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase, or international normalized ratio.[95] Male patients should be counseled on the risk for irreversible effects on male fertility based on testicular toxicity observed in animal studies **(AII).**[95] Individuals of childbearing potential should use effective contraception and/or condoms during treatment and for at least 4 months after the last dose **(AIII).**[95]

Managing Treatment Failure

Clinical failure of therapy for mpox might be more likely in patients who do not have substantial immune reconstitution after initiation or optimization of ART or who are otherwise severely immunocompromised. Treatment failure can also result from inadequate tecovirimat levels secondary to inadequate gastrointestinal absorption, drug resistance, or nonadherence.

Lesions may continue to develop after a 14-day course of tecovirimat. If clinical manifestations do not improve, symptoms progress despite the use of oral tecovirimat, or there are concerns about gastrointestinal absorption, IV tecovirimat should be initiated if not already being used **(BIII).** In these cases, the addition of other therapeutics, including brincidofovir or cidofovir and VIGIV should also be assessed. Extending the duration of tecovirimat treatment should be done carefully, through short increments of time and close clinical monitoring for safety signals and clinical response **(BIII).**

The use of topical or ablative therapies for progressive hypertrophic lesions has been reported, but their role is still under exploration.[96] Consultation with an infectious diseases specialist, dermatology, and wound care services should be sought. CDC offers a clinical consultation service (email eocevent482@cdc.gov), or health care providers may contact the CDC Emergency Operations Center (EOC) at 770-488-7100, where CDC can provide additional guidance to clinicians with patient management questions.

Tecovirimat has a relatively low barrier to viral resistance. Single amino acid substitutions at various locations in the F13L gene coding the viral VP37 drug target confer substantial reductions in tecovirimat's antiviral activity.[69] Genotypic and phenotypic resistance to tecovirimat has been documented in patients with severe immunocompromising conditions who have disseminated and progressive mpox infection and have received or are undergoing prolonged tecovirimat treatment.[97]

Patients for whom resistance is suspected (e.g., new lesions form after at least 7 days of treatment) or documented can be considered for additional therapeutics, including cidofovir or brincidofovir, and VIGIV. Efforts should be made to restore immune function, such as ensuring people with HIV are receiving effective ART and limiting the use of immunocompromising therapies.[41]

Clinicians may consider sending repeat sample swabs to the CDC to assess for the continued presence of virus and to assess for evidence of potential viral resistance based on genetic sequencing. Formal tecovirimat sensitivity testing results cannot be used to guide treatment decisions for individual patients for two reasons: first, they require culture-based resistance testing techniques that take weeks to perform (i.e., results cannot be returned in a timely manner); and second, reporting of these results is not permitted under Clinical Laboratory Improvement Amendments. However, the results of tecovirimat susceptibility testing are helpful to public health efforts to monitor for the emergence of tecovirimat resistance.

Persistently positive PCR test results are expected until lesions resolve; therefore, subsequent testing of lesion specimens may not be informative unless new lesions or progressive lesions are occurring despite 14 days of tecovirimat treatment. Evaluating trends in PCR cycle threshold (Ct) values may be informative; Ct values ≥35 might suggest that minimal replication-competent virus is present.[98] Certain laboratories may be able to test for presence of viable virus with culture techniques, but these results may not be available in a clinically relevant timeframe.

Other possible reasons for treatment failure may include a dysregulated immune response with associated inflammation or the presence of another opportunistic infection. If viable mpox virus is still detected by culture, viral replication and ongoing infection may be driving the disease process and antiviral medications should be continued. Biopsy of the affected tissue can be performed in cases with new or atypical lesions where it is unclear if the lesions are primarily due to mpox or another infectious cause, including secondary bacterial or fungal infections, and in cases with significant complications (e.g., mucosal or bowel lesions, severe lymphadenopathy, pulmonary nodular lesions, or severe conjunctivitis). Consultation with infectious diseases specialists and CDC is encouraged.

Preventing Recurrence and Reinfection

The durability of immunity after infection with mpox or after vaccination is unknown, including among people with HIV. No clinical correlates of immunity have yet been established to guide when booster vaccination may be needed following infection or a primary vaccination series.

Special Considerations During Pregnancy

Data regarding mpox infection in pregnancy are limited.[99,100] It is unknown if pregnant people, including people with HIV, are more susceptible to mpox or if infection is more severe in pregnancy. Mpox can be transmitted to the fetus during pregnancy or to the newborn by close contact during and after birth. Adverse pregnancy outcomes, including spontaneous pregnancy loss and stillbirth, have

been reported in cases of confirmed mpox infection during pregnancy.[4,101] Preterm delivery and neonatal mpox infection have also been reported.[50]

The signs and symptoms of mpox infection in pregnant people appear similar to those in non-pregnant people, including prodromal symptoms and rash. The approach to diagnosis of mpox in pregnant people is the same as in non-pregnant people.

For people who are pregnant, breastfeeding, or trying to become pregnant and who require vaccination, JYNNEOS should be used because it is non-replication competent **(AIII).** Studies of JYNNEOS vaccine in animals have shown no evidence of harm to the developing fetus.[102] Vaccination with ACAM2000, which contains a replication-competent virus, is **contraindicated** in people who are pregnant or breastfeeding due to risk of pregnancy loss, congenital defects, and vaccinia virus infection in fetuses and newborns and the availability of alternative non-replicating viral vaccine **(AII).**[57]

Treatment for mpox should be offered to people who are pregnant, recently pregnant, or breastfeeding **(AIII).** Tecovirimat can be used as a first-line antiviral for people who are pregnant, recently pregnant, or breastfeeding **(BIII).** Information about the impact of tecovirimat on reproductive development is limited to animal studies, in which no specific fetal effects were observed.[69] It is not known if treatment with tecovirimat during pregnancy prevents congenital mpox. Animal reproduction studies have not been conducted with VIGIV; therefore, it is not known whether VIGIV can cause fetal harm when administered during pregnancy or affect future fertility.[68] However, other immune globulins have been widely used during pregnancy for many years without any apparent negative reproductive effects. In animal studies, cidofovir and brincidofovir have been shown to be teratogenic; therefore, these agents are **not recommended** for use in pregnancy **(AIII).**[94,95]

References

1. Ladnyj ID, Ziegler P, Kima E. A human infection caused by monkeypox virus in Basankusu Territory, Democratic Republic of the Congo. *Bull World Health Organ*. 1972;46(5):593-597. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4340218.

2. Chen N, Li G, Liszewski MK, et al. Virulence differences between monkeypox virus isolates from West Africa and the Congo basin. *Virology*. 2005;340(1):46-63. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16023693.

3. Likos AM, Sammons SA, Olson VA, et al. A tale of two clades: monkeypox viruses. *J Gen Virol*. 2005;86(Pt 10):2661-2672. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16186219.

4. Mbala PK, Huggins JW, Riu-Rovira T, et al. Maternal and fetal outcomes among pregnant women with human monkeypox infection in the Democratic Republic of Congo. *J Infect Dis*. 2017;216(7):824-828. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29029147.

5. Bunge EM, Hoet B, Chen L, et al. The changing epidemiology of human monkeypox-A potential threat? A systematic review. *PLoS Negl Trop Dis*. 2022;16(2):e0010141. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35148313.

6. Centers for Disease Control Prevention. Update: multistate outbreak of monkeypox--Illinois, Indiana, Kansas, Missouri, Ohio, and Wisconsin, 2003. *MMWR Morb Mortal Wkly Rep*. 2003;52(27):642-646. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12855947.

7. Ogoina D, Yinka-Ogunleye A. Sexual history of human monkeypox patients seen at a tertiary hospital in Bayelsa, Nigeria. *Int J STD AIDS*. 2022;33(10):928-932. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35969500.

8. Yinka-Ogunleye A, Aruna O, Dalhat M, et al. Outbreak of human monkeypox in Nigeria in 2017-18: a clinical and epidemiological report. *Lancet Infect Dis*. 2019;19(8):872-879. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31285143.

9. Vaughan A, Aarons E, Astbury J, et al. Two cases of monkeypox imported to the United Kingdom, September 2018. *Euro Surveill*. 2018;23(38). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30255836.

10. ECDC. Rapid Risk Assessment: Monkeypox cases in the UK imported by travellers returning from Nigeria, 2018. 2018. Available at: https://ecdc.europa.eu/sites/portal/files/documents/13-09-2018-RRA-Monkeypox-Nigeria-United-Kingdom.pdf.

11. Erez N, Achdout H, Milrot E, et al. Diagnosis of imported monkeypox, Israel, 2018. *Emerg Infect Dis*. 2019;25(5):980-983. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30848724.

12. Yong SEF, Ng OT, Ho ZJM, et al. Imported monkeypox, Singapore. *Emerg Infect Dis*. 2020;26(8):1826-1830. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32338590.

13. Costello V, Sowash M, Gaur A, et al. Imported Monkeypox from International Traveler, Maryland, USA, 2021. *Emerg Infect Dis*. 2022;28(5):1002-1005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35263559.

14. Rao AK, Schulte J, Chen TH, et al. Monkeypox in a traveler returning from Nigeria - Dallas, Texas, July 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(14):509-516. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35389974.

15. Gigante CM, Korber B, Seabolt MH, et al. Multiple lineages of monkeypox virus detected in the United States, 2021-2022. *Science*. 2022;378(6619):560-565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36264825.

16. Centers for Disease Control and Prevention. Science Brief: Detection and transmission of monkeypox virus. Available at: https://archive.cdc.gov/#/details?url=https://www.cdc.gov/poxvirus/mpox/about/science-behind-transmission.html.

17. Curran KG, Eberly K, Russell OO, et al. HIV and sexually transmitted infections among persons with monkeypox - eight U.S. jurisdictions, May 17-July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(36):1141-1147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36074735.

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

19. Saunders KE, Van Horn AN, Medlin HK, et al. Monkeypox in a young infant - Florida, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(38):1220-1221. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36136958.

20. Aguilera-Alonso D, Alonso-Cadenas JA, Roguera-Sopena M, Lorusso N, Miguel LGS, Calvo C. Monkeypox virus infections in children in Spain during the first months of the 2022 outbreak. *Lancet Child Adolesc Health*. 2022;6(11):e22-e23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36058226.

21. Alonso-Cadenas JA, Andina-Martinez D, Garcia-Garcia CJ, Gaitero-Tristan J, Garcia-Ascaso MT, Torrelo A. Monkeypox disease in a breastfeeding infant. *Pediatr Dermatol*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36180382.

22. Carvalho LB, Casadio LVB, Polly M, et al. Monkeypox Virus Transmission to Healthcare Worker through Needlestick Injury, Brazil. *Emerg Infect Dis*. 2022;28(11):2334-2336. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36121391.

23. Mendoza R, Petras JK, Jenkins P, et al. Monkeypox virus infection resulting from an occupational needlestick - Florida, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1348-1349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36264845.

24. Choi Y, Jeon EB, Kim T, et al. Case report and literature review of occupational transmission of monkeypox virus to healthcare workers, South Korea. *Emerg Infect Dis*. 2023;29(5):997-1001. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36856759.

25. Caldas JP, Valdoleiros SR, Rebelo S, Tavares M. Monkeypox after occupational needlestick injury from pustule. *Emerg Infect Dis*. 2022;28(12):2516-2519. Available at: https://www.pubmed.ncbi.nlm.nih.gov/36252152.

26. Tarin-Vicente EJ, Alemany A, Agud-Dios M, et al. Clinical presentation and virological assessment of confirmed human monkeypox virus cases in Spain: a prospective observational cohort study. *Lancet*. 2022;400(10353):661-669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35952705.

27. Philpott D, Hughes CM, Alroy KA, et al. Epidemiologic and clinical characteristics of monkeypox cases - United States, May 17-July 22, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1018-1022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35951487.

28. Philpott D, Bonacci R, Weidle P, et al. CD4 count <350 cells/mm3 increases risk of hospitalization with mpox in PWH. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/cd4-count-350-cells-mm3-increases-risk-of-hospitalization-with-mpox-in-pwh/.

29. Cholli PA, Miller MJ, Paromita P, et al. Characteristics of patients hospitalized with mpox during the 2022 U.S. outbreak. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/characteristics-of-patients-hospitalized-with-mpox-during-the-2022-us-outbreak/.

30. Corma-Gómez A, Santos M, Cabello A, et al. Mpox virus infection is more severe in patients with uncontrolled HIV infection. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/mpox-virus-infection-is-more-severe-in-patients-with-uncontrolled-hiv-infection/.

31. Garcia EA, Lash MK, McPherson TD, et al. Severe mpox among people living with HIV receiving tecovirimat in New York city. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/severe-mpox-among-people-living-with-hiv-receiving-tecovirimat-in-new-york-city/.

32. Garneau WM, Jones JL, Dashler G, et al. Clinical outcomes among in- and outpatients with mpox in an urban health system. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/clinical-outcomes-among-in-and-outpatients-with-mpox-in-an-urban-health-system/.

33. Silva M, Coutinho C, Torres T, et al. Impact of HIV infection on mpox-related hospitalizations in Brazil. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/impact-of-hiv-infection-on-mpox-related-hospitalizations-in-brazil/.

34. Vo C, Zomorodi R, Silvera R, et al. Demographic and clinical characteristics of mpox within a New York city health system. Presented at: Conference on Retroviruses and Opportunistic Infections 2023; 2023. Seattle, US. Available at: https://www.croiconference.org/abstract/demographic-and-clinical-characteristics-of-mpox-within-a-new-york-city-health-system/.

35. Mitja O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. *Lancet*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36828001.

36. WHO. Multi-country outbreak of mpox, External situation report#12- 14 December 2022. 2022. Available at: https://www.who.int/publications/m/item/multi-country-outbreak-of-mpox--external-situation-report-12--14-december-2022.

37. NCDC. NCDC Weekly Epidemiological Report: Volume 9, No. 51: 16th – 22nd December 2019. 2019. Available at: https://reliefweb.int/report/nigeria/ncdc-weekly-epidemiological-report-volume-9-no-51-16th-22nd-december-2019.

38. Ogoina D, Iroezindu M, James HI, et al. Clinical course and outcome of human monkeypox in Nigeria. *Clin Infect Dis*. 2020;71(8):e210-e214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32052029.

39. Miller MJ, Cash-Goldwasser S, Marx GE, et al. Severe monkeypox in hospitalized patients - United States, August 10-October 10, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1412-1417. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36327164.

40. Centers for Disease Control and Prevention. Health Alert Network (HAN) No. 466: Monkeypox Virus Infection in the United States and Other Non-endemic Countries--2022. 2022. Available at: https://emergency.cdc.gov/han/2022/han00466.asp.

41. Rao AK, Schrodt CA, Minhaj FS, et al. Interim clinical treatment considerations for severe manifestations of mpox - United States, February 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(9):232-243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36862595.

42. Lucar J, Roberts A, Saardi KM, Yee R, Siegel MO, Palmore TN. Monkeypox virus-associated severe proctitis treated with oral tecovirimat: a report of two cases. *Ann Intern Med*. 2022;175(11):1626-1627. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35981225.

43. Patel A, Bilinska J, Tam JCH, et al. Clinical features and novel presentations of human monkeypox in a central London centre during the 2022 outbreak: descriptive case series. *BMJ*. 2022;378:e072410. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35902115.

44. Centers for Disease Control and Prevention. Health Alert Network (HAN) No. 475: Severe Manifestations of Monkeypox among People who are Immunocompromised Due to HIV or Other Conditions. 2022. Available at: https://emergency.cdc.gov/han/2022/han00475.asp.

45. Cash-Goldwasser S, Labuda SM, McCormick DW, et al. Ocular monkeypox - United States, July-September 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(42):1343-1347. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36264836.

46. Nogueira Filho PA, Lazari CDS, Granato CFH, et al. Ocular manifestations of monkeypox: a case report. *Arq Bras Oftalmol*. 2022;85(6):632-635. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36350927.

47. Kaufman AR, Chodosh J, Pineda R, 2nd. Monkeypox virus and ophthalmology-a primer on the 2022 monkeypox outbreak and monkeypox-related ophthalmic disease. *JAMA Ophthalmol*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36326768.

48. Pastula DM, Copeland MJ, Hannan MC, et al. Two cases of monkeypox-associated encephalomyelitis - Colorado and the District of Columbia, July-August 2022. *MMWR Morb*

Mortal Wkly Rep. 2022;71(38):1212-1215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36136957.

49. Fonti M, Mader T, Burmester-Kiang J, et al. Monkeypox associated acute arthritis. *Lancet Rheumatol*. 2022;4(11):e804. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36247685.

50. Khalil A, Samara A, O'Brien P, et al. Monkeypox in pregnancy: update on current outbreak. *Lancet Infect Dis*. 2022;22(11):1534-1535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36115375.

51. Hennessee I, Shelus V, McArdle CE, et al. Epidemiologic and clinical features of children and adolescents Aged <18 Years with monkeypox - United States, May 17-September 24, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(44):1407-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36331124.

52. Carrubba S, Geevarghese A, Solli E, et al. Novel severe oculocutaneous manifestations of human monkeypox virus infection and their historical analogues. *Lancet Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36702137.

53. Centers for Disease Control and Prevention. Case Definitions for Use in the 2022 Mpox Response. 2022. Available at: https://www.cdc.gov/mpox/hcp/case-definitions/?CDC_AAref_Val=https://www.cdc.gov/poxvirus/mpox/clinicians/case-definition.html

54. Centers for Disease Control and Prevention. Infection Prevention and Control of Mpox in Healthcare Settings. 2022. Available at: https://www.cdc.gov/mpox/hcp/infection-control/healthcare-settings.html?CDC_AAref_Val=https://www.cdc.gov/poxvirus/mpox/clinicians/infection-control-healthcare.html.

55. O'Shea J, Filardo TD, Morris SB, Weiser J, Petersen B, Brooks JT. Interim guidance for prevention and treatment of monkeypox in persons with HIV infection - United States, August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(32):1023-1028. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35951495.

56. Centers for Disease Control and Prevention. JYNNEOS Vaccine. 2022. Available at: https://www.cdc.gov/mpox/?CDC_AAref_Val=https://www.cdc.gov/poxvirus/mpox/interim-considerations/jynneos-vaccine.html.

57. FDA. ACAM2000 [package insert]. 2018. Available at: https://www.fda.gov/media/75792/download.

58. Overton ET, Lawrence SJ, Stapleton JT, et al. A randomized phase II trial to compare safety and immunogenicity of the MVA-BN smallpox vaccine at various doses in adults with a history of AIDS. *Vaccine*. 2020;38(11):2600-2607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32057574.

59. Overton ET, Stapleton J, Frank I, et al. Safety and immunogenicity of modified vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced human immunodeficiency virus-infected individuals: an open-label, controlled clinical Phase II trial. *Open Forum Infect Dis*. 2015;2(2):ofv040. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26380340.

60. Greenberg RN, Overton ET, Haas DW, et al. Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects. *J Infect Dis*. 2013;207(5):749-758. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23225902.

61. Centers for Disease Control and Prevention. Preliminary JYNNEOS Vaccine Effectiveness Estimates Against Medically Attended Mpox Disease in the U.S., August 15, 2022 – October 29, 2022. 2022. Available at: https://www.cdc.gov/mpox/?CDC_AAref_Val=https://www.cdc.gov/poxvirus/mpox/cases-data/mpx-JYENNOS-vaccine-effectiveness.html.

62. Payne AB, Ray LC, Cole MM, et al. Reduced risk for mpox after receipt of 1 or 2 doses of JYNNEOS vaccine compared with risk among unvaccinated persons - 43 U.S. jurisdictions, July 31-October 1, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(49):1560-1564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36480479.

63. Bertran M, Andrews N, Davison C, et al. Effectiveness of one dose of MVA-BN smallpox vaccine against mpox in England using the case-coverage method: an observational study. *Lancet Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36924787.

64. Arbel R, Sagy YW, Zucker R, et al. Effectiveness of a single-dose modified vaccinia Ankara in human monkeypox: an observational study. *Research Square*. 2022. Available at: https://europepmc.org/article/ppr/ppr550023.

65. Dalton AF, Diallo AO, Chard AN, et al. Estimated effectiveness of JYNNEOS vaccine in preventing mpox: a multijurisdictional case-control study - United States, August 19, 2022-March 31, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):553-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37200229.

66. Deputy NP, Deckert J, Chard AN, et al. Vaccine effectiveness of JYNNEOS against mpox disease in the United States. *N Engl J Med*. 2023. Available at: https://www.pubmed.ncbi.nlm.nih.gov/37199451.

67. Rosenberg ES, Dorabawila V, Hart-Malloy R, et al. Effectiveness of JYNNEOS Vaccine Against Diagnosed Mpox Infection — New York, 2022. *MMWR Morb Mortal Wkly Rep*. 2023;72(20):559–563. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10205166/.

68. FDA. Vaccine Immune Globulin Intravenous [package insert]. 2005. Available at: https://www.fda.gov/media/78174/download.

69. FDA. TPOXX (tecovirimat) [package insert]. 2018. Available at: https://www.fda.gov/media/75792/download.

70. Merchlinsky M, Albright A, Olson V, et al. The development and approval of tecoviromat (TPOXX((R))), the first antiviral against smallpox. *Antiviral Res*. 2019;168:168-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31181284.

71. Grosenbach DW, Honeychurch K, Rose EA, et al. Oral Tecovirimat for the Treatment of Smallpox. *N Engl J Med*. 2018;379(1):44-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29972742.

72. Smith SK, Self J, Weiss S, et al. Effective antiviral treatment of systemic orthopoxvirus disease: ST-246 treatment of prairie dogs infected with monkeypox virus. *J Virol*. 2011;85(17):9176-9187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21697474.

73. Desai AN, Thompson GR, 3rd, Neumeister SM, Arutyunova AM, Trigg K, Cohen SH. Compassionate use of tecovirimat for the treatment of monkeypox infection. *JAMA*. 2022;328(13):1348-1350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35994281.

74. O'Laughlin K, Tobolowsky FA, Elmor R, et al. Clinical use of tecovirimat (Tpoxx) for treatment of monkeypox under an Investigational New Drug protocol - United States, May-August 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(37):1190-1195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36107794.

75. Adler H, Gould S, Hine P, et al. Clinical features and management of human monkeypox: a retrospective observational study in the UK. *Lancet Infect Dis*. 2022;22(8):1153-1162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35623380.

76. NIH. Study of Tecovirimat for Human Monkeypox Virus (STOMP). 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05534984.

77. NIH. Tecovirimat for Treatment of Monkeypox Virus. 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT05559099.

78. NIHR. New clinical trial to test treatment for mpox (PLATINUM). 2022. Available at: https://www.nihr.ac.uk/news/new-clinical-trial-to-test-treatment-for-mpox/31352.

79. Rice AD, Adams MM, Wallace G, et al. Efficacy of CMX001 as a post exposure antiviral in New Zealand White rabbits infected with rabbitpox virus, a model for orthopoxvirus infections of humans. *Viruses*. 2011;3(1):47-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21373379.

80. Parker S, Chen NG, Foster S, et al. Evaluation of disease and viral biomarkers as triggers for therapeutic intervention in respiratory mousepox - an animal model of smallpox. *Antiviral Res*. 2012;94(1):44-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22381921.

81. Baker RO, Bray M, Huggins JW. Potential antiviral therapeutics for smallpox, monkeypox and other orthopoxvirus infections. *Antiviral Res*. 2003;57(1-2):13-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12615299.

82. Smee DF. Progress in the discovery of compounds inhibiting orthopoxviruses in animal models. *Antivir Chem Chemother*. 2008;19(3):115-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19024628.

83. Stittelaar KJ, Neyts J, Naesens L, et al. Antiviral treatment is more effective than smallpox vaccination upon lethal monkeypox virus infection. *Nature*. 2006;439(7077):745-748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16341204.

84. Hutson CL, Kondas AV, Mauldin MR, et al. Pharmacokinetics and efficacy of a potential smallpox therapeutic, brincidofovir, in a lethal monkeypox virus animal model. *mSphere*. 2021;6(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33536322.

85. Quenelle DC, Prichard MN, Keith KA, et al. Synergistic efficacy of the combination of ST-246 with CMX001 against orthopoxviruses. *Antimicrob Agents Chemother*. 2007;51(11):4118-4124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17724153.

86. Sobral-Costas TG, Escudero-Tornero R, Servera-Negre G, et al. Human monkeypox outbreak: epidemiological data and therapeutic potential of topical cidofovir in a prospective cohort study. *J Am Acad Dermatol*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36455826.

87. Rubio-Muniz CA, Montero-Menárguez J, López-Valle A, et al. Monkeypox: is topical cidofovir a good idea? *Clinical and Experimental Dermatology*. 2022. Available at: https://doi.org/10.1093/ced/llac038.

88. Parkhurst JR, Danenberg PV, Heidelberger C. Growth inhibition of cells in cultures and of vaccinia virus infected HeLa cells by derivatives of trifluorothymidine. *Chemotherapy*. 1976;22(3-4):221-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/178485.

89. Hyndiuk RA, Seideman S, Leibsohn JM. Treatment of vaccinial keratitis with trifluorothymidine. *Arch Ophthalmol*. 1976;94(10):1785-1786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/823931.

90. Maudgal PC, Van Damme B, Missotten L. Corneal epithelial dysplasia after trifluridine use. *Graefes Arch Clin Exp Ophthalmol*. 1983;220(1):6-12. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6403411.

91. Agrati C, Cossarizza A, Mazzotta V, et al. Immunological signature in human cases of monkeypox infection in 2022 outbreak: an observational study. *Lancet Infect Dis*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36356606.

92. Lum FM, Torres-Ruesta A, Tay MZ, et al. Monkeypox: disease epidemiology, host immunity and clinical interventions. *Nat Rev Immunol*. 2022;22(10):597-613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36064780.

93. Hermanussen L, Grewe I, Tang HT, et al. Tecovirimat therapy for severe monkeypox infection: Longitudinal assessment of viral titers and clinical response pattern-A first case-series experience. *J Med Virol*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36177717.

94. FDA. Cidofovir [package insert]. 2000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/020638s003lbl.pdf).

95. FDA. Brincidofovir [package insert]. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214460s000,214461s000lbl.pdf.

96. Scotti B, Piraccini BM, Gaspari V. Hypertrophic verrucous lesions after monkeypox virus infection. *Lancet Infect Dis*. 2022. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36309035.

97. Centers for Disease Control and Prevention. Update on Managing Monkeypox in Patients Receiving Therapeutics. 2022. Available at: https://emergency.cdc.gov/han/2022/han00481.asp.

98. Paran N, Yahalom-Ronen Y, Shifman O, et al. Monkeypox DNA levels correlate with virus infectivity in clinical samples, Israel, 2022. *Euro Surveill*. 2022;27(35). Available at: https://www.ncbi.nlm.nih.gov/pubmed/36052723.

99. Jamieson DJ, Cono J, Richards CL, Treadwell TA. The role of the obstetrician-gynecologist in emerging infectious diseases: monkeypox and pregnancy. *Obstet Gynecol*. 2004;103(4):754-756. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15051569.

100. Meaney-Delman DM, Galang RR, Petersen BW, Jamieson DJ. A Primer on monkeypox virus for obstetrician-gynecologists: diagnosis, prevention, and treatment. *Obstet Gynecol*. 2022;140(3):391-397. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36356237.

101. Jezek Z; Fenner Z. Human monkeypox. *Monographs in Virology*. 1988;17:127-140. Available at: https://www.karger.com/DOI/10.1159/000416465.

102. FDA. JYNNEOS [package insert]. 2022. Available at: https://www.fda.gov/media/131078/download.

Disseminated *Mycobacterium avium* Complex Disease

Updated: August 15, 2024
Reviewed: August 15, 2024

Epidemiology

Organisms of the *Mycobacterium avium* complex (MAC) are ubiquitous in the environment.[1-6] In the era before effective antiretroviral therapy (ART) was available, *M. avium* was the etiologic agent in >95% of people with HIV with advanced immunosuppression who acquired disseminated MAC disease.[4,7-12] Newer bacterial typing technology suggests organisms causing bacteremia in people with HIV represent a diversity of species, including the *M. avium* subspecies *hominissuis* and *M. colombiense* and other non-MAC species, including *M. genavense*, *M. kansasii*, *M. simiae*, *M. mycogenicum*, and others.[13-16] These comprise what was historically referred to as disseminated MAC. An estimated 7% to 12% of adults with HIV have been previously infected with MAC, although rates of disease vary in different geographic locations.[2,4,8,11,12] In particular, disseminated MAC in people with HIV has been described more frequently in the United States and Europe than in resource-limited settings.[17]

Although epidemiologic associations with infection have been identified, no singular environmental exposure or behavior has been consistently linked to subsequent increased risk of developing MAC disease. The mode of MAC infection is thought to be through repeated inhalation or ingestion of MAC bacteria via the respiratory or gastrointestinal (GI) tract, likely from environmental exposure.[1,18] Household or close contacts of those with MAC disease do not appear to be at increased risk of disease, and person-to-person transmission is unlikely.[19]

MAC disease typically occurs in people with HIV with CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. The previously reported incidence of disseminated MAC disease ranged from 20% to 40% in people with HIV with advanced immunosuppression in the absence of effective ART or chemoprophylaxis.[20,21] However, the overall incidence of MAC disease among people with HIV has declined substantially in the modern ART era to current levels of <2 cases of MAC as the first opportunistic infection [OI] per 1,000 person-years for individuals in care, even among those not receiving effective ART.[22-26] In addition to a CD4 count <50 cells/mm^3, factors associated with increased risk for MAC disease are ongoing HIV viral replication despite ART, previous or concurrent OIs, reduced *in vitro* lymphoproliferative immune responses to *M. avium* antigens (possibly reflecting defects in T-cell repertoire), and genetic predisposition in some populations.[24-27] While effective ART has clearly been associated with dramatic reductions in risk of developing MAC disease, MAC disease still can occur in people with HIV on suppressive ART, and the clinical presentation may differ from what is seen in people with untreated HIV. In one retrospective case series following people with HIV mostly on ART, nontuberculous mycobacterial (NTM) disease occurred in nine people who were virologically suppressed on ART at the time of their diagnosis—seven with pulmonary NTM only and two with extrapulmonary disease. MAC was the most common NTM pathogen, isolated in 19 of the 34 cases.[13] Those with extrapulmonary disease were younger and had higher viral loads and lower CD4 counts at diagnosis.

Clinical Manifestations

In people with HIV with advanced immunosuppression who are not on ART, MAC disease generally presents as a disseminated, multi-organ infection, although localized disease may also be seen.[28-32] Early symptoms may be minimal and can precede mycobacteremia or positive tissue cultures by several weeks. Symptoms are nonspecific and include fever, night sweats, weight loss, fatigue, diarrhea, and abdominal pain.[8,13-15]

Laboratory abnormalities particularly associated with disseminated MAC disease include anemia (often out of proportion to that expected for the stage of HIV disease) and elevated liver alkaline phosphatase levels.[4,5,7-12,20,21,33,34] Hepatomegaly, splenomegaly, or lymphadenopathy (paratracheal, retroperitoneal, para-aortic, or less commonly peripheral) may be identified on physical examination or by radiographic or other imaging studies. Other focal physical findings or laboratory abnormalities may occur with localized disease.

Localized MAC disease occurs more often in people with HIV on suppressive ART with increased CD4 counts than in people with HIV not on ART, suggesting improved immune function is associated with more localized disease. Localized syndromes include cervical, intraabdominal, or mediastinal lymphadenitis; pneumonia; pericarditis; osteomyelitis; skin or soft-tissue abscesses; bursitis; genital ulcers; and central nervous system infection. Localized syndromes may also be manifestations of immune reconstitution inflammatory syndrome (IRIS), as discussed below.

Diagnosis

A confirmed diagnosis of disseminated MAC disease is based on compatible clinical signs and symptoms coupled with the isolation of MAC from cultures of blood, lymph fluid, bone marrow, or other normally sterile tissue or body fluids, although data suggest that bone marrow cultures have low yield for detection of MAC in this setting, particularly if blood cultures are negative.[21,31,32,35-40] Species identification should be performed using molecular techniques, polymerase chain reaction-based assays, whole-genome sequencing, high-performance liquid chromatography, or biochemical tests.

Other ancillary studies provide supportive diagnostic information, including acid-fast bacilli smear and culture of tissue, radiographic imaging, or other studies aimed at isolating organisms from focal infection sites.

Although isolated pulmonary MAC disease is not often observed in people with advanced HIV-associated immunosuppression, occasionally MAC disease may be limited to the lung in people with HIV who are virologically suppressed on ART. Diagnostic criteria for disease limited to the lung in this setting should follow those established by the American Thoracic Society (ATS), European Respiratory Society (ERS), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the Infectious Disease Society of America (IDSA) joint guideline on Treatment of Nontuberculous Mycobacterial Pulmonary Disease, which include pulmonary clinical signs and symptoms, exclusion of other alternative diagnoses, nodular or cavitary disease on lung imaging, and a positive culture for MAC from at least two sputum specimens or at least one bronchoalveolar lavage or biopsy sample.[41]

Detection of MAC organisms in the respiratory or GI tract may represent colonization of these sites and may be a harbinger of disseminated MAC infection. However, no data are available regarding

efficacy of treatment for asymptomatic colonization with MAC organisms at these sites. Therefore, routine screening of respiratory or GI specimens and preemptive treatment for MAC **is not recommended.**

Preventing Exposure

MAC organisms commonly contaminate environmental sources of infection, such as food and water. Available information does not support specific recommendations regarding avoidance of exposure.

Preventing Disease

Recommendations for Preventing Disseminated *Mycobacterium avium* Complex Disease

Preventing First Episode of Disseminated MAC Disease (Primary Prophylaxis)
• Primary prophylaxis **is not recommended** for adults and adolescents who immediately initiate ART (AII). Indications for Primary Prophylaxis • CD4 count <50 cells/mm^3 AND not receiving ART or remains viremic on ART or has no options for a fully suppressive ART regimen (AI) • Before primary prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, and if appropriate, by obtaining a blood culture for MAC (AI). If blood culture is obtained, prophylaxis should be delayed until results are available to avoid exposing patients to monotherapy and the attendant risk of drug resistance (AI). Preferred Therapy • Azithromycin 1,200 mg PO once weekly (AI), *or* • Clarithromycin 500 mg PO twice daily (AI), *or* • Azithromycin 600 mg PO twice weekly (BIII) Alternative Therapy • Rifabutin 300 mg PO daily (BI) in people who cannot tolerate azithromycin or clarithromycin o Dose adjustment of rifabutin may be necessary based on drug–drug interactions, please refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosing recommendation when used with certain ARV drugs. o Active TB should be ruled out before starting rifabutin to avoid monotherapy in the setting of active TB. Indication for Discontinuing Primary Prophylaxis • If previously initiated, primary prophylaxis should be discontinued if the patient is continuing on a fully suppressive ART regimen (AI).
Pregnancy Considerations
• Primary prophylaxis for MAC disease in pregnant people who immediately initiate ART **is not recommended** (AIII). • When primary prophylaxis is required for a pregnant person who is not being treated with effective ART, azithromycin is the preferred agent (BIII).

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; MAC = *Mycobacterium avium* complex; PO = orally; TB = tuberculosis

Indication for Primary Prophylaxis

Primary prophylaxis against disseminated MAC disease **is not recommended** for adults and adolescents with HIV who immediately initiate ART, regardless of CD4 count **(AII).** People with HIV who have CD4 counts <50 cells/mm^3 and who are not receiving ART, remain viremic on ART, or have no options for a fully suppressive ART regimen should receive chemoprophylaxis against disseminated MAC **(AI).** Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment and, if appropriate based on that assessment, by obtaining a blood culture for MAC. MAC prophylaxis should be delayed until results are available to avoid exposing patients to monotherapy and the attendant risk of drug resistance **(AI).**

When to Stop Primary Prophylaxis

Primary MAC prophylaxis, if previously initiated, should be discontinued in adults and adolescents who are continuing on a fully suppressive ART regimen **(AI).** Two randomized, placebo-controlled trials and several large observational cohort studies have demonstrated that people with HIV taking ART can discontinue primary prophylaxis with minimal risk of developing MAC disease, particularly if they are virologically suppressed.[42-47] Conclusions from these studies indicate that the overall incidence of disseminated MAC within 6 to 12 months after stopping primary prophylaxis in these circumstances, regardless of CD4 count, was 0.6 to 0.8 per 100 person-years. In each of these studies, plasma HIV RNA level >1,000 copies/mL was the principal risk factor for developing MAC disease regardless of MAC prophylaxis. However, in a study from the TREAT Asia HIV Observational Database, which evaluated the impact of MAC prophylaxis on AIDS-defining conditions and HIV-associated mortality in people with HIV on ART from September 2015 onward, macrolide use within 3 months of starting ART for those with a CD4 count <50 at ART initiation was associated with a decreased risk of HIV-associated mortality (HR 0.10; 95% CI, 0.01–0.80; P = 0.031) but not with the combined outcome of developing an AIDS-defining condition or death.[48] Despite this finding, only 10.6% of the 1,345 participants in the cohort eligible for MAC prophylaxis received it. The authors concluded that there may be an additive protective effect of macrolide prophylaxis in reducing overall HIV-related mortality among Asians with HIV and CD4 counts <50 even though they received effective ART. Despite some differences among these published data, for most individuals, particularly in higher resourced settings, the preponderance of current data suggest that primary MAC prophylaxis provides no additional benefit in people started on effective ART that results in viral suppression. Additional arguments against primary MAC prophylaxis while prioritizing effective ART to achieve viral suppression include (1) the potential for adding additional cost and adverse effects of the drugs used for prophylaxis; (2) the likelihood that only a small number of people with HIV will develop "unmasking MAC IRIS" (i.e., active MAC disease after starting ART); (3) the potential for acquired drug resistance if people fail monotherapy for MAC prophylaxis; and (4) limiting polypharmacy to assist with adherence to ART.[49-51]

Preferred and Alternative Drugs for Prophylaxis

As previously stated, primary prophylaxis for MAC is not recommended for people on effective ART, but for those for whom prophylaxis is being considered, azithromycin[52] and clarithromycin[5,53] are the preferred prophylactic agents **(AI).**[1,54] The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and **should not be used (AI).**[5] The combination of azithromycin and rifabutin is more effective than azithromycin alone in preventing MAC disease.[52] However, based on the additional cost, increased occurrence of adverse effects, potential for drug

interactions, and lack of greater survival benefit than with azithromycin alone, the combination regimen of azithromycin and rifabutin **is not recommended (AI).** In people with HIV who cannot tolerate azithromycin or clarithromycin, rifabutin can be used as a prophylactic agent for MAC disease **(BI),** although drug interactions may complicate use of this agent. Moreover, tuberculosis (TB) should be excluded before rifabutin is used to avoid monotherapy in the setting of active TB, which could result in acquired rifamycin resistance.

Treating Disease

Recommendations for Treating Disseminated *Mycobacterium avium* Complex Disease

Treating Disseminated MAC Disease

Preferred Therapy
• At least two drugs as initial therapy to prevent or delay emergence of resistance (AI)
  o Clarithromycin 500 mg PO twice daily (AI) plus ethambutol 15 mg/kg PO daily (AI), *or*
  o Azithromycin 500–600 mg (AII) plus ethambutol 15 mg/kg PO daily (AI) when drug interactions or intolerance precludes the use of clarithromycin (AII)
  o Note: Testing of susceptibility to clarithromycin or azithromycin is recommended.
• Some experts would add rifabutin when more severe disease manifestations are present.
  o Rifabutin 300 mg PO daily (CI). Dose adjustment of rifabutin may be necessary based on drug–drug interactions. Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for more information.
• Some experts would also add a fourth drug if more severe disease is present, the risk of mortality is high, emergence of drug resistance is likely (e.g., after failure of MAC prophylaxis), CD4 count is <50 cells/mm^3, mycobacterial loads are high (>2 $\log_{10}$ CFU/mL of blood), or effective ART is absent (CIII). Fourth drug options may include:
  o A fluoroquinolone (CIII) (e.g., levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily), *or*
  o An injectable aminoglycoside (CIII) (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily) (generally avoided unless in the setting of refractory disease when other alternatives are not available or tolerated)
  o Bedaquiline, tedizolid, linezolid, and omadacycline have demonstrated *in vitro* activity against clinical isolates of MAC; these might also be considered in people with refractory MAC disease.
Duration of Therapy
• At least 12 months (AII)
• Shorter duration may be considered depending on the degree of immunologic recovery following initiation of ART. CD4 count should be >100 cells/mm^3 for ≥6 months before discontinuation of therapy (CIII).
Chronic Maintenance Therapy (Secondary Prophylaxis)
• Same as treatment regimens
• If ART does not result in immune reconstitution, people with HIV and disseminated MAC disease should continue chronic maintenance therapy (AII).
Criteria for Discontinuing Chronic Maintenance Therapy (Secondary Prophylaxis) (AI)
• Completed at least 12 months of therapy, *and*

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

Indication for Restarting Chronic Maintenance Therapy (Secondary Prophylaxis)

- If a fully suppressive ART regimen is not possible and CD4 is consistently <100 cells/mm^3 (BIII)

Pregnancy Considerations

- For secondary prophylaxis (chronic maintenance therapy), azithromycin plus ethambutol is the preferred drug combination (BIII).

Other Considerations

- NSAIDs may be used for people with HIV who experience moderate to severe symptoms attributed to IRIS (BIII).
- If IRIS symptoms persist, a short-term course (4–8 weeks) of systemic corticosteroid therapy (equivalent to prednisone 20–40 mg/day) can be used (BII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CFU = colony-forming units; IM = intramuscular; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; MAC = *Mycobacterium avium* complex; NSAID = nonsteroidal anti-inflammatory drug; PO = orally

Initial treatment of MAC disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance **(AI).**[1,6,11,12,18,55-63] Clarithromycin **(AI)** or azithromycin **(AII)** are preferred first agents; published data are more extensive for clarithromycin than for azithromycin in people with advanced HIV disease, and clarithromycin appears to be associated with more rapid clearance of MAC from the blood.[6,55,57,61,62,64] However, azithromycin is acceptable when drug interactions or intolerance preclude the use of clarithromycin **(AII).** Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI).**[65] Testing MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for all people with HIV, particularly those who developed MAC disease while receiving prophylaxis with one of these agents.[66,67] In three randomized clinical trials, clarithromycin-resistant isolates were reported in 29% and 58% of people with HIV who developed MAC bacteremia during prophylaxis with clarithromycin, and azithromycin-resistant isolates were recovered from 11% of those who developed bacteremia while on azithromycin prophylaxis.[5,52,53,68] More advanced immunosuppression at prophylaxis initiation and longer duration of MAC prophylaxis are associated with higher rates of clarithromycin resistance at the time of MAC prophylaxis failure.[68]

Ethambutol is the recommended second drug for the initial treatment of MAC disease **(AI)** based on randomized trials of MAC therapy that indicate its use in the regimen is associated with lower rates of relapse.[56,58,64,69] Rifabutin can be used as a third drug **(CI)** with or without a fluoroquinolone (levofloxacin or moxifloxacin) (**CIII),** or an injectable aminoglycoside (amikacin or streptomycin) **(CIII)** can be used as a fourth drug if more severe disease is present; the risk of mortality is high; emergence of drug resistance is likely (e.g., after failure of MAC prophylaxis); or in the setting of advanced immunosuppression (CD4 count <50 cells/mm^3), high mycobacterial loads (>2 $\log_{10}$ colony-forming units/mL of blood), or the absence of effective ART **(CIII).** One randomized clinical trial demonstrated that adding rifabutin to the combination of clarithromycin and ethambutol improved survival, and in two randomized clinical trials, this approach reduced emergence of drug resistance[6,57] in individuals with advanced HIV and disseminated MAC disease. These studies were completed before the availability of effective ART. It has not been established whether similar results would be observed for people with HIV receiving effective ART. The fluoroquinolones levofloxacin and moxifloxacin and amikacin have *in vitro* and animal model

activity against MAC, although randomized trials evaluating the efficacy of adding a fluoroquinolone or injectable aminoglycoside as part of a multidrug regimen for treatment of MAC have not been done. Injectable aminoglycosides should generally be avoided except in the setting of refractory disease when other alternative agents are not available or tolerated.[66,70] Additional drugs with *in vitro* activity against clinical isolates of MAC include bedaquiline, tedizolid, linezolid, and omadacycline; these might also be considered in people with refractory MAC disease.[71-75]

While not specifically applicable to people with HIV (who more often have disseminated MAC disease than isolated pulmonary disease), in 2020, the ATS/ERS/ESCMID/IDSA updated their jointly sponsored clinical guideline for treatment of nontuberculous mycobacterial pulmonary disease, including pulmonary MAC.[41] People with HIV fully suppressed on ART with higher CD4 counts may present with localized pulmonary or other local organ system MAC disease that may clinically resemble such disease in people without HIV. Following the ATS/ERS/ESCMID/IDSA guidelines would be reasonable in such settings. The recommended treatment includes an initial three-drug regimen containing a macrolide and ethambutol for those with macrolide-susceptible pulmonary MAC disease. Addition of an aminoglycoside, which in refractory cases can be given as inhalation suspension, is recommended if cavitary or severe bronchiectatic disease is present or if macrolide resistance is suspected.[76]

People with HIV and disseminated MAC disease should be treated for a minimum duration of 12 months **(AII).** Shorter duration of treatment may be considered depending on the degree of immunologic recovery following initiation of ART **(CIII);** the CD4 count should be maintained above 100 cells/mm^3 for at least 6 months before discontinuing MAC treatment.[77-79]

Special Considerations Regarding Antiretroviral Therapy Initiation

ART should be started as soon as possible after the diagnosis of MAC disease, preferably at the same time as initiation of antimycobacterial therapy in people with HIV and disseminated MAC disease who are not receiving effective ART **(BIII).** ART is recommended as soon as possible to reduce the risk of further AIDS-defining OIs and to further improve the response to antimycobacterial therapy in the setting of advanced immunosuppression **(BIII).** If ART has already been initiated, it should be continued. The regimens should be modified when there is any potential for an adverse drug–drug interaction(s) between the antiretroviral (ARV) and antimycobacterial drugs **(BIII).** Information on drug–drug interactions can be found in the Adult and Adolescent Antiretroviral Guidelines. People with HIV will need continuous antimycobacterial treatment until ART results in sustained immune reconstitution, as indicated above (CD4 count maintained above 100 cells/mm^3 for at least 6 months).

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

A repeat blood culture for MAC should be obtained 4 to 8 weeks after initiating antimycobacterial therapy in people with HIV who do not have a clinical response to their initial treatment regimens. Improvement in fever and other systemic symptoms and a decline in quantity of mycobacteria in blood or tissue can be expected within 2 to 4 weeks after initiation of appropriate therapy; clinical response may be delayed, however, in those with more extensive MAC disease or advanced immunosuppression.

Adverse effects of clarithromycin and azithromycin include GI upset, metallic taste, elevations in liver transaminase levels, and hypersensitivity reactions. Clarithromycin's adverse effects may be exacerbated when drug levels are increased due to drug interactions associated with some ARV

drugs. Doses of clarithromycin >1 g/day for treatment of disseminated MAC disease have been associated with increased mortality and **should not be used (AI).**[65] Protease inhibitors (PIs) can increase clarithromycin levels; clarithromycin dose adjustment or switching clarithromycin to azithromycin may be necessary. Azithromycin metabolism is not affected by the cytochrome P450 (CYP) system; azithromycin can be used safely in the presence of PIs, non-nucleoside reverse transcriptase inhibitors, or integrase inhibitors without concerns about drug interactions.

When used with clarithromycin or other drugs that inhibit CYP isoenzyme 3A4, rifabutin has been associated with a higher risk of adverse drug interactions, in particular sight-threatening uveitis and neutropenia.[80-82] Rifabutin adverse effects are concentration related; therapeutic drug level monitoring may be considered to reduce the potential for adverse effects. Rifabutin must be dose adjusted in people with HIV receiving PIs or efavirenz. Rifabutin should not be coadministered with cobicistat-boosted PIs, long-acting injectable cabotegravir/rilpivirine, bictegravir, elvitegravir/cobicistat, fostemsavir, or lenacapavir.[82-86] Rilpivirine and doravirine must be dose adjusted if either is coadministered with rifabutin. No dose adjustment for rifabutin or the integrase inhibitors dolutegravir or raltegravir or injectable cabotegravir alone is currently recommended, although at least one study suggested that compared with people without TB or MAC, lower trough concentrations were observed when once daily dolutegravir was used together with rifabutin.[87-89] The most updated drug–drug interaction information can be found in the Adult and Adolescent Antiretroviral Guidelines. Therapeutic drug monitoring may be helpful for optimizing drug dosing in the context of complex drug–drug interactions.[90]

IRIS associated with MAC disease is recognized as a systemic inflammatory syndrome, with signs and symptoms clinically indistinguishable from active MAC infection, although bacteremia is generally absent. Similar to TB, MAC-associated IRIS can occur as "unmasking" IRIS in people with HIV with subclinical (undiagnosed) MAC or "paradoxical" IRIS in those with previously established MAC disease.[91-95] Both variants occur primarily in those with advanced immunosuppression who begin ART and have a rapid and marked reduction in plasma HIV RNA.[95,96] Elevated alkaline phosphatase levels may be a predictor of MAC-associated IRIS.[97] The syndrome may be benign and self-limited or may result in severe, unremitting symptoms that improve with the use of systemic anti-inflammatory therapy or corticosteroids.

People with HIV on ART who develop moderate to severe symptoms typical of IRIS should receive initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) **(BIII).** If IRIS symptoms do not improve, short-term (4–8 weeks) systemic corticosteroid therapy, in doses equivalent to 20 to 40 mg of oral prednisone daily, can be used to reduce symptoms and morbidity **(BII).**[92,98] Severe forms of MAC IRIS with a hemophagocytic lymphohistiocytosis (HLH) phenotype may occur, and a lower hemoglobin prior to ART may help predict this more severe form of IRIS.[97,99] Patients with this more severe form may have a genetic predisposition, and cases of MAC IRIS and other NTM IRIS requiring additional immunosuppression in addition to corticosteroids have been reported.[99,100]

Managing Treatment Failure

MAC treatment failure is defined by the absence of a clinical response and the persistence of mycobacteremia (or persistently positive tissue cultures from other sites) after 4 to 8 weeks of treatment. Repeat testing of MAC isolates for susceptibility to clarithromycin or azithromycin is recommended for people with HIV whose disease relapses after an initial response to treatment.

Because the number of drugs with demonstrated clinical activity against MAC is limited, results of susceptibility testing should be used to construct a new multidrug regimen. The regimen should consist of at least two new drugs (i.e., not previously used) to which the isolate is susceptible. Drugs from which to choose include rifabutin, fluoroquinolone (levofloxacin or moxifloxacin), an injectable aminoglycoside (amikacin or streptomycin), or possibly bedaquiline, tedizolid, linezolid, or omadacycline, although data supporting a survival or microbiologic benefit when these agents are added are limited.[11,12,41,56-60,64,69,72-75,101-104] Continuing clarithromycin or azithromycin despite resistance **is not recommended (BIII),** as there is likely to be no additional benefit and may have added toxicity. Clofazimine **should generally not be used** because randomized trials have demonstrated lack of efficacy and an association with increased mortality **(AI).**[56,58,69] Optimization of ART is an important adjunct to second-line or salvage therapy for MAC disease in people with HIV for whom initial treatment is unsuccessful or who have disease that is resistant to antimycobacterial drugs **(AIII).**

Although anecdotal data and individual case reports suggest potential benefit, adjunctive treatment of MAC disease with immunomodulators has not been thoroughly studied, and data are insufficient to support a recommendation for routine use, except in the setting of familial immunodeficiencies associated with increased risk of MAC disease.[105]

Preventing Recurrence

As indicated above, people with HIV and disseminated MAC disease should be treated for a minimum duration of 12 months **(AII).** Shorter duration of treatment may be considered depending on the degree of immunologic recovery following initiation of ART; the CD4 count should be maintained above 100 cells/mm^3 for at least 6 months before discontinuing MAC treatment. If ART initiation does not result in immune reconstitution, people with HIV and disseminated MAC disease should continue chronic maintenance therapy **(AII).**[77-79]

When to Stop Secondary Prophylaxis or Chronic Maintenance Therapy

The risk of MAC recurrence is low in people with HIV who have completed at least a 12-month MAC treatment course, remain asymptomatic with respect to MAC signs and symptoms, and sustain an increase in CD4 count to >100 cells/mm^3 for ≥6 months after initiation of ART. In this setting, it is reasonable to discontinue maintenance therapy based on data from studies in people with HIV and inferences from more extensive study data that indicate the safety of discontinuing secondary prophylaxis for other OIs **(AI).**[44,60,77-79,106-108] Reintroducing chronic maintenance therapy or secondary prophylaxis for people with HIV for whom a fully suppressive ART regimen is not possible and who have a decline in their CD4 count to levels consistently below 100 cells/mm^3 may be indicated **(BIII).**

Special Considerations During Pregnancy

Primary prophylaxis for MAC disease in pregnant people who immediately initiate ART **is not recommended (AIII).** When primary prophylaxis is required for a pregnant person 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).** Because clarithromycin is associated with an increased risk of birth defects based on evidence from certain animal studies, it **is not recommended** as the first-line agent for prophylaxis or treatment of MAC in pregnancy **(BIII).** Two studies, each with slightly more than 100 women with

first-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although an increased risk of spontaneous abortion was noted in one study.[109,110]

Azithromycin did not produce defects in animal studies, but experience with use in humans during the first trimester is limited. A nested case-control study conducted within the large Quebec Pregnancy cohort found an association between azithromycin use and spontaneous miscarriage[111]; however the authors were not able to adjust for severity of infection, an important confounder. Multiple studies, including large cohort studies, have found no association between the use of azithromycin in the first trimester and major congenital malformations, including heart defects.[112-114] A systematic review of pregnancy outcomes following macrolide use found no significant increased risks for major congenital malformations or congenital heart defects following all macrolide use in the first trimester, but a small but significant increased rate of major congenital malformations with azithromycin though maternal confounders could not be excluded. In a Cochrane systematic review of *Chlamydia trachomatis* infection treatment in pregnancy, there was no apparent difference between azithromycin and other agents in terms of efficacy and pregnancy complications.[115]

References

1. Karakousis PC, Moore RD, Chaisson RE. *Mycobacterium avium* complex in patients with HIV infection in the era of highly active antiretroviral therapy. *Lancet Infect Dis*. 2004;4(9):557-565. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15336223.

2. Hoefsloot W, van Ingen J, Andrejak C, et al. The geographic diversity of nontuberculous mycobacteria isolated from pulmonary samples: an NTM-NET collaborative study. *Eur Respir J*. 2013;42(6):1604-1613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23598956.

3. Reed C, von Reyn CF, Chamblee S, et al. Environmental risk factors for infection with *Mycobacterium avium* complex. *Am J Epidemiol*. 2006;164(1):32-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16675537.

4. Inderlied CB. Microbiology and minimum inhibitory concentration testing for *Mycobacterium avium* complex prophylaxis. *Am J Med*. 1997;102(5):2-10. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0002934397000375?showall=true.

5. Benson CA, Williams PL, Cohn DL, et al. Clarithromycin or rifabutin alone or in combination for primary prophylaxis of *Mycobacterium avium* complex disease in patients with AIDS: a randomized, double-blind, placebo-controlled trial. The AIDS Clinical Trials Group 196/Terry Beirn Community Programs for Clinical Research on AIDS 009 Protocol Team. *J Infect Dis*. 2000;181(4):1289-1297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10762562.

6. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons with acquired immunodeficiency syndrome. *Clin Infect Dis*. 2003;37(9):1234-1243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14557969.

7. Kemper CA, Havlir D, Bartok AE, et al. Transient bacteremia due to *Mycobacterium avium* complex in patients with AIDS. *J Infect Dis*. 1994;170(2):488-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8035044.

8. Gordin FM, Cohn DL, Sullam PM, Schoenfelder JR, Wynne BA, Horsburgh CR, Jr. Early manifestations of disseminated *Mycobacterium avium* complex disease: a prospective evaluation. *J Infect Dis*. 1997;176(1):126-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9207358.

9. Benson CA, Ellner JJ. *Mycobacterium avium* complex infection and AIDS: advances in theory and practice. *Clin Infect Dis*. 1993;17(1):7-20. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8353249.

10. Havlik JA, Jr., Horsburgh CR, Jr., Metchock B, Williams PP, Fann SA, Thompson SE, 3rd. Disseminated *Mycobacterium avium* complex infection: clinical identification and epidemiologic trends. *J Infect Dis*. 1992;165(3):577-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1347060.

11. Benson CA. Treatment of disseminated disease due to the *Mycobacterium avium* complex in patients with AIDS. *Clin Infect Dis*. 1994;18 Suppl 3:S237-242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8204776.

12. Benson CA. Disease due to the *Mycobacterium avium* complex in patients with AIDS: epidemiology and clinical syndrome. *Clin Infect Dis*. 1994;18 Suppl 3:S218-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8204773.

13. Lee EH, Chin B, Kim YK, et al. Clinical characteristics of nontuberculous mycobacterial disease in people living with HIV/AIDS in South Korea: a multi-center, retrospective study. *PLoS One*. 2022;17(11):e0276484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36355915.

14. Ricotta EE, Adjemian J, Blakney RA, Lai YL, Kadri SS, Prevots DR. Extrapulmonary nontuberculous mycobacteria infections in hospitalized patients, United States, 2009–2014. *Emerg Infect Dis*. 2021;27(3):845-852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33622461.

15. Wetzstein N, Geil A, Kann G, et al. Disseminated disease due to non-tuberculous mycobacteria in HIV positive patients: a retrospective case control study. *PLoS One*. 2021;16(7):e0254607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34255788.

16. Lee MR, Chien JY, Huang YT, et al. Clinical features of patients with bacteraemia caused by *Mycobacterium avium* complex species and antimicrobial susceptibility of the isolates at a medical centre in Taiwan, 2008-2014. *Int J Antimicrob Agents*. 2017;50(1):35-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28478210.

17. Heidary M, Nasiri MJ, Mirsaeidi M, et al. *Mycobacterium avium* complex infection in patients with human immunodeficiency virus: a systematic review and meta-analysis. *J Cell Physiol*. 2019;234(7):9994-10001. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30548598.

18. Corti M, Palmero D. *Mycobacterium avium* complex infection in HIV/AIDS patients. *Expert Rev Anti Infect Ther*. 2008;6(3):351-363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18588499.

19. Carbonne A, Lemaitre N, Bochet M, et al. *Mycobacterium avium* complex common-source or cross-infection in AIDS patients attending the same day-care facility. *Infect Control Hosp Epidemiol*. 1998;19(10):784-786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9801289.

20. Nightingale SD, Byrd LT, Southern PM, Jockusch JD, Cal SX, Wynne BA. Incidence of *Mycobacterium avium-intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. *J Infect Dis*. 1992;165(6):1082-1085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1349906.

21. Chaisson RE, Moore RD, Richman DD, Keruly J, Creagh T. Incidence and natural history of *Mycobacterium avium*-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. The Zidovudine Epidemiology

Study Group. *Am Rev Respir Dis*. 1992;146(2):285-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1362634.

22. Marochi-Telles JP, Muniz R, Jr., Sztajnbok J, Cosme-de Oliveira A. Disseminated *Mycobacterium avium* on HIV/AIDS: historical and current literature review. *AIDS Rev*. 2020;22(1):9-15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32167509.

23. Buchacz K, Baker RK, Palella FJ, Jr., et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study. *AIDS*. 2010;24(10):1549-1559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20502317.

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

25. Collins LF, Clement ME, Stout JE. Incidence, long-term outcomes, and healthcare utilization of patients with human immunodeficiency virus/acquired immune deficiency syndrome and disseminated *Mycobacterium avium* complex from 1992-2015. *Open Forum Infect Dis*. 2017;4(3):ofx120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28748197.

26. Jung Y, Song KH, Choe PG, et al. Incidence of disseminated *Mycobacterium avium*-complex infection in HIV patients receiving antiretroviral therapy with use of *Mycobacterium avium*-complex prophylaxis. *Int J STD AIDS*. 2017;28(14):1426-1432. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28592210.

27. Hsu DC, Breglio KF, Pei L, et al. Emergence of polyfunctional cytotoxic CD4+ T cells in *Mycobacterium avium* immune reconstitution inflammatory syndrome in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 2018;67(3):437-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29538651.

28. Barbaro DJ, Orcutt VL, Coldiron BM. *Mycobacterium avium-Mycobacterium intracellulare* infection limited to the skin and lymph nodes in patients with AIDS. *Rev Infect Dis*. 1989;11(4):625-628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2772468.

29. Hellyer TJ, Brown IN, Taylor MB, Allen BW, Easmon CS. Gastro-intestinal involvement in *Mycobacterium avium-intracellulare* infection of patients with HIV. *J Infect*. 1993;26(1):55-66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8454889.

30. Torriani FJ, McCutchan JA, Bozzette SA, Grafe MR, Havlir DV. Autopsy findings in AIDS patients with *Mycobacterium avium* complex bacteremia. *J Infect Dis*. 1994;170(6):1601-1605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7996004.

31. Roth RI, Owen RL, Keren DF, Volberding PA. Intestinal infection with *Mycobacterium avium* in acquired immune deficiency syndrome (AIDS): histological and clinical comparison with Whipple's disease. *Dig Dis Sci*. 1985;30(5):497-504. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2580679.

32. Gillin JS, Urmacher C, West R, Shike M. Disseminated *Mycobacterium avium-intracellulare* infection in acquired immunodeficiency syndrome mimicking Whipple's disease.

Gastroenterology. 1983;85(5):1187-1191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6194041.

33. Inderlied CB, Kemper CA, Bermudez LE. The *Mycobacterium avium* complex. *Clin Microbiol Rev*. 1993;6(3):266-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8358707.

34. Packer SJ, Cesario T, Williams JH, Jr. *Mycobacterium avium* complex infection presenting as endobronchial lesions in immunosuppressed patients. *Ann Intern Med*. 1988;109(5):389-393. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3165608.

35. Shanson DC, Dryden MS. Comparison of methods for isolating *Mycobacterium avium-intracellulare* from blood of patients with AIDS. *J Clin Pathol*. 1988;41(6):687-690. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3385000.

36. Hafner R, Inderlied CB, Peterson DM, et al. Correlation of quantitative bone marrow and blood cultures in AIDS patients with disseminated *Mycobacterium avium* complex infection. *J Infect Dis*. 1999;180(2):438-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10395860.

37. Cornejo-Juárez P, Islas-Muñoz B, Ramírez-Ibarguen AF, et al. Bone marrow culture yield for the diagnosis of opportunistic diseases in patients with AIDS and disseminated Kaposi sarcoma. *Curr HIV Res*. 2020;18(4):277-282. Available at: https://pubmed.ncbi.nlm.nih.gov/32493198.

38. Prabhu V, Coelho S, Achappa B, Baliga S, Sharon L, Shah J. Role of fluorescence in situ hybridization in detecting *Mycobacterium avium* complex presenting as fever in treatment failure HIV. *J Clin Tuberc Other Mycobact Dis*. 2020;21:100188. Available at: https://pubmed.ncbi.nlm.nih.gov/32995570.

39. Sharma S, Latawa R, Wanchu A, Verma I. Differential diagnosis of disseminated *Mycobacterium avium* and *Mycobacterium tuberculosis* infection in HIV patients using duplex PCR. *Future Microbiol*. 2021;16(3):159-173. Available at: https://pubmed.ncbi.nlm.nih.gov/33528278.

40. Sharvit G, Schwartz D, Heering G, et al. Evaluation of the clinical impact of bone marrow cultures in current medical practice. *Sci Rep*. 2022;12(1):9664. Available at: https://pubmed.ncbi.nlm.nih.gov/35690634/.

41. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. *Clin Infect Dis*. 2020;71(4):e1-e36. Available at: https://pubmed.ncbi.nlm.nih.gov/32628747.

42. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10915098.

43. El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to

antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. 2000;342(15):1085-1092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10766581.

44. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count: a randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. *Ann Intern Med*. 2000;133(7):493-503. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11015162.

45. Furrer H, Telenti A, Rossi M, Ledergerber B. Discontinuing or withholding primary prophylaxis against *Mycobacterium avium* in patients on successful antiretroviral combination therapy. The Swiss HIV Cohort Study. *AIDS*. 2000;14(10):1409-1412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10930156.

46. Brooks JT, Song R, Hanson DL, et al. Discontinuation of primary prophylaxis against *Mycobacterium avium* complex infection in HIV-infected persons receiving antiretroviral therapy: observations from a large national cohort in the United States, 1992–2002. *Clin Infect Dis*. 2005;41(4):549-553. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16028167.

47. Chene G, Phillips A, Costagliola D, et al. Cohort profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. *Int J Epidemiol*. 2017;46(3):797-797n. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27864413.

48. Pasayan MKU, ML SM, Boettiger D, et al. Effect of macrolide prophylactic therapy on AIDS-defining conditions and HIV-associated mortality. *J Acquir Immune Defic Syndr*. 2019;80(4):436-443. Available at: https://pubmed.ncbi.nlm.nih.gov/30550488.

49. Lange CG, Woolley IJ, Brodt RH. Disseminated *Mycobacterium avium-intracellulare* complex (MAC) infection in the era of effective antiretroviral therapy: is prophylaxis still indicated? *Drugs*. 2004;64(7):679-692. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15025543.

50. Sax PE. "Choosing wisely" in HIV medicine — should we stop giving MAC prophylaxis? *HIV and ID Observations*. 2016;2018(3/20/2016). Available at: https://blogs.jwatch.org/hiv-id-observations/index.php/choosing-wisely-in-hiv-medicine-should-we-stop-giving-mac-prophylaxis/2016/03/20.

51. Vervoort SC, Borleffs JC, Hoepelman AI, Grypdonck MH. Adherence in antiretroviral therapy: a review of qualitative studies. *AIDS*. 2007;21(3):271-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17255734.

52. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med*. 1996;335(6):392-398. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8676932.

53. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced

acquired immunodeficiency syndrome. *N Engl J Med*. 1996;335(6):384-391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8663871.

54. Uthman MM, Uthman OA, Yahaya I. Interventions for the prevention of *Mycobacterium avium* complex in adults and children with HIV. *Cochrane Database Syst Rev*. 2013(4):CD007191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23633339.

55. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. *Ann Intern Med*. 1994;121(12):905-911. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7978715.

56. May T, Brel F, Beuscart C, et al. Comparison of combination therapy regimens for treatment of human immunodeficiency virus-infected patients with disseminated bacteremia due to *Mycobacterium avium*. ANRS Trial 033 Curavium Group. Agence Nationale de Recherche sur le Sida. *Clin Infect Dis*. 1997;25(3):621-629. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9314450.

57. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. *Clin Infect Dis*. 1999;28(5):1080-1085. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10452638.

58. Dube MP, Sattler FR, Torriani FJ, et al. A randomized evaluation of ethambutol for prevention of relapse and drug resistance during treatment of *Mycobacterium avium* complex bacteremia with clarithromycin-based combination therapy. California Collaborative Treatment Group. *J Infect Dis*. 1997;176(5):1225-1232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9359722.

59. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Terry Beirn Community Programs for Clinical Research on AIDS. *Clin Infect Dis*. 1999;29(1):125-133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10433575.

60. Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated *Mycobacterium avium* complex infection after 12 months of antimycobacterial therapy combined with highly active antiretroviral therapy. *J Infect Dis*. 1998;178(5):1446-1449. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9780266.

61. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. Veterans Affairs HIV Research Consortium. *Clin Infect Dis*. 1998;27(5):1278-1285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9827282.

62. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with human immunodeficiency virus. *Clin Infect Dis*. 2000;31(5):1245-1252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11073759.

63. Xu HB, Jiang RH, Li L. Treatment outcomes for *Mycobacterium avium* complex: a systematic review and meta-analysis. *Eur J Clin Microbiol Infect Dis*. 2014;33(3):347-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23979729.

64. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group. *N Engl J Med*. 1996;335(6):377-383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8676931.

65. Food and Drug Administration. Clarithromycin [package insert]. 2017. Accessed May 25. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/050662s058,050698s038,050775s026lbl.pdf.

66. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175(4):367-416. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17277290.

67. Gardner EM, Burman WJ, DeGroote MA, Hildred G, Pace NR. Conventional and molecular epidemiology of macrolide resistance among new *Mycobacterium avium* complex isolates recovered from HIV-infected patients. *Clin Infect Dis*. 2005;41(7):1041-1044. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16142672.

68. Craft JC, Notario GF, Grosset JH, Heifets LB. Clarithromycin resistance and susceptibility patterns of *Mycobacterium avium* strains isolated during prophylaxis for disseminated infection in patients with AIDS. *Clin Infect Dis*. 1998;27(4):807-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9798037.

69. Chaisson RE, Keiser P, Pierce M, et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic *Mycobacterium avium* complex disease in patients with HIV infection. *AIDS*. 1997;11(3):311-317. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9147422.

70. Koh WJ, Hong G, Kim SY, et al. Treatment of refractory *Mycobacterium avium* complex lung disease with a moxifloxacin-containing regimen. *Antimicrob Agents Chemother*. 2013;57(5):2281-2285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23478956.

71. Chapagain M, Pasipanodya JG, Athale S, et al. Omadacycline efficacy in the hollow fibre system model of pulmonary *Mycobacterium avium* complex and potency at clinically attainable doses. *J Antimicrob Chemother*. 2022;77(6):1694-1705. Available at: https://pubmed.ncbi.nlm.nih.gov/35257162.

72. Litvinov V, Makarova M, Kudlay D, Nikolenko N, Mikhailova J. In vitro activity of bedaquiline against *Mycobacterium avium* complex. *J Med Microbiol*. 2021;70(10). Available at: https://pubmed.ncbi.nlm.nih.gov/34668850.

73. Lin S, Hua W, Wang S, et al. In vitro assessment of 17 antimicrobial agents against clinical *Mycobacterium avium* complex isolates. *BMC Microbiol*. 2022;22(1):175. Available at: https://pubmed.ncbi.nlm.nih.gov/35804298.

74. Gil E, Sweeney N, Barrett V, et al. Bedaquiline as treatment for disseminated nontuberculous mycobacteria infection in 2 patients co-infected with HIV. *Emerg Infect Dis*. 2021;27(3):944-948. Available at: https://pubmed.ncbi.nlm.nih.gov/33622490.

75. Philley JV, Wallace RJ, Jr., Benwill JL, et al. Preliminary results of bedaquiline as salvage therapy for patients with nontuberculous mycobacterial lung disease. *Chest*. 2015;148(2):499-506. Available at: https://pubmed.ncbi.nlm.nih.gov/25675393.

76. Shirley M. Amikacin liposome inhalation suspension: a review in *Mycobacterium avium* complex lung disease. *Drugs*. 2019;79(5):555-562. Available at: https://pubmed.ncbi.nlm.nih.gov/30877642.

77. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex: AIDS Clinical Trial Group 393 Study Team. *J Infect Dis*. 2003;187(7):1046-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12660918.

78. Shafran SD, Mashinter LD, Phillips P, et al. Successful discontinuation of therapy for disseminated *Mycobacterium avium* complex infection after effective antiretroviral therapy. *Ann Intern Med*. 2002;137(9):734-737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12416943.

79. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med*. 2002;137(4):239-250. Available at: https://pubmed.ncbi.nlm.nih.gov/12186514.

80. Shafran SD, Deschenes J, Miller M, Phillips P, Toma E. Uveitis and pseudojaundice during a regimen of clarithromycin, rifabutin, and ethambutol. MAC Study Group of the Canadian HIV Trials Network. *N Engl J Med*. 1994;330(6):438-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8284019.

81. Hafner R, Bethel J, Power M, et al. Tolerance and pharmacokinetic interactions of rifabutin and clarithromycin in human immunodeficiency virus-infected volunteers. *Antimicrob Agents Chemother*. 1998;42(3):631-639. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9517944.

82. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. 2023. Available at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-overview?view=full.

83. Hennig S, Svensson EM, Niebecker R, et al. Population pharmacokinetic drug-drug interaction pooled analysis of existing data for rifabutin and HIV PIs. *J Antimicrob Chemother*. 2016;71(5):1330-1340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26832753.

84. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV-infected tuberculosis patients on lopinavir/ritonavir-based

antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25406657.

85. Kakuda TN, Woodfall B, De Marez T, et al. Pharmacokinetic evaluation of the interaction between etravirine and rifabutin or clarithromycin in HIV-negative, healthy volunteers: results from two phase 1 studies. *J Antimicrob Chemother*. 2014;69(3):728-734. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24155058.

86. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet*. 2011;50(4):229-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21348537.

87. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23075918.

88. Brainard DM, Kassahun K, Wenning LA, et al. Lack of a clinically meaningful pharmacokinetic effect of rifabutin on raltegravir: *in vitro/in vivo* correlation. *J Clin Pharmacol*. 2011;51(6):943-950. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20852006.

89. Le X, Guo X, Sun J, et al. Pharmacokinetic features of dolutegravir with rifampicin and rifabutin among patients coinfected with human immunodeficiency virus and tuberculosis/*Mycobacterium avium* complex. *Int J Infect Dis*. 2022;116:147-150. Available at: https://pubmed.ncbi.nlm.nih.gov/34999246.

90. Alffenaar JW, Martson AG, Heysell SK, et al. Therapeutic drug monitoring in non-tuberculosis mycobacteria infections. *Clin Pharmacokinet*. 2021;60(6):711-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33751415.

91. Phillips P, Kwiatkowski MB, Copland M, Craib K, Montaner J. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr*. 1999;20(2):122-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10048898.

92. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis*. 2005;41(10):1483-1497. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16231262.

93. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet*. 1998;351(9098):252-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9457095.

94. Cabie A, Abel S, Brebion A, Desbois N, Sobesky G. Mycobacterial lymphadenitis after initiation of highly active antiretroviral therapy. *Eur J Clin Microbiol Infect Dis*. 1998;17(11):812-813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9923530.

95. Smibert OC, Trubiano JA, Cross GB, Hoy JF. Short communication: *Mycobacterium avium* complex infection and immune reconstitution inflammatory syndrome remain a challenge in

the era of effective antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2017;33(12):1202-1204. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28791872.

96. Barber DL, Andrade BB, McBerry C, Sereti I, Sher A. Role of IL-6 in *Mycobacterium avium*—associated immune reconstitution inflammatory syndrome. *J Immunol*. 2014;192(2):676-682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24337386.

97. Breglio KF, Vinhaes CL, Arriaga MB, et al. Clinical and immunologic predictors of *Mycobacterium avium* complex immune reconstitution inflammatory syndrome in a contemporary cohort of patients with human immunodeficiency virus. *J Infect Dis*. 2021;223(12):2124-2135. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205640.

98. Wormser GP, Horowitz H, Dworkin B. Low-dose dexamethasone as adjunctive therapy for disseminated *Mycobacterium avium* complex infections in AIDS patients. *Antimicrob Agents Chemother*. 1994;38(9):2215-2217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7811052.

99. Rocco JM, Laidlaw E, Galindo F, et al. Severe mycobacterial immune reconstitution inflammatory syndrome (IRIS) in advanced human immunodeficiency virus (HIV) has features of hemophagocytic lymphohistiocytosis and requires prolonged immune suppression. *Clin Infect Dis*. 2023;76(3):e561-e570. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36048425.

100. Rocco JM, Laidlaw E, Galindo F, et al. Mycobacterial immune reconstitution inflammatory syndrome in HIV is associated with protein-altering variants in hemophagocytic lymphohistiocytosis-related genes. *J Infect Dis*. 2023;228(2):111-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37040388.

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

102. Kemper CA, Meng TC, Nussbaum J, et al. Treatment of *Mycobacterium avium* complex bacteremia in AIDS with a four-drug oral regimen: rifampin, ethambutol, clofazimine, and ciprofloxacin. The California Collaborative Treatment Group. *Ann Intern Med*. 1992;116(6):466-472. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1739237.

103. Chiu J, Nussbaum J, Bozzette S, et al. Treatment of disseminated *Mycobacterium avium* complex infection in AIDS with amikacin, ethambutol, rifampin, and ciprofloxacin. California Collaborative Treatment Group. *Ann Intern Med*. 1990;113(5):358-361. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2382918.

104. Rodriguez Diaz JC, Lopez M, Ruiz M, Royo G. *In vitro* activity of new fluoroquinolones and linezolid against non-tuberculous mycobacteria. *Int J Antimicrob Agents*. 2003;21(6):585-588. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12791475.

105. Liu L, Song Z, Xun J, et al. PD-1 inhibitor for disseminated Mycobacterium avium infection in a person with HIV. *Open Forum Infect Dis*. 2023;10(1):ofac700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36686637.

106. Aberg J, Powderly W. HIV: primary and secondary prophylaxis for opportunistic infections. *BMJ Clin Evid*. 2010;2010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21418688.

107. Green H, Hay P, Dunn DT, McCormack S, Investigators S. A prospective multicentre study of discontinuing prophylaxis for opportunistic infections after effective antiretroviral therapy. *HIV Med*. 2004;5(4):278-283. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15236617.

108. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9862944.

109. Einarson A, Phillips E, Mawji F, et al. A prospective controlled multicentre study of clarithromycin in pregnancy. *Am J Perinatol*. 1998;15(9):523-525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9890248.

110. Drinkard CR, Shatin D, Clouse J. Postmarketing surveillance of medications and pregnancy outcomes: clarithromycin and birth malformations. *Pharmacoepidemiol Drug Saf*. 2000;9(7):549-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11338912.

111. Muanda FT, Sheehy O, Berard A. Use of antibiotics during pregnancy and risk of spontaneous abortion. *CMAJ*. 2017;189(17):E625-E633. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28461374.

112. Berard A, Sheehy O, Zhao JP, Nordeng H. Use of macrolides during pregnancy and the risk of birth defects: a population-based study. *Pharmacoepidemiol Drug Saf*. 2015;24(12):1241-1248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26513406.

113. Lin KJ, Mitchell AA, Yau WP, Louik C, Hernandez-Diaz S. Safety of macrolides during pregnancy. *Am J Obstet Gynecol*. 2013;208(3):221 e221-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23254249.

114. Bahat Dinur A, Koren G, Matok I, et al. Fetal safety of macrolides. *Antimicrob Agents Chemother*. 2013;57(7):3307-3311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23650169.

115. Cluver C, Novikova N, Eriksson DO, Bengtsson K, Lingman GK. Interventions for treating genital chlamydia trachomatis infection in pregnancy. *Cochrane Database Syst Rev*. 2017;9(9):CD010485. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28937705.

Mycobacterium tuberculosis Infection and Disease

Updated: May 2, 2024
Reviewed: May 2, 2024

Epidemiology

Tuberculosis (TB) is the leading cause of morbidity and mortality among people with HIV worldwide. In 2020 and 2021, progress towards reducing TB morbidity and mortality slowed amidst the widespread disruption of health services from the COVID-19 pandemic. Globally, the annual number of estimated TB deaths increased in 2020 and 2021, to 1.5 million and 1.6 million, respectively.[1,2] Among people with HIV, there were an estimated 703,000 people who had TB, but only 52% were diagnosed and reported. A total of 187,000 deaths among people with HIV were attributed to TB in 2021, the first time there has been an increase in HIV-associated TB deaths since 2006.[2] People with HIV still account for a disproportionate number of TB deaths worldwide (11.8% of deaths vs. 6.7% of TB cases); however, a 47% reduction in deaths has occurred since 2010.[2]

In the United States, more than two-thirds (5,456; 71.4%) of people newly reported with TB in 2021 were born outside the United States, similar to 2019 and 2020 proportions.[3] The incidence of HIV-related TB in the United States has declined substantially, in part because of the widespread use of antiretroviral therapy (ART).[4,5] Among all people reported with TB with known HIV status in the United States in 2021, 293 people (4.2%) were coinfected with HIV (6.3% among people with TB aged 25–44 years vs. 5.6% among those aged 45–64 years).[6] Overall, the proportion of reported people with TB and HIV co-infection has been steadily declining over the past decade (7.4% in 2011).

Latent TB Infection

TB infection occurs when a person inhales droplet nuclei containing *Mycobacterium tuberculosis* organisms. Usually within 2 to 12 weeks after infection, the immune response limits the multiplication of tubercle bacilli. However, viable bacilli can persist for years, a condition referred to as latent TB infection (LTBI). People with LTBI are asymptomatic and are not infectious. TB disease (defined as clinically active disease, often with positive smears and cultures) can develop soon after exposure to *M. tuberculosis* organisms (primary disease) or after reactivation of latent infection.[7,8] The risk of TB disease due to reactivation of LTBI for people with untreated HIV has been estimated as 3% to 16% per year, which approximates the lifetime risk of TB disease for people with LTBI who do not have HIV (approximately 5%).[9-14] The risk of TB disease begins in the first year following HIV infection.[15] TB disease can occur at any CD4 T lymphocyte (CD4) cell count, although the risk increases with progressive immunodeficiency.[15,16] The estimated annual risk of developing TB disease among people with LTBI (diagnosed by a positive tuberculin skin test [TST] or interferon-gamma release assay [IGRA] in the absence of a TB disease diagnosis) is 3 to 12 times greater for people with untreated HIV than for those without HIV.[17] Even with effective ART, the risk of TB disease among people with HIV remains greater than that among the general population.[18] Since 2006, the TB incidence rate in people with HIV has been lower than in previous years, but the TB risk is still substantially higher than among people without HIV.[19] In the United States, the most common predisposing factor for TB infection is birth or residence outside of the United States.[20]

The risk of progression from LTBI to TB disease in people with HIV is reduced both by ART and by the treatment of LTBI.[18,21-24] In combination with ART, isoniazid preventive therapy decreased the risk of TB disease by 76% among people with HIV in Brazil.[25] Furthermore, isoniazid preventive therapy and ART independently and additively decreased the risk of death and severe HIV-related illness.[21,23]

Diagnosing Latent TB Infection

All people with HIV should be evaluated for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure**.** In programmatic settings in the United States, TB screening has been suboptimal, with only 47% to 69% of people with HIV presenting to care completing initial screening, and 42% of those with LTBI initiating therapy.[26-30] The two current diagnostics available for the detection of *M. tuberculosis* infection in the United States, IGRA and TST, help differentiate those with and without TB infection. However, the diagnostic accuracy of TST and IGRA is limited; a negative test does not exclude the diagnosis of LTBI or TB disease, and a positive test does not, by itself, mean LTBI therapy is warranted. Decisions about medical and public health management should include epidemiological risk factors, medical history, and other clinical information when interpreting IGRA or TST results.

People with advanced HIV (CD4 count <200 cells/mm^3) and negative diagnostic tests for LTBI, and no indications for initiating empiric LTBI treatment (i.e., no recent exposure to a culture-confirmed TB case) should be retested for LTBI once they start ART and attain a CD4 count ≥200 cells/mm^3 to ensure that the initial test result was a true negative result.[31-33] Annual testing for LTBI using TST or IGRA is recommended only for people with HIV who have a history of a negative test for infection and are at high risk for repeated or ongoing exposure to people with active TB disease (e.g., during incarceration, travel to a high-TB incidence country, homelessness, living in a congregate setting).[34]

Traditionally, LTBI has been defined by the presence of a positive TST (≥5 mm of induration at 48–72 hours in people with HIV) in people with no clinical or radiographic evidence of TB disease. Despite the extensive experience with the TST among people with HIV, the test has several disadvantages: the requirement for two visits to place and read the test, decreased specificity (false positive results) among people who received Bacillus Calmette-Guérin (BCG) vaccination, and decreased sensitivity (false negative results) among people with advanced immunodeficiency.[33,35] The first two limitations of the TST have led to broader use of IGRAs for the detection of LTBI.

IGRAs include the T-SPOT.TB and QFT-TB Gold Plus (QFT-Plus). Systematic reviews and meta-analyses, as well as a large study in the United States, have found that IGRAs generally have higher specificity than the TST, may correlate better with exposure to *M. tuberculosis*, and are less likely to cross-react with BCG vaccination or exposure to nontuberculous mycobacteria.[19,36,37] A systematic review among people with HIV did not find robust evidence that IGRAs were superior to TST in diagnosing either active TB or LTBI.[33] However, in a prospective study of 1,510 people with HIV in the United States (median CD4 count of 532 cells/mm^3), T.SPOT.TB was significantly more specific (99.7%) and had a significantly higher positive predictive value (PPV; 90.0%) than the older QuantiFERON Gold In-Tube (QFT-GIT) (96.5% specificity, 50.7% PPV) and TST (96.8% specificity, 45.4% PPV). QFT-GIT was significantly more sensitive (72.2%) than TST (54.2%) and T.SPOT.TB (51.9%).[38]

As with the TST, progressive immunodeficiency is associated with decreased sensitivity of IGRAs.[39] In addition, the reproducibility of positive results of IGRAs may be limited. Among 46 people with HIV who had initial positive tests with the QFT-GIT assay, 33 (72%) had negative repeat tests, particularly those whose responses were at the lower range of the manufacturer's suggested range of positive results.[40] Similar to recommendations for healthcare workers, annual testing for people with HIV is no longer recommended unless high risk exists for repeated or ongoing exposure to people with active TB disease.[41]

Among people with HIV, the correlation between the TST and IGRA test results is poor to moderate.[42,43] In prospective studies not limited to people with HIV, positive results with either the TST or IGRA were associated with an increased risk of developing TB disease.[19,44-46] In some studies (again not limited to people with HIV), patients with a positive IGRA were at a higher risk of subsequently developing TB disease than those with a positive TST.[19,47,48] Despite its limitations, a positive TST result strongly predicts that the treatment of LTBI will decrease the risk of TB progression among people with HIV.[18] Studies are underway to formally evaluate if IGRAs are similarly predictive.[49]

Although no definitive comparisons of the TST and IGRAs for screening people with HIV in low-burden settings have been published, both the TST and the approved IGRAs are considered appropriate for TB screening among people with HIV in the United States.[17,38] Some experts have suggested using both the TST and an IGRA in a stepwise or sequential manner to screen for LTBI, but the predictive value of this approach is not clear, and it may be challenging to implement. The routine use of both TST and IGRAs in a single patient to screen for LTBI is not recommended in the United States.[50]

As tests of immune reactivity against *M. tuberculosis*, TST and IGRAs are often positive among people with TB disease. Therefore, all people with a positive TST or IGRA should be evaluated for the possibility of active TB disease.[17] Most, but not all, people with HIV and TB disease have symptoms (e.g., cough, fever, sweats, weight loss, lymphadenopathy); the absence of these symptoms had a 98% negative predictive value for culture-positive TB in low-resource settings, although this varied depending on pretest probability.[51] The addition of a chest radiograph improved the sensitivity of this screening algorithm but decreased specificity.[52] It is important to note that in a symptomatic patient with clinical suspicion of TB disease, a negative TST or IGRA does not rule out TB disease, particularly in those with CD4 count <200 cells/mm^3.

Obtaining a sputum specimen for *M. tuberculosis* identification is the gold standard for diagnosing pulmonary TB disease, but it is not high yield in screening people with HIV without pulmonary symptoms, particularly in low-prevalence settings. Therefore, a negative symptom screen (including absent cough of *any* duration) coupled with a normal chest radiograph is usually sufficient to exclude TB disease in a patient with a positive TST or IGRA in low TB incidence settings.[17] Sub-clinical TB among people with HIV is of greater concern in high TB burden settings.[53]

Treating Latent TB Infection

Recommendations for Treating LTBI to Prevent TB Disease in People with HIV

Indications

- Positive screening test[a] for LTBI (≥5 mm of induration at 48–72 hours in people with HIV or positive IGRA) regardless of BCG status, no evidence of active TB disease, and no prior history of treatment for active disease or latent TB infection (AI).
- Close contact with a person with infectious TB (such as someone who has shared air space, such as in a household or close congregate setting, with a person with active pulmonary TB according to the Centers for Disease Control and Prevention Guidelines for the Investigation of Contacts of Persons with Infectious Tuberculosis) regardless of screening test result and CD4 count (AII).

Preferred Therapy

- Isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus rifapentine (see weight-based dosing below) PO once weekly plus pyridoxine 50 mg PO once weekly (3HP) for 12 weeks (AI). Note: 3HP is recommended only for virally-suppressed patients receiving an efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen (AII).
  - Rifapentine Weekly Dose (maximum 900 mg)
    - *Weighing 25.1–32 kg:* 600 mg
    - *Weighing 32.1–49.9 kg*: 750 mg
    - *Weighing ≥50.0 kg*: 900 mg
- Isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25–50 mg PO daily (AI) for 3 months (3HR). See the Dosing Recommendations for use of ARV and Anti-TB Drugs When Treating Latent TB table for the list of ARV drugs not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (i.e., raltegravir, dolutegravir, or maraviroc).

Alternative Therapy

- Isoniazid 300 mg PO daily plus pyridoxine 25–50 mg PO daily for 6–9 months (AII) *or*
- Rifampin 600 mg PO daily for 4 months (BI) (4R)
  - Consult the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for the list of ARV drugs not recommended for use with rifampin (e.g., protease inhibitors, bictegravir) and those which require dosage adjustment (e.g., raltegravir, dolutegravir, or maraviroc).
- Isoniazid 300 mg PO daily plus rifapentine (see weight-based dosing below) PO daily plus pyridoxine 25–50 mg PO daily for 4 weeks (BI) (1HP) Note: 1HP is recommended only for patients receiving an efavirenz-based ARV regimen (AI).
  - Rifapentine Daily Dose (maximum 600 mg)
    - *Weighing <35 kg*: 300 mg
    - *Weighing 35–45 kg*: 450 mg
    - *Weighing >45 kg*: 600 mg
- For people exposed to drug-resistant TB, select drugs for prevention of TB after consultation with experts and with public health authorities (AIII).

Pregnancy Considerations

- 4R and 3HR are acceptable alternative regimens for pregnant people with HIV (BIII).
- For pregnant people receiving effective ART and without close household contact with infectious TB or recent test for TB infection (TST or IGRA) conversion from negative to positive, therapy for LTBI may be deferred until after delivery (BIII).

- Although rifampin generally is considered safe in pregnancy, data on the use of rifapentine are extremely limited and its use in pregnant people is not currently recommended (BIII).

Additional Considerations

- Deferring ART until after completion of treatment for LTBI is not recommended (AI).
- Given the important drug–drug interactions between rifamycins and several antiretroviral (ARV) agents, selection of an LTBI regimen will depend on a patient's current or planned ARV regimen.

[a] Screening tests for LTBI include a tuberculin skin test (TST) or interferon-gamma release assay (IGRA); see text for details regarding these tests.

Key: H = Isoniazid; P = Rifapentine; R = Rifampin; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; CD4 = CD4 T lymphocyte; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; IPT = isoniazid preventive therapy; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally; TB = tuberculosis

Once active TB disease is excluded and in the absence of other medical contraindications, people with HIV with a positive TB screening test should receive LTBI treatment **(AI),** unless there is documentation of prior treatment for active TB or LTBI.[54] Additionally, people with HIV who are in close contact with anyone with infectious TB should receive LTBI treatment, regardless of their TB screening test results and CD4 count **(AII).** Selection of an LTBI regimen may depend on the potential for drug interactions, toxicity concerns, as well as medication availability and/or cost (see Recommendations for Treating LTBI to Prevent TB Disease in People with HIV table above). People with HIV who have been treated successfully for LTBI should not have repeat testing with TST or IGRA; a previously positive test result generally will not revert to negative.

People with HIV in the United States who have a negative TST or IGRA and no recent contact with a person with infectious TB likely will not benefit from the treatment of LTBI, and preventive therapy is not generally recommended **(AIII);** this is in contrast to high TB prevalence countries where isoniazid (i.e., isoniazid preventive therapy; IPT) decreased TB risk and mortality in people with HIV, regardless of TST or IGRA result.[24]

LTBI treatment and ART act independently to decrease the risk of TB disease.[22,23,25,55,56] Therefore, the use of both interventions is recommended for people with LTBI and HIV **(AI).** Given the important drug–drug interactions between rifamycins and several antiretroviral (ARV) agents, selection of an LTBI regimen will depend on a patient's current or planned ARV regimen. Deferring ART until after completion of treatment for LTBI is not recommended **(AI).**[23]

Preferred Drugs for Treatment of Latent TB Infection

3HP

- Rifapentine (weight-based dosing) orally (PO) once weekly plus isoniazid 15 mg/kg PO once weekly (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks is one of two preferred regimens for the treatment of LTBI **(AI).**[54]

In two randomized controlled trials, rifapentine plus isoniazid once weekly for 12 weeks (3HP) was as effective and well-tolerated as 6 to 9 months of daily isoniazid, including in people with HIV whose CD4 counts were generally >350 cells/mm^3 and who were not yet on ART.[57,58] 3HP treatment completion rates with self-administered therapy were inferior to those with directly observed therapy (DOT) but non-inferior among study participants enrolled in the United States—and generally high overall.[59]

Although individuals taking ART were not included in the Phase 3 trial of 3HP,[57] the pharmacokinetic (PK) profile of efavirenz with daily rifapentine and isoniazid is favorable.[60,61] Raltegravir concentrations were modestly increased when it was given with once-weekly rifapentine in healthy volunteers.[62] In a Phase 1/2 single-arm study of people with HIV treated with dolutegravir and 3HP, rifapentine decreased dolutegravir exposure by 26%. However, trough concentrations remained above the 90% maximum inhibitory concentration for all but one participant, and all participants maintained an undetectable viral load throughout the study period.[63] Based on these PK data and limited outcome data, 3HP is recommended in virally suppressed people receiving efavirenz, raltegravir, or once-daily dolutegravir without dose adjustment of rifapentine, isoniazid, or ART **(AII).**[64] A trial is currently underway examining the use of 3HP in ART-naive participants who are initiating therapy with a dolutegravir-based regimen.[65] 3HP has not been studied in patients receiving twice-daily dolutegravir and is therefore not recommended **(AIII)**.

3HR

- Daily isoniazid 300 mg PO daily plus rifampin 600 mg PO daily plus pyridoxine 25 mg to 50 mg PO daily for 3 months is also a preferred option for the treatment of LTBI in people with HIV **(AI).**

In studies of adults and children without HIV who had a positive TST, those who received 3HR had a similar decreased risk of TB disease, hepatotoxicity, and adverse effects requiring treatment discontinuation compared with those who received ≥6 months of daily isoniazid.[66-70] Among people with HIV, several studies found no difference in the incidence of TB disease between those who received 3HR and those who received ≥6 months of daily isoniazid, regardless of TST status;[71-74] hepatotoxicity was less frequent among those receiving 3HR, but treatment-limiting adverse effects were more common.[54] When using rifampin for LTBI treatment, either dose adjustment or substitution of many commonly used ARVs may be needed (see Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB table).

Alternative Drugs for Treatment of Latent TB Infection

Isoniazid

- Isoniazid 300 mg PO daily plus pyridoxine 25 mg to 50 mg PO daily for 6 to 9 months is an alternative regimen for the treatment of LTBI, particularly when drug–drug interactions between rifamycins and ARV regimens limit the use of rifamycin-containing LTBI therapies **(AII).**

Daily isoniazid for 6 to 9 months is effective and reasonably well-tolerated; severe toxicity is infrequent.[23,74-78] However, treatment completion rates are suboptimal, decreasing its effectiveness.[79] Longer courses of isoniazid (e.g., 12 months) are more effective at preventing TB but carry a higher risk of toxicity[80,81] and patients are more likely to complete shorter regimens.[57,59,79,82-85] Peripheral neuropathy, hepatitis, and rash may be caused by either isoniazid or some ARV drugs. Isoniazid, when used, should be supplemented with pyridoxine at a dose of 25 to 50 mg per day to prevent peripheral neuropathy **(AIII).**

4R

- Rifampin 600 mg PO daily for 4 months (4R) is an alternative regimen for the treatment of LTBI in people with HIV **(BI).**

A large trial compared 4 months of daily rifampin (4R) to 9 months of daily isoniazid (9H) in more than 6,000 participants who were predominantly HIV-seronegative.[77] Although rates of incident active TB were low in both arms, the 4R regimen was non-inferior to 9H. Treatment completion rates were significantly higher and adverse events were less common in the 4R arm than in the 9H arm (78.8% vs. 63.2%; $P < 0.001$ and 1.5% vs. 2.6%; $P = 0.003$, respectively). However, only 255 participants were people with HIV, which limits the generalizability of the findings for this population. Although the National Tuberculosis Controllers Association (NTCA)/CDC guidelines recommend 4R as a preferred treatment for LTBI in people without HIV,[54] given the lack of trial data in people with HIV, the 4R regimen is recommended only as an alternative to 3HP, 3HR, and 6 or 9 months of isoniazid in people with HIV **(BI).** When using rifampin for LTBI treatment, either dose adjustment or substitution of key ARVs may be needed. Given the theoretical but unproven risk of selecting for drug-resistant TB with rifamycin monotherapy in undiagnosed early-stage TB disease and the relatively poor performance of symptom screens alone in people with HIV on ART,[86,87] some clinicians would obtain a specimen for *M. tuberculosis* testing before starting 4R for LTBI. Due to limited data on 4R in people with HIV, concerns about using this regimen in people with low CD4 cell counts, and an absence of data on the use of 4 months of rifabutin either in people with or without HIV, rifabutin monotherapy is not recommended **(AIII).**[88-90]

1HP

- Isoniazid 300 mg PO daily plus rifapentine (weight-based dosing to a maximum of 600 mg) PO daily plus pyridoxine 25 mg to 50 mg PO daily for 4 weeks (1HP) is an alternative therapy for the treatment of LTBI in people with HIV treated with efavirenz **(BI).**

The BRIEF-TB study (AIDS Clinical Trials Group [ACTG] 5279) evaluated 1 month of daily rifapentine plus isoniazid (1HP) versus 9 months of daily isoniazid (9H) in people with HIV residing in mostly high TB burden settings (TB incidence >60 per 100,000 population).[83] The median CD4 count of study participants was 470 cells/mm^3, 50% of the study population was on efavirenz or nevirapine-based ART regimens at study entry, and 21% of the study population was TST positive. 1HP was non-inferior to 9H when comparing the composite outcome of confirmed or probable TB, death due to TB, and death due to unknown cause. Treatment completion rates (by self-report) were 97% in the 1HP arm and 90% in the 9H arm. Of note, although the population of people with HIV enrolled was at increased risk for LTBI due to high endemic exposure, the number of participants with documented LTBI based on TST or IGRA testing was low (23%), and the overall event rate (i.e., the number of participants who developed active TB in either arm) was also low (0.56/100 person-years) after more than 3 years of follow-up. Based on these data, 1HP is recommended as an alternative regimen for treatment of LTBI in people with HIV **(BI).** The NTCA/CDC guidelines do not include 1HP as a preferred or alternative regimen given that the BRIEF-TB study was performed largely in people with HIV living in high TB burden settings, most of whom did not have positive tests for LTBI.[54] In light of the strengths of the study results and the convenience and safety of the regimen, some clinicians may choose to use 1HP for treatment of LTBI as an alternative option to those recommended in the current NTCA/CDC guidelines. If ART is administered together with 1HP, an efavirenz-based regimen should be used **(AI).**[60,91] A study evaluating co-administration of 1HP with dolutegravir is in progress; the use of dolutegravir-based ART should await results from this trial.[92]

Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB Infection

TB Drug	ARV Drugs	Dose of TB Drug
Isoniazid (INH)	• All ARVs • Note: for information on coadministration of ARVs with rifampin or rifapentine, see entries below	Use INH with pyridoxine 25–50 mg PO daily (50 mg once weekly if used with 3HP) *For 3HP (weekly INH + rifapentine x 12 weeks)* • 15 mg/kg PO once weekly (900 mg maximum) *For 3HR (daily INH + rifampin x 3 months), or 1HP (daily INH + rifapentine x 4 weeks), or INH alone (daily INH x 6–9 months)* • 300 mg PO daily
Rifampin[a]	• NRTIs (TAF with caution[b]) • EFV 600 mg • DTG, RAL (twice daily), and MVC without a strong CYP3A4 inhibitor (note: doses of these ARV drugs need to be adjusted when used with rifampin) • IBA, T-20	*For 3HR (daily rifampin + INH x 3 months), or 4R (daily rifampin x 4 months)* • 600 mg PO daily
	• All other ARVs	Not recommended
Rifapentine[a] 3HP *Weekly rifapentine + INH x 12 weeks*	• EFV 600 mg, RAL or once daily DTG • NRTIs (TAF with caution[b]) • IBA, T-20	• Weighing 32.1–49.9 kg: 750 mg PO weekly • Weighing ≥50.0 kg: 900 mg PO weekly
	• All other ARVs	Not recommended
Rifapentine[a] 1HP *Daily rifapentine + INH x 4 weeks*	• NRTIs (TAF with caution[b]) • EFV 600 mg • IBA, T-20	• Weighing <35 kg: 300 mg PO daily • Weighing 35–45 kg: 450 mg PO daily • Weighing >45 kg: 600 mg PO daily
	• All other ARVs	Not Recommended

[a] For additional drug—drug interaction information between antiretrovirals and anti-TB drugs, see Drug-Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines.

[b] If TAF and rifamycins are coadministered, monitor for HIV treatment efficacy. Note that FDA labeling recommends not to coadminister. See Drug-Drug Interactions in the Treatment of HIV-Related TB below and Significant Pharmacokinetic Interactions between Drugs Used to Treat or Prevent Opportunistic Infections table for more information.

Key: ARV = antiretroviral; BIC = bictegravir; DTG = dolutegravir; EFV = efavirenz; IBA = ibalizumab; IM = intramuscular; INH = isoniazid; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PO = oral; RAL = raltegravir; RTV = ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TB = tuberculosis

Treatment of LTBI Following Exposure to Drug-Resistant TB

For people exposed to drug-resistant TB, a regimen for LTBI should be selected after consultation with experts or with public health authorities **(AIII).**[93] A large randomized clinical trial of 26 weeks of either isoniazid or delamanid for people at high risk for TB, including people with HIV, following household exposure to drug-resistant TB is in progress.[94]

Monitoring for Adverse Events Related to Treating Latent TB Infection

Individuals receiving TB-preventive therapy should be evaluated by a clinician monthly to assess adherence and evaluate for possible drug toxicity. Although people with HIV may not have a higher risk of hepatitis from isoniazid than people without HIV, people with HIV should have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin levels measured before starting LTBI treatment and repeated if abnormal.[54] People with concomitant chronic viral hepatitis and older individuals have an increased risk of isoniazid-related hepatotoxicity, and such people should be monitored closely when being treated for LTBI.[95,96]

Following initiation of isoniazid, ALT and AST levels often increase during the first 3 months of treatment but return to normal despite continued therapy. Hepatotoxicity also can occur with rifamycins, although it is less common than with isoniazid.[78,83] Factors that increase the risk of drug-induced clinical hepatitis include daily alcohol consumption, underlying liver disease, pregnancy and early postpartum, and concurrent treatment with other hepatotoxic drugs.[97] At each visit, patients should be asked about adherence, new medications, and alcohol use and should be screened for potential adverse effects of treatment for LTBI (e.g., unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesia of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness, easy bruising or bleeding, arthralgia) and told to stop medications immediately and return to the clinic for an assessment should any of these occur **(AIII).**

If the serum ALT or AST levels increase to (1) greater than five times the upper limit of normal without symptoms or (2) greater than three times the upper limit of normal AND total bilirubin greater than two times the upper limit of normal without symptoms or (3) greater than three times the upper limit of normal with symptoms (or greater than two times the baseline value for patients with baseline abnormal transaminases), LTBI treatment should be stopped **(AIII).**

The ultimate decision regarding resumption of therapy with the same or different agents for LTBI treatment should be made after weighing the risk for additional hepatic injury against the benefit of preventing progression to TB disease,[97] and ideally in consultation with an expert in treating LTBI in people with HIV. If a local expert is not available through the public health department, clinicians and TB programs can contact the CDC (tbinfo@cdc.gov) and utilize remote TB medical consultation services available through the CDC-funded TB Center of Excellence that serves their region.

Clinical Manifestations of TB Disease

Similar to people without HIV, people with HIV and TB disease may be asymptomatic but have positive sputum cultures with or without abnormal findings on chest radiograph (subclinical TB).[98,99] In ambulatory people with HIV, the presence of any one of the classic symptoms of TB disease (i.e., cough, fever, night sweats, weight loss) has high sensitivity but low specificity for diagnosing TB as assessed in resource-limited settings.[51] Compared to treatment-naive patients with HIV, the sensitivity of classic TB symptoms is lower in people with HIV on ART.[86]

The presentation of TB disease is influenced by the degree of immunodeficiency.[100-102] In people with HIV and CD4 counts >200 cells/mm^3, HIV-related TB generally resembles TB among people without HIV. Most people with or without HIV have disease limited to the lungs, and common chest radiographic manifestations are upper lobe infiltrates with or without cavitation.[103]

In people with HIV and CD4 counts <200 cells/mm^3, the chest radiographic findings of pulmonary TB are markedly different, with infiltrates showing no predilection for the upper lobes, and cavitation uncommon.[100,103,104] Normal chest radiographs can be seen in some people with respiratory symptoms and positive sputum cultures. Thoracic CT scans may demonstrate mild reticulonodular infiltrates despite a normal chest radiograph.[105]

With increasing degrees of immunodeficiency, extrapulmonary (especially lymphadenitis, pleuritis, pericarditis, and meningitis) or disseminated TB are more common. In people with HIV who are markedly immune-suppressed, TB can be a severe systemic disease with high fevers, rapid progression, and features of sepsis.[106] Clinical manifestations of extrapulmonary TB in people with HIV are not substantially different from those described in people without HIV. TB must be considered in disease processes involving any site in the body,[107] especially in those with central nervous system (CNS) disease, when early TB treatment is essential to improve outcomes.[108-111]

After initiation of ART, immune reconstitution can unmask subclinical TB disease, resulting in pronounced inflammatory reactions at the sites of infection (see Unmasking TB-IRIS below).

Diagnosis

Initial diagnostic testing for TB disease should be directed at the anatomic site of symptoms or signs (e.g., lungs, lymph nodes, urine, cerebrospinal fluid).[17] Pulmonary involvement is common at all CD4 counts.[99,112] The initial evaluation of a person suspected of having HIV-related TB should always include chest imaging, even in the absence of pulmonary symptoms or signs. However, chest radiography is an imperfect screen for pulmonary TB, particularly among individuals with advanced immunodeficiency who can have TB culture-positive sputum despite normal chest radiographs.[113,114] Therefore, sputum acid-fast bacilli (AFB) smear, nucleic acid amplification (NAA) testing, and AFB culture should be performed in people with HIV with symptoms of TB disease who have a normal chest radiograph, as well as in those with no pulmonary symptoms but evidence of TB disease elsewhere in the body.[17]

Sputum culture yield is not affected by HIV or the degree of immunodeficiency. Sputum smear-negative, culture-positive TB disease is common among people with HIV, particularly those with advanced immunodeficiency and non-cavitary disease.[115,116] NAA tests have a higher sensitivity for culture-positive disease than smear.[17,117] Smear and culture of three sputum specimens is recommended based on a large study in people with HIV that showed a 10% incremental yield for broth culture between the second and third specimens.[118] Additionally, up-front NAA testing for *M. tuberculosis* can expedite diagnosis.[17]

Lymph node involvement is common in HIV-related TB, and the combined yield of histopathology, smear, and culture from needle aspirates of enlarged lymph nodes is quite high.[119,120] While NAA testing on specimens other than sputum is an off-label use of the test, a positive NAA test result can be useful as evidence of extrapulmonary TB and for clinical decision-making.[121] Histopathologic findings also are affected by the degree of immunodeficiency. People with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With progressive immunodeficiency, granulomas become poorly formed or can be completely absent.[101,122]

Pleural fluid, pericardial fluid, ascites, and cerebrospinal fluid should be sampled if there is clinical evidence of involvement. Polymerase chain reaction (PCR) testing to aid with molecular identification of *M. tuberculosis* on formalin-fixed tissue is available through reference laboratories

and, in special situations, through the CDC. Clinical providers and pathologists should contact their state or local health department for consultation with the CDC (tbinfo@cdc.gov) and the CDC-funded TB Center of Excellence for assistance with referring specimens for evaluation. The yield of mycobacterial urine and blood cultures depends on the clinical setting; among people with HIV and advanced immunodeficiency, the yield of culture from these two readily available body fluids can be relatively high[101,107] and may allow definitive diagnosis and be the only source of an isolate for drug-susceptibility testing (DST).[123]

Nucleic-Acid Amplification Testing

NAA tests provide rapid diagnosis of TB, and some assays also provide rapid detection of drug resistance. NAA assays, if positive, are highly predictive of TB disease when performed on Acid-Fast Bacillus (AFB) smear-positive specimens. However, because nontuberculous mycobacterial infections (NTM) may occur in people with HIV with advanced immunodeficiency, negative NAA results in the setting of smear-positive specimens may indicate NTM infection and can be used to direct further workup and guide decisions about the need for respiratory isolation.

NAA tests are more sensitive than AFB smears, being positive in 50% to 80% of smear-negative, culture-positive sputum specimens[124,125] and up to 90% when three NAA tests are performed. Therefore, it is recommended that for all patients with suspected pulmonary TB, an NAA test be performed on at least one sputum specimen.[17,126] NAA tests also can be used on extrapulmonary specimens with the caveat that the sensitivity is often lower than with sputum specimens.[17] Importantly, a smear-negative specimen with a negative NAA test result does not rule out active TB disease.

The Xpert MTB/RIF assay is an automated NAA test that can detect both *M. tuberculosis* and mutations in the *rpoB* gene associated with rifampin resistance. It has been implemented widely in resource-limited settings with high TB prevalence and as a frontline TB diagnostic test in people with HIV.[127] This assay combines simple processing requirements in the laboratory and rapid turnaround (results within 2 hours). In a meta-analysis, the overall sensitivity and specificity of the Xpert MTB/RIF assay were 88% (95% confidence interval [CI], 83% to 92%) and 98% (95% CI, 97% to 99%), respectively. The assay is somewhat less sensitive among people with HIV overall,[128] however, this may be, in part, attributed to a higher prevalence of smear-negative disease in people with HIV.[129] In one key study from South Africa, the sensitivity of Xpert MTB/RIF a relationship with CD4 count was demonstrated, indicating higher sensitivity among people with HIV as the CD4 count declined below 500 cells/mm^3.[130] Importantly, patients in this study with the lowest CD4 count (<100 cells/mm^3) actually had higher rates of smear-positivity and higher markers of severe TB disease (C-reactive protein, anemia, and WHO symptom screen).

Xpert MTB/RIF sensitivity in extrapulmonary specimens is up to 95% in smear-positive specimens and 69% in smear-negative specimens.[131] Median sensitivity varied by specimen type, with higher yield from lymph nodes (96%), cerebrospinal fluid (85%), and gastric aspirates (78%) and lower yield from pleural fluid (34%) and other non-pleural serous fluids (67%). Xpert MTB/RIF also has been applied with excellent diagnostic accuracy to stool specimens in people with pulmonary TB,[132] which may provide an alternative for people with HIV who are being evaluated for TB and unable to expectorate.

The next-generation Xpert MTB/RIF Ultra improved the sensitivity of the existing test platform, but it is not currently approved by the U.S. Food and Drug Administration (FDA) or available in the

United States. Similarly, the Xpert MTB/XDR cartridge incorporates other drug-resistance targets that may be relevant for constructing a treatment regimen for drug-resistant TB, particularly in settings without access to conventional growth-based or sequencing-based DST, but is also not currently approved by the U.S. FDA and is unavailable in the United States (see Drug-Resistance Testing, below).[133]

Lipoarabinomannan (LAM)

LAM is an *M. tuberculosis* cell wall polysaccharide that can be detected in the urine of people with TB.[134-137] LAM has been shown to be more sensitive and specific as an adjunct diagnostic test in people with HIV with advanced immunosuppression. The Alere Determine TB LAM is a lateral flow strip applied to a urine sample and recommended by the WHO as an additional diagnostic test for TB among people with HIV.[138] Newer generation LAM assays have increased sensitivity and may be particularly useful in paucibacillary clinical specimens such as cerebrospinal fluid. In a study of 101 patients with suspected TB meningitis, 95 of whom were people with HIV, the SILVAMP TB LAM (Fujifilm) sensitivity from cerebrospinal fluid was 52% for definite or probable TB meningitis (with specificity of 98%), which compared favorably to the sensitivity of 55% for Xpert Ultra. LAM assays are not commercially available in the United States at this time.[139]

Drug-Resistance Testing

Evaluation for TB drug resistance should be considered in all people with HIV, especially those who meet any of the following criteria:

- Known exposure to a person with drug-resistant TB,
- Residence in a setting with high rates of primary drug-resistant TB,
- Persistently positive smear or culture results at or after 4 months of treatment, *or*
- Previous TB treatment, particularly if it was not directly observed or was interrupted for any reason.

Rapid molecular DST for rifampin (and isoniazid, if available) should be performed on the initial isolates from all patients suspected of having TB, because resistance to rifampin is associated with an increased risk of treatment failure, recurrent TB, and amplification of resistance to additional TB medications.[140,141]

The presence of multidrug-resistant TB (MDR TB; defined as resistance to at least isoniazid and rifampin) or extensively drug-resistant TB (XDR TB; defined as MDR TB with additional resistance to a fluoroquinolone and either bedaquiline or linezolid) is associated with a markedly increased risk of death.[142-144] Therefore, early identification of drug resistance, with appropriate adjustment of the treatment regimen based on both full molecular and conventional DST results, is critical to the successful treatment of TB disease and to curbing transmission of drug-resistant *M. tuberculosis*.[17]

For all patients with TB disease, phenotypic DST to first-line TB drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) should be performed, regardless of the source of the specimen. Given the alternative of a shorter drug-susceptible TB regimen containing moxifloxacin (see Treating TB Disease), public health laboratories in the U.S. may add routine moxifloxacin susceptibility testing as well. Molecular resistance testing should be performed, and resistance testing should be repeated if

sputum cultures remain positive for *M. tuberculosis* at or after 4 months of treatment or become positive again 1 month or longer after culture conversion to negative. Resistance testing for second-line TB medications (including bedaquiline, linezolid, clofazimine, pretomanid, cycloserine, ethionamide, and others) should be limited to specimens with resistance to first-line TB medications and should be performed in reference laboratories with substantial experience in these techniques.[126]

Conventional Growth-Based Drug-Susceptibility Testing

Conventional DST is used widely and has been validated for first-line drugs. The disadvantage of this technique, however, is that the combined turnaround time of a conventional broth or agar-based culture followed by DST may be as long as 8 weeks,[145] due to the slow growth of *M. tuberculosis*. During this time, people with drug-resistant TB may be receiving ineffective, empiric first-line TB therapy, which could allow ongoing transmission, further clinical deterioration, acquisition of additional drug resistance, and death, particularly in individuals with HIV.[144] Yet, for many second-line drugs used to treat MDR and XDR TB, conventional DST remains either the gold standard or the only available technique because molecular correlates of phenotypic drug resistance are incomplete.

Molecular Tests for Drug Resistance

Genotypic testing to identify mutations that confer drug resistance allows rapid detection of resistance. The relationship between these mutations and drug resistance has been studied for a number of TB medications.[146,147] Commercial NAA tests—such as Xpert MTB/RIF—identify resistance mutations associated with rifampin, and commercially available line probe assays (LPAs) identify genotypic resistance to other drugs.[129,148] All probe-based assays, including Xpert MTB/RIF and LPAs, should be confirmed with sequence-based tests and growth-based DST. For initial evaluation of drug resistance or confirmation of drug resistance identified by the aforementioned assays, the CDC Division of Tuberculosis Elimination has a Molecular Detection of Drug Resistance (MDDR) service that offers rapid sequencing-based testing for first-and second-line TB medications at no charge for providers evaluating people for drug-resistant TB. State TB programs and state laboratories also should be consulted for resistance testing options. Several assays can be performed on cultured isolates or directly on sputum specimens. Molecular resistance testing also can be performed on extrapulmonary specimens that are NAA-positive; if unable to be performed by local or state public health laboratories, this testing can be arranged through the CDC's Division of TB Elimination Laboratory (TBLab@cdc.gov).

In low TB prevalence settings—such as the United States—the positive predictive value for NAA tests of rifampin resistance is low.[149] False-positive rifampin resistance on Xpert MTB/RIF is associated with lower sputum bacillary burden (i.e., high cycle thresholds on Xpert).[150] Therefore, isolates with an initial reading of rifampin resistance by commercial NAA test should always undergo confirmatory testing (*rpoB* gene sequencing and phenotypic DST), with results taken into consideration for treatment decisions. Clinicians who suspect drug-resistant TB in a patient with HIV should make every effort to expedite a diagnosis and consult with their state TB program and then the CDC as needed.

Treating TB Disease

Treating Active TB Disease in People with HIV

- After collecting a specimen for culture and molecular diagnostic tests, empiric treatment should be initiated in people with HIV with clinical and radiographic presentation suggestive of HIV-related TB (AIII).
- DOT is recommended for all patients requiring treatment for HIV-related TB (AII).
- Please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB (below) for specific TB drug dosing recommendations and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations of ARV drugs when used with rifampin or rifabutin.
- Recommendations for monitoring during TB treatment and when to start ART in the context of TB treatment are described in the text.

For Drug-Susceptible TB

Preferred Therapy

Intensive Phase (8 weeks)

- Isoniazid plus (rifampin or rifabutin) plus pyrazinamide plus ethambutol plus pyridoxine 25–50 mg PO daily (AI)
- If molecular or phenotypic drug susceptibility reports show sensitivity to isoniazid and rifampin, then ethambutol may be discontinued before the end of 8 weeks (AI).

Continuation Phase (for Drug-Susceptible TB)

- Isoniazid plus (rifampin or rifabutin) plus pyridoxine 25–50 mg PO daily (AII)

Total Duration of Therapy

- Pulmonary, drug-susceptible, uncomplicated TB: 6 months (BII)
- Pulmonary TB and positive culture at 8 weeks of TB treatment, severe cavitary disease or disseminated extrapulmonary TB: 9 months (BII)
- Extrapulmonary TB with TB meningitis: 9–12 months (BII)
- Extrapulmonary TB in other sites: 6 months (BII)

Alternative Therapy (only for patients receiving an efavirenz-based ARV regimen; not recommended for extrapulmonary TB)

Intensive Phase (8 weeks)

- Isoniazid plus rifapentine 1,200 mg plus moxifloxacin 400 mg plus pyrazinamide plus pyridoxine 25–50 mg PO daily (AI).[a]

Continuation Phase (9 weeks)

- Isoniazid plus rifapentine 1,200 mg plus moxifloxacin 400 mg plus pyridoxine 25–50 mg PO daily (AI).

For Drug-Resistant TB

Empiric Therapy for Suspected Resistance to Rifamycin With or Without Resistance to Other Drugs

- Isoniazid[b] plus pyrazinamide plus ethambutol plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin[c]) (BII)

Resistant to Isoniazid

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

Resistant to Rifamycins With or Without Other Antimycobacterial Agents

Preferred Therapy

- For 14 days: pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg plus bedaquiline 400 PO daily, *followed by*
- For 24 weeks: pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily, *and* bedaquiline 200 mg PO three times per week
- Note: Omit moxifloxacin if resistant to fluoroquinolones (AI).

Alternative Therapy

- An individualized regimen including based on drug susceptibility test results and clinical and microbiological responses, to include ≥5 active drugs, and with close consultation with experienced specialists (BIII).

Duration

- 6–24 months (see Managing Drug-Resistant TB section below for discussion of treatment duration)

Treatment of TB for Pregnant People

- TB therapy should not be withheld because of pregnancy (AIII).
- Treatment of TB disease for pregnant people should be the same as for nonpregnant people, but with attention to the following considerations (AIII):
  - Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended (BIII).
  - If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB (AII). The decision regarding whether to include pyrazinamide in treatment regimens for a pregnant person should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.
  - Fluoroquinolones are typically not recommended for pregnant people because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero* (CIII). Fluoroquinolones can, however, be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing (BII).
  - Based on data derived from studies of streptomycin and kanamycin, and the theoretical risk of ototoxicity with *in utero* exposure to amikacin, aminoglycosides should be avoided during pregnancy, if possible (AIII).

TB-Associated IRIS

Preventing Paradoxical TB-IRIS

- In high-risk patients (i.e., starting ART within 30 days after TB treatment initiation and a CD4 count ≤100/mm^3) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (BI): prednisone 40 mg/day for 2 weeks, then 20 mg/day for 2 weeks

Managing Paradoxical TB-IRIS

- Paradoxical reaction/IRIS that is not severe may be treated symptomatically (CIII).
- For moderately severe paradoxical TB-IRIS, use of prednisone is recommended (AI).
- In patients on a rifampin-based regimen: prednisone 1.5 mg/kg/day for 2 weeks, then 0.75 mg/kg/day for 2 weeks
- In patients on a rifabutin plus boosted PI-based regimen: prednisone 1.0 mg/kg/day for 2 weeks, then 0.5 mg/kg/day for 2 weeks
- Taper over 4 weeks (or longer) based on clinical symptoms; a more gradual tapering schedule over 2 to 3 months is recommended for patients whose signs and symptoms have not improved or have worsened due to tapering (BIII).

Other Considerations in TB Management
• Adjunctive corticosteroid is recommended for patients with HIV-related TB involving the CNS (AII). • Dexamethasone has been used for CNS disease with the following dosing schedule: 0.3–0.4 mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day and taper by 1 mg/week; total duration of 12 weeks[d] • Despite the potential of drug–drug interactions, rifamycins remain the most potent TB drug and should remain as part of the TB regimen, unless a rifamycin-resistant isolate is detected or the patient has a severe adverse effect that is likely due to the rifamycin (please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB below and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations involving concomitant use of rifampin or rifabutin and different ARV drugs). • Intermittent rifamycin use can result in the development of resistance in patients with HIV and is not recommended (AI).

[a] This regimen was not studied and is not recommended for people who are pregnant, breastfeeding, <40kg, or who have most types of extrapulmonary TB (other than pleural TB or lymphadenitis).

[b] Many patients with rifampin resistance also have resistance to isoniazid. Susceptibility should be confirmed in any patient with rifampin resistance to determine if isoniazid can be included in the treatment regimen.

[c] Given the risk of ototoxicity and nephrotoxicity with aminoglycosides, use of amikacin should generally be restricted to bridging regimens, while awaiting availability of less toxic medications and/or results of drug-susceptibility testing.

[d] At doses above 16 mg, dexamethasone is a CYP3A4 inducer and can decrease certain ARVs that are substrates of CYP3A4 (e.g., DOR, RPV, and protease inhibitors). Consultation with a pharmacist is recommended.

Key: ARV = antiretroviral; CNS = central nervous system; DOT = directly observed therapy; IRIS = immune reconstitution inflammatory syndrome; LTBI = latent tuberculosis infection; PI = protease inhibitor; PO = orally

TB among people with advanced immunodeficiency can be a rapidly progressive and fatal illness if treatment is delayed. Therefore, after collection of available specimens for culture and molecular diagnostic tests, empiric treatment for TB is recommended in patients with clinical and radiographic findings suggestive of HIV-related TB **(AIII).**

Treatment of TB for people with HIV is the same as for individuals without HIV[151] although the current standard of care continues to evolve as new data emerge from clinical trials. Recommended dosing of drugs for treating active TB disease is summarized in the following table.

Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB

TB Drug	ARV Drugs	Daily Dose of TB Drug
Isoniazid	• All ARVs	5 mg/kg (usual dose 300 mg) Use INH with pyridoxine 25–50 mg PO daily
Rifampin[a,b]	• NRTIs (use TAF with caution[c]) • EFV 600 mg • DTG, RAL (twice daily), MVC without a strong CYP3A4 inhibitor (note: doses of these ARVs need to be adjusted when used with rifampin) • IBA, T-20	10 mg/kg (usual dose 600 mg)
	• DOR, ETR, EFV 400 mg, NVP, RPV (PO) • BIC, EVG/c, RAL (daily) • CAB/RPV (IM/PO) • HIV PIs	Not recommended

TB Drug	ARV Drugs	Daily Dose of TB Drug
	• LEN (SC/PO), FTR, MVC with a strong CYP3A4 inhibitor	
Rifabutin[a]	• NRTIs (use TAF with caution[c]) • ETR without boosted PIs • DOR and RPV (PO) (note: doses need to be adjusted when used with rifabutin) • DTG, RAL • MVC without a strong CYP3A4 inhibitor • IBA, T-20, FTR	5 mg/kg (usual dose 300 mg)
	• PIs with RTV • MVC with a strong CYP3A4 inhibitor	150 mg daily[e]
	• EFV	450–600 mg
	• ETR with boosted PIs • BIC, EVG/c • CAB/RPV (IM/PO) • PIs with COBI • LEN (SC/PO)	Not recommended
Rifapentine	• EFV • NRTIs (use TAF with caution[c])	1,200 mg/day for people weighing ≥40 kg
	• All other ARVs	Not recommended
Pyrazinamide	• All ARVs	Weight-based dosing • *40–55 kg*: 1,000 mg • *56–75 kg*: 1,500 mg • *76–90 kg*: 2,000 mg • *>90 kg*: 2,000 mg[f]
Ethambutol	• All ARVs	Weight-based dosing • *40–55 kg*: 800 mg • *56–75 kg*: 1,200 mg • *76–90 kg*: 1,600 mg • *>90 kg*: 1,600 mg[f]
Moxifloxacin	• All ARVs	• 400 mg daily for those weighing ≥40 kg

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

[b] Higher doses may be needed in the treatment of TB meningitis. Expert consultation is advised.

[c] If TAF and rifamycins are coadministered, monitor for HIV treatment efficacy. Note that FDA labeling recommends not to coadminister. See text below and Table 4 for more information.

[e] Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150 mg three times per week dosing together with RTV-boosted PIs. May consider therapeutic drug monitoring (TDM) when rifabutin is used with an RTV-boosted PI and adjust dose accordingly.

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

Note: For drug-drug interaction information between antiretrovirals and anti-TB drugs for treatment of drug-resistant TB, see the Adult and Adolescent Antiretroviral Guidelines.

Key: ARV = antiretroviral; BIC = bictegravir; BID = twice a day; CAB = cabotegravir; COBI = cobicistat; DOR = doravirine; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; FTR = fostemsavir; IBA = ibalizumab; IM = intramuscular; INH = isoniazid; LEN = lenacapavir; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SC = subcutaneous; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TB = tuberculosis; TDM = Therapeutic Drug Monitoring

The preferred regimen for drug-susceptible TB includes a 2-month (8-week) intensive phase of isoniazid, rifampin, ethambutol, and pyrazinamide **(AI).** Ethambutol can be discontinued when susceptibility to isoniazid and rifampin has been confirmed. Thereafter, isoniazid and a rifamycin are used in the continuation phase of therapy, generally recommended as an additional 4 months (18 weeks) of treatment for uncomplicated TB **(AI).**[151] Extension of therapy to 9 months is recommended for patients who have a positive sputum culture after 2 months of treatment or severe cavitary or disseminated extrapulmonary disease **(BII).**

A recently completed large, randomized clinical trial that enrolled 2,516 participants at 34 clinical sites in 13 countries established that a 4-month regimen of 2 months (8 weeks) of rifapentine, moxifloxacin, isoniazid, and pyrazinamide followed by 2 months (9 weeks) of rifapentine, moxifloxacin, and isoniazid was as effective as the standard 6-month regimen of isoniazid, rifampin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampin for an additional four months.[152] In this study, the four-month regimen was non-inferior to the control regimen in both the microbiologically eligible and the assessable populations, with unfavorable outcome rates of 15.5% vs. 14.6% (95% CI, -2.6 to 4.5) and 11.6% vs. 9.6% (95% CI, -1.1 to 5.1) respectively. Additionally, the four-month regimen had slightly lower rates of grade 3 or higher adverse events than the control arm. While participants with HIV were included in the trial, the only antiretroviral therapy regimen allowed during the study was efavirenz-containing.[153] This four-month regimen is now recommended as an alternative option for people with and without HIV who are 12 years of age or older **(AI).** It is not recommended for children under 12 years of age, pregnant people, people with extrapulmonary TB, or people with HIV who are taking a non-efavirenz-based antiretroviral regimen **(AI)**.[154] The trial also evaluated a four-month regimen with the same high dose of rifapentine but without moxifloxacin, which was found to be inferior to the control arm.

If rapid DST results indicate resistance to rifampin, with or without resistance to other drugs, an initial MDR TB regimen, as indicated below, should be used **(BIII)** and adjusted as molecular sequencing and conventional DST results become available.

Directly Observed Therapy (DOT)

DOT monitored by trained health care workers, who can be community-based or clinic-based, is recommended for all people with HIV-related TB **(AII).** Digital technology—such as video-DOT and pill sensors—may be useful alternatives to clinic-based or health care worker–based DOT.[155-160] The likelihood of treatment success is further enhanced with comprehensive case management; assistance with housing and other social support; and, if needed, assistance to help people establish or re-engage with HIV care.[151]

Dosing and Duration of Therapy

Although intermittent dosing (administration less often than daily) facilitates DOT, regimens that included twice- or thrice-weekly dosing during the intensive or continuation phase have been

associated with an increased risk of treatment failure or relapse with acquired drug resistance to the rifamycin class, particularly in people with HIV.[161-169] Intermittent rifamycin use can result in the development of resistance in patients with HIV and is not recommended **(AI).** Therefore, daily therapy is recommended during both the intensive and continuation treatment phases **(AII).**[151,167,168,170]

Earlier recommendations[171] for TB treatment in people without HIV indicated that therapy should be based on the number of doses received rather than the duration of therapy. However, no data substantiate the minimum number of doses needed within a specified time interval in people with HIV.[151] Every effort should be made to ensure that people with HIV receive daily therapy as previously described.

The optimal duration of TB treatment for people with HIV and drug-susceptible TB disease has not been fully established. In general, the outcomes of 6-month regimens given as DOT to people with HIV have been favorable.[2,151] A 1998 randomized but underpowered trial in the United States showed excellent and comparable outcomes of TB therapy among people with HIV assigned to 6 months or 9 months of therapy.[172]

Two trials in high-burden settings showed a higher risk of recurrent TB among people treated with 6 months of therapy than among those assigned to 9-month[161] or 12-month regimens.[173] However, the applicability of these two trials to low-burden settings—such as the United States—and in the context of universal ART is uncertain. In people with HIV receiving an efavirenz-based ART regimen, the 4-month alternative regimen of rifapentine, moxifloxacin, isoniazid, and pyrazinamide previously described was not associated with a higher rate of recurrent TB compared to the standard of care arm after follow-up out to at least 18 months post-TB treatment initiation.[152,154] Whether outcomes with this 4-month regimen will be similar to standard 6-month anti-TB therapy in people with HIV treated with non-efavirenz-based ART is not known. Additional TB treatment shortening trials using alternative strategies in participants with HIV and TB coinfection are ongoing.

Treatment of TB Meningitis

With regard to the treatment of tuberculous meningitis, data regarding optimal drugs and doses to use are sparse. Many experts suggest that TB meningitis should be treated for an extended period of 9 to 12 months, but there is no evidence to support this recommended treatment duration.[174] Recent clinical trials have suggested that the use of higher rifampin doses (up to 30–35 mg/kg/day) or the addition of fluoroquinolones or linezolid to initial treatment for TB meningitis may be beneficial, but the data are limited, particularly in people with HIV, and are insufficient to support a clear recommendation at this time.[175-183] Adjunctive corticosteroid therapy is recommended for all individuals who have TB involving the CNS **(AII)** including those with HIV, as indicated below.

Adjunctive Corticosteroid Use in TB Treatment

Several clinical trials have demonstrated that adjunctive corticosteroid therapy increases survival overall for people with TB meningitis, improves treatment effectiveness, and reduces adverse event rates. These trials, however, either excluded people with HIV or were underpowered for detecting statistically significant outcome benefits in that group.[111,184,185] A recent clinical trial compared adjunctive corticosteroids to placebo in people with HIV—the majority of whom had advanced HIV (52% of participants had a CD4 ≤50 cells/mm^3)—and failed to find a statistically significant benefit (HR for death 0.85 [95% CI, 0.66–1.10]).[186] The trial was powered to detect a 31% improvement in

survival and it is possible that corticosteroids have a more modest effect. Importantly, the study found no evidence of harm with corticosteroids and, given the high morbidity and mortality associated with TB meningitis, adjunctive corticosteroids are still recommended in people with HIV and TB meningitis. Dexamethasone should be administered in a dose of 0.3 mg/kg/day to 0.4 mg/kg/day for 2 to 4 weeks, then tapered by 0.1 mg/kg per week until a dose of 0.1 mg/kg is reached, then 4 mg per day and tapered by 1 mg/week) for a total duration of 12 weeks **(BII).**[111,151]

TB involving the CNS is currently the only organ system manifestation for which corticosteroids are recommended.[151] Adjunctive corticosteroid therapy is **not recommended** in the treatment of TB pericarditis **(AI).** In a randomized trial that compared adjunctive prednisolone with placebo—each administered for 6 weeks in individuals with tuberculous pericarditis, with and without HIV—prednisolone was not associated with a significant reduction in the composite endpoint of death, cardiac tamponade, or constrictive pericarditis. Those receiving prednisolone also had a higher incidence of some cancers.[187] A Cochrane review similarly found no mortality benefit from adjunctive corticosteroids and a nonsignificant reduction in constrictive pericarditis. Notably, however, <20% of people with HIV in the trials analyzed were receiving ART.[188] No trials have been conducted comparing different doses and treatment durations of adjunctive corticosteroids.

Special Considerations Regarding ART Initiation

The preponderance of data from several large randomized trials in people with HIV and TB, as well as subsequent systematic reviews and meta-analyses, supports the recommendation that ART should not be withheld until completion of TB treatment **(AI).**[108,189-196] ART is recommended for all people with HIV and TB **(AI).** For ART-naive patients, ART should be started within 2 weeks after TB treatment initiation in those with CD4 count <50 cells/mm^3 when TB meningitis is not suspected **(AI).** For ART-naive patients with higher CD4 cell counts, ART should be started within 2-8 weeks of starting anti-TB treatment when TB meningitis is not suspected **(AI).** For ART-naïve patients with TB meningitis, ART should be started once the TB meningitis is under control—with either clinical improvement or improvement in CSF parameters—after at least 2 weeks of anti-TB treatment, to reduce the risk of immune reconstitution causing life-threatening inflammation in a closed space **(AIII).** Rifamycin-associated drug interactions should be considered when selecting the ARV drug regimen. Preemptive prednisone therapy should be offered to patients starting ART within 30 days after TB treatment initiation, have a CD4 count ≤100/mm^3, are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B **(BI)** (see TB-Associated IRIS below for details).[197]

American Thoracic Society (ATS)/CDC/Infectious Diseases Society of America (IDSA) guidelines recommend that people with TB meningitis should not start ART before 8 weeks of TB treatment is completed, regardless of CD4 count, based primarily on a randomized trial in 253 people with HIV and TB meningitis conducted in Vietnam. This trial compared immediate ART within 7 days of starting TB treatment with delayed ART started two months after starting TB treatment.[151,193] The study showed no difference in mortality or TB outcomes, but those receiving immediate ART had a higher rate of severe adverse events. It is unclear whether the study's findings are generalizable to higher-resourced settings with access to frequent monitoring and adjustment of dosing. We recommend that for ART-naive people with HIV and TB meningitis, ART should be started once the TB meningitis is under control, after at least 2 weeks of anti-TB treatment **(AIII).** The greatest risk of early ART is the occurrence of intracerebral TB-IRIS after starting ART, which has been reported in up to 50% of people with HIV and TB meningitis and may increase morbidity and mortality[198] (although mortality was similar in both early and delayed ART arms in the only randomized trial

completed to date).[193] However, adjunctive corticosteroid therapy is recommended for all people with HIV and TB meningitis **(AII)** and precludes the need for pre-emptive use of prednisone to prevent IRIS. Whether the corticosteroid regimen recommended as adjunctive therapy for TB meningitis also further reduces the risk of TB IRIS and its consequences has not been evaluated.

In summary, early ART initiation requires close collaboration between HIV and TB care clinics, expertise in the management of ARV regimen selection, close monitoring, potential adjunctive corticosteroid therapy, and support and adherence services. The prevention and management of IRIS are discussed in detail below (see TB-Associated IRIS, below).

When TB occurs in people already on ART, treatment for TB must be started immediately **(AIII),** and ART should be modified to reduce the risk of drug interactions and to maintain virologic suppression. When TB occurs in the setting of virologic failure, ART drug-resistance testing should be performed, and intensified adherence counseling should be provided. A new ARV regimen may be required to achieve virologic suppression and minimize drug interactions with the anti-TB regimen.

Drug–Drug Interactions in the Treatment of HIV-Related TB

Dolutegravir in combination with two nucleoside(tide) reverse transcriptase inhibitors, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), abacavir, emtricitabine, or lamivudine, is the preferred regimen for co-treatment of HIV in most ART-naive people with TB **(AI).** This regimen can be managed with rifamycin-based anti-TB treatment (see Integrase Inhibitor section below for recommendations about dolutegravir dose adjustment if coadministered with rifampin). The following text summarizes the most important drug-drug interactions for antiretroviral drugs and anti-TB drugs to guide choices if other ART regimens are considered.

The rifamycin class of antibiotics is the cornerstone of effective and shorter-course first-line treatments for drug-sensitive TB. The currently available rifamycins (rifampin, rifabutin, and rifapentine) have clinically significant interactions with several ARV drugs. Most of these result from the rifamycin's potent induction of genes involved in the metabolism and transport of ARV agents, and these interactions should be taken into consideration before initiating therapy (see Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB above, and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines). Every effort should be made to include a rifamycin in the TB treatment regimen. Rifamycins remain the most potent drug class for TB treatment. Older regimens that included only 2 months of rifampin were associated with increased risks of treatment failure and TB recurrence among people with HIV-related TB.[199,200] If a rifamycin cannot be used, TB treatment duration must be extended, and treatment complexity increases substantially. Thus, individuals with rifamycin-susceptible *M. tuberculosis* isolates should be treated with a regimen that includes a rifamycin unless a serious adverse event is highly likely due to a rifamycin **(AIII).**

No clinical trial has specifically compared rifampin- and rifabutin-containing anti-TB regimens among people with HIV and TB taking ART. Rifabutin is generally regarded as a reasonable substitute for rifampin for the treatment of active TB disease in people with HIV who concurrently receive ARVs that have adverse drug interactions with rifamycins, because rifabutin is a less potent inducer of CYP3A4 than rifampin.[201] Although clinical trial data among people with HIV are limited to one small study, observational data among people with HIV, and several trials among people without HIV have found similar outcomes between those treated with rifampin or rifabutin.[202-205]

Nucleoside Reverse Transcriptase Inhibitor Backbone

Nucleoside(tide) backbone drugs—including tenofovir disoproxil fumarate (TDF), abacavir, emtricitabine, and lamivudine—can be given together with rifampin-containing TB treatment without dose adjustment. Tenofovir alafenamide (TAF), a substrate of drug transporters including P-glycoprotein, may be more likely to have drug–drug interactions than TDF. A study conducted among healthy volunteers without HIV showed that concentrations of intracellular tenofovir-diphosphate (TFV-DP) were higher with TAF/emtricitabine given with rifampin than with TDF given alone, suggesting that TAF may be given together with rifampin-containing TB treatment without dose adjustment.[206] Neither TDF nor TAF has been fully evaluated with rifabutin. In one small study, though, HIV virologic suppression was sustained during TAF-rifabutin co-administration.[207] In one study of TAF (as part of Biktarvy™) taken with daily high-dose rifapentine and isoniazid (1HP) for the treatment of LTBI, plasma tenofovir concentration was similar when TAF was taken alone versus together with 1HP, suggesting that TAF can be taken with rifapentine for short periods of time for prevention of TB.[208]

Non-Nucleoside Reverse Transcriptase Inhibitors—Efavirenz, Nevirapine, Etravirine, Doravirine, and Rilpivirine

One alternative co-treatment regimen for HIV-related TB disease is rifampin-based TB therapy with an ARV regimen of efavirenz (600 mg daily) plus two nucleoside(tide) analogues **(AII).** Studies in people with HIV and TB (including patients with higher body weight) have not shown a significant effect of rifampin-containing TB treatment on efavirenz plasma concentrations when used at the standard 600 mg per day dose in the majority of patients.[209-211] Given the preponderance of data and the excellent treatment outcomes of co-treatment with standard-dose efavirenz,[212,213] the 600 mg daily dose of efavirenz is recommended **(AII).** A small study among people with HIV found similar efavirenz concentrations when the 400 mg dose was taken with isoniazid and rifampicin versus when it was taken alone,[214] suggesting that, while not recommended, rifampicin-based TB treatment could be given with efavirenz without a need for efavirenz dose adjustment. Pharmacokinetic studies also support the use of the 600mg efavirenz dose with the new 4-month rifapentine-moxifloxacin-isoniazid-pyrazinamide regimen.[215]

Nevirapine is **not recommended** for HIV and TB co-treatment **(AII).**[216] The use of rifampin or rifapentine with doravirine, etravirine, or rilpivirine **is not recommended (AIII)** (see Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB, above, and the Tuberculosis/HIV Coinfection section of the Adult and Adolescent Antiretroviral Guidelines).

Some experts might consider substitution of rifabutin for rifampin with an appropriate dose adjustment of rifabutin (e.g., increasing to 450–600 mg daily when given with efavirenz) or of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) (e.g., increasing doravirine dosing to 100 mg twice daily and increasing oral rilpivirine to 50 mg daily), where appropriate,[217,218] for patients who require one of these NNRTIs;[219] however, IM rilpivirine, as used in long-acting ARV combinations, is **not recommended (AIII).** Rifabutin has not been evaluated in combination with rilpivirine, doravirine, or etravirine in people with HIV requiring treatment for active TB disease.

Integrase Inhibitors—Bictegravir, Dolutegravir, Elvitegravir, Raltegravir, and Cabotegravir

As indicated above, dolutegravir in combination with nucleoside reverse transcriptase inhibitors is the preferred option for co-treatment of HIV in most patients with TB **(AI).** A PK study in healthy volunteers showed that increasing the dose of dolutegravir to 50 mg twice a day with rifampin resulted in similar exposure to dolutegravir dosed 50 mg daily without rifampin, and that rifabutin 300 mg daily did not significantly reduce the area under the concentration curve of dolutegravir.[220] A Phase 2 trial in people with HIV and TB (INSPIRING) demonstrated that PK targets and virologic suppression were favorable at 24 and 48 weeks when dolutegravir 50 mg twice daily was administered with rifampin-containing TB treatment.[221] Dolutegravir is currently recommended at a dose of 50 mg twice daily when used together with a rifampin-containing TB regimen **(AI)** (and for two weeks following the completion of TB therapy), though randomized trials evaluating standard once-daily dosing are underway.[222] Dolutegravir should be used at a standard 50 mg once-daily dose when used with rifabutin **(AII).**

Another alternative co-treatment regimen is the combination of raltegravir-based ART, using raltegravir 800 mg twice daily, with standard rifampin dosing **(BI).**[223] Raltegravir concentrations are decreased significantly when co-administered with rifampin. Increasing the dose of raltegravir to 800 mg twice daily mitigates this PK interaction.[224] No PK or clinical data exist regarding the use of rifampin with the once-daily, extended-release 600 mg formulation of raltegravir, and co-administration **is not recommended (AIII).** Alternatively, raltegravir can be given with a rifabutin-containing TB regimen without a dose adjustment of either drug **(BII).**[225]

At this time, bictegravir **should not be used** together with rifamycin-containing TB treatment (rifampin, rifabutin, or rifapentine) **(AII).** A trial conducted among healthy participants without HIV evaluated bictegravir concentrations when given twice daily together with rifampin versus once daily alone.[226] Bictegravir trough concentrations, with the dose adjustment, were reduced by 80%. Although studied only with rifabutin, elvitegravir/cobicistat **is not recommended** with TB treatment that contains rifamycins **(AII).**[227,228] When given at steady-state with oral cabotegravir, rifampin decreased cabotegravir AUC by 59% in healthy volunteers.[229] The long-acting injectable formulation of cabotegravir has not been studied with rifamycins, but a pharmacokinetic model of long-acting, injectable, co-formulated cabotegravir-rilpivirine predicted that concurrent rifampin would decrease cabotegravir AUC by 41% to 46%.[230] As a result, oral and long-acting injectable cabotegravir **is not recommended for use** with rifampin or rifapentine **(AII).**[229] Oral and long-acting injectable cabotegravir may be coadministered with rifabutin **(AIII)**; however, long-acting injectable cabotegravir plus rilpivirine is not recommended for use with rifabutin due to the rilpivirine component **(AIII)**.

Protease Inhibitors with Rifampin or Rifabutin

Rifampin decreases the plasma concentrations and exposure of co-administered PIs by >75%.[231-234] One trial tested adjusted doses of ritonavir-boosted darunavir (1600/200 mg once daily and 800/100 mg twice daily) with rifampicin in people with HIV without TB.[235] The trial was stopped early because of high rates of hepatotoxicity, and trough concentrations in the once-daily group were reduced substantially. Thus, boosted darunavir **is not recommended for use** together with rifampin, even with dose adjustment **(AI).**

The effects of rifampin on lopinavir/ritonavir PK may be overcome by doubling the dose of lopinavir/ritonavir.[233,236] In a study of 71 people with HIV and TB, double doses of lopinavir/ritonavir were reasonably well tolerated in those on rifampin-based TB treatment.[205] Some experts would consider this an alternative when a PI-based ART regimen is required during TB treatment **(BI).** Regular monitoring of transaminases and HIV RNA is recommended when double-dose lopinavir/ritonavir is used (e.g., more frequently initially, then monthly once transaminase levels are stable on full dose).

Use of rifabutin with a boosted PI is preferred to the use of rifampin with double-dose PI in settings where rifabutin is readily available. Co-administered rifabutin has little effect on ritonavir-boosted lopinavir[205,237] or atazanavir[238] and only moderately increases concentrations of ritonavir-boosted darunavir[239] and fosamprenavir.[240] However, all PIs markedly increase serum concentrations of rifabutin (and one of its principal active metabolites, 25-O-desacetyl-rifabutin). Therefore, the dose of rifabutin must be decreased from 300 mg to 150 mg daily with all ritonavir-boosted PIs to avoid dose-related toxicity, such as uveitis and neutropenia **(AI).**[205,241] Coadministration of cobicistat-boosted PIs with rifabutin is not recommended **(AII)**.

In studies in people with HIV, rifabutin exposures were significantly lower when rifabutin was dosed at 150 mg three times weekly (with lopinavir/ritonavir) than when dosed at 300 mg daily without a PI, but concentrations of the active desacetyl metabolite were high.[242,243] Among people with HIV and TB, cases have been reported of acquired rifamycin resistance when doses of rifabutin of 150 mg three times weekly were co-administered with a boosted PI-based ARV regimen.[244,245] Based on available PK data, it is generally recommended that rifabutin be dosed 150 mg daily in patients who are on a ritonavir-boosted PI-containing ARV regimen **(AI).** However, given the potential risk of adverse events related to high levels of rifabutin's metabolite with this dosing strategy, close monitoring for toxicity (especially neutropenia and uveitis) is required.[205] Close monitoring of adherence to ART is essential because these reduced doses of rifabutin would be inadequate if the patient stopped taking the PI, putting the patient at risk of rifamycin-resistant TB.

Monitoring the Response to Therapy

Patients with pulmonary TB should have at least monthly sputum smears and cultures performed to document culture conversion on therapy (defined as two consecutive negative cultures) **(AII).** Sputum cultures from patients with susceptible TB typically convert to negative within 2 months of first-line TB therapy, although sputum culture conversion to negative may take longer for people with cavitary TB disease.[246-248] Sputum cultures that do not convert to negative at or after 4 months of therapy indicate treatment failure and should prompt further evaluation, including drug-resistance testing of available specimens.

In patients with extrapulmonary TB, obtaining follow-up specimens can be challenging, making it difficult to assess a bacteriologic response to therapy. Instead, the response typically is measured by an improvement in clinical and radiographic findings, but the frequency of such evaluations will depend on the infected sites, the severity of disease, and the ease with which specimens can be obtained.

Managing Suspected Treatment Failure

The causes of treatment failure include undetected primary drug resistance, inadequate adherence to therapy, incorrect or inadequate prescribed regimen, subtherapeutic drug levels due to malabsorption

or drug interactions, reinfection or mixed infection with drug-resistant *M. tuberculosis*, and acquired drug resistance.

People with suspected treatment failure should be evaluated with a medical history, physical exam, and chest radiograph to determine whether a clinical response to therapy has occurred despite the absence of sputum culture conversion. The initial culture results and drug-resistance tests, treatment regimen, and adherence to the regimen also should be reviewed. Some experts would perform therapeutic drug monitoring to determine if serum concentrations of the TB drugs are within expected ranges and adjust dosage as necessary.[151,249] In addition, samples from all available sites (e.g., sputum, blood, urine) should be collected for repeat culture and DST, and strong consideration should be given to performing rapid resistance testing on direct specimens or positive cultures to identify acquired drug resistance or mixed infection with a drug-resistant strain.

While awaiting results of repeat cultures and rapid resistance testing, broadening empiric TB treatment to include at least two additional second-line TB drugs should be considered in consultation with an expert in the field **(BIII).**

Adverse Drug Reactions in TB Patients on Antiretroviral Therapy

Retrospective observational studies reported an increased risk of adverse drug reactions in patients treated with concomitant ART and anti-TB therapy. Many of these studies, however, included patients receiving older antiretrovirals which carried more frequent side effects.[250] Three later randomized controlled trials reported similar rates of adverse events during anti-TB therapy with and without concomitant ART, suggesting no significant additive toxicity when ART is co-administered with anti-TB therapy.[153,189,191] Nevertheless, managing suspected adverse drug reactions in this setting is complex because assigning causality to individual drugs in patients on anti-TB drugs, ART, and other agents is very difficult.

Because first-line anti-TB drugs are more effective and have fewer toxicities than alternative drugs, first-line drugs (especially isoniazid and rifampin or rifabutin) should not be stopped permanently, unless strong evidence exists that a severe drug reaction was caused by a specific anti-TB drug **(AIII).** In such situations, decisions regarding rechallenge with first-line drugs and/or substitution of second-line drugs may be made in consultation with a specialist in treating TB disease in people with HIV.

Liver transaminases should be monitored at baseline and monthly for those with underlying risk factors for hepatotoxicity.[151] Drug-induced liver injury (DILI) can be caused by isoniazid, rifamycins, pyrazinamide, some ARV drugs, and trimethoprim-sulfamethoxazole (TMP-SMX). Anti-TB DILI is defined as an ALT elevation ≥3 times the upper limit of normal (ULN) in the presence of symptoms (e.g., fever, rash, fatigue, nausea, anorexia, jaundice); ALT ≥3 times the ULN plus total bilirubin 2 times the ULN in the absence of symptoms; or ALT ≥5 times the ULN alone in the absence of symptoms. An increase in ALT concentration occurs in approximately 5% to 30% of people treated with the standard four-drug anti-TB regimen,[97,251] but many of these have only transient, mild elevations of ALT.[97]

If the criteria for anti-TB DILI are fulfilled, all potentially hepatotoxic drugs should be stopped, and the patient should be evaluated immediately **(AIII)**. Serologic testing for syphilis and hepatitis A, B, and C should be performed, and the patient should be questioned regarding symptoms suggestive of biliary tract disease and exposures to alcohol and other hepatotoxins. At least three anti-TB drugs not

associated with hepatoxicity should be started (e.g., ethambutol, linezolid, and moxifloxacin or levofloxacin)[252] as a "bridging regimen" until the specific cause of hepatotoxicity can be determined and an alternative longer-term regimen constructed **(BIII)**.

After the ALT level returns to <2.5 times the ULN (or to near baseline for those with preexisting abnormalities), rechallenge with the hepatotoxic first-line anti-TB medications can be started by adding each drug individually to the bridging regimen at 7-day intervals. During the rechallenge, ALT levels should be monitored frequently.

Rechallenge was successful in almost 90% of people without HIV in one randomized controlled trial of different rechallenge regimens.[252] Because the rifamycins are a critical part of the TB regimen, they should be restarted first. Rechallenge with pyrazinamide is controversial because some studies have reported high rates of recurrent ALT elevations with reintroduction of the drug. Other studies, however, have demonstrated successful reintroduction of pyrazinamide,[253,254] and some experts would therefore recommend rechallenge with pyrazinamide in people with severe forms of TB (e.g., meningitis or disseminated TB).

Bridging drugs can be stopped once three active nonbridging drugs are reinstated successfully. Depending on the outcome of the rechallenge, the anti-TB therapy regimen and duration may need to be altered, in which case, expert consultation is advised. After successful anti-TB drug rechallenge (i.e., if appropriate), relevant ARV drugs and TMP-SMX may be restarted.

Cutaneous adverse drug reactions may occur with all anti-TB drugs, notably rifampin and isoniazid[255]; some ARV drugs, notably the NNRTIs; and TMP-SMX. If the rash is minor, affects a limited area, and causes pruritus, antihistamines should be administered for symptomatic relief and all anti-TB medications should be continued. If the rash is generalized or associated with fever or DILI or involves mucous membrane or desquamation, all anti-TB medications, relevant ARVs, and TMP-SMX should be stopped. When the rash improves substantially, the TB drugs should be restarted as described in the section on DILI above. If the rash recurs, the last drug that had been added should be stopped and the TB regimen modified. Thereafter, if appropriate, relevant ARV drugs and TMP-SMX may be restarted.

Managing Drug-Resistant TB

Although drug-resistant TB represents a small fraction of the TB cases in the United States, the increasing number of people with drug-resistant TB globally plus the high proportion of TB cases in the United States in people who are from TB-endemic areas make it increasingly likely that local TB programs will be faced with this complex disease. The most active and effective TB drugs are those used in first-line TB treatment regimens. When resistance to these medications develops, alternative combinations of TB medications must be used, but clinical trial data on their optimal use are limited, and most recent studies have been conducted primarily in TB-endemic resource-constrained settings.

In the United States, approximately 7% of people with TB have baseline isoniazid mono-resistance.[256] Growing evidence demonstrates an increased risk of treatment failure associated with isoniazid monoresistance,[257] particularly in people with HIV and TB.[258] For people with isoniazid monoresistance, it is recommended that a fluoroquinolone (levofloxacin or moxifloxacin) be substituted for isoniazid and given together with rifampin or rifabutin, pyrazinamide, and ethambutol for 6 months **(BII).**[93,259-261] Though rifampin reduces concentrations of moxifloxacin by 20% to 40%, there is no clinical evidence that a moxifloxacin dose adjustment improves outcomes.[262-264]

The treatment of rifampin-resistant (RR) and MDR TB (resistance to both isoniazid and rifampin) is an area of active investigation and is evolving rapidly. Historically, RR/MDR TB has been treated with individualized regimens taking into account the results of drug resistance testing and prior treatment exposure. In 2019, ATS, CDC, IDSA, and the European Respiratory Society (ERS) issued MDR TB treatment guidelines recommending a fully oral regimen consisting of at least 5 active drugs for most patients with drug-resistant TB, including people with HIV.[93]

Since the publication of the 2019 guidelines, however, several clinical trials have examined the efficacy and safety of a 6-month, all-oral regimen comprised of bedaquiline, pretomanid, and linezolid ("BPaL"). Pretomanid is a novel oral antimycobacterial agent that was approved by the FDA in 2019 exclusively as part of the BPaL regimen. The initial study ("Nix-TB") on which approval was based, was a single-arm study in 109 patients, of whom 51% were people with HIV.[265] Although the study had no control arm, 90% of participants had a favorable outcome. High rates of peripheral neuropathy were seen in Nix-TB study participants, and this was attributed to the high dose of linezolid used (1200 mg daily). The follow-up ZeNix study (n=181) compared outcomes of patients receiving the BPaL regimen at different linezolid doses and showed similarly favorable outcomes with a lower dose of 600 mg daily.[266] The TB-PRACTECAL study compared a regimen in which moxifloxacin was added to BPaL (aka "BPaLM") to longer injectable-based regimens, which were the standard of care at the time.[267,268] In modified intention-to-treat analyses, 121 of 138 (88%) participants in the BPaLM arm achieved treatment success compared with 81 of 137 (59%) of those receiving standard of care. Disease recurrence occurred in one participant in the BPaLM group (n=151) and four in the BPaL group (n=123); new resistance to bedaquiline was observed in the BPaL group in isolates from three of four recurrences, with no new resistance to other drugs in the regimens.[267]

The BPaL and BPaLM regimens have been used in the United States, and treatment outcomes thus far have been very successful among 152 patients with culture-positive pulmonary TB, most of whom received the 600 mg daily dose of linezolid.[269,270] Three recurrences after treatment completion were reported among 116 who received BPaL and none among 36 patients who received BPaLM.

Based on these data, **BPaLM is recommended as the preferred therapy for people with HIV with pulmonary RR-TB and without known resistance to the component medications (AI).**[271] Patients with RR-TB with fluoroquinolone resistance should receive BPaL without moxifloxacin **(AI)**. This recommendation is similar to that of WHO, which conditionally recommends both the BPaL and BPaLM regimens to patients ≥15 years of age with RR-TB who have not had previous exposure or resistance to the drugs in the regimen.[272] BPaLM and BPaL regimens should be given for a total of 26 weeks (6 months) **(AI).** Treatment should be extended up to a total of 39 weeks (9 months) if sputum cultures are positive between months 4 and 6 **(AI)**.

For patients who have not been included in BPaL or BPaLM studies—such as those with extrapulmonary TB or those with known or suspected resistance to bedaquiline, pretomanid, or linezolid—we recommend an individualized regimen consisting of at least 5 active drugs, based on the results of resistance testing and prior treatment exposure **(AI)**. Component medications should be selected using the ranking outlined in the ATS/CDC/IDSA/ERS guidelines.[93] When possible, an initial individualized regimen should contain bedaquiline, linezolid, a fluoroquinolone (levofloxacin or moxifloxacin), clofazimine, and a D-alanine analog (cycloserine or terizidone). All remaining drugs should be used to complete the regimen only when the recommended drugs cannot be used. Kanamycin and capreomycin are no longer recommended due to the increased risk of treatment

failure and relapse with their use.[273] Such an association was not seen for amikacin, which may be used when other, less toxic drugs cannot be used. The duration of therapy with such a regimen will depend on the component drugs and the patient's response to therapy. The ATS/CDC/IDSA/ERS guidelines currently recommend a treatment duration of 15 to 24 months *after culture conversion* when using an individualized regimen, although these guidelines are currently undergoing revision.[93] Several clinical trials have examined different regimens with total durations as short as 9 months and show TB treatment success rates comparable to or better than longer duration therapy.[274-278] Consultation with an expert who has experience managing drug-resistant TB is advised.

An important concern regarding BPaL(M) regimens is the growing prevalence of bedaquiline resistance and the lack of widespread availability of phenotypic second-line TB drug susceptibility testing.[279,280] Rapid molecular testing with confirmatory sequencing for fluoroquinolones and first-line drugs should ideally be performed prior to the initiation of treatment for RR/MDR TB; phenotypic testing should also be undertaken. This testing, as well as susceptibility testing for second-line agents, is available at many local or state public health laboratories or through the CDC's Molecular Detection of Drug Resistance (MDDR) service. To submit a sample for the MDDR service, complete the CDC's MDDR Request Form.

Importantly, as with all TB drugs, there is incomplete concordance between purported bedaquiline resistance-conferring mutations and phenotypic resistance.[281] If bedaquiline is being used, then bedaquiline phenotypic testing should be pursued, if available. Treatment with BPaLM need not be delayed, however, while awaiting the results of bedaquiline susceptibility testing. Of note, pretomanid resistance testing is not currently available.

For people with HIV with RR-TB, several important drug–drug interactions occur between bedaquiline and some ARV drugs. Specifically, efavirenz decreases bedaquiline plasma concentrations.[282] For people with HIV with RR-TB, efavirenz **should not be used** concurrently with bedaquiline **(AI).** Lopinavir/ritonavir increases bedaquiline plasma concentrations approximately twofold when given at steady-state,[283,284] but this has not been associated with additional prolongation of the QT-interval or other adverse events.[285]

Given the options for regimen choice and individual drug dosing within regimens, as well as variations in local drug susceptibilities, the treatment of RR-TB should involve an expert with experience in treating drug-resistant TB.[267,269] If a local expert is not available through the public health department, clinicians and TB programs can contact the CDC (tbinfo@cdc.gov) and one of the CDC's TB Centers of Excellence for Training, Education, and Medical Consultation.

TB-Associated IRIS

TB-IRIS is a frequent, early complication of ART in people with HIV with active TB. The condition is thought to result from the recovering immune system driving inflammatory reactions directed at *M. tuberculosis* antigen present at sites of disease.[286-288] TB-IRIS is characterized by excessive local or systemic inflammation. Two forms of TB-IRIS are recognized: paradoxical TB-IRIS and unmasking TB-IRIS. Proposed clinical case definitions for these syndromes have been published.[289]

Paradoxical TB-IRIS

Paradoxical TB-IRIS occurs in people who are diagnosed with active TB disease before starting ART. Typically, people experiencing paradoxical TB-IRIS have had clinical improvement on TB

treatment before starting ART, and within the first 1 to 4 weeks of ART (though sometimes later), they develop new or recurrent symptoms and worsening or recurrent clinical and radiologic features of TB. Common and important manifestations of paradoxical TB-IRIS include fevers, new or enlarging lymphadenopathy, and new or worsening pulmonary infiltrates. Mortality due to paradoxical TB-IRIS is uncommon,[287,290] but life-threatening manifestations include enlarging cerebral tuberculomas, meningitis, enlargement of pericardial effusions causing cardiac tamponade, extensive pulmonary involvement with respiratory failure, nodal enlargement causing airway obstruction, and splenic rupture due to rapid enlargement.[287,291,292] In people with disseminated TB, hepatic TB-IRIS is common, manifesting with nausea and vomiting, tender hepatic enlargement, cholestatic liver function derangement, and occasionally jaundice.[288,293] A liver biopsy often reveals granulomatous hepatitis.[294] Hepatic TB-IRIS may be difficult to differentiate from drug-induced liver injury.

Paradoxical TB-IRIS is relatively common among patients starting ART while on TB treatment. A meta-analysis of 40 studies reported a pooled incidence of TB-IRIS of 18% in adults with HIV-associated TB initiating ART, with death attributed to TB-IRIS in 2% of the cases.[295] The onset of paradoxical TB-IRIS symptoms is typically between 1 to 4 weeks after ART is initiated.[296-301] The syndrome lasts for 2 to 3 months on average,[300,302] but in some cases, symptoms may continue for several more months, and in rare cases, local manifestations may persist or recur over a year after onset.[289,302,303] In such cases of prolonged TB-IRIS, manifestations usually include suppurative lymphadenitis and abscess formation.

The most consistently identified risk factors for paradoxical TB-IRIS are a low CD4 count at the start of ART, especially a CD4 count[239,244] <100 cells/mm^3;[299,304] high HIV viral load before ART[305,306]; disseminated or extrapulmonary TB[291,298,300,304]; and a short interval between starting TB treatment and initiating ART, particularly if ART is started within the first 1 to 2 months of TB treatment.[291,297,299] Although early ART increases the risk for TB-IRIS, ART should be started within 2 weeks of TB diagnosis in patients with CD4 counts <50 cells/mm^3 and within 2 to 8 weeks of TB diagnosis in those with higher CD4 counts, as previously discussed, to reduce the risk of HIV progression and death (see Special Considerations Regarding ART Initiation, above) **(AI)**.[295]

The diagnosis of paradoxical TB-IRIS may be challenging, and no definitive confirmatory test exists. Thus, diagnosis relies upon a characteristic clinical presentation: improvement of TB symptoms with treatment before ART, deterioration with inflammatory features of TB soon after starting ART, or demonstration of a response to ART (CD4 rise and/or HIV viral load reduction). In addition, diagnosis of paradoxical TB-IRIS requires investigations to exclude alternative causes for deterioration, particularly another opportunistic infection, undetected TB drug resistance, or other cause of treatment failure (see Managing Suspected Treatment Failure, above).[307]

Prevention of Paradoxical TB-IRIS

Pre-emptive treatment with prednisone may prevent or reduce the consequences of TB-IRIS. A randomized, double-blind, placebo-controlled trial of prednisone (40 mg/day for 2 weeks, then 20 mg/day for 2 weeks) versus placebo in 240 ART-naive adults at high risk of developing IRIS at the time of ART initiation demonstrated that preemptive prednisone treatment was effective in reducing the risk of paradoxical TB-IRIS.[197] The incidence of TB-IRIS was 47% in the placebo arm and 33% in the prednisone arm (RR = 0.70; 95% CI, 0.51–0.96). No excess risk was observed for malignancy, severe infections, or other complications. Based on these study findings, preemptive prednisone therapy should be offered for high-risk patients as defined in this study (i.e., starting ART

within 30 days after TB treatment initiation and a CD4 count ≤100/mm^3) who are responding well to TB therapy and who do not have rifampin resistance, Kaposi sarcoma, or active hepatitis B (**BI)**.

Managing Paradoxical TB-IRIS

Most cases of paradoxical TB-IRIS are self-limiting. Many people require symptomatic therapy (e.g., analgesia, anti-emetics), and if symptoms are significant, anti-inflammatory therapy is appropriate. Clinicians may use non-steroidal anti-inflammatory drugs to provide symptomatic relief in patients with mild TB-IRIS **(CIII)**. Needle aspiration of enlarging serous effusions, large tuberculous abscesses, or suppurative lymphadenitis may also provide symptom relief **(CIII)**. Repeated aspirations may be required as abscesses and effusions often re-accumulate.[291]

In people with moderately severe paradoxical TB-IRIS, treatment with prednisone is recommended **(AI)**. One randomized, placebo-controlled trial among patients with moderately severe paradoxical TB-IRIS showed that treatment with prednisone (1.5 mg/kg/day for 2 weeks followed by 0.75 mg/kg/day for 2 weeks) resulted in a reduction in a combined endpoint of days hospitalized plus outpatient therapeutic procedures.[308] In that study, however, 4 weeks of prednisone treatment was insufficient in a subset of participants. If clinical assessment indicates that signs and symptoms have not improved or have worsened as corticosteroids are tapered, a more gradual tapering of steroids over 2 to 3 months is recommended **(BIII)**.[308] Patients on prednisone experienced more rapid symptoms and radiographic improvement. No reduction in mortality was demonstrated, but immediately life-threatening cases (e.g., those with neurological involvement) were excluded from this study.[111,292,308] Rifampin increases the clearance of prednisolone (the active metabolite of prednisone),[309] but no such effect is expected with rifabutin; dosing of prednisone should therefore be adjusted in patients receiving rifampin or rifabutin-containing regimens (See the Treating TB-Associated IRIS section of the Treating TB Disease table). Corticosteroids should be avoided in people with Kaposi sarcoma because life-threatening exacerbations can occur. Case reports have been published of patients with steroid-refractory and prolonged IRIS or paradoxical reactions responding to TNF-blockers, IL-1 inhibitors, JAK inhibitors, or thalidomide.[310-317]

Unmasking TB-IRIS

Unmasking TB-IRIS may occur in people who have unrecognized TB (because TB is either symptomatic or it has eluded diagnosis) at the start of ART. These people may present with a particularly accelerated and inflammatory presentation of TB in the first weeks of ART.[289] A common presentation is pulmonary TB with rapid symptom onset and clinical features similar to bacterial pneumonia with high fever, respiratory distress, sepsis syndrome, and consolidation on chest radiograph.[289,308,318-320] Focal inflammatory manifestations—such as abscesses and lymphadenitis— also may develop.[321] In cases of unmasking TB-IRIS, the treatment should be standard TB treatment and, if the manifestations are life-threatening, adjunctive corticosteroid therapy is recommended, although steroid use in this setting has not been studied in a clinical trial **(BIII).**

Prevention of Recurrent TB

Among patients receiving the same TB treatment regimen in the same setting, the risk of recurrent TB appears to be higher among those with HIV than among those without HIV.[322,323] In TB-endemic settings, much of the increased risk of recurrent TB appears to be due to the higher risk of re-infection with a new strain of *M. tuberculosis*, with subsequent rapid progression to TB disease.[324,325]

In settings with low rates of TB—such as the United States—recurrent TB due to re-infection is uncommon, even among people with HIV.[326]

Several interventions may decrease the risk of recurrent TB among people with HIV: longer TB treatment regimens, administering therapy daily throughout the course of the intensive and continuation phases, post-treatment isoniazid therapy, and use of ART. None of these interventions has been adequately evaluated in randomized trials in settings with low TB burdens. Post-treatment isoniazid (6–9 months of daily isoniazid therapy after the completion of standard multidrug therapy) has been shown to be effective in high-burden settings in which the risk of re-exposure is high,[327,328] suggesting that this intervention decreases the risk of re-infection. Post-treatment isoniazid **is not recommended** for patients in the United States or other low-burden settings due to a lack of evidence of effectiveness supporting a reduced risk of re-infection for these settings **(AIII).** Given that ART reduces the risk of initially developing TB disease, it is likely that ART also decreases the risk of re-infection with TB.

Special Considerations During Pregnancy

Pregnant people with HIV who do not have documentation of a prior negative TB screening test result or who are at high risk for repeated or ongoing exposure to individuals with active TB disease should be tested for TB during pregnancy **(AIII).** TB rates in pregnant and postpartum women are higher than in non-pregnant adults, after adjusting for age,[329] and this is likely due to pregnancy-related immunologic shifts.[330-334] Several studies have examined the performance of IGRAs for diagnosis of LTBI in pregnant women. In pregnant women with or without HIV, the test appears to perform well.[335,336] Longitudinal studies conducted in high-burden countries, however, suggest that test performance may be compromised in late pregnancy versus postpartum, especially at delivery.[337-343]

A clinical trial of isoniazid preventive therapy (IPT) among HIV-infected women in high TB prevalence settings (TB APPRISE) found increased adverse pregnancy outcomes in women treated with isoniazid during pregnancy compared to postpartum initiation of isoniazid.[344] Importantly, however, none of the women were close household TB contacts, and most of the women in the trial were IGRA-negative and were receiving efavirenz-based ART. Two smaller observational studies of isoniazid given to pregnant women with HIV in South Africa did not find an increased risk of adverse pregnancy outcomes with isoniazid.[345,346] Similarly, a study of participants in Botswana who became pregnant in a trial of 36 months of isoniazid for people with HIV also did not report increased adverse pregnancy outcomes.[347] A subsequent systematic review of the association of adverse pregnancy outcomes and isoniazid found inconsistent associations.[348] Among people enrolled in the BRIEF-TB study who became pregnant while taking isoniazid for TB prevention, first-trimester IPT exposure was associated with increased risk of fetal demise, though this association was attenuated when adjusted for covariates proximal to pregnancy outcome including ART use. [349]

Studies in individuals with HIV who are not receiving ART have shown a high risk of progression from LTBI to active TB disease (10% per year), and a high risk exists for maternal and infant mortality in pregnant women with HIV who have active TB disease.[350,351] Although the risk of progression from LTBI to active TB disease in individuals on ART is decreased significantly, risk in these individuals with HIV appears higher than in pregnant and postpartum people without HIV.[337,352] Pregnant people with HIV should be receiving ART both for their own health and for prevention of perinatal transmission **(AI).** In the United States, isoniazid preventive therapy is

recommended for pregnant women with HIV whose close household contacts include a person with active TB disease **(AI).** For those receiving effective ART and without recent TST or IGRA conversion or close household contacts with infectious TB, therapy for LTBI may be deferred until after delivery **(BIII).** The risk of isoniazid-associated hepatotoxicity may be increased in pregnancy and in the first 2 to 3 months post-partum.[344] Therefore, if isoniazid is prescribed, frequent monitoring is needed.[34] Pregnant people receiving isoniazid should receive daily pyridoxine supplementation **(AII)** because they are at risk of isoniazid-associated peripheral neuropathy.[151,353] Limited data exist on alternatives to isoniazid for LTBI therapy in pregnant people with HIV. In the IMPAACT 2001 study, pregnant women with and without HIV received 3HP and no serious adverse pregnancy outcomes were observed. Drug exposures were similar to non-pregnant adults, suggesting this regimen does not require dose adjustment in pregnancy.[354] Despite these promising data and although rifampin generally is considered safe in pregnancy, data on the use of rifapentine remain extremely limited and the use of rifapentine in pregnant people is not currently recommended **(BIII).**[355-357] The DOLPHIN Moms trial (NCT05122026) currently underway is examining the pharmacokinetics and safety of 3HP and 1HP in pregnant people with HIV who are virally suppressed on a dolutegravir-based regimen.

The diagnostic evaluation for TB disease in pregnant people is the same as for nonpregnant adults. It is important to recognize that standard symptom screens have lower sensitivity in pregnant women than in non-pregnant adults, and that some TB symptoms may be masked by common symptoms of pregnancy (e.g. poor appetite).[358-360] In addition to standard sputum testing, chest radiographs with abdominal shielding are recommended and result in minimal fetal radiation exposure.[361] An increase in pregnancy complications—including preterm birth, low birthweight, and fetal growth restriction—can be seen among pregnant women with either pulmonary or extrapulmonary TB not confined to the lymph nodes, especially when TB treatment is delayed until late in pregnancy.[34,330,333,335,336,339,344,351,362-366] Congenital TB infection has been reported, although it appears relatively uncommon; history of maternal infertility and acid-fast bacilli from placenta or endometrial biopsy may be found with this rare diagnosis.[367-372] While rare, congenital TB might be more common among children born to mothers with TB/HIV coinfection, especially when those children also have perinatally acquired HIV.[373,374]

TB therapy should not be withheld because of pregnancy **(AIII).** Treatment of TB disease should be the same for pregnant people and nonpregnant people, but with attention to the following considerations **(AIII):**

- Although isoniazid is not teratogenic in animals or humans, hepatotoxicity caused by isoniazid might occur more frequently during pregnancy and the postpartum period.[375] Monthly monitoring of liver transaminases during pregnancy and the postpartum period is recommended **(BIII).**
- Rifampin is not teratogenic in humans.
- Ethambutol is teratogenic in rodents and rabbits at doses that are much higher than those used in humans. No evidence of teratogenicity has been observed in humans. Ocular toxicity has been reported in adults taking ethambutol but changes in visual acuity have not been detected in infants exposed to ethambutol *in utero*.
- Pyrazinamide is not teratogenic in animals. The WHO and the International Union Against Tuberculosis and Lung Diseases have made recommendations for the routine use of pyrazinamide in pregnant individuals.[272,376] Pyrazinamide has been recommended for use in pregnant people in the United States, although data characterizing its safety in this setting are

limited and the CDC guidance suggests that clinicians consider the use of this agent based on individual patient considerations weighing benefit and risks.[151,377] If pyrazinamide is not included in the initial treatment regimen, the minimum duration of TB therapy with isoniazid, rifampin, and ethambutol should be 9 months for drug-susceptible TB **(AII).** The decision regarding whether to include pyrazinamide in treatment regimens for a pregnant person should be made after consultation among obstetricians, TB specialists, and the patient, while considering gestational age and likely susceptibility pattern of the TB strain.

Experience using the majority of the second-line drugs for TB during pregnancy is limited.[378-381] MDR TB in pregnancy should be managed in consultation with a specialist. In a small prospective study of pregnant patients who received second-line MDR/RR-TB regimens that contained bedaquiline or delamanid (including linezolid, clofazimine, amikacin, capreomycin, and kanamycin) 98% had successful treatment outcomes, and at least 81% of continued pregnancies resulted in live births with 68% normal birthweight neonates.[378] The following concerns should be considered when selecting second-line anti-TB drugs for use in pregnant people:

- **Bedaquiline:** Data on the use of bedaquiline in pregnancy are limited, but a study of 108 pregnant women from South Africa found an increased frequency of low birthweight (<2,500 g) among children exposed to bedaquiline *in utero* compared to those who were not exposed (45% vs. 26%; $P = 0.034$).[382] The median birthweight between the two groups, however, was not statistically significant (2690 vs. 2900 grams [$P = 0.18$]) and after 1 year, most children exposed to bedaquiline had gained weight and were doing well. Bedaquiline concentrations in breast milk may be as high or higher than concentrations in maternal plasma, which may have implications for the infant.[383,384]
- **Cycloserine:** No data are available from animal studies or reports of cycloserine use in humans during pregnancy.
- **Ethionamide** has been associated with an increased risk for several anomalies in rats after high-dose exposure, but not in mice or rabbits.[385-387] Case reports have documented cases of CNS defects in humans and hypothyroidism, but overall experience is limited with use during human pregnancy.[388] Ethionamide is likely present in the breast milk, which could be associated with thyroid issues in the infant. Thus, ethionamide should be avoided, unless its use is required on the basis of susceptibility testing **(CIII).**
- **Fluoroquinolones:** Because arthropathy has been noted in immature animals exposed to fluoroquinolones *in utero*, quinolones are typically not recommended for pregnant people or children aged <18 years **(CIII).** However, studies evaluating fluoroquinolone use in pregnant women did not find an increased risk of birth defects or congenital musculoskeletal abnormalities.[389-393] Furthermore, fluoroquinolones were used in a larger South African case series of MDR TB treatment in pregnancy with generally good outcomes.[382] Thus, fluoroquinolones can be used in pregnancy for drug-resistant TB if they are required on the basis of susceptibility testing **(BII).**[394]
- **Linezolid:** Animal studies of linezolid in pregnancy report decreased fetal body weight and increased fusion of costal cartilage.[395] There are few studies in human pregnancy, but linezolid has been used for the treatment of DR-TB in some high-burden countries.[378,382] In these case studies, monitoring complete blood counts for anemia and thrombocytopenia and advising iron supplementation has been recommended.[384,396]

- **Delamanid:** Delamanid appears to be safe in animal reproductive toxicity studies. It has been used in small cohorts of pregnant women for DR-TB with favorable outcomes.[378,397]
- **Pretomanid**: Animal studies of pretomanid do not indicate direct or indirect harmful effects with respect to embryo-fetal development. However, pretomanid has been associated with reproductive toxicity in animal models; specifically, reduced fertility in male rats.[398] There has been very limited use in human pregnancies. Therefore, pretomanid should be avoided in pregnancy until more data is available **(AIII)**.
- **Para-aminosalicylic acid** is not teratogenic in rats or rabbits.[377] In one study, a possible increase in limb and ear anomalies was reported among 143 infants delivered by women who were exposed to para-aminosalicylic acid during the first trimester of pregnancy.[399] No specific pattern of defects and no increase in the rate of defects have been detected in other human studies, indicating that this agent can be used with caution, if needed **(CIII).**
- **Aminoglycosides/polypeptides:** Streptomycin use has been associated with a 10% rate of vestibulocochlear nerve toxicity in infants exposed to the drug *in utero*; its use during pregnancy should be avoided, if possible **(AIII).** Hearing loss has been detected in approximately 2% of children exposed to long-term kanamycin therapy *in utero*; like streptomycin, this agent should typically be avoided, if possible **(AIII).** The fetus is at a theoretical risk for ototoxicity with *in utero* exposure to amikacin and capreomycin, but this risk has not been documented. Capreomycin is no longer recommended, but amikacin might be used as an alternative when an aminoglycoside is required for the treatment of MDR TB **(CIII).**

References

1. World Health Organization. Global tuberculosis report 2021. 2021. Available at: https://www.who.int/publications/i/item/9789240037021.

2. World Health Organization. Global tuberculosis report 2022. 2022. Available at: https://www.who.int/publications/i/item/9789240061729.

3. Filardo TD, Feng PJ, Pratt RH, Price SF, Self JL. Tuberculosis - United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(12):441-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35324877.

4. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000;30 Suppl 1:S5-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10770911.

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

6. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2021. 2021. Available at: https://www.cdc.gov/tb/statistics/reports/2021/table19.htm.

7. Drain PK, Bajema KL, Dowdy D, et al. Incipient and subclinical tuberculosis: a clinical review of early stages and progression of infection. *Clin Microbiol Rev*. 2018;31(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30021818.

8. Pai M, Behr MA, Dowdy D, et al. Tuberculosis. *Nat Rev Dis Primers*. 2016;2(16076). Available at: https://www.nature.com/articles/nrdp201676.

9. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320(9):545-550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2915665.

10. Selwyn PA, Sckell BM, Alcabes P, Friedland GH, Klein RS, Schoenbaum EE. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA*. 1992;268(4):504-509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1619742.

11. Moreno S, Baraia-Etxaburu J, Bouza E, et al. Risk for developing tuberculosis among anergic patients infected with HIV. *Ann Intern Med*. 1993;119(3):194-198. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8100693.

12. Antonucci G, Girardi E, Raviglione MC, Ippolito G. Risk factors for tuberculosis in HIV-infected persons. A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS

(GISTA). *JAMA*. 1995;274(2):143-148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7596002.

13. Markowitz N, Hansen NI, Hopewell PC, et al. Incidence of tuberculosis in the United States among HIV-infected persons. The Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1997;126(2):123-132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9005746.

14. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol*. 1974;99(2):131-138. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4810628.

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

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

17. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis*. 2017;64(2):111-115. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28052967.

18. Akolo C, Adetifa I, Shepperd S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2010(1):CD000171. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20091503.

19. Campbell JR, Winters N, Menzies D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. *BMJ*. 2020;368:m549. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32156698.

20. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011-2012. *PLoS One*. 2015;10(11):e0140881. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26536035.

21. Badje A, Moh R, Gabillard D, et al. Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial. *Lancet Glob Health*. 2017;5(11):e1080-e1089. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29025631.

22. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet*. 2014;384(9944):682-690. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24835842.

23. Temprano ANRS Study Group, Danel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med*. 2015;373(9):808-822. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26193126.

24. Ross JM, Badje A, Rangaka MX, et al. Isoniazid preventive therapy plus antiretroviral therapy for the prevention of tuberculosis: a systematic review and meta-analysis of individual participant data. *Lancet HIV*. 2021;8(1):e8-e15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33387480.

25. Golub JE, Saraceni V, Cavalcante SC, et al. The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. *AIDS*. 2007;21(11):1441-1448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17589190.

26. Holzman SB, Perry A, Saleeb P, et al. Evaluation of the latent tuberculosis care cascade among public health clinics in the United States. *Clin Infect Dis*. 2022;75(10):1792-1799. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35363249.

27. Wilson IB, Landon BE, Hirschhorn LR, et al. Quality of HIV care provided by nurse practitioners, physician assistants, and physicians. *Ann Intern Med*. 2005;143(10):729-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16287794.

28. Backus LI, Boothroyd DB, Phillips BR, et al. National quality forum performance measures for HIV/AIDS care: the Department of Veterans Affairs' experience. *Arch Intern Med*. 2010;170(14):1239-1246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660844.

29. Lee LM, Lobato MN, Buskin SE, Morse A, Costa OS. Low adherence to guidelines for preventing TB among persons with newly diagnosed HIV infection, United States. *Int J Tuberc Lung Dis*. 2006;10(2):209-214. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16499263.

30. Reaves EJ, Shah NS, France AM, et al. Latent tuberculous infection testing among HIV-infected persons in clinical care, United States, 2010-2012. *Int J Tuberc Lung Dis*. 2017;21(10):1118-1126. Available at: https://pubmed.ncbi.nlm.nih.gov/28911355/.

31. Fisk TL, Hon HM, Lennox JL, Fordham von Reyn C, Horsburgh CR, Jr. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *AIDS*. 2003;17(7):1102-1104. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12700468.

32. Girardi E, Palmieri F, Zaccarelli M, et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *AIDS*. 2002;16(14):1976-1979. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12351964.

33. Overton K, Varma R, Post JJ. Comparison of interferon-gamma release assays and the tuberculin skin test for diagnosis of tuberculosis in human immunodeficiency virus: a systematic review. *Tuberc Respir Dis (Seoul)*. 2018;81(1):59-72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29256218.

34. Centers for Disease Control and Prevention. Latent tuberculosis infection: a guide for primary health care providers. 2020. Available at: https://www.cdc.gov/tb/hcp/education/latent-tb-infection-guide-primary-care-providers.html?CDC_AAref_Val=https://www.cdc.gov/tb/publications/ltbi/default.htm.

35. Markowitz N, Hansen NI, Wilcosky TC, et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. *Ann Intern Med*. 1993;119(3):185-193. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8100692.

36. Auguste P, Tsertsvadze A, Pink J, et al. Comparing interferon-gamma release assays with tuberculin skin test for identifying latent tuberculosis infection that progresses to active tuberculosis: systematic review and meta-analysis. *BMC Infect Dis*. 2017;17(1):200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28274215.

37. Ho CS, Feng PI, Narita M, et al. Comparison of three tests for latent tuberculosis infection in high-risk people in the USA: an observational cohort study. *Lancet Infect Dis*. 2022;22(1):85-96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34499863.

38. Pettit AC, Stout JE, Belknap R, et al. Optimal testing choice and diagnostic strategies for latent tuberculosis infection among US-born people living with human immunodeficiency virus (HIV). *Clin Infect Dis*. 2021;73(7):e2278-e2284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32761083.

39. Cattamanchi A, Smith R, Steingart KR, et al. Interferon-gamma release assays for the diagnosis of latent tuberculosis infection in HIV-infected individuals: a systematic review and meta-analysis. *J Acquir Immune Defic Syndr*. 2011;56(3):230-238. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21239993.

40. Gray J, Reves R, Johnson S, Belknap R. Identification of false-positive QuantiFERON-TB Gold In-Tube assays by repeat testing in HIV-infected patients at low risk for tuberculosis. *Clin Infect Dis*. 2012;54(3):e20-23. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22057704.

41. Sosa LE, Njie GJ, Lobato MN, et al. Tuberculosis screening, testing, and treatment of U.S. health care personnel: recommendations from the National Tuberculosis Controllers Association and CDC, 2019. *MMWR Morb Mortal Wkly Rep*. 2019;68(19):439-443. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31099768.

42. Luetkemeyer AF, Charlebois ED, Flores LL, et al. Comparison of an interferon-gamma release assay with tuberculin skin testing in HIV-infected individuals. *Am J Respir Crit Care Med*. 2007;175(7):737-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17218620.

43. Talati NJ, Seybold U, Humphrey B, et al. Poor concordance between interferon-gamma release assays and tuberculin skin tests in diagnosis of latent tuberculosis infection among HIV-infected individuals. *BMC Infect Dis*. 2009;9:15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19208218.

44. Rangaka MX, Wilkinson KA, Glynn JR, et al. Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(1):45-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21846592.

45. Hill PC, Jackson-Sillah DJ, Fox A, et al. Incidence of tuberculosis and the predictive value of ELISPOT and Mantoux tests in Gambian case contacts. *PLoS One*. 2008;3(1):e1379. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18167540.

46. Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and prediction of active tuberculosis disease by a whole-blood interferon-gamma release assay in HIV-1-infected individuals. *Clin Infect Dis*. 2009;48(7):954-962. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19245343.

47. Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. *Am J Respir Crit Care Med*. 2008;177(10):1164-1170. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18276940.

48. Leung CC, Yam WC, Yew WW, et al. T-Spot.TB outperforms tuberculin skin test in predicting tuberculosis disease. *Am J Respir Crit Care Med*. 2010;182(6):834-840. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20508217.

49. Ledesma JR, Ma J, Zheng P, Ross JM, Vos T, Kyu HH. Interferon-gamma release assay levels and risk of progression to active tuberculosis: a systematic review and dose-response meta-regression analysis. *BMC Infect Dis*. 2021;21(1):467. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34022827.

50. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR Recomm Rep*. 2010;59(RR-5):1-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20577159.

51. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. 2011;8(1):e1000391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21267059.

52. Hamada Y, Lujan J, Schenkel K, Ford N, Getahun H. Sensitivity and specificity of WHO's recommended four-symptom screening rule for tuberculosis in people living with HIV: a systematic review and meta-analysis. *Lancet HIV*. 2018;5(9):e515-e523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30139576.

53. Stuck L, van Haaster AC, Kapata-Chanda P, Klinkenberg E, Kapata N, Cobelens F. How "subclinical" is subclinical tuberculosis? An analysis of National Prevalence Survey data from Zambia. *Clin Infect Dis*. 2022;75(5):842-848. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34984431.

54. Sterling TR, Njie G, Zenner D, et al. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep*. 2020;69(1):1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32053584.

55. Golub JE, Pronyk P, Mohapi L, et al. Isoniazid preventive therapy, HAART and tuberculosis risk in HIV-infected adults in South Africa: a prospective cohort. *AIDS*. 2009;23(5):631-636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19525621.

56. Samandari T, Agizew TB, Nyirenda S, et al. 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9777):1588-1598. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21492926.

57. Sterling TR, Scott NA, Miro JM, et al. Three months of weekly rifapentine plus isoniazid for treatment of *Mycobacterium tuberculosis* infection in HIV co-infected persons. *AIDS*. 2016;30(10):1607-1615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26990624.

58. Martinson NA, Barnes GL, Moulton LH, et al. New regimens to prevent tuberculosis in adults with HIV infection. *N Engl J Med*. 2011;365(1):11-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21732833.

59. Belknap R, Holland D, Feng PJ, et al. Self-administered versus directly observed once-weekly isoniazid and rifapentine treatment of latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2017;167(10):689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29114781.

60. Podany AT, Bao Y, Swindells S, et al. Efavirenz pharmacokinetics and pharmacodynamics in HIV-infected persons receiving rifapentine and isoniazid for tuberculosis prevention. *Clin Infect Dis*. 2015;61(8):1322-1327. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26082504.

61. Farenc C, Doroumian S, Cantalloube C, et al. Rifapentine once-weekly dosing effect on efavirenz emtricitabine and tenofovir PKs. Presented at: Conference on Retroviruses and Opportunistic Infections; 2014. Boston, MA. Available at: https://www.croiconference.org/abstract/rifapentine-once-weekly-dosing-effect-efavirenz-emtricitabine-and-tenofovir-pks.

62. Weiner M, Egelund EF, Engle M, et al. Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother*. 2014;69(4):1079-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24343893.

63. Dooley KE, Savic R, Gupte A, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial.

Lancet HIV. 2020;7(6):e401-e409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32240629.

64. Borisov AS, Bamrah Morris S, Njie GJ, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regimen to treat latent *Mycobacterium tuberculosis* infection. *MMWR Morb Mortal Wkly Rep*. 2018;67(25):723-726. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29953429.

65. U.S. National Library of Medicine. Safety tolerability DDI short course treatment of LTBI infection with high-dose rifapentine and isoniazid or standard isoniazid preventive therapy in HIV+ patients (DOLPHIN & DOLPHIN TOO) (IMPAACT4TB). 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT03435146.

66. Hong Kong Chest Service/Tuberculosis Research Centre; Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *Am Rev Respir Dis*. 1992;145(1):36-41. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1731596.

67. Geijo MP, Herranz CR, Vano D, Garcia AJ, Garcia M, Dimas JF. [Short-course isoniazid and rifampin compared with isoniazid for latent tuberculosis infection: a randomized clinical trial]. *Enferm Infecc Microbiol Clin*. 2007;25(5):300-304. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504682.

68. Jimenez-Fuentes MA, de Souza-Galvao ML, Mila Auge C, Solsona Peiro J, Altet-Gomez MN. Rifampicin plus isoniazid for the prevention of tuberculosis in an immigrant population. *Int J Tuberc Lung Dis*. 2013;17(3):326-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23407221.

69. Martinez Alfaro E, Solera J, Serna E, et al. [Compliance, tolerance and effectiveness of a short chemoprophylaxis regimen for the treatment of tuberculosis]. *Med Clin (Barc)*. 1998;111(11):401-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9834911.

70. Ena J, Valls V. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. *Clin Infect Dis*. 2005;40(5):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15714411.

71. Fitzgerald DW, Severe P, Joseph P, et al. No effect of isoniazid prophylaxis for purified protein derivative-negative HIV-infected adults living in a country with endemic tuberculosis: results of a randomized trial. *J Acquir Immune Defic Syndr*. 2001;28(3):305-307. Available at: https://pubmed.ncbi.nlm.nih.gov/11694842/.

72. Johnson JL, Okwera A, Hom DL, et al. Duration of efficacy of treatment of latent tuberculosis infection in HIV-infected adults. *AIDS*. 2001;15(16):2137-2147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11684933.

73. Rivero A, Lopez-Cortes L, Castillo R, et al. [Randomized clinical trial investigating three chemoprophylaxis regimens for latent tuberculosis infection in HIV-infected patients]. *Enferm Infecc Microbiol Clin*. 2007;25(5):305-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17504683.

74. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. *N Engl J Med*. 1997;337(12):801-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9295239.

75. Gordin FM, Matts JP, Miller C, et al. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. *N Engl J Med*. 1997;337(5):315-320. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9233868.

76. Hawken MP, Meme HK, Elliott LC, et al. Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial. *AIDS*. 1997;11(7):875-882. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9189212.

77. Menzies D, Adjobimey M, Ruslami R, et al. Four months of rifampin or nine months of isoniazid for latent tuberculosis in adults. *N Engl J Med*. 2018;379(5):440-453. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30067931.

78. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med*. 2011;365(23):2155-2166. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22150035.

79. Horsburgh CR, Jr., Goldberg S, Bethel J, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. *Chest*. 2010;137(2):401-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19793865.

80. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis*. 1999;3(10):847-850. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10524579.

81. International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bull World Health Organ*. 1982;60(4):555-564. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6754120.

82. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. *JAMA*. 2000;283(11):1445-1450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10732934.

83. Swindells S, Ramchandani R, Gupta A, et al. One Month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *N Engl J Med*. 2019;380(11):1001-1011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865794.

84. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. *Ann Intern Med*. 2008;149(10):689-697. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19017587.

85. Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. *Int J Infect Dis*. 2010;14(4):e292-297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19656705.

86. Rangaka MX, Wilkinson RJ, Glynn JR, et al. Effect of antiretroviral therapy on the diagnostic accuracy of symptom screening for intensified tuberculosis case finding in a South African HIV clinic. *Clin Infect Dis*. 2012;55(12):1698-1706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22955441.

87. den Boon S, Matteelli A, Getahun H. Rifampicin resistance after treatment for latent tuberculous infection: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2016;20(8):1065-1071. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27393541.

88. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection: experience from three public health tuberculosis clinics. *Int J Tuberc Lung Dis*. 2002;6(11):995-1000. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12475146.

89. McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis: improved completion rates but more hepatotoxicity. *Chest*. 2003;123(1):102-106. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12527609.

90. Centers for Disease Control and Prevention. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC Recommendations--United States, 2001. *MMWR*. 2001. Available at: https://www.cdc.gov/mmwr/PDF/wk/mm5034.pdf.

91. Podany AT, Leon-Cruz J, Hakim J, et al. Nevirapine pharmacokinetics in HIV-infected persons receiving rifapentine and isoniazid for TB prevention. *J Antimicrob Chemother*. 2021;76(3):718-721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33241266.

92. U.S. National Library of Medicine. Drug-drug interactions between rifapentine and dolutegravir in HIV/LTBI co-infected individuals. 2023. Available at: https://clinicaltrials.gov/study/NCT04272242.

93. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis. an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200(10). Available at: https://www.atsjournals.org/doi/ref/10.1164/rccm.201909-1874ST.

94. U.S. National Library of Medicine. Protecting households on exposure to newly diagnosed index multidrug-resistant tuberculosis patients (PHOENIx MDR-TB). 2023. Available at: https://clinicaltrials.gov/study/NCT03568383?cond=NCT03568383&rank=1.

95. Bliven-Sizemore EE, Sterling TR, Shang N, et al. Three months of weekly rifapentine plus isoniazid is less hepatotoxic than nine months of daily isoniazid for LTBI. *Int J Tuberc Lung Dis*. 2015;19(9):1039-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26260821.

96. Ngongondo M, Miyahara S, Hughes MD, et al. Hepatotoxicity during isoniazid preventive therapy and antiretroviral therapy in people living with HIV with severe immunosuppression: a secondary analysis of a multi-country open-label randomized controlled clinical trial. *J Acquir Immune Defic Syndr*. 2018;78(1):54-61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29406428.

97. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174(8):935-952. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17021358.

98. Kendall EA, Shrestha S, Dowdy DW. The epidemiological importance of subclinical tuberculosis. A critical reappraisal. *Am J Respir Crit Care Med*. 2021;203(2):168-174. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33197210.

99. Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med*. 2010;362(8):707-716. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20181972.

100. Batungwanayo J, Taelman H, Dhote R, Bogaerts J, Allen S, Van de Perre P. Pulmonary tuberculosis in Kigali, Rwanda. Impact of human immunodeficiency virus infection on clinical and radiographic presentation. *Am Rev Respir Dis*. 1992;146(1):53-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1626814.

101. Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. *Am Rev Respir Dis*. 1993;148(5):1292-1297. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7902049.

102. Dhana A, Hamada Y, Kengne AP, et al. Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis. *Lancet Infect Dis*. 2022;22(4):507-518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34800394.

103. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25(2):242-246. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9332519.

104. Post F, Wood R, Pillay G. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD4+ T-lymphocyte count. *Tuber Lung Dis*. 1995;76:518-21. Available at https://pubmed.ncbi.nlm.nih.gov/8593372.

105. Pepper T, Joseph P, Mwenya C, et al. Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. *Int J Tuberc Lung Dis*. 2008;12(4):397-403. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18371265.

106. Ahuja SS, Ahuja SK, Phelps KR, Thelmo W, Hill AR. Hemodynamic confirmation of septic shock in disseminated tuberculosis. *Crit Care Med*. 1992;20(6):901-903. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1597048.

107. Shafer RW, Kim DS, Weiss JP, Quale JM. Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. *Medicine*. 1991;70(6):384-397. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1956280.

108. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med*. 2011;365(16):1471-1481. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010913.

109. Whalen C, Horsburgh CR, Jr., Hom D, Lahart C, Simberkoff M, Ellner J. Site of disease and opportunistic infection predict survival in HIV-associated tuberculosis. *AIDS*. 1997;11(4):455-460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9084792.

110. Kourbatova EV, Leonard MK, Jr., Romero J, Kraft C, del Rio C, Blumberg HM. Risk factors for mortality among patients with extrapulmonary tuberculosis at an academic inner-city hospital in the US. *Eur J Epidemiol*. 2006;21(9):715-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17072539.

111. Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351(17):1741-1751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15496623.

112. Lewis JJ, Charalambous S, Day JH, et al. HIV infection does not affect active case finding of tuberculosis in South African gold miners. *Am J Respir Crit Care Med*. 2009;180(12):1271-1278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19745207.

113. Cavanaugh JS, Modi S, Musau S, et al. Comparative yield of different diagnostic tests for tuberculosis among people living with HIV in western Kenya. *PLoS One*. 2016;11(3):e0152364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27023213.

114. Henostroza G, Harris JB, Chitambi R, et al. High prevalence of tuberculosis in newly enrolled HIV patients in Zambia: need for enhanced screening approach. *Int J Tuberc Lung Dis*. 2016;20(8):1033-1039. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27393536.

115. Arpagaus A, Franzeck FC, Sikalengo G, et al. Extrapulmonary tuberculosis in HIV-infected patients in rural Tanzania: The prospective Kilombero and Ulanga antiretroviral cohort. *PLoS One*. 2020;15(3):e0229875. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130279.

116. Elliott AM, Halwiindi B, Hayes RJ, et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. *J Trop Med Hyg*. 1993;96(1):1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8429569.

117. Reid MJ, Shah NS. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. *Lancet Infect Dis*. 2009;9(3):173-184. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19246021.

118. Monkongdee P, McCarthy KD, Cain KP, et al. Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. *Am J Respir Crit Care Med*. 2009;180(9):903-908. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19628775.

119. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial lymphadenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis*. 1992;15(4):601-605. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1420673.

120. Razack R, Louw M, Wright CA. Diagnostic yield of fine needle aspiration biopsy in HIV-infected adults with suspected mycobacterial lymphadenitis. *S Afr Med J*. 2013;104(1):27-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24388082.

121. Cheng VC, Yew WW, Yuen KY. Molecular diagnostics in tuberculosis. *Eur J Clin Microbiol Infect Dis*. 2005;24(11):711-720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16283213.

122. Diedrich CR, O'Hern J, Gutierrez MG, et al. Relationship between HIV coinfection, interleukin 10 production, and *Mycobacterium tuberculosis* in human lymph node granulomas. *J Infect Dis*. 2016;214(9):1309-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27462092.

123. Heysell SK, Moll AP, Gandhi NR, et al. Extensively drug-resistant *Mycobacterium tuberculosis* from aspirates, rural South Africa. *Emerg Infect Dis*. 2010;16(3):557-560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20202446.

124. Boehme CC, Nabeta P, Hillemann D, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med*. 2010;363(11):1005-1015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20825313.

125. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess*. 2007;11(3):1-196. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17266837.

126. Forbes BA, Hall GS, Miller MB, et al. Practice guidelines for clinical microbiology laboratories: mycobacteria. *Clin Microbiol Rev*. 2018. Available at: https://cmr.asm.org/content/cmr/31/2/e00038-17.full.pdf.

127. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. 2011. Available at: https://www.who.int/publications/i/item/9789241501545.

128. Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2014;1:CD009593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24448973.

129. Luetkemeyer AF, Kendall MA, Wu X, et al. Evaluation of two line probe assays for rapid detection of *Mycobacterium tuberculosis*, tuberculosis (TB) drug resistance, and non-TB mycobacteria in HIV-infected individuals with suspected TB. *J Clin Microbiol*. 2014;52(4):1052-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24430455.

130. Lawn SD, Kerkhoff AD, Vogt M, Wood R. HIV-associated tuberculosis: relationship between disease severity and the sensitivity of new sputum-based and urine-based diagnostic assays. *BMC Med*. 2013;11:231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24168211.

131. Maynard-Smith L, Larke N, Peters JA, Lawn SD. Diagnostic accuracy of the Xpert MTB/RIF assay for extrapulmonary and pulmonary tuberculosis when testing non-respiratory samples: a systematic review. *BMC Infect Dis*. 2014;14:709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25599808.

132. Rahman SMM, Maliha UT, Ahmed S, et al. Evaluation of Xpert MTB/RIF assay for detection of *Mycobacterium tuberculosis* in stool samples of adults with pulmonary tuberculosis. *PLoS One*. 2018;13(9):e0203063. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30212505.

133. Xie YL, Chakravorty S, Armstrong DT, et al. Evaluation of a rapid molecular drug-susceptibility test for tuberculosis. *N Engl J Med*. 2017;377(11):1043-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28902596.

134. Drain PK, Losina E, Coleman SM, et al. Diagnostic accuracy of a point-of-care urine test for tuberculosis screening among newly-diagnosed HIV-infected adults: a prospective, clinic-based study. *BMC Infect Dis*. 2014;14:110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24571362.

135. Drain PK, Losina E, Coleman SM, et al. Value of urine lipoarabinomannan grade and second test for optimizing clinic-based screening for HIV-associated pulmonary tuberculosis. *J Acquir Immune Defic Syndr*. 2015;68(3):274-280. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25415288.

136. Lawn SD, Dheda K, Kerkhoff AD, et al. Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. *BMC Infect Dis*. 2013;13:407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24004840.

137. Broger T, Moyoyeta M, Kerkhoff AD, Denkinger CM, Moreau E. Tuberculosis test results using fresh versus biobanked urine samples with FujiLAM. *The Lancet: Infectious Diseases*. 2020;20(1):22-23. Available at: https://pubmed.ncbi.nlm.nih.gov/31876492.

138. World Health Organization. Lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis of active tuberculosis in people living with HIV, 2019 Update. 2019. Available at: https://www.who.int/publications/i/item/9789241550604.

139. Quinn CM, Kagimu E, Okirworth M, et al. Fujifilm SILVAMP TB LAM assay on cerebrospinal fluid for the detection of tuberculous meningitis in adults with Human Immunodeficiency Virus. *Clin Infect Dis*. 2021;73(9):e3428-e3434. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33388751.

140. Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med*. 2017. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28344011.

141. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and tuberculosis treatment outcomes: systematic review and meta-analysis. *Ann Intern Med*. 2008;149(2):123-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18626051.

142. Centers for Disease Control and Prevention. Surveillance definitions for extensively drug resistant (XDR) and pre-XDR tuberculosis. 2022. Available at: https://archive.cdc.gov/#/details?url=https://www.cdc.gov/tb/php/dear-colleague-letters/2022-xdr-surveillance-definitions.html.

143. Viney K, Linh NN, Gegia M, et al. New definitions of pre-extensively and extensively drug-resistant tuberculosis: update from the World Health Organization. *Eur Respir J*. 2021;57(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/33833074.

144. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. 2010;181(1):80-86. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19833824.

145. Moore DA, Evans CA, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med*. 2006;355(15):1539-1550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17035648.

146. Walker TM, Miotto P, Koser CU, et al. The 2021 WHO catalogue of *Mycobacterium tuberculosis* complex mutations associated with drug resistance: A genotypic analysis. *Lancet Microbe*. 2022;3(4):e265-e273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35373160.

147. Heysell SK, Houpt ER. The future of molecular diagnostics for drug-resistant tuberculosis. *Expert Rev Mol Diagn*. 2012;12(4):395-405. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22616704.

148. Barnard M, Warren R, Gey Van Pittius N, et al. Genotype MTBDRsl line probe assay shortens time to diagnosis of extensively drug-resistant tuberculosis in a high-throughput diagnostic laboratory. *Am J Respir Crit Care Med*. 2012;186(12):1298-1305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23087027.

149. Rice JP, Seifert M, Moser KS, Rodwell TC. Performance of the Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis and rifampin resistance in a low-incidence, high-resource setting. *PLoS One*. 2017;12(10):e0186139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29016684.

150. Ocheretina O, Byrt E, Mabou MM, et al. False-positive rifampin resistant results with Xpert MTB/RIF version 4 assay in clinical samples with a low bacterial load. *Diagn Microbiol Infect Dis*. 2016;85(1):53-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26915638.

151. Nahid P, Dorman SE, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible tuberculosis. *Clin Infect Dis*. 2016;63(7):e147-e195. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27516382.

152. Dorman SE, Nahid P, Kurbatova EV, et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. *N Engl J Med*. 2021;384(18):1705-1718. Available at: https://pubmed.ncbi.nlm.nih.gov/33951360/.

153. Pettit AC, Phillips PPJ, Kurbatova E, et al. Rifapentine with and without moxifloxacin for pulmonary tuberculosis in people with human immunodeficiency virus (S31/A5349). *Clin Infect Dis*. 2023;76(3):e580-e589. Available at: https://pubmed.ncbi.nlm.nih.gov/36041016/.

154. Carr W, Kurbatova E, Starks A, Goswami N, Allen L, Winston C. Interim guidance: 4-month rifapentine-moxifloxacin regimen for the treatment of drug-susceptible pulmonary tuberculosis - United States, 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(8):285-289. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35202353.

155. Mangan JM, Woodruff RS, Winston CA, et al. Recommendations for use of video directly observed therapy during tuberculosis treatment - United States, 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(12):313-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36952279.

156. Burzynski J, Mangan JM, Lam CK, et al. In-person vs electronic directly observed therapy for tuberculosis treatment adherence: a randomized noninferiority trial. *JAMA Netw Open*. 2022;5(1):e2144210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35050357.

157. Alipanah N, Jarlsberg L, Miller C, et al. Adherence interventions and outcomes of tuberculosis treatment: A systematic review and meta-analysis of trials and observational studies. *PLoS Med*. 2018;15(7):e1002595. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29969463.

158. Story A, Aldridge RW, Smith C, Garber E, Hall J, Ferenando G. Smartphone-enabled video-observed versus directly observed treatment for tuberculosis: a multicenter, analyst-blinded

randomized, controlled superiority trial. *Lancet*. 2019;393(10177):1216-1224. Available at: https://pubmed.ncbi.nlm.nih.gov/30799062.

159. Browne SH, Umlauf A, Tucker AJ, et al. Wirelessly observed therapy compared to directly observed therapy to confirm and support tuberculosis treatment adherence: A randomized controlled trial. *PLoS Med*. 2019;16(10):e1002891. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31584944.

160. Centers for Disease Control and Prevention. Implementing an electronic directly observed therapy (eDOT) Program: A Toolkit for Tuberculosis (TB) Programs. 2017. Available at: https://www.cdc.gov/tb-programs/php/edot-toolkit/?CDC_AAref_Val=https://www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm.

161. Swaminathan S, Narendran G, Venkatesan P, et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. *Am J Respir Crit Care Med*. 2010;181(7):743-751. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19965813.

162. Nettles RE, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. *Clin Infect Dis*. 2004;38(5):731-736. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14986259.

163. Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. *Clin Infect Dis*. 2005;41(1):83-91. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15937767.

164. Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis*. 2010;50(9):1288-1299. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20353364.

165. Vashishtha R, Mohan K, Singh B, et al. Efficacy and safety of thrice weekly DOTS in tuberculosis patients with and without HIV co-infection: an observational study. *BMC Infect Dis*. 2013;13:468. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24099345.

166. Narendran G, Menon PA, Venkatesan P, et al. Acquired rifampicin resistance in thrice-weekly antituberculosis therapy: impact of HIV and antiretroviral therapy. *Clin Infect Dis*. 2014;59(12):1798-1804. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25156114.

167. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*. 1999;353(9167):1843-1847. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10359410.

168. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am J Respir Crit Care Med*. 2006;173(3):350-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16109981.

169. Gopalan N, Santhanakrishnan RK, Palaniappan AN, et al. Daily vs intermittent antituberculosis therapy for pulmonary tuberculosis in patients with HIV: a randomized clinical trial. *JAMA Intern Med*. 2018;178(4):485-493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29507938.

170. Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nat Med*. 2018;24(11):1708-1715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30397355.

171. Centers for Disease Control and Prevention. Treatment of tuberculosis. *MMWR Recomm Rep*. 2003;52(RR11):1-77. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

172. el-Sadr WM, Perlman DC, Matts JP, et al. Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1998;26(5):1148-1158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9597244.

173. Perriens JH, St Louis ME, Mukadi YB, et al. Pulmonary tuberculosis in HIV-infected patients in Zaire: a controlled trial of treatment for either 6 or 12 months. *N Engl J Med*. 1995;332(12):779-784. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7862181.

174. Jullien S, Ryan H, Modi M, Bhatia R. Six months therapy for tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;9(9):CD012091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27581996.

175. Cresswell FV, Meya DB, Kagimu E, et al. High-dose oral and intravenous rifampicin for the treatment of tuberculous meningitis in predominantly human immunodeficiency virus (HIV)-positive Ugandan adults: a Phase II open-label randomized controlled trial. *Clin Infect Dis*. 2021;73(5):876-884. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33693537.

176. Smith AGC, Gujabidze M, Avaliani T, et al. Clinical outcomes among patients with tuberculous meningitis receiving intensified treatment regimens. *Int J Tuberc Lung Dis*. 2021;25(8):632-639. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34330348.

177. Huynh J, Donovan J, Phu NH, Nghia HDT, Thuong NTT, Thwaites GE. Tuberculous meningitis: progress and remaining questions. *Lancet Neurol*. 2022;21(5):450-464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35429482.

178. Dian S, Yunivita V, Ganiem AR, et al. Double-blind, randomized, placebo-controlled phase II dose-finding study to evaluate high-dose rifampin for tuberculous meningitis. *Antimicrob Agents Chemother*. 2018;62(12). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30224533.

179. Heemskerk AD, Bang ND, Mai NT, et al. Intensified antituberculosis therapy in adults with tuberculous meningitis. *N Engl J Med*. 2016;374(2):124-134. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26760084.

180. Te Brake L, Dian S, Ganiem AR, et al. Pharmacokinetic/pharmacodynamic analysis of an intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis. *Int J Antimicrob Agents*. 2015;45(5):496-503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25703312.

181. Yunivita V, Dian S, Ganiem AR, et al. Pharmacokinetics and safety/tolerability of higher oral and intravenous doses of rifampicin in adult tuberculous meningitis patients. *Int J Antimicrob Agents*. 2016;48(4):415-421. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27526979.

182. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomised controlled trial. *Lancet Infect Dis*. 2017;17(1):39-49. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28100438.

183. Ruslami R, Ganiem AR, Aarnoutse RE, van Crevel R, study t. Rifampicin and moxifloxacin for tuberculous meningitis--authors' reply. *Lancet Infect Dis*. 2013;13(7):570. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23809224.

184. Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*. 2016;4:CD002244. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27121755.

185. Wang W, Gao J, Liu J, Qi J, Zhang Q. Clinical efficacy of dexamethasone in the treatment of patients with tuberculous meningitis: a meta-analysis. *Contrast Media Mol Imaging*. 2022;2022:2180374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35418812.

186. Donovan J, Bang ND, Imran D, et al. Adjunctive dexamethasone for tuberculous meningitis in HIV-positive adults. *N Engl J Med*. 2023;389(15):1357-1367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37819954.

187. Mayosi BM, Ntsekhe M, Bosch J, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. *N Engl J Med*. 2014;371(12):1121-1130. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25178809.

188. Wiysonge CS, Ntsekhe M, Thabane L, et al. Interventions for treating tuberculous pericarditis. *Cochrane Database Syst Rev*. 2017;9:CD000526. Available at: http://www.ncbi.nlm.nih.gov/pubmed/28902412.

189. Mfinanga SG, Kirenga BJ, Chanda DM, et al. Early versus delayed initiation of highly active antiretroviral therapy for HIV-positive adults with newly diagnosed pulmonary tuberculosis (TB-HAART): a prospective, international, randomised, placebo-controlled trial. *Lancet Infect Dis*. 2014;14(7):563-571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24810491.

190. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med*. 2011;365(16):1482-1491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22010914.

191. Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med*. 2010;362(8):697-706. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20181971.

192. Nahid P, Gonzalez LC, Rudoy I, et al. Treatment outcomes of patients with HIV and tuberculosis. *Am J Respir Crit Care Med*. 2007;175(11):1199-1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17290042.

193. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis*. 2011;52(11):1374-1383. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21596680.

194. Li L, Li J, Chai C, et al. Association of CD4 T cell count and optimal timing of antiretroviral therapy initiation with immune reconstitution inflammatory syndrome and all-cause mortality for HIV-infected adults with newly diagnosed pulmonary tuberculosis: a systematic review and meta-analysis. *Int J Clin Exp Pathol*. 2021;14(6):670-679. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34239668.

195. Chelkeba L, Fekadu G, Tesfaye G, Belayneh F, Melaku T, Mekonnen Z. Effects of time of initiation of antiretroviral therapy in the treatment of patients with HIV/TB co-infection: A systemic review and meta-analysis. *Ann Med Surg (Lond)*. 2020;55:148-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32477514.

196. Burke RM, Rickman HM, Singh V, et al. What is the optimum time to start antiretroviral therapy in people with HIV and tuberculosis coinfection? A systematic review and meta-analysis. *J Int AIDS Soc*. 2021;24(7):e25772. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34289243.

197. Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the prevention of paradoxical tuberculosis-associated IRIS. *N Engl J Med*. 2018;379(20):1915-1925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30428290.

198. Marais S, Meintjes G, Pepper DJ, et al. Frequency, severity, and prediction of tuberculous meningitis immune reconstitution inflammatory syndrome. *Clin Infect Dis*. 2013;56(3):450-460. Available at: https://pubmed.ncbi.nlm.nih.gov/23097584/.

199. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. *Lancet*. 2004;364(9441):1244-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15464185.

200. Johnson JL, Okwera A, Nsubuga P, et al. Efficacy of an unsupervised 8-month rifampicin-containing regimen for the treatment of pulmonary tuberculosis in HIV-infected adults. Uganda-

Case Western Reserve University Research Collaboration. *Int J Tuberc Lung Dis*. 2000;4(11):1032-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11092715.

201. Blaschke TF, Skinner MH. The clinical pharmacokinetics of rifabutin. *Clin Infect Dis*. 1996;22 Suppl 1:S15-21; discussion S21-12. Available at: https://pubmed.ncbi.nlm.nih.gov/8785251/.

202. Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev*. 2007(4):CD005159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17943842.

203. Singh R, Marshall N, Smith CJ, et al. No impact of rifamycin selection on tuberculosis treatment outcome in HIV coinfected patients. *AIDS*. 2013;27(3):481-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23014518.

204. McGregor MM, Olliaro P, Wolmarans L, et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J Respir Crit Care Med*. 1996;154(5):1462-1467. Available at: https://pubmed.ncbi.nlm.nih.gov/8912765/.

205. Kendall MA, Lalloo U, Fletcher CV, et al. Safety and pharmacokinetics of double-dose lopinavir/ritonavir + rifampin versus lopinavir/ritonavir + daily rifabutin for treatment of human immunodeficiency virus-tuberculosis coinfection. *Clin Infect Dis*. 2021;73(4):706-715. Available at: https://pubmed.ncbi.nlm.nih.gov/34398956/.

206. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *J Antimicrob Chemother*. 2019;74(6):1670-1678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30815689.

207. Martin TCS, Hill LA, Tang ME, Balcombe SM. Tenofovir alafenamide and rifabutin co-administration does not lead to loss of HIV-1 suppression: A retrospective observational study. *Int J Infect Dis*. 2020;100:470-472. Available at: https://pubmed.ncbi.nlm.nih.gov/32979587/.

208. Liou BH, Cheng CN, Lin YT, et al. Short-course daily isoniazid and rifapentine for latent tuberculosis infection in people living with HIV who received coformulated bictegravir/emtricitabine/tenofovir alafenamide. *J Int AIDS Soc*. 2021;24(11):e25844. Available at: https://pubmed.ncbi.nlm.nih.gov/34822220/.

209. Cohen K, Grant A, Dandara C, et al. Effect of rifampicin-based antitubercular therapy and the cytochrome P450 2B6 516G>T polymorphism on efavirenz concentrations in adults in South Africa. *Antivir Ther*. 2009;14(5):687-695. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19704172.

210. Ramachandran G, Hemanth Kumar AK, Rajasekaran S, et al. CYP2B6 G516T polymorphism but not rifampin coadministration influences steady-state pharmacokinetics of efavirenz in human immunodeficiency virus-infected patients in South India. *Antimicrob Agents Chemother*. 2009;53(3):863-868. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19124658.

211. Luetkemeyer AF, Rosenkranz SL, Lu D, et al. Relationship between weight, efavirenz exposure, and virologic suppression in HIV-infected patients on rifampin-based tuberculosis treatment in the AIDS Clinical Trials Group A5221 STRIDE Study. *Clin Infect Dis*. 2013;57(4):586-593. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23592830.

212. Manosuthi W, Kiertiburanakul S, Sungkanuparph S, et al. Efavirenz 600 mg/day versus efavirenz 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. *AIDS*. 2006;20(1):131-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16327334.

213. Boulle A, Van Cutsem G, Cohen K, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA*. 2008;300(5):530-539. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18677025.

214. Cerrone M, Wang X, Neary M, et al. Pharmacokinetics of efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus-infected individuals. *Clin Infect Dis*. 2019;68(3):446-452. Available at: https://pubmed.ncbi.nlm.nih.gov/30084943/.

215. Podany AT, Pham M, Sizemore E, et al. Efavirenz pharmacokinetics and human immunodeficiency virus type 1 (HIV-1) viral suppression among patients receiving tuberculosis treatment containing daily high-dose rifapentine. *Clin Infect Dis*. 2022;75(4):560-566. Available at: https://pubmed.ncbi.nlm.nih.gov/34918028/.

216. Yee KL, Khalilieh SG, Sanchez RI, et al. The effect of single and multiple doses of rifampin on the pharmacokinetics of doravirine in healthy subjects. *Clin Drug Investig*. 2017;37(7):659-667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28353169.

217. Khalilieh SG, Yee KL, Sanchez RI, et al. Multiple doses of rifabutin reduce exposure of doravirine in healthy subjects. *J Clin Pharmacol*. 2018;58(8):1044-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29723418.

218. Janssen Therapeutics. Edurant [package insert]. 2021. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/EDURANT-pi.pdf.

219. Kakuda TN, Woodfall B, De Marez T, et al. Pharmacokinetic evaluation of the interaction between etravirine and rifabutin or clarithromycin in HIV-negative, healthy volunteers: results from two Phase 1 studies. *J Antimicrob Chemother*. 2014;69(3):728-734. Available at: https://pubmed.ncbi.nlm.nih.gov/24155058/.

220. Dooley KE, Sayre P, Borland J, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr*. 2013;62(1):21-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23075918.

221. Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-based antiretroviral therapy for patients coinfected with tuberculosis and human immunodeficiency virus: a multicenter, noncomparative, open-label, randomized trial. *Clin Infect Dis*. 2020;70(4):549-556. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30918967.

222. Griesel R, Hill A, Meintjes G, Maartens G. Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase 2 non-comparative randomised controlled (RADIANT-TB) trial. *Wellcome Open Res*. 2021;6:1. Available at: https://pubmed.ncbi.nlm.nih.gov/33954265/.

223. Grinsztejn B, De Castro N, Arnold V, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): a multicentre, phase 2, non-comparative, open-label, randomised trial. *Lancet Infect Dis*. 2014;14(6):459-467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24726095.

224. Wenning LA, Hanley WD, Brainard DM, et al. Effect of rifampin, a potent inducer of drug-metabolizing enzymes, on the pharmacokinetics of raltegravir. *Antimicrob Agents Chemother*. 2009;53(7):2852-2856. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19433563.

225. Brainard DM, Wenning LA, Stone JA, Wagner JA, Iwamoto M. Clinical pharmacology profile of raltegravir, an HIV-1 integrase strand transfer inhibitor. *J Clin Pharmacol*. 2011;51(10):1376-1402. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21209233.

226. Custodio JM, West SK, Collins S, et al. Pharmacokinetics of bictegravir administered twice daily in combination with rifampin. Presented at: Conference on Retroviruses and Opportunistic Infections; 2018. Boston, MA. Available at: https://www.croiconference.org/abstract/pharmacokinetics-bictegravir-administered-twice-daily-combination-rifampin.

227. Ramanathan S, Mathias AA, German P, Kearney BP. Clinical pharmacokinetic and pharmacodynamic profile of the HIV integrase inhibitor elvitegravir. *Clin Pharmacokinet*. 2011;50(4):229-244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21348537.

228. Toomey CB, Lee J, Spencer DB. Rifabutin-cobicistat drug interaction resulting in severe bilateral panuveitis. *Case Rep Ophthalmol*. 2020;11(1):156-160. Available at: https://pubmed.ncbi.nlm.nih.gov/32399018/.

229. Ford SL, Sutton K, Lou Y, et al. Effect of rifampin on the single-dose pharmacokinetics of oral cabotegravir in healthy subjects. *Antimicrob Agents Chemother*. 2017;61(10). Available at: https://pubmed.ncbi.nlm.nih.gov/28739783/.

230. Rajoli RKR, Curley P, Chiong J, et al. Predicting drug-drug interactions between rifampicin and long-acting cabotegravir and rilpivirine using physiologically based pharmacokinetic modeling. *J Infect Dis*. 2019;219(11):1735-1742. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30566691.

231. Burger DM, Agarwala S, Child M, Been-Tiktak A, Wang Y, Bertz R. Effect of rifampin on steady-state pharmacokinetics of atazanavir with ritonavir in healthy volunteers. *Antimicrob Agents Chemother*. 2006;50(10):3336-3342. Available at: https://pubmed.ncbi.nlm.nih.gov/17005814/.

232. Justesen US, Andersen AB, Klitgaard NA, Brøsen K, Gerstoft J, Pedersen C. Pharmacokinetic interaction between rifampin and the combination of indinavir and low-dose ritonavir in HIV-infected patients. *Clin Infect Dis*. 2004;38(3):426-429. Available at: https://pubmed.ncbi.nlm.nih.gov/14727216/.

233. la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother*. 2004;48(5):1553-1560. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15105105.

234. Regazzi M, Carvalho AC, Villani P, Matteelli A. Treatment optimization in patients co-infected with HIV and *Mycobacterium tuberculosis* infections: focus on drug-drug interactions with rifamycins. *Clin Pharmacokinet*. 2014;53(6):489-507. Available at: https://pubmed.ncbi.nlm.nih.gov/24777631/.

235. Ebrahim I, Maartens G, Wiesner L, Orrell C, Smythe W, McIlleron H. Pharmacokinetic profile and safety of adjusted doses of darunavir/ritonavir with rifampicin in people living with HIV. *J Antimicrob Chemother*. 2020;75(4):1019-1025. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31942627.

236. Decloedt EH, McIlleron H, Smith P, Merry C, Orrell C, Maartens G. Pharmacokinetics of lopinavir in HIV-infected adults receiving rifampin with adjusted doses of lopinavir-ritonavir tablets. *Antimicrob Agents Chemother*. 2011;55(7):3195-3200. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21537021.

237. Food and Drug Adminstration. Kaletra [package insert]. 2020. Available at: https://www.rxabbvie.com/pdf/kaletratabpi.pdf.

238. Bristol-Myers Squibb. Atazanavir [package insert]. 2018. Available at: https://packageinserts.bms.com/pi/pi_reyataz.pdf.

239. Sekar V, Lavreys L, Van de Casteele T, et al. Pharmacokinetics of darunavir/ritonavir and rifabutin coadministered in HIV-negative healthy volunteers. *Antimicrob Agents Chemother*. 2010;54(10):4440-4445. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20660678.

240. Ford SL, Chen YC, Lou Y, et al. Pharmacokinetic interaction between fosamprenavir-ritonavir and rifabutin in healthy subjects. *Antimicrob Agents Chemother*. 2008;52(2):534-538. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18056271.

241. Lin HC, Lu PL, Chang CH. Uveitis associated with concurrent administration of rifabutin and lopinavir/ritonavir (Kaletra). *Eye (Lond)*. 2007;21(12):1540-1541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17962822.

242. Lan NT, Thu NT, Barrail-Tran A, et al. Randomised pharmacokinetic trial of rifabutin with lopinavir/ritonavir-antiretroviral therapy in patients with HIV-associated tuberculosis in Vietnam. *PLoS One*. 2014;9(1):e84866. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24465443.

243. Naiker S, Connolly C, Wiesner L, et al. Randomized pharmacokinetic evaluation of different rifabutin doses in African HIV- infected tuberculosis patients on lopinavir/ritonavir-based antiretroviral therapy. *BMC Pharmacol Toxicol*. 2014;15:61. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25406657.

244. Jenny-Avital ER, Joseph K. Rifamycin-resistant *Mycobacterium tuberculosis* in the highly active antiretroviral therapy era: a report of 3 relapses with acquired rifampin resistance following alternate-day rifabutin and boosted protease inhibitor therapy. *Clin Infect Dis*. 2009;48(10):1471-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19368504.

245. Boulanger C, Hollender E, Farrell K, et al. Pharmacokinetic evaluation of rifabutin in combination with lopinavir-ritonavir in patients with HIV infection and active tuberculosis. *Clin Infect Dis*. 2009;49(9):1305-1311. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19807276.

246. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360(9332):528-534. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12241657.

247. Dorman SE, Goldberg S, Stout JE, et al. Substitution of rifapentine for rifampin during intensive phase treatment of pulmonary tuberculosis: study 29 of the Tuberculosis Trials Consortium. *The Journal of Infectious Diseases*. 2012;206(7):1030-1040. Available at: https://pubmed.ncbi.nlm.nih.gov/22850121.

248. Su WJ, Feng JY, Chiu YC, Huang SF, Lee YC. Role of 2-month sputum smears in predicting culture conversion in pulmonary tuberculosis. *Eur Respir J*. 2011;37(2):376-383. Available at: https://pubmed.ncbi.nlm.nih.gov/20516049/.

249. Alsultan A, Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis: an update. *Drugs*. 2014;74(8):839-854. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24846578.

250. McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. *J Infect Dis*. 2007;196 Suppl 1:S63-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17624828.

251. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis. *Chest*. 1991;99(2):465-471. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1824929.

252. Sharma SK, Singla R, Sarda P, et al. Safety of 3 different reintroduction regimens of antituberculosis drugs after development of antituberculosis treatment-induced hepatotoxicity.

Clin Infect Dis. 2010;50(6):833-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20156055.

253. Tahaoglu K, Atac G, Sevim T, et al. The management of anti-tuberculosis drug-induced hepatotoxicity. *Int J Tuberc Lung Dis*. 2001;5(1):65-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11263519.

254. Abbara A, Chitty S, Roe JK, et al. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. *BMC Infect Dis*. 2017;17(1):231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28340562.

255. Lehloenya RJ, Todd G, Badri M, Dheda K. Outcomes of reintroducing anti-tuberculosis drugs following cutaneous adverse drug reactions. *Int J Tuberc Lung Dis*. 2011;15(12):1649-1657. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22118173.

256. Centers for Disease Control and Prevention. Reported tuberculosis in the United States, 2019. 2019. Available at: https://www.cdc.gov/tb-programs/php/edot-toolkit/?CDC_AAref_Val=https://www.cdc.gov/tb/publications/guidestoolkits/tbedottoolkit.htm.

257. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis*. 2017;17(2):223-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27865891.

258. van der Heijden YF, Karim F, Mufamadi G, et al. Isoniazid-monoresistant tuberculosis is associated with poor treatment outcomes in Durban, South Africa. *Int J Tuberc Lung Dis*. 2017;21(6):670-676. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28482962.

259. Fregonese F, Ahuja SD, Akkerman OW, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. *Lancet Respir Med*. 2018;6(4):265-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29595509.

260. World Health Organization. WHO treatment guidelines for isoniazid-resistant tuberculosis: supplement to the WHO treatment guidelines for drug-resistant tuberculosis. 2018. Available at: http://apps.who.int/iris/bitstream/handle/10665/260494/9789241550079-eng.pdf.

261. World Health Organization. WHO consolidated guidelines on drug-resistant tuberculosis treatment. 2019. Available at: https://www.who.int/publications/i/item/9789241550529.

262. Vogensen VB, Bolhuis MS, Sturkenboom MGG, et al. Clinical relevance of rifampicin-moxifloxacin interaction in isoniazid-resistant/intolerant tuberculosis patients. *Antimicrob Agents Chemother*. 2022;66(2):e0182921. Available at: https://pubmed.ncbi.nlm.nih.gov/34807758/.

263. Weiner M, Burman W, Luo CC, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother*. 2007;51(8):2861-2866. Available at: https://pubmed.ncbi.nlm.nih.gov/17517835/.

264. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis*. 2007;45(8):1001-1007. Available at: https://pubmed.ncbi.nlm.nih.gov/17879915/.

265. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. *N Engl J Med*. 2020;382(10):893-902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32130813.

266. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. *N Engl J Med*. 2022;387(9):810-823. Available at: https://pubmed.ncbi.nlm.nih.gov/36053506/.

267. Nyang'wa BT, Berry C, Kazounis E, et al. Short oral regimens for pulmonary rifampicin-resistant tuberculosis (TB-PRACTECAL): an open-label, randomised, controlled, phase 2B-3, multi-arm, multicentre, non-inferiority trial. *Lancet Respir Med*. 2024;12(2):117-128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37980911.

268. Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. *N Engl J Med*. 2022;387(25):2331-2343. Available at: https://pubmed.ncbi.nlm.nih.gov/36546625/.

269. Labuda SM, Seaworth B, Dasgupta S, Goswami ND, Team BPAMP. Bedaquiline, pretomanid, and linezolid with or without moxifloxacin for tuberculosis. *Lancet Respir Med*. 2024;12(2):e5-e6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38043563.

270. Haley CA, Schechter MC, Ashkin D, et al. Implementation of BPaL in the United States: experience using a novel all-oral treatment regimen for treatment of rifampin-resistant or rifampin-intolerant TB disease. *Clin Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37249079.

271. Centers for Disease Control and Prevention. Provisional CDC guidance for the use of pretomanid as part of a regimen [bedaquiline, pretomanid, and linezolid (BPaL)] to treat drug-resistant tuberculosis disease. 2024. Accessed February 21. Available at: https://www.cdc.gov/tb/hcp/treatment/bpal.html.

272. World Health Organization. WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. 2022. Accessed May 12. Available at: https://www.who.int/publications/i/item/9789240065116.

273. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet*. 2018;392(10150):821-834. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30215381.

274. Mok J, Lee M, Kim DK, et al. 9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in

South Korea. *Lancet*. 2022;400(10362):1522-1530. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36522208.

275. Goodall RL, Meredith SK, Nunn AJ, et al. Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial. *Lancet*. 2022;400(10366):1858-1868. Available at: https://pubmed.ncbi.nlm.nih.gov/36368336/.

276. Nunn AJ, Phillips PPJ, Meredith SK, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med*. 2019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30865791.

277. World Health Organization. WHO consolidated guidelines on tuberculosis: module 4: treatment - drug-resistant tuberculosis treatment. 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32603040.

278. Esmail A, Oelofse S, Lombard C, et al. An all-oral 6-month regimen for multidrug-resistant tuberculosis: a multicenter, randomized controlled clinical trial (the NExT Study). *Am J Respir Crit Care Med*. 2022;205(10):1214-1227. Available at: https://pubmed.ncbi.nlm.nih.gov/35175905/.

279. Barilar I, Fernando T, Utpatel C, et al. Emergence of bedaquiline-resistant tuberculosis and of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis* strains with rpoB Ile491Phe mutation not detected by Xpert MTB/RIF in Mozambique: a retrospective observational study. *Lancet Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37956677.

280. Perumal R, Bionghi N, Nimmo C, et al. Baseline and treatment-emergent bedaquiline resistance in drug-resistant tuberculosis: a systematic review and meta-analysis. *Eur Respir J*. 2023;62(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/37945030.

281. Nimmo C, Bionghi N, Cummings MJ, et al. Opportunities and limitations of genomics for diagnosing bedaquiline-resistant tuberculosis: a systematic review and individual isolate meta-analysis. *Lancet Microbe*. 2024;5(2):e164-e172. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38215766.

282. Svensson EM, Aweeka F, Park JG, Marzan F, Dooley KE, Karlsson MO. Model-based estimates of the effects of efavirenz on bedaquiline pharmacokinetics and suggested dose adjustments for patients coinfected with HIV and tuberculosis. *Antimicrob Agents Chemother*. 2013;57(6):2780-2787. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23571542.

283. Svensson EM, Dooley KE, Karlsson MO. Impact of lopinavir-ritonavir or nevirapine on bedaquiline exposures and potential implications for patients with tuberculosis-HIV coinfection. *Antimicrob Agents Chemother*. 2014;58(11):6406-6412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25114140.

284. Pandie M, Wiesner L, McIlleron H, et al. Drug-drug interactions between bedaquiline and the antiretrovirals lopinavir/ritonavir and nevirapine in HIV-infected patients with drug-resistant TB. *J Antimicrob Chemother*. 2016;71(4):1037-1040. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26747099.

285. Brust JCM, Gandhi NR, Wasserman S, et al. Effectiveness and cardiac safety of bedaquiline-based therapy for drug-resistant tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2021;73(11):2083-2092. Available at: https://pubmed.ncbi.nlm.nih.gov/33882121/.

286. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS*. 2004;18(12):1615-1627. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15280772.

287. Lawn SD, Bekker LG, Miller RF. Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *Lancet Infect Dis*. 2005;5(6):361-373. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15919622.

288. Meintjes G, Rabie H, Wilkinson RJ, Cotton MF. Tuberculosis-associated immune reconstitution inflammatory syndrome and unmasking of tuberculosis by antiretroviral therapy. *Clin Chest Med*. 2009;30(4):797-810, x. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19925968.

289. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis*. 2008;8(8):516-523. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18652998.

290. Muller M, Wandel S, Colebunders R, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(4):251-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20334848.

291. Burman W, Weis S, Vernon A, et al. Frequency, severity and duration of immune reconstitution events in HIV-related tuberculosis. *Int J Tuberc Lung Dis*. 2007;11(12):1282-1289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18229435.

292. Pepper DJ, Marais S, Maartens G, et al. Neurologic manifestations of paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome: a case series. *Clin Infect Dis*. 2009;48(11):e96-107. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19405867.

293. Lawn SD, Wood R. Hepatic involvement with tuberculosis-associated immune reconstitution disease. *AIDS*. 2007;21(17):2362-2363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18090294.

294. Sonderup MW, Wainwright H, Hall P, Hairwadzi H, Spearman CW. A clinicopathological cohort study of liver pathology in 301 patients with human immunodeficiency virus/acquired immune deficiency syndrome. *Hepatology*. 2015;61(5):1721-1729. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25644940.

295. Namale PE, Abdullahi LH, Fine S, Kamkuemah M, Wilkinson RJ, Meintjes G. Paradoxical TB-IRIS in HIV-infected adults: a systematic review and meta-analysis. *Future Microbiol*. 2015;10(6):1077-1099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26059627.

296. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158(1):157-161. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9655723.

297. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax*. 2004;59(8):704-707. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15282393.

298. Breton G, Duval X, Estellat C, et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin Infect Dis*. 2004;39(11):1709-1712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15578375.

299. Lawn SD, Myer L, Bekker LG, Wood R. Tuberculosis-associated immune reconstitution disease: incidence, risk factors and impact in an antiretroviral treatment service in South Africa. *AIDS*. 2007;21(3):335-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17255740.

300. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *J Infect*. 2006;53(6):357-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16487593.

301. Serra FC, Hadad D, Orofino RL, et al. Immune reconstitution syndrome in patients treated for HIV and tuberculosis in Rio de Janeiro. *Braz J Infect Dis*. 2007;11(5):462-465. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17962870.

302. Olalla J, Pulido F, Rubio R, et al. Paradoxical responses in a cohort of HIV-1-infected patients with mycobacterial disease. *Int J Tuberc Lung Dis*. 2002;6(1):71-75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11931404.

303. Huyst V, Lynen L, Bottieau E, Zolfo M, Kestens L, Colebunders R. Immune reconstitution inflammatory syndrome in an HIV/TB co-infected patient four years after starting antiretroviral therapy. *Acta Clin Belg*. 2007;62(2):126-129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17547295.

304. Michailidis C, Pozniak AL, Mandalia S, Basnayake S, Nelson MR, Gazzard BG. Clinical characteristics of IRIS syndrome in patients with HIV and tuberculosis. *Antivir Ther*. 2005;10(3):417-422. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15918332.

305. Luetkemeyer AF, Kendall MA, Nyirenda M, et al. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity, and implications for HIV-TB

programs. *J Acquir Immune Defic Syndr*. 2014;65(4):423-428. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24226057.

306. Narendran G, Andrade BB, Porter BO, et al. Paradoxical tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS) in HIV patients with culture confirmed pulmonary tuberculosis in India and the potential role of IL-6 in prediction. *PLoS One*. 2013;8(5):e63541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23691062.

307. Meintjes G, Rangaka MX, Maartens G, et al. Novel relationship between tuberculosis immune reconstitution inflammatory syndrome and antitubercular drug resistance. *Clin Infect Dis*. 2009;48(5):667-676. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19191655.

308. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS*. 2010;24(15):2381-2390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20808204.

309. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J (Clin Res Ed)*. 1983;286(6369):923-925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6403136.

310. Xie YL, Ita-Nagy F, Chen RY, et al. Neurotuberculosis: control of steroid-refractory paradoxical inflammatory reaction with ruxolitinib. *Open Forum Infect Dis*. 2019;6(10):ofz422. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31687418.

311. Brunel AS, Reynes J, Tuaillon E, et al. Thalidomide for steroid-dependent immune reconstitution inflammatory syndromes during AIDS. *AIDS*. 2012;26(16):2110-2112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22874513.

312. Hsu DC, Faldetta KF, Pei L, et al. A paradoxical treatment for a paradoxical condition: infliximab use in three cases of mycobacterial IRIS. *Clin Infect Dis*. 2015. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26394669.

313. Fourcade C, Mauboussin JM, Lechiche C, Lavigne JP, Sotto A. Thalidomide in the treatment of immune reconstitution inflammatory syndrome in HIV patients with neurological tuberculosis. *AIDS Patient Care STDS*. 2014;28(11):567-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25285462.

314. Keeley AJ, Parkash V, Tunbridge A, et al. Anakinra in the treatment of protracted paradoxical inflammatory reactions in HIV-associated tuberculosis in the United Kingdom: a report of two cases. *Int J STD AIDS*. 2020;31(8):808-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32631210.

315. Marais BJ, Cheong E, Fernando S, et al. Use of infliximab to treat paradoxical tuberculous meningitis reactions. *Open Forum Infect Dis*. 2021;8(1):ofaa604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33542942.

316. Abo YN, Curtis N, Osowicki J, et al. Infliximab for paradoxical reactions in pediatric central nervous system tuberculosis. *J Pediatric Infect Dis Soc*. 2021;10(12):1087-1091. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34608937.

317. van Toorn R, Rabie H, Dramowski A, Schoeman JF. Neurological manifestations of TB-IRIS: a report of 4 children. *Eur J Paediatr Neurol*. 2012;16(6):676-682. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22658306.

318. John L, Baalwa J, Kalimugogo P, et al. Response to 'Does immune reconstitution promote active tuberculosis in patients receiving highly active antiretroviral therapy?'. *AIDS*. 2005;19(17):2049-2050. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16260919.

319. Goldsack NR, Allen S, Lipman MC. Adult respiratory distress syndrome as a severe immune reconstitution disease following the commencement of highly active antiretroviral therapy. *Sex Transm Infect*. 2003;79(4):337-338. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12902592.

320. Lawn SD, Wainwright H, Orrell C. Fatal unmasking tuberculosis immune reconstitution disease with bronchiolitis obliterans organizing pneumonia: the role of macrophages. *AIDS*. 2009;23(1):143-145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19050399.

321. Chen WL, Lin YF, Tsai WC, Tsao YT. Unveiling tuberculous pyomyositis: an emerging role of immune reconstitution inflammatory syndrome. *Am J Emerg Med*. 2009;27(2):251 e251-252. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19371548.

322. Korenromp EL, Scano F, Williams BG, Dye C, Nunn P. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis*. 2003;37(1):101-112. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12830415.

323. Vega V, Rodríguez S, Van der Stuyft P, Seas C, Otero L. Recurrent TB: a systematic review and meta-analysis of the incidence rates and the proportions of relapses and reinfections. *Thorax*. 2021;76(5):494-502. Available at: https://pubmed.ncbi.nlm.nih.gov/33547088/.

324. Sonnenberg P, Murray J, Glynn JR, Shearer S, Kambashi B, Godfrey-Faussett P. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet*. 2001;358(9294):1687-1693. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11728545.

325. Narayanan S, Swaminathan S, Supply P, et al. Impact of HIV infection on the recurrence of tuberculosis in South India. *J Infect Dis*. 2010;201(5):691-703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20121433.

326. Jasmer RM, Bozeman L, Schwartzman K, et al. Recurrent tuberculosis in the United States and Canada: relapse or reinfection? *Am J Respir Crit Care Med*. 2004;170(12):1360-1366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15477492.

327. Fitzgerald DW, Desvarieux M, Severe P, Joseph P, Johnson WD, Jr., Pape JW. Effect of post-treatment isoniazid on prevention of recurrent tuberculosis in HIV-1-infected individuals: a randomised trial. *Lancet*. 2000;356(9240):1470-1474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11081529.

328. Haller L, Sossouhounto R, Coulibaly IM, Dosso M, al e. Isoniazid plus sulphadoxine-pyrimethamine can reduce morbidity of HIV-positive patients treated for tuberculosis in Africa: a controlled clinical trial. *Chemotherapy*. 1999;45(6):452-465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10567776.

329. Sugarman J, Colvin C, Moran AC, Oxlade O. Tuberculosis in pregnancy: an estimate of the global burden of disease. *Lancet Glob Health*. 2014;2(12):e710-716. Available at: https://pubmed.ncbi.nlm.nih.gov/25433626/.

330. Mofenson LM, Rodriguez EM, Hershow R, et al. *Mycobacterium tuberculosis* infection in pregnant and nonpregnant women infected with HIV in the Women and Infants Transmission Study. *Arch Intern Med*. 1995;155(10):1066-1072. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7748050.

331. Eriksen NL, Helfgott AW. Cutaneous anergy in pregnant and nonpregnant women with human immunodeficiency virus. *Infect Dis Obstet Gynecol*. 1998;6(1):13-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9678142.

332. Jana N, Vasishta K, Jindal SK, Khunnu B, Ghosh K. Perinatal outcome in pregnancies complicated by pulmonary tuberculosis. *Int J Gynaecol Obstet*. 1994;44(2):119-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7911094.

333. Jana N, Vasishta K, Saha SC, Ghosh K. Obstetrical outcomes among women with extrapulmonary tuberculosis. *N Engl J Med*. 1999;341(9):645-649. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10460815.

334. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. *N Engl J Med*. 2014;370(23):2211-2218. Available at: https://pubmed.ncbi.nlm.nih.gov/24897084/.

335. Jonnalagadda S, Lohman Payne B, Brown E, et al. Latent tuberculosis detection by interferon gamma release assay during pregnancy predicts active tuberculosis and mortality in human immunodeficiency virus type 1-infected women and their children. *J Infect Dis*. 2010;202(12):1826-1835. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21067370.

336. Jonnalagadda SR, Brown E, Lohman-Payne B, et al. Consistency of *Mycobacterium tuberculosis*-specific interferon-gamma responses in HIV-1-infected women during pregnancy and postpartum. *Infect Dis Obstet Gynecol*. 2012;2012:950650. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22496602.

337. Bhosale R, Alexander M, Deshpande P, et al. Stages of pregnancy and HIV affect diagnosis of tuberculosis infection and *Mycobacterium tuberculosis* (MTB)-induced immune response:

Findings from PRACHITi, a cohort study in Pune, India. *Int J Infect Dis*. 2021;112:205-211. Available at: https://pubmed.ncbi.nlm.nih.gov/34517050/.

338. Kaplan SR, Escudero JN, Mecha J, et al. Interferon gamma release assay and tuberculin skin test performance in pregnant women living with and without HIV. *J Acquir Immune Defic Syndr*. 2022;89(1):98-107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34629414.

339. Lighter-Fisher J, Surette AM. Performance of an interferon-gamma release assay to diagnose latent tuberculosis infection during pregnancy. *Obstet Gynecol*. 2012;119(6):1088-1095. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22569120.

340. Mathad JS, Bhosale R, Balasubramanian U, et al. Quantitative IFN-γ and IL-2 response associated with latent tuberculosis test discordance in HIV-infected pregnant women. *Am J Respir Crit Care Med*. 2016;193(12):1421-1428. Available at: https://pubmed.ncbi.nlm.nih.gov/26765255/.

341. Mathad JS, Bhosale R, Sangar V, et al. Pregnancy differentially impacts performance of latent tuberculosis diagnostics in a high-burden setting. *PLoS One*. 2014;9(3):e92308. Available at: https://pubmed.ncbi.nlm.nih.gov/24658103/.

342. LaCourse SM, Cranmer LM, Matemo D, et al. Effect of pregnancy on interferon gamma release assay and tuberculin skin test detection of latent TB infection among HIV-infected women in a high burden setting. *J Acquir Immune Defic Syndr*. 2017;75(1):128-136. Available at: https://pubmed.ncbi.nlm.nih.gov/28141782/.

343. Weinberg A, Aaron L, Montepiedra G, et al. Effects of pregnancy and isoniazid preventive therapy on *Mycobacterium tuberculosis* interferon gamma response assays in women with HIV. *Clin Infect Dis*. 2021;73(9):e3555-e3562. Available at: https://pubmed.ncbi.nlm.nih.gov/32720695/.

344. Gupta A, Montepiedra G, Aaron L, Theron G. isoniazid preventive therapy in HIV-infected pregnant and postpartum women. *N Engl J Med*. 2019;381:1333-1346. Available at: https://pubmed.ncbi.nlm.nih.gov/31577875.

345. Salazar-Austin N, Cohn S, Lala S, et al. Isoniazid preventive therapy and pregnancy outcomes in women living with human immunodeficiency virus in the Tshepiso cohort. *Clin Infect Dis*. 2020;71(6):1419-1426. Available at: https://pubmed.ncbi.nlm.nih.gov/31631221/.

346. Kalk E, Heekes A, Mehta U, et al. Safety and effectiveness of isoniazid preventive therapy in pregnant women living with human immunodeficiency virus on antiretroviral therapy: An Observational Study Using Linked Population Data. *Clin Infect Dis*. 2020;71(8):e351-e358. Available at: https://pubmed.ncbi.nlm.nih.gov/31900473/.

347. Taylor AW, Mosimaneotsile B, Mathebula U, et al. Pregnancy outcomes in HIV-infected women receiving long-term isoniazid prophylaxis for tuberculosis and antiretroviral therapy. *Infect Dis Obstet Gynecol*. 2013;2013:195637. Available at: https://pubmed.ncbi.nlm.nih.gov/23533318/.

348. Hamada Y, Figueroa C, Martín-Sánchez M, Falzon D, Kanchar A. The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis. *Eur Respir J*. 2020;55(3). Available at: https://pubmed.ncbi.nlm.nih.gov/32217619/.

349. Gupta A, Hughes MD, Cruz JL, et al. Adverse pregnancy outcomes among HIV-infected women taking isoniazid preventive therapy during the first trimester. *Clin Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37768207.

350. Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis*. 2010;10(7):489-498. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20610331.

351. Gupta A, Nayak U, Ram M, et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clin Infect Dis*. 2007;45(2):241-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17578786.

352. Middelkoop K, Bekker LG, Myer L, et al. Antiretroviral program associated with reduction in untreated prevalent tuberculosis in a South African township. *Am J Respir Crit Care Med*. 2010;182(8):1080-1085. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20558626.

353. Miele K, Bamrah Morris S, Tepper NK. Tuberculosis in pregnancy. *Obstet Gynecol*. 2020;135(6):1444-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32459437.

354. Mathad JS, Savic R, Britto P, et al. Pharmacokinetics and safety of 3 months of weekly rifapentine and isoniazid for tuberculosis prevention in pregnant women. *Clin Infect Dis*. 2022;74(9):1604-1613. Available at: https://pubmed.ncbi.nlm.nih.gov/34323955/.

355. Moro RN, Scott NA, Vernon A, et al. Exposure to latent tuberculosis treatment during pregnancy. the PREVENT TB and the iAdhere Trials. *Ann Am Thorac Soc*. 2018;15(5):570-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29393655.

356. Food and Drug Administration. PRIFTIN (rifapentine). 2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021024s009lbl.pdf.

357. Mathad JS, Savic R, Britto P, et al. Pharmacokinetics and safety of three months of weekly rifapentine and isoniazid for tuberculosis prevention in pregnant women. *Clin Infect Dis*. 2021. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34323955.

358. Hoffmann CJ, Variava E, Rakgokong M, et al. High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa. *PLoS One*. 2013;8(4):e62211. Available at: https://pubmed.ncbi.nlm.nih.gov/23614037/.

359. LaCourse SM, Cranmer LM, Matemo D, et al. Tuberculosis case finding in HIV-infected pregnant women in Kenya reveals poor performance of symptom screening and rapid diagnostic

tests. *J Acquir Immune Defic Syndr*. 2016;71(2):219-227. Available at: https://pubmed.ncbi.nlm.nih.gov/26334736/.

360. Kosgei RJ, Szkwarko D, Callens S, et al. Screening for tuberculosis in pregnancy: do we need more than a symptom screen? Experience from western Kenya. *Public Health Action*. 2013;3(4):294-298. Available at: https://pubmed.ncbi.nlm.nih.gov/26393049/.

361. Committee Opinion. Committee Opinion No. 723: Guidelines for diagnostic imaging during pregnancy and lactation. *Obstet Gynecol*. 2017;130(4):e210-e216. Available at https://pubmed.ncbi.nlm.nih.gov/28937575.

362. Mnyani CN, McIntyre JA. Tuberculosis in pregnancy. *BJOG*. 2011;118(2):226-231. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21083862.

363. Brost BC, Newman RB. The maternal and fetal effects of tuberculosis therapy. *Obstet Gynecol Clin North Am*. 1997;24(3):659-673. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9266585.

364. Bothamley G. Drug treatment for tuberculosis during pregnancy: safety considerations. *Drug Saf*. 2001;24(7):553-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11444726.

365. Czeizel AE, Rockenbauer M, Olsen J, Sorensen HT. A population-based case-control study of the safety of oral anti-tuberculosis drug treatment during pregnancy. *Int J Tuberc Lung Dis*. 2001;5(6):564-568. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11409585.

366. Efferen LS. Tuberculosis and pregnancy. *Curr Opin Pulm Med*. 2007;13(3):205-211. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17414128.

367. Vilarinho LC. Congenital tuberculosis: a case report. *Braz J Infect Dis*. 2006;10(5):368-370. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17293929.

368. Lee LH, LeVea CM, Graman PS. Congenital tuberculosis in a neonatal intensive care unit: case report, epidemiological investigation, and management of exposures. *Clin Infect Dis*. 1998;27(3):474-477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9770143.

369. Cantwell MF, Shehab ZM, Costello AM, et al. Brief report: congenital tuberculosis. *N Engl J Med*. 1994;330(15):1051-1054. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8127333.

370. Rinsky JL, Farmer D, Dixon J, et al. Notes from the field: contact investigation for an infant with congenital tuberculosis infection - North Carolina, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67(23):670-671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29902167.

371. Chang CW, Wu PW, Yeh CH, Wong KS, Wang CJ, Chang CC. Congenital tuberculosis: case report and review of the literature. *Paediatr Int Child Health*. 2018;38(3):216-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28421876.

372. Stuart RL, Lewis A, Ramsden CA, Doherty RR. Congenital tuberculosis after in-vitro fertilisation. *Med J Aust*. 2009;191(1):41-42. Available at: https://pubmed.ncbi.nlm.nih.gov/19580539/.

373. Pillay T, Sturm AW, Khan M, et al. Vertical transmission of *Mycobacterium tuberculosis* in KwaZulu Natal: impact of HIV-1 co-infection. *Int J Tuberc Lung Dis*. 2004;8(1):59-69. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14974747.

374. Adhikari M, Pillay T, Pillay DG. Tuberculosis in the newborn: an emerging disease. *Pediatr Infect Dis J*. 1997;16(12):1108-1112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9427454.

375. Franks AL, Binkin NJ, Snider DE, Jr., Rokaw WM, Becker S. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Public Health Rep*. 1989;104(2):151-155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2495549.

376. Dlodlo RA, Brigden G, Heldal E, et al. Management of tuberculosis: a guide to essential practice. Paris, France: International Union Against Tuberculosis and Lung Disease; October 2019. Available at: https://theunion.org/sites/default/files/2020-08/TheUnion_Orange_2019.pdf.

377. Dluzniewski A, Gastol-Lewinska L. The search for teratogenic activity of some tuberlostatic drugs. *Diss Pharm Pharmacol*. 1971;23:383-392.

378. Lotia Farrukh I, Lachenal N, Adenov MM, et al. Pregnancy and birth outcomes in patients with multidrug-resistant tuberculosis treated with regimens that include new and repurposed drugs. *Clin Infect Dis*. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37606512.

379. Lessnau KD, Qarah S. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. *Chest*. 2003;123(3):953-956. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12628902.

380. Drobac PC, del Castillo H, Sweetland A, et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. *Clin Infect Dis*. 2005;40(11):1689-1692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15889370.

381. Alene KA, Murray MB, van de Water BJ, et al. Treatment outcomes among pregnant patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(6):e2216527. Available at: https://pubmed.ncbi.nlm.nih.gov/35687333/.

382. Loveday M, Hughes J, Sunkari B, et al. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. *Clinical Infectious Diseases*. 2020;72(7):1158-1168. Available at: https://pubmed.ncbi.nlm.nih.gov/32141495.

383. Court R, Gausi K, Mkhize B, et al. Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis. *Br J Clin Pharmacol*. 2022;88(8):3548-3558. Available at: https://pubmed.ncbi.nlm.nih.gov/35526837/.

384. Jaspard M, Elefant-Amoura E, Melonio I, De Montgolfier I, Veziris N, Caumes E. Bedaquiline and linezolid for extensively drug-resistant tuberculosis in pregnant woman. *Emerg Infect Dis*. 2017;23(10):1731-1732. Available at: https://pubmed.ncbi.nlm.nih.gov/28792382/.

385. Fujimori H, et al. The effect of tuberculostatics on the fetus: an experimental production of congenital anomaly in rats by ethionamide. *Proc Congen Anom Res Assoc Jpn*. 1965;5:34-35.

386. Takekoshi S. Effects of hydroxymethylpyrimidine on isoniazid- and ethionamide-induced teratosis. *Gunma J Med Sci*. 1965;14:233-244.

387. Khan I, Azam A. Study of teratogenic activity of trifluoperazine, amitriptyline, ethionamide and thalidomide in pregnant rabbits and mice. *Proc Eur Soc Study Drug Toxic*. 1969;10:235-242.

388. Potworowska M, Sianoz-Ecka E, Szufladowica R. Treatment with ethionamide in pregnancy. *Pol Med J*. 1966;5(5):1152-1158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/5958801.

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

390. Yefet E, Schwartz N, Chazan B, Salim R, Romano S, Nachum Z. The safety of quinolones and fluoroquinolones in pregnancy: a meta-analysis. *BJOG*. 2018;125(9):1069-1076. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29319210.

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

392. Ziv A, Masarwa R, Perlman A, Ziv D, Matok I. Pregnancy Outcomes Following exposure to quinolone antibiotics - a systematic-review and meta-analysis. *Pharm Res*. 2018;35(5):109. Available at: https://pubmed.ncbi.nlm.nih.gov/29582196/.

393. Acar S, Keskin-Arslan E, Erol-Coskun H, Kaya-Temiz T, Kaplan YC. Pregnancy outcomes following quinolone and fluoroquinolone exposure during pregnancy: A systematic review and meta-analysis. *Reprod Toxicol*. 2019;85:65-74. Available at: https://pubmed.ncbi.nlm.nih.gov/30738954/.

394. Nahum GG, Uhl K, Kennedy DL. Antibiotic use in pregnancy and lactation: what is and is not known about teratogenic and toxic risks. *Obstet Gynecol*. 2006;107(5):1120-1138. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648419.

395. ZYVOX [package insert]. Food and Drug Administration. 2008. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021130s016,021131s013,021132s014lbl.pdf.

396. Van Kampenhout E, Bolhuis MS, Alffenaar JC, et al. Pharmacokinetics of moxifloxacin and linezolid during and after pregnancy in a patient with multidrug-resistant tuberculosis. *Eur Respir J*. 2017;49(3). Available at: https://pubmed.ncbi.nlm.nih.gov/28331037/.

397. Acquah R, Mohr-Holland E, Daniels J, et al. Outcomes of children born to pregnant women with drug-resistant tuberculosis treated with novel drugs in Khayelitsha, South Africa: A Report of Five Patients. *Pediatr Infect Dis J*. 2021;40(5):e191-e192. Available at: https://pubmed.ncbi.nlm.nih.gov/33847295/.

398. PRETOMANID [package insert]. Food and Drug Administration. 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212862s004lbl.pdf.

399. Varpela E. On the effect exerted by first-line tuberculosis medicines on the foetus. *Acta Tuberc Pneumol Scand*. 1964;45:53-69. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14209270.

Pneumocystis Pneumonia

Updated: September 16, 2024
Reviewed: September 16, 2024

Epidemiology

Pneumocystis pneumonia (PCP) is caused by *Pneumocystis jirovecii*, a ubiquitous fungus. The taxonomy of the organism has been changed; *Pneumocystis carinii* now refers only to the *Pneumocystis* that infects rats, and *P. jirovecii* refers to the distinct species that infects humans. However, the abbreviation PCP is still the preferred acronym to designate the clinical syndrome of *Pneumocystis* pneumonia,[1] although PJP is commonly used. Initial infection with *P. jirovecii* usually occurs in early childhood; two-thirds of healthy children have antibodies to *P. jirovecii* by age 2 years to 4 years.[2]

Rodent studies and case clusters in immunosuppressed patients suggest that *Pneumocystis* spreads by the airborne route. Disease probably occurs by both new acquisition of infection and by reactivation of latent infection.[3-12] Before the widespread use of PCP prophylaxis and antiretroviral therapy (ART), PCP occurred in 70% to 80% of people with advanced HIV,[13] with a 20% to 40% mortality rate in individuals despite anti-*Pneumocystis* therapy. Approximately 90% of PCP cases occur in people with HIV with CD4 T lymphocyte (CD4) cell counts <200 cells/mm^3.

The incidence of PCP has declined substantially with widespread use of PCP prophylaxis and ART; incidence among people with HIV in Western Europe and the United States is <1 case per 100 person-years.[14-16] Most cases of PCP now occur in people with HIV who are unaware of their HIV status or are not receiving ongoing care for HIV,[17] and in those with advanced immunosuppression (i.e., CD4 counts <100 cells/mm^3).[18]

Clinical Manifestations

In people with HIV, the most common manifestations of PCP are subacute onset of progressive dyspnea, fever, non-productive cough, and chest discomfort that worsens within days to weeks. The fulminant pneumonia observed in people who do not have HIV is less common among people with HIV. A more fulminant course can occur particularly after initiation of therapy.[19-21]

In mild cases, pulmonary examination while the patient is at rest usually is normal. With exertion, tachypnea, tachycardia, and diffuse dry (cellophane) rales may be observed.[20] Fever is present in most cases and may be the predominant symptom in some people. Pneumonia limited to the apices and extrapulmonary disease, which can occur in any organ, are rare and have been associated with use of aerosolized pentamidine prophylaxis.[22]

Hypoxemia, the most characteristic laboratory abnormality, can range from mild (room air arterial oxygen partial pressure [PaO_2] ≥70 mmHg or alveolar-arterial gradient [A-a gradient] <35 mmHg) to moderate (A-a gradient ≥35 to <45 mmHg) to severe (A-a gradient ≥45 mmHg). Oxygen desaturation with exercise is often abnormal but is 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[20]; however, in people with HIV with early disease, a chest radiograph may

be normal.[25] Atypical radiographic presentations (such as nodules, blebs and cysts, asymmetric disease, upper lobe localization, intrathoracic adenopathy, and pneumothorax) also occur. Spontaneous pneumothorax in a person with HIV should raise the suspicion of PCP.[26,27] Cavitation and pleural effusion are uncommon in the absence of other pulmonary pathogens or malignancies, and their presence may indicate an alternative diagnosis or an additional pathology. People with HIV who have documented PCP may have another concurrent cause of pulmonary dysfunction, such as tuberculosis (TB), Kaposi sarcoma, toxoplasmosis, or fungal or bacterial pneumonia.[28,29]

Thin-section computed tomography (CT) without contrast is a useful adjunctive study, since even in patients with mild-to-moderate symptoms and a normal chest radiograph, a CT scan will be abnormal, demonstrating "ground-glass" attenuation that may be patchy. A normal CT has a high negative predictive value, and alternate diagnoses should be excluded.[30,31]

Diagnosis

Because clinical presentation, blood tests, and chest radiographs are not pathognomonic for PCP (and because the organism cannot be cultivated routinely), histopathologic or cytopathologic demonstration of organisms in tissue, bronchoalveolar lavage (BAL) fluid, or induced sputum samples[19,28,29,32] is required for a definitive diagnosis of PCP. Spontaneously expectorated sputum has low sensitivity for the diagnosis of PCP and should not be submitted to the laboratory to diagnose PCP. Giemsa, Diff-Quik, and Wright stains detect both main life forms of P. *jirovecii*—cysts and trophic forms—but do not stain the cyst wall; Grocott-Gomori methenamine silver, Gram-Weigert, cresyl violet, and toluidine blue stain only the cyst wall. Some laboratories prefer direct immunofluorescent staining, which has higher sensitivity than the colorimetric stains.[33] The sensitivity and specificity of respiratory samples for PCP depend on the stain being used, the experience of the microbiologist or pathologist, the pathogen load, and specimen quality. Studies of stained respiratory tract samples obtained by various methods indicate the following relative diagnostic sensitivities: <50% to >90% for induced sputum, 90% to 99% for bronchoscopy with BAL, 95% to 100% for transbronchial biopsy, and 95% to 100% for open lung biopsy.[34-40]

Polymerase chain reaction (PCR) is an increasingly utilized method for diagnosing PCP and has replaced staining methods in many laboratories. PCR is highly sensitive and specific for detecting *Pneumocystis*. While PCR cannot reliably distinguish colonization from active disease, quantitative PCR (qPCR) is favored over qualitative assays, as a higher organism load by qPCR is likely to represent clinically significant disease.[41-43] However, the broad range of organism loads in patients with PCP and the lack of commercially available U.S. Food and Drug Administration (FDA)–approved qPCR kits for diagnosis makes establishment of cutoffs for colonization versus disease difficult to standardize.

1,3 β-D-glucan (β-glucan), which is a component of the cell wall of *Pneumocystis* cysts, is often elevated in people with HIV who also have PCP. The sensitivity of the β-glucan assay for diagnosis of PCP appears to be high, thus PCP is less likely in people with HIV with a low level of β-glucan (e.g., <80 pg/mL using the Fungitell assay). However, the specificity of β-glucan testing for establishing a PCP diagnosis is low,[44-48] since many other fungal diseases, cellulose membranes used for hemodialysis, and some drugs can elevate β-glucan levels.[47,48]

Because the clinical manifestations of several disease processes are similar, it is important to seek a definitive diagnosis of PCP disease rather than rely on a presumptive diagnosis, especially in patients with moderate-to-severe disease. However, PCP treatment should be initiated before a definitive

diagnosis is established if clinical suspicion is high. *P. jirovecii* persist in clinical specimens for days or weeks after effective therapy is initiated, allowing definitive diagnosis to be established even after initiating therapy.[32]

Preventing Exposure

There are insufficient data to support isolation as standard practice to prevent PCP **(CIII).** *Pneumocystis* can be quantified in the air near people with PCP,[49] and multiple outbreaks, each caused by a distinct strain of *Pneumocystis*, have been documented among kidney transplant patients as well as other immunosuppressed populations.[6-12,50] Although these findings strongly suggest that isolating people with known PCP from people at high risk for PCP may be beneficial, no study to date has documented the benefit of such an approach.

Preventing Disease

Recommendations for Preventing First Episode of *Pneumocystis* Pneumonia (Primary Prophylaxis)

Indications for Initiating Primary Prophylaxis

- CD4 count 100–200 cells/mm^3, if plasma HIV RNA level above detection limits (AI), *or*
- CD4 count <100 cells/mm^3, regardless of plasma HIV RNA level (AIII)
- Note: Patients who are receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).

Preferred Therapy

- TMP-SMX, 1 DS tablet PO daily (AI), *or*
- TMP-SMX, 1 SS tablet PO daily (AI)
- Note: TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections.

Alternative Therapy

- The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*:
  - TMP-SMX 1 DS tablet PO three times weekly (BI), *or*
  - Dapsone[a] 50 mg PO daily with pyrimethamine 50 mg plus leucovorin 25 mg PO weekly (BI), *or*
  - Dapsone[a] 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg PO weekly (BI), *or*
  - Atovaquone 1,500 mg PO daily with food (BI)
- The following regimens should only be used in people who are seronegative for *Toxoplasma gondii*:
  - Dapsone[a] 100 mg PO daily or dapsone 50 mg PO twice a day (BI), *or*
  - Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month (BI), *or*
  - Intravenous pentamidine 300 mg every 28 days (CIII)

Indication for Discontinuing Primary Prophylaxis

- CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months in response to ART (AI)
- Can consider when CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limit of detection of the assay used for ≥3 to 6 months (BII)

Indication for Restarting Primary Prophylaxis
• CD4 count <100 cells/mm^3 regardless of HIV RNA (AIII) • CD4 count 100–200 cells/mm^3 and HIV RNA consistently above detection limit of the assay used (AIII)
Pre-pregnancy and Pregnancy Considerations
• Clinicians who are providing pre-pregnancy care for people with HIV receiving PCP prophylaxis can discuss the option of deferring pregnancy until PCP prophylaxis can be safely discontinued with their patients (BIII). • Chemoprophylaxis for PCP should be administered to pregnant adults and adolescents as for nonpregnant adults and adolescents (AIII). TMP-SMX is the recommended prophylactic agent (AIII). Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX if they are capable of becoming pregnant prior to pregnancy or as soon as possible in their first trimester (BIII). • Given theoretical concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, clinicians may consider using alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone during the first trimester (CIII) rather than withholding chemoprophylaxis.
Other Considerations/Comments
• For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible. • If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution of therapy should be considered after the reaction has resolved (AII). The dose of TMP-SMX can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII). • TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse reactions including suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for primary PCP prophylaxis.

[a] G6PD levels should be checked before administration of dapsone. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole

Indication for Primary Prophylaxis

Chemoprophylaxis against PCP should be given to adults and adolescents with HIV (including pregnant people) with CD4 counts <100 cells/mm^3 regardless of plasma HIV levels **(AIII)** and those with CD4 counts between 100 and 200 cells/mm^3 with plasma HIV RNA levels above detection limits **(AI).**[13,51] Patients receiving pyrimethamine-sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP **(AII).**[52]

Trimethoprim-sulfamethoxazole (TMP-SMX) is the recommended prophylactic agent for PCP **(AI).**[51,53-55] One double-strength TMP-SMX tablet daily or one single-strength tablet daily[55] are the preferred regimens **(AI)**; there is greater experience with the double-strength tablet, but the single-strength tablet may be better tolerated. One double-strength TMP-SMX tablet three times weekly is also effective **(BI).**[56] TMP-SMX confers cross-protection against toxoplasmosis[57] and many respiratory bacterial infections.[53,58] TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in people with HIV who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction (e.g., rash without vesicles, bullae, or ulcerations), reinstitution of the drug should be considered after the reaction has resolved **(AII).**[59] Therapy should be permanently discontinued (with no rechallenge) in people with HIV with life-

threatening adverse reactions, including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis **(AIII).** Patients who have experienced adverse events, including fever and rash, may better tolerate reinstitution of TMP-SMX if the dose is gradually increased according to published regimens **(BI)**[60,61] or if the drug is given at a reduced dose or frequency **(CIII).** As many as 70% of people with HIV can tolerate such reinstitution of TMP-SMX therapy.[58]

For people with HIV in whom TMP-SMX use may need to be avoided (e.g., intolerance, severe renal dysfunction, early pregnancy, significant myelosuppression), alternative prophylactic regimens include dapsone **(BI),**[53] dapsone plus pyrimethamine plus leucovorin **(BI),**[62-64] aerosolized pentamidine administered with the Respirgard II nebulizer (manufactured by Marquest; Englewood, Colorado) **(BI),**[54] intravenous (IV) pentamidine **(CIII),**[65-67] and atovaquone **(BI).**[68,69] For people with HIV who are seropositive for *Toxoplasma gondii* and cannot tolerate TMP-SMX, recommended alternatives for prophylaxis against both PCP and toxoplasmosis include dapsone plus pyrimethamine plus leucovorin **(BI)**[62-64] or atovaquone **(CIII).** Dapsone alone and pentamidine (aerosol or IV) have not been shown to have activity against toxoplasmosis, and should only be used in people who are seronegative for anti-*Toxoplasma* antibodies.[57,70,71] Glucose-6-phosphate dehydrogenase (G6PD) levels should be checked prior to starting dapsone, and an alternative regimen should be used if G6PD deficiency is present, given the risks of hemolysis and methemoglobinemia in patients with G6PD deficiency.[72]

The utility of IV pentamidine as PCP prophylaxis has been evaluated primarily in retrospective/observational studies in immunosuppressed patients without HIV, especially in pediatric populations; experience in people with HIV is limited. Aerosolized pentamidine should be administered in an appropriately configured negative pressure room.[73] Pyrimethamine has become extremely expensive and can be difficult to obtain in the United States, and atovaquone has variable and unpredictable bioavailability. Atovaquone is as effective as aerosolized pentamidine[68] or dapsone[69] but substantially more expensive than the other regimens, and less preferred by patients due to the taste of the suspension.

The following regimens **are NOT recommended** as alternatives to TMP-SMX for PCP prophylaxis **(AIII):**

- Aerosolized pentamidine administered by nebulization devices other than the Respirgard II nebulizer[74]
- Oral clindamycin plus primaquine, given that this regimen has not been studied for PCP prophylaxis, and clindamycin alone was poorly tolerated as a potential prophylactic regimen for toxoplasmosis.[75]

Discontinuing Primary Prophylaxis

Primary *Pneumocystis* prophylaxis should be discontinued in adult and adolescent people with HIV who have responded to ART with an increase in CD4 counts from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months **(AI).** In observational and randomized studies whose findings support this recommendation, most people with HIV had CD4 counts >200 cells/mm^3 for >3 months before discontinuing PCP prophylaxis.[76-85] At discontinuation of prophylaxis, the median CD4 count was >300 cells/mm^3, most participants had a CD4 cell percentage ≥14%, and many had sustained suppression of HIV plasma RNA levels below detection limits for the assay employed. Median follow-up was 6 to 19 months.

A combined analysis of European cohorts,[86,87] a small randomized trial,[88] and a case series[89] found a low incidence of PCP in people with HIV with CD4 counts between 100 cells/mm^3 and 200 cells/mm^3, who were receiving ART and had HIV plasma viral loads <50 to <400 copies/mL, and who had stopped or never received PCP prophylaxis; this suggests that primary and secondary PCP prophylaxis can be safely discontinued in people with HIV with CD4 counts between 100 cells/mm^3 to 200 cells/mm^3 and HIV plasma RNA levels below limits of detection of commercial assays. Data on which to base specific recommendations are inadequate, but some clinicians would stop primary prophylaxis in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 if HIV plasma RNA levels remain below limits of detection for ≥3 months to 6 months **(BII).** Similar observations have been made with regard to stopping primary prophylaxis for *Toxoplasma* encephalitis.[90]

Prophylaxis should be reintroduced if the patient's CD4 count decreases to 100 to 200 cells/mm^3 in the setting of sustained increases in plasma HIV RNA levels **(AIII)** and in any people with HIV whose CD4 count drops to <100 cells/mm^3 **(AIII).**

Treating Disease

Recommendations for Treating *Pneumocystis* Pneumonia

People with HIV who develop PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX (BIII).

If not already started, ART should be initiated in patients within 2 weeks of diagnosis of PCP, if possible (AI).

For Moderate-to-Severe PCP

Preferred Therapy

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) IV given in divided doses every 6 or 8 hours (AI); may switch to PO formulation after clinical improvement (AI)

Alternative Therapy

- Primaquine[a] 30 mg (base) PO once daily plus clindamycin (IV [600 mg every 6 hours or 900 mg every 8 hours] or PO [450 mg every 6 hours or 600 mg every 8 hours]) (AI), *or*
- Pentamidine 4 mg/kg IV once daily infused over ≥60 minutes (AI); may reduce the dose to pentamidine 3 mg/kg IV once daily in the event of toxicities (BI)
- Note: Some clinicians prefer primaquine plus clindamycin because it is more effective and less toxic than pentamidine.

Adjunctive Corticosteroids For Moderate-to-Severe PCP Based on the Following Criteria (AI)

- PaO_2 <70 mmHg at room air, *or*
- A-a gradient ≥35 mmHg

Corticosteroid Dosing Schedule

- Prednisone doses (beginning as soon as possible and ideally within 72 hours of initiating PCP therapy) (AI)
  - Days 1–5: 40 mg PO twice daily
  - Days 6–10: 40 mg PO daily
  - Days 11–21: 20 mg PO daily
- IV methylprednisolone can be given as 80% of prednisone dose.

- Benefit of corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate-to-severe PCP (BIII).

For Mild-to-Moderate PCP

Preferred Therapy

- TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg)/day) PO given in three divided doses (AI), *or*
- TMP-SMX, two DS tablets PO three times daily (AI)

Alternative Therapy

- Dapsone[a] 100 mg PO daily plus TMP 15 mg/kg/day PO given in three divided doses (BI), *or*
- Primaquine[a] 30 mg (base) PO daily plus clindamycin PO (450 mg every 6 hours or 600 mg every 8 hours) (BI), *or*
- Atovaquone 750 mg PO twice daily with food (BI)

Duration of Therapy

- The recommended duration of therapy (irrespective of regimen) is 21 days (AII).
- Secondary prophylaxis should be initiated immediately after completion of treatment (see Recurrence table below).

Pregnancy Considerations

For Moderate-to-Severe PCP

Preferred Therapy

- TMP-SMX, regardless of disease (AI)
- Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, people in their first trimester with PCP should be treated with TMP-SMX because of its considerable benefit in reducing morbidity and mortality, which outweighs potential risk (AIII).
- Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX before pregnancy if they are capable of becoming pregnant, or as soon as possible in their first trimester (BIII). Doses of supplemental folic acid of 4 mg/day should be limited to the first trimester during the teratogenic window and can be reduced to 0.4 mg at 12 weeks continuing to 4–6 weeks postpartum or discontinuation of breastfeeding (AIII).
- Whether or not a person receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for follow-up scans subsequently (BIII).

Alternative Therapy

- IV pentamidine (BIII)
- If other alternatives are not available or tolerated, primaquine plus clindamycin (BIII)
    - Because of concerns about hemolytic anemia in exposed fetuses who are G6PD deficient (which cannot be diagnosed antenatally), primaquine (plus clindamycin) should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk (AIII).

For Mild-to-Moderate PCP

Preferred Therapy

- TMP-SMX, regardless of disease (AI)

Alternative Therapy

- Atovaquone suspension (BIII)
- If atovaquone is not available or tolerated, dapsone plus TMX (BIII)

- Because of concerns about hemolytic anemia in exposed fetuses who are G6PD deficient, primaquine or dapsone should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk (AIII).

Note: As with nonpregnant adults, G6PD levels should be checked before administration of primaquine or dapsone. While the G6PD level in a fetus generally is unknown during pregnancy, G6PD deficiency is an X-linked inherited condition and primaquine or dapsone can be considered if both the pregnant person and biologic father have normal G6PD activity.

Adjunctive Corticosteroid Therapy

- Adjunctive corticosteroid therapy should be used to improve the pregnant person's treatment outcome as indicated in nonpregnant adults (AIII). Maternal glucose levels and blood pressure should be monitored closely when corticosteroids are used in pregnancy, as well as fetal growth (AIII).
- Pregnant persons who are on chronic steroid therapy during pregnancy for non-hypothalamic-pituitary-adrenal axis disorders do not need stress doses of steroids for vaginal or cesarean delivery but should be continued on their therapeutic dose of steroids without interruption (BIII).

Other Considerations/Comments

- For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution of therapy should be considered after the reaction has resolved (AII). The dose of TMP-SMX can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII).
- TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse reactions including suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for PCP treatment.

[a] G6PD levels should be checked before administration of dapsone or primaquine. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: A-a gradient = alveolar-arterial gradient; ART = antiretroviral therapy; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PaO_2 = room air arterial oxygen partial pressure; PCP = *Pneumocystis* pneumonia; PO = orally; SMX = sulfamethoxazole; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

TMP-SMX is the treatment of choice for PCP **(AI).**[91,92] Standard doses are summarized in the table above; lower doses may also be effective, potentially with less toxicity, though randomized controlled data addressing this possibility are unavailable.[93] The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that TMP-SMX is as effective as parenteral pentamidine and more effective than other regimens for PCP treatment.[91,92,94] Adding leucovorin to prevent myelosuppression during acute treatment **is not recommended** because efficacy in preventing this toxicity is questionable and some evidence exists for a higher failure rate in preventing PCP **(AII).**[95] Outpatient therapy with oral TMP-SMX is highly effective in people with HIV with mild-to-moderate PCP **(AI).**[92] TMP-SMX should be permanently discontinued (with no rechallenge) in people with HIV who experience life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis **(AIII).**

Mutations associated with resistance to sulfa drugs have been documented, but their effect on clinical outcome is uncertain.[96-99] Patients who have PCP despite TMP-SMX prophylaxis usually can be treated effectively with standard doses of TMP-SMX **(BIII).**

Patients with documented or suspected PCP and moderate-to-severe disease, defined by room air PaO_2 <70 mmHg or A-a gradient ≥35 mmHg, should receive adjunctive corticosteroids as soon as possible and certainly within 72 hours after starting specific PCP therapy **(AI).**[100-105] The benefits of starting steroids later are unclear, but most clinicians would administer them even after 72 hours for

people with HIV who have moderate-to-severe PCP **(BIII).** Intravenous methylprednisolone at 80% of the corresponding oral prednisone dose can be used if parenteral administration is necessary.

Alternative therapeutic regimens for mild-to-moderate disease include: dapsone plus trimethoprim (TMP) **(BI),**[92,106] which may have efficacy similar to TMP-SMX with fewer side effects, but is less convenient given the number of pills; primaquine plus clindamycin **(BI)**[107-109] (clindamycin can be administered IV for more severe cases, but primaquine is only available in an oral formulation); and atovaquone suspension **(BI),**[91,110] which is less effective than TMP-SMX for mild-to-moderate PCP but has fewer side effects. Clinicians should be aware that the absorption of atovaquone is highly variable; plasma concentrations ≥15 μg/mL are associated with an improved response rate, but atovaquone therapeutic drug monitoring is not routinely available.[91,111] People with HIV should be tested for G6PD levels before primaquine or dapsone is administered. An alternative agent should be used if the patient is found to have G6PD deficiency.

Alternative therapeutic regimens for people with HIV who have moderate-to-severe PCP include primaquine plus clindamycin **(AI)** or IV pentamidine **(AI).**[109,112,113] Some clinicians prefer primaquine plus clindamycin because this combination is more effective and less toxic than pentamidine.[109,114-116]

Aerosolized pentamidine **should not be used** to treat PCP because it has limited efficacy and is associated with more frequent relapse **(AI).**[112,117,118]

The recommended duration of therapy for PCP (irrespective of regimen) is 21 days **(AII)**[19]; shorter durations may also be effective but have not been systematically studied.[119] The probability and rate of response to therapy depend on the agent used, number of previous PCP episodes, severity of pulmonary illness, degree of immunodeficiency, timing of initiation of therapy, and comorbidities.

Although the overall prognosis for people with HIV with PCP-associated respiratory failure is poor, over the past decades, survival for people with HIV who require intensive care unit (ICU) care has improved as management of respiratory failure and HIV comorbidities has improved.[120-123] Special attention is necessary regarding the use of ART in such critically ill patients.[124]

Special Considerations With Regards to Starting ART (Including IRIS)

If not already started, ART should be initiated in patients, when possible, within 2 weeks of PCP diagnosis **(AI).** In a randomized controlled trial of 282 people with HIV with opportunistic infections (OIs) other than TB, 63% of whom had definite or presumptive PCP, the incidence of AIDS progression or death (a secondary study endpoint) was significantly lower among participants who initiated ART early than among those who delayed ART (median 12 days and 45 days after OI therapy initiation, respectively).[125] Of note, none of the participants with PCP enrolled in the study had respiratory failure requiring intubation.[125] Initiating ART in such people with HIV can be managed with attention to formulations that can be crushed for administration, awareness of the unpredictable absorption of oral medications, and potential drug–drug or drug–nutrient interactions commonly encountered in the ICU.[126]

Paradoxical immune reconstitution inflammatory syndrome (IRIS) following an episode of PCP is rare but has been reported.[127,128] Most cases occurred within weeks of the PCP episode; symptoms included fever and recurrence or exacerbation of pulmonary symptoms including cough and shortness of breath, as well as worsening of a previously improving chest radiograph. Although IRIS

in the setting of PCP has rarely been life-threatening,[129] people with HIV should be closely followed for recurrence of symptoms after initiation of ART. Management of PCP-associated IRIS is not well defined; some experts recommend use of corticosteroids in people with HIV with respiratory deterioration if other causes are ruled out.

Monitoring of Response to Pneumocystis Pneumonia Therapy and Adverse Events

Careful monitoring during PCP therapy is important to evaluate treatment response and to detect toxicity as soon as possible. Follow-up after therapy includes assessment for early relapse, especially if therapy has been with an agent other than TMP-SMX or was shortened because of toxicity.

In people with HIV, rates of adverse reactions to TMP-SMX are high (20% to 85% of patients).[91,92,106,108,113,130-134] Common adverse effects are rash (30% to 55% of patients) (including Stevens-Johnson syndrome), fever (30% to 40% of patients), leukopenia (30% to 40% of patients), thrombocytopenia (15% of patients), azotemia (1% to 5% of patients), hepatitis (20% of patients), hyperkalemia, and rarely, aseptic meningitis. Supportive care for common adverse effects should be attempted before TMP-SMX is discontinued **(AIII)**. Mild rashes (e.g., rash without vesicles, bullae, or ulcerations), nausea, and fever can often be "treated through" with antihistamines, antiemetics, and antipyretics, respectively.[59] High-dose trimethoprim inhibits tubular secretion of creatinine without affecting glomerular filtration rate, and this may be additive with other medications. As noted above, therapy should be permanently discontinued in the setting of **life-threatening adverse reactions *including*** possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis **(AIII).**

The most common adverse effects of alternative therapies include methemoglobinemia and hemolysis with dapsone or primaquine (especially in those with G6PD deficiency); rash and fever with dapsone[92,106]; azotemia, pancreatitis, hypoglycemia or hyperglycemia, leukopenia, electrolyte abnormalities, and cardiac dysrhythmia with pentamidine[110,112,113,133]; anemia, rash, fever, and diarrhea with primaquine and clindamycin[92,107,108]; and headache, nausea, diarrhea, rash, and transaminase elevations with atovaquone.[91,132] Patients who exhibit persistent hypoxemia despite an apparent positive clinical response should undergo evaluation for methemoglobinemia if they are taking potentially causative medications.

Managing Treatment Failure

Clinical failure is defined as lack of improvement or worsening of respiratory function documented by arterial blood gases after 4 to 8 days of anti-PCP treatment. Failure attributed to lack of drug efficacy occurs in approximately 10% of people with HIV with mild-to-moderate PCP disease.[91,92] However, there are not any convincing clinical trial data on which to base recommendations for the management of PCP treatment failure due to lack of drug efficacy.

Clinicians should wait 4 to 8 days before switching therapy for lack of clinical improvement **(BIII).** In the absence of corticosteroid therapy, early and reversible deterioration within the first 3 to 5 days of therapy is typical, probably because of the inflammatory response caused by antibiotic-induced lysis of organisms in the lung. Other concomitant infectious and non-infectious processes must be excluded as a cause of clinical failure[28,29]; bronchoscopy with BAL should be strongly considered to evaluate for this possibility, even if bronchoscopy was used to make the initial diagnosis.

Treatment-limiting toxicities occur in up to one-third of patients.[92] Switching to another regimen is the appropriate management for treatment-related toxicity **(BII).** When TMP-SMX is not effective or cannot be used for moderate-to-severe disease because of toxicity, the common practice is to use parenteral pentamidine **(BII)** or oral primaquine combined with IV clindamycin **(BII).**[108,109,113] For mild disease, atovaquone is a reasonable alternative **(BII).** Although a meta-analysis, systematic review, and cohort study concluded that the combination of primaquine and clindamycin might be the most effective regimen for salvage therapy,[109,115,116] no prospective clinical trials have evaluated the optimal approach for people with HIV who experience a therapy failure with TMP-SMX.

Preventing Recurrence

Recommendations for Preventing Recurrence of *Pneumocystis* Pneumonia (Secondary Prophylaxis)

Indications for Initiating Secondary Prophylaxis

- Prior PCP

Preferred Therapy

- TMP-SMX, 1 DS tablet PO daily[a] (AI), *or*
- TMP-SMX, 1 SS tablet PO daily[a] (AI)
- Note: TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections. Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional prophylaxis for PCP (AII).

Alternative Therapy

- The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*:
  - TMP-SMX one DS tablet PO three times weekly (BI), or
  - Dapsone[a] 50 mg PO daily with pyrimethamine 50 mg plus leucovorin 25 mg PO weekly (BI), or
  - Dapsone[a] 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg PO weekly (BI), or
  - Atovaquone 1,500 mg PO daily with food (BI)
- The following regimens should only be used in people who are seronegative for *Toxoplasma gondii*:
  - Dapsone[a] 100 mg PO daily (BI), or
  - Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month (BI), or
  - Intravenous pentamidine 300 mg every 28 days (CIII)

Indications for Discontinuing Secondary Prophylaxis

- CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3 for ≥3 months as a result of ART (AII), *or*
- Can consider if CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limits of detection of assay used for 3 to 6 months (BII)
- For people with HIV in whom PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 to 6 months, although there are no data to support recommendations in this setting (CIII).
- Note: If an episode of PCP occurs at a CD4 count >200 cells/mm^3 while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, especially with plasma HIV RNA below level of detection, regardless of how high the CD4 cell count rises as a consequence of ART (BIII).

Indications for Restarting Secondary Prophylaxis

- CD4 count <100 cells/mm^3 regardless of HIV RNA (AIII), *or*
- CD4 count 100–200 cells/mm^3 and HIV RNA above detection limit of the assay used (AIII)

Pre-pregnancy and Pregnancy Considerations

- Clinicians who are providing pre-pregnancy care for people with HIV receiving PCP prophylaxis can discuss with their patients the option of deferring pregnancy until PCP prophylaxis can be safely discontinued (BIII) due to potential concerns about possible adverse effects of trimethoprim on the fetus.
- Persons of childbearing potential who choose not to defer pregnancy while on TMP-SMX should consider increasing the dose of folic acid to 4 mg/day (BIII).
- Chemoprophylaxis for PCP should be administered to pregnant adults and adolescents as for nonpregnant adults and adolescents (AIII). TMP-SMX is the recommended prophylactic agent (AIII). Clinicians should consider giving supplemental folic acid 4 mg/day to people in their first trimester who are on TMP-SMX (BIII).
- Given theoretical concerns about possible teratogenicity associated with first-trimester TMP-SMX exposures, alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone can be used in during the first trimester (BII).
- Dapsone should be used in the first trimester only if the other alternatives are not available or tolerated due to concerns about hemolytic anemia in mothers or exposed fetuses (BIII).

Note regarding G6PD deficiency and use of primaquine or dapsone in pregnancy: As with nonpregnant adults, G6PD levels should be checked before administration of primaquine or dapsone. While G6PD level in a fetus are generally unknown during pregnancy, G6PD deficiency is an X-linked inherited condition and primaquine or dapsone can be considered if both the pregnant person and biologic father have normal G6PD activity.

Other Considerations/Comments

- For people with HIV with non-life-threatening adverse reactions to TMP-SMX, the drug should be continued if clinically feasible.
- If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution of therapy should be considered after the reaction has resolved (AII). The dose of TMP-SMX can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII).
- TMP-SMX should be permanently discontinued, with no rechallenge, in people with HIV with life-threatening adverse events, ***including*** suspected or confirmed Stevens-Johnson Syndrome or toxic epidermal necrolysis (AIII). See above for alternative options for secondary PCP prophylaxis.

[a] Whenever possible, people with HIV should be tested for G6PD deficiency before administration of dapsone. An alternative agent should be used if the patient is found to have G6PD deficiency.

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; G6PD = glucose-6-phosphate dehydrogenase; IV = intravenously; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole

When to Start Secondary Prophylaxis

Secondary PCP prophylaxis with TMP-SMX should be initiated immediately upon successful completion of PCP therapy and maintained until immune reconstitution occurs as a result of ART (see below) **(AI).**[135] For people with HIV who are intolerant of TMP-SMX, the alternatives are dapsone **(BI),** dapsone plus pyrimethamine plus leucovorin **(BI),** atovaquone **(BI),** and aerosolized **(BI)** or IV pentamidine **(CIII).**

When to Stop Secondary Prophylaxis

Secondary prophylaxis should be discontinued in adult and adolescent patients whose CD4 counts have increased from <200 cells mm^3 to ≥200 cells mm^3 for ≥3 months as a result of ART **(AII).** Reports from observational studies[77,83,136,137] and from two randomized trials[84,138] and a combined analysis of European cohorts being followed prospectively[139,140] support this recommendation. In these studies, people with HIV responded to ART with an increase in CD4 counts to ≥200 cells/mm^3 for ≥3 months. At the time secondary PCP prophylaxis was discontinued, the median CD4 count was >300 cells/mm^3 and most people with HIV had a CD4 cell percentage >14%. Most people with HIV had sustained suppression of plasma HIV RNA levels below the limits of detection for the assay employed; the longest follow-up was 40 months. Based on results from the COHERE study, secondary prophylaxis in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 can potentially be discontinued if HIV plasma RNA levels remain below limits of detection for 3 to 6 months **(BII).**[141]

When to Restart Primary or Secondary Prophylaxis

Primary or secondary PCP prophylaxis should be reintroduced if the patient's CD4 count decreases to <100 cells/mm^3 **(AIII)** regardless of the HIV plasma viral load. Prophylaxis should also be reintroduced for people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 with HIV plasma viral load above detection limits of the assay used **(AIII).** Based on results from the COHERE study, primary or secondary PCP prophylaxis may not need to be restarted in people with HIV with CD4 counts of 100 cells/mm^3 to 200 cells/mm^3 who have had HIV plasma RNA levels below limits of detection for 3 to 6 months **(BII).**[86,139]

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

Special Considerations Regarding Pregnancy

Some data suggest an increased risk of PCP-associated mortality in pregnancy.[142] All-cause pneumonia during pregnancy increases rates of preterm labor and delivery.[143]

People at >20 weeks gestation who have PCP should be closely monitored for signs or symptoms of preterm labor (e.g., abdominal cramping, uterine tightening, fluid leakage) **(BIII).**

Pre-pregnancy Care

Clinicians who are providing pre-pregnancy care for people with HIV receiving PCP prophylaxis can discuss with their patients the option of deferring pregnancy until PCP prophylaxis can be safely discontinued **(BIII)** due to concerns about possible adverse effects of trimethoprim on the fetus (see the Primary and Secondary Prophylaxis section below). All persons of childbearing potential should take supplemental folic acid at a dose of 0.4 mg/day **(AI);** those who choose not to defer pregnancy while on TMP-SMX should consider increasing the dose of folic acid to 4 mg/day **(BIII)** (see below).

Pregnancy Care

Note: Specific drugs recommended for prophylaxis are discussed in the section on Primary and Secondary Prophylaxis. This information is not repeated in the Treating Disease section and only medications recommended exclusively for treatment are discussed in this section.

Primary and Secondary Prophylaxis

Chemoprophylaxis for PCP should be administered to pregnant adults and adolescents as for nonpregnant adults and adolescents **(AIII).** The preferred regimen for prophylaxis is TMP-SMX **(AIII).** Given concerns about possible teratogenicity associated with first-trimester TMP-SMX exposure, alternative prophylactic regimens such as aerosolized pentamidine or oral atovaquone can be used during the first trimester **(BII).** Dapsone should be used in the first trimester only if the other alternatives are not available or tolerated due to concerns about hemolytic anemia in pregnant persons or exposed fetuses **(BIII).** As with nonpregnant adults, G6PD levels should be checked before dapsone administration.

No adequate and well-controlled large studies of pregnancy outcomes after exposure to sulfamethoxazole and trimethoprim have been published. Trimethoprim is classified as a folic acid antagonist, acting as a dihydrofolate reductase inhibitor; older case-control studies found that first-trimester exposure has been associated with an increased risk of neural tube defects and cardiovascular, oral clefts, urinary tract, and multiple anomalies.[144-146] A systematic review and meta-analysis in 2014, including 24 studies,[147] reported congenital anomalies in 232 infants among 4,196 women receiving TMP-SMX in pregnancy, with a pooled prevalence of 3.5% (95% confidence interval [CI], 1.8% to 5.1%) and three studies reported 31 infants with neural tube defects associated with first-trimester exposure, with a crude prevalence of 0.7% (95% CI, 0.5% to 1.0%). The quality of the evidence was considered very low and the authors supported continued recommendation for TMP-SMX when indicated for pregnant persons with HIV. A recent systematic review of antimicrobials used for management of plague during pregnancy included 23,602 prenatal exposures to TMP-SMX found that first-trimester exposure was associated with an increased risk of neural tube defects (pooled odds ratio [OR] 2.5; 95% CI, 1.4–4.3).[148] This study also found increased odds of spontaneous abortion (OR 3.5; 95% CI, 2.3–5.6), preterm delivery (OR 1.5; 95% CI, 1.1–2.1) and the fetus being small for gestational age (OR 1.6; 95% CI, 1.2–2.2). In a nested case-control study (n = 77,429; 7,039 cases of spontaneous abortion) based on prescription fills, first-trimester exposure to TMP-SMX, after adjusting for potential confounders, was associated with increased odds of spontaneous abortion (adjusted odds ratio [aOR] 2.94, 95% CI, 1.89–4.57, including 25 exposed cases and 77 controls).[149] Exposure to TMP-SMX in the last two trimesters of pregnancy was associated with low birth weight, adjusted for gestational age and gender (OR 1.61; 95% CI, 1.16–2.23) in a case-control study within the Quebec Pregnancy Registry (8,192 cases, 55,146 controls).[150] Data from a large Canadian administrative database was used to retrospectively compare the occurrence of placenta-mediated adverse pregnancy outcomes between pregnant women exposed to folic acid antagonists and women without exposure to these agents.[151] TMP-SMX was the most frequently prescribed dihydrofolate reductase inhibitor (11,386 exposures during the preconception period and all three trimesters compared to 45,456 unexposed women) and exposure was associated with increased odds of preeclampsia (aOR 1.13; 95% CI, 1.01–1.26), placental abruption (aOR 1.26; 95% CI, 1.03–1.55), and fetal growth restriction defined as less than the third percentile (aOR 1.20; 95% CI, 1.07–1.33).

Folic acid supplementation at 0.4 mg/day is routinely recommended for all women of reproductive potential,[152] to reduce the risk of neural tube defects **(AI).** Since neural tube closure occurs early in pregnancy, often before pregnancy is diagnosed, all persons planning a pregnancy or with reproductive potential should take daily folic acid supplementation. There is also evidence that folic acid supplementation may decrease risk of congenital heart defects, cleft lip and palate,[153] preterm birth,[154] low birth weight, and the fetus being small for gestational age.[155,156] There are no trials evaluating whether supplementation at higher levels (e.g., 4 mg/day as recommended for pregnant women who previously had an infant with a neural tube defect) would reduce the risk of birth defects associated with first-trimester TMP-SMX use. A multicenter double-blind randomized clinical trial in women of childbearing age who planned pregnancy within 12 months failed to show an advantage of folic acid 4 mg versus 0.4 mg daily on the occurrence of congenital malformations; however, the higher dose was associated with lower occurrence of spontaneous abortion, the fetus being small for gestational age, and preterm delivery.[157] The authors noted that the study was underpowered for the outcome of congenital malformations.[157] Other studies have found that higher doses of folic acid (4–6 mg/day) are associated with less frequent neural tube defects, oral clefts, and recurrent preeclampsia.[158-160] In a large, population-based, case-control study, the increased odds of congenital cardiovascular anomalies associated with TMP-SMX use in pregnancy were not seen in women also receiving folic acid supplementation, most of whom received folic acid 6 mg/day (OR 1.24; 95% CI, 0.94–1.62).[144]

Although the risk of multiple congenital abnormalities associated with TMP-SMX use persisted despite supplemental folic acid, the OR decreased from 6.4 for TMP-SMX without folic acid to 1.9 for TMP-SMX plus folic acid. Based on these findings, with the suggestion of a dose-response effect of folic acid supplementation and the known effects of TMP-SMX as a folic acid antagonist, clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX prior to pregnancy in those who are capable of becoming pregnant, or as soon as possible in the first trimester in those who are pregnant **(BIII).** Leucovorin (folinic acid) is an active form of folate and is commonly used to counteract the effect of folic acid antagonists, especially as an adjunct in the treatment of various cancers. However, it is chemically different from folic acid and is not interchangeable. A randomized, controlled trial demonstrated that adding leucovorin to TMP-SMX for the treatment of PCP was associated with an increased risk of therapeutic failure and death.[95] In addition, there are case reports of failure of TMP-SMX prophylaxis in the setting of concurrent leucovorin use.[161] If a higher dose of supplemental folic acid is given, its use should be limited to the first trimester **(AIII).** Whether or not a person receives supplemental folic acid during the first trimester, a follow-up ultrasound is recommended at 18 weeks to 20 weeks to assess fetal anatomy with consideration for subsequent follow-up scans **(BIII).**

Although historically there has been concern about the risk of neonatal kernicterus in the setting of maternal sulfonamide or dapsone use near delivery, reviews have found no cases of kernicterus reported in neonates after maternal ingestion of sulfonamides or with the use of TMP-SMX in neonates.[162-164] For several decades, dapsone has been used safely to treat leprosy, malaria, and various dermatologic conditions during pregnancy.[165,166] Long-term therapy is associated with a risk of mild maternal hemolysis, and exposed fetuses with G6PD deficiency are at potential risk (albeit extremely low) of acute hemolytic anemia.[167]

Data on atovaquone in human pregnancy are limited but preclinical studies have not demonstrated teratogenicity in rats or rabbits at plasma concentrations corresponding to estimated human exposure during malaria treatment.[168] A systematic review of the safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy found miscarriages in 21 of 260 women (8.08%;

95% CI, 5.07% to 12.08%) and congenital anomalies in 11 of 430 women (2.56%; 95% CI, 1.28% to 4.53%), both well within expected rates.[169] When considering only results from this one randomized clinical trial of atovaquone-proguanil, there was no significant difference in these outcomes when compared to quinine, although the number was extremely small (n = 81).[170]

Pentamidine is embryotoxic but not teratogenic in rats and rabbits.[171] There is limited experience with systemic use in human pregnancy and no human studies of pregnancy outcomes after exposure to pentamidine have been published. It is unknown if pentamidine crosses the placental barrier at significant concentrations when administered via the aerosolized route. Given anecdotal experience to date during pregnancy without signs of adverse effects or teratogenicity, pentamidine should be considered an alternative when indicated either via aerosolized or IV route.

Treating Disease

The preferred initial therapy for PCP during pregnancy, regardless of disease severity, is TMP-SMX **(AI).**[134]

Although a small increased risk of birth defects may be associated with first-trimester exposure to trimethoprim, people with PCP in the first trimester should be treated with TMP-SMX because of its considerable benefit in reducing morbidity and mortality, which outweighs the potential risk **(AIII).** Clinicians should consider giving supplemental folic acid 4 mg/day to people who are on TMP-SMX and capable of pregnancy or as soon as possible in the first trimester **(BIII).** Doses of supplemental folic acid of 4 mg/day should be limited to the first trimester during the teratogenic window and can be reduced to 0.4 mg at 12 weeks continuing to 4 to 6 weeks postpartum or discontinuation of breastfeeding **(AIII).**

If an alternative therapeutic regimen is required for moderate-to-severe PCP, IV pentamidine is preferred **(BIII).** Primaquine plus clindamycin should be used only if other alternatives are not available or tolerated **(BIII).** If an alternative therapeutic regimen is required for mild-to-moderate PCP, atovaquone suspension is preferred **(BIII);** dapsone plus TMP can be used if atovaquone is not available or tolerated **(BIII).** As with nonpregnant adults, G6PD levels should be checked before administration of dapsone**.** Because of concerns about hemolytic anemia in exposed fetuses who are G6PD-deficient (which cannot be diagnosed antenatally), primaquine or dapsone should be used in pregnancy only if other alternatives are not available or tolerated and benefit is felt to outweigh the risk **(AIII).**

Adjunctive corticosteroid therapy should be used to improve the mother's treatment outcome as indicated in nonpregnant adults **(AIII).**[172-175] Patients with documented or suspected PCP and moderate-to-severe disease, as defined by room air PO_2 <70 mmHg or A-a gradient PO_2 ≥35 mmHg, should receive adjunctive corticosteroids as early as possible. Corticosteroids have commonly been used in pregnancy for autoimmune conditions and are considered low risk for use in pregnancy.[176] Although an earlier systematic review of case-control studies evaluating women with first-trimester exposure to corticosteroids found a 3.4-fold increase in the odds of delivering a baby with an oral cleft,[177] more recent data from a prospective controlled study in Israel, a large population-based registry in Sweden,[178] and an updated analysis from the National Birth Defect Prevention Study,[179,180] have failed to demonstrate an association between first-trimester corticosteroids and major congenital anomalies, including orofacial clefts. A recent systematic review and meta-analysis also found no association between first-trimester corticosteroid exposure and risk of congenital heart defects.[181] Long-term corticosteroid use in pregnancy may be associated with an increased risk of maternal

hypertension, preeclampsia, hyperglycemia, premature rupture of membranes, intrauterine growth restriction,[182] and infection, although the magnitude is not known.[183]

Maternal glucose levels and blood pressure as well as fetal growth should be monitored closely when corticosteroids are used in pregnancy **(AIII).** Based on available observational data from pregnant and nonpregnant surgical patients, pregnant persons who are on chronic steroid therapy during pregnancy for non-hypothalamic-pituitary-adrenal axis disorders do not need stress doses of steroids for vaginal or cesarean delivery, but they should be continued on their therapeutic dose of steroids without interruption **(BIII).** HPA axis suppression is rarely seen among neonates born to women who received chronic corticosteroids during pregnancy.

Clindamycin is considered safe for use throughout pregnancy **(BIII).** Clindamycin is recommended as an alternative antibiotic for prevention of group B streptococcal disease in newborns and for antimicrobial prophylaxis during cesarean delivery.[184,185] However, there are no well-controlled studies of clindamycin use in pregnant women during the first trimester. In animal studies, clindamycin was not teratogenic following oral doses up to six times the maximum recommended adult human dose.[186] During clinical trials, the systemic administration of clindamycin to pregnant women during the second and third trimesters did not increase the frequency of congenital abnormalities.[186]

There are no adequate or well-controlled studies of primaquine use in pregnant women, and animal data is scant. Although some data from animal studies suggest evidence of genotoxicity, as well as fetal abnormalities at doses multiple times the maximal dose in humans,[187] another animal study at doses 0.25 to 3.0 mg/kg early in gestation found no harmful effects on mother or offspring.[188] In an observational study from Brazil, 59 women were found to have been prescribed primaquine for malaria during pregnancy, approximately one-third in the first trimester; no adverse birth outcomes were found, although G6PD testing was not done on the infants.[189] The Centers for Disease Control and Prevention recommend that primaquine not be administered during pregnancy because of the risk of hemolytic anemia in a G6PD-deficient fetus.[190] The degree of intravascular hemolysis appears to be associated with both the dose of primaquine and severity of G6PD deficiency.[168] G6PD deficiency is an X-linked inherited condition and primaquine can be considered if both the pregnant person and biologic father have normal G6PD activity.[191] Primaquine should be used in pregnancy only if other alternatives are not available or tolerated and the benefit is felt to outweigh the risk **(AIII).**

References

1. Nevez G, Totet A, Matos O, Calderon EJ, Miller RF, Le Gal S. It is still PCP that can stand for *Pneumocystis* pneumonia: appeal for generalized use of only one acronym. *Med Mycol*. 2021;59(8):842-844. Available at: https://pubmed.ncbi.nlm.nih.gov/34003930.

2. Pifer LL, Hughes WT, Stagno S, Woods D. *Pneumocystis carinii* infection: evidence for high prevalence in normal and immunosuppressed children. *Pediatrics*. 1978;61(1):35-41. Available at: http://www.ncbi.nlm.nih.gov/pubmed/400818.

3. Keely SP, Stringer JR, Baughman RP, Linke MJ, Walzer PD, Smulian AG. Genetic variation among *Pneumocystis carinii hominis* isolates in recurrent pneumocystosis. *J Infect Dis*. 1995;172(2):595-598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7542688.

4. Helweg-Larsen J, Tsolaki AG, Miller RF, Lundgren B, Wakefield AE. Clusters of *Pneumocystis carinii* pneumonia: analysis of person-to-person transmission by genotyping. *QJM*. 1998;91(12):813-820. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10024946.

5. Huang L, Beard CB, Creasman J, et al. Sulfa or sulfone prophylaxis and geographic region predict mutations in the *Pneumocystis carinii* dihydropteroate synthase gene. *J Infect Dis*. 2000;182(4):1192-1198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10979917.

6. Sassi M, Ripamonti C, Mueller NJ, et al. Outbreaks of *Pneumocystis* pneumonia in 2 renal transplant centers linked to a single strain of *Pneumocystis*: implications for transmission and virulence. *Clin Infect Dis*. 2012;54(10):1437-1444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22431811.

7. de Boer MG, Kroon FP, le Cessie S, de Fijter JW, van Dissel JT. Risk factors for *Pneumocystis jirovecii* pneumonia in kidney transplant recipients and appraisal of strategies for selective use of chemoprophylaxis. *Transpl Infect Dis*. 2011;13(6):559-569. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21689251.

8. Arichi N, Kishikawa H, Mitsui Y, et al. Cluster outbreak of *Pneumocystis* pneumonia among kidney transplant patients within a single center. *Transplant Proc*. 2009;41(1):170-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19249506.

9. Gianella S, Haeberli L, Joos B, et al. Molecular evidence of interhuman transmission in an outbreak of *Pneumocystis jirovecii* pneumonia among renal transplant recipients. *Transpl Infect Dis*. 2010;12(1):1-10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19744285.

10. Mori S, Cho I, Sugimoto M. A cluster of *Pneumocystis jirovecii* infection among outpatients with rheumatoid arthritis. *J Rheumatol*. 2010;37(7):1547-1548. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20595296.

11. Schmoldt S, Schuhegger R, Wendler T, et al. Molecular evidence of nosocomial *Pneumocystis jirovecii* transmission among 16 patients after kidney transplantation. *J Clin Microbiol*. 2008;46(3):966-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18216217.

12. Yazaki H, Goto N, Uchida K, Kobayashi T, Gatanaga H, Oka S. Outbreak of *Pneumocystis jiroveci* pneumonia in renal transplant recipients: *P. jiroveci* is contagious to the susceptible host. *Transplantation*. 2009;88(3):380-385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19667941.

13. Phair J, Munoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. 1990;322(3):161-165. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1967190.

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

15. Sezgin E, Van Natta ML, Thorne JE, Puhan MA, Jabs DA, Longitudinal Studies of the Ocular Complications of AIDS Research Group. Secular trends in opportunistic infections, cancers and mortality in patients with AIDS during the era of modern combination antiretroviral therapy. *HIV Med*. 2018;19(6):411-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29573311.

16. Bielick C, Strumpf A, Ghosal S, McMurry T, McManus KA. National hospitalization rates and in-hospital mortality rates of HIV-related opportunistic infections in the United States, 2011–2018. *Clin Infect Dis*. 2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38306316.

17. Lundberg BE, Davidson AJ, Burman WJ. Epidemiology of *Pneumocystis carinii* pneumonia in an era of effective prophylaxis: the relative contribution of non-adherence and drug failure. *AIDS*. 2000;14(16):2559-2566. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11101068.

18. Wolff AJ, O'Donnell AE. Pulmonary manifestations of HIV infection in the era of highly active antiretroviral therapy. *Chest*. 2001;120(6):1888-1893. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11742918.

19. Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. *Ann Intern Med*. 1984;100(5):663-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6231873.

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

21. Chiliza N, Du Toit M, Wasserman S. Outcomes of HIV-associated *Pneumocystis* pneumonia at a South African referral hospital. *PLoS One*. 2018;13(8):e0201733. Available at: https://pubmed.ncbi.nlm.nih.gov/30071089.

22. Ng VL, Yajko DM, Hadley WK. Extrapulmonary pneumocystosis. *Clin Microbiol Rev*. 1997;10(3):401-418. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9227859.

23. Smith DE, McLuckie A, Wyatt J, Gazzard B. Severe exercise hypoxaemia with normal or near normal x-rays: a feature of *Pneumocystis carinii* infection. *Lancet*. 1988;2(8619):1049-1051. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2903279.

24. Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia. Diagnostic and prognostic significance. *Am Rev Respir Dis*. 1988;137(4):796-800. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3258483.

25. Opravil M, Marincek B, Fuchs WA, et al. Shortcomings of chest radiography in detecting *Pneumocystis carinii* pneumonia. *J Acquir Immune Defic Syndr*. 1994;7(1):39-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8263751.

26. Metersky ML, Colt HG, Olson LK, Shanks TG. AIDS-related spontaneous pneumothorax. Risk factors and treatment. *Chest*. 1995;108(4):946-951. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7555166.

27. Sepkowitz KA, Telzak EE, Gold JW, et al. Pneumothorax in AIDS. *Ann Intern Med*. 1991;114(6):455-459. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1994791.

28. Baughman RP, Dohn MN, Frame PT. The continuing utility of bronchoalveolar lavage to diagnose opportunistic infection in AIDS patients. *Am J Med*. 1994;97(6):515-522. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7985710.

29. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med*. 1984;101(1):1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6375497.

30. Gruden JF, Huang L, Turner J, et al. High-resolution CT in the evaluation of clinically suspected *Pneumocystis carinii* pneumonia in AIDS patients with normal, equivocal, or nonspecific radiographic findings. *AJR Am J Roentgenol*. 1997;169(4):967-975. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9308446.

31. Hidalgo A, Falco V, Mauleon S, al. e. Accuracy of high-resolution CT in distinguishing between *Pneumocystis carinii* pneumonia and non-*Pneumocystis carinii* pneumonia in AIDS patients. *Eur Radiol*. 2003;13:1179-1184. Available at: https://pubmed.ncbi.nlm.nih.gov/12695843.

32. Roger PM, Vandenbos F, Pugliese P, et al. Persistence of *Pneumocystis carinii* after effective treatment of *P. carinii* pneumonia is not related to relapse or survival among patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1998;26(2):509-510. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9502487.

33. Cruciani M, Marcati P, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of diagnostic procedures for *Pneumocystis carinii* pneumonia in HIV-1-infected patients. *Eur Respir J*. 2002;20(4):982-989. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12412693.

34. Flori P, Bellete B, Durand F, et al. Comparison between real-time PCR, conventional PCR and different staining techniques for diagnosing *Pneumocystis jiroveci* pneumonia from

bronchoalveolar lavage specimens. *J Med Microbiol*. 2004;53(Pt 7):603-607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15184529.

35. Armbruster C, Pokieser L, Hassl A. Diagnosis of *Pneumocystis carinii* pneumonia by bronchoalveolar lavage in AIDS patients. Comparison of Diff-Quik, fungifluor stain, direct immunofluorescence test and polymerase chain reaction. *Acta Cytol*. 1995;39(6):1089-1093. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7483981.

36. Aderaye G, Woldeamanuel Y, Asrat D, et al. Evaluation of Toluidine Blue O staining for the diagnosis of *Pneumocystis jiroveci* in expectorated sputum sample and bronchoalveolar lavage from HIV-infected patients in a tertiary care referral center in Ethiopia. *Infection*. 2008;36(3):237-243. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18483698.

37. Raab SS, Cheville JC, Bottles K, Cohen MB. Utility of Gomori methenamine silver stains in bronchoalveolar lavage specimens. *Mod Pathol*. 1994;7(5):599-604. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7524071.

38. Tiley SM, Marriott DJ, Harkness JL. An evaluation of four methods for the detection of *Pneumocystis carinii* in clinical specimens. *Pathology*. 1994;26(3):325-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7527514.

39. Procop GW, Haddad S, Quinn J, et al. Detection of *Pneumocystis jiroveci* in respiratory specimens by four staining methods. *J Clin Microbiol*. 2004;42(7):3333-3335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15243109.

40. Thomas CF, Jr., Limper AH. *Pneumocystis* pneumonia. *N Engl J Med*. 2004;350(24):2487-2498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15190141.

41. Guegan H, Roojee M, Le Gal S, et al. Evaluation of the PneumoGenius® PCR assay for the diagnosis of *Pneumocystis pneumonia* and the detection of *Pneumocystis* dihydropteroate synthase mutations in respiratory samples. *Med Mycol*. 2023;61(4). Available at: https://pubmed.ncbi.nlm.nih.gov/37028929.

42. Lussac-Sorton F, Fleur T, Voisin T, et al. Interest of a commercialized *Pneumocystis jirovecii* quantitative PCR to discriminate colonization from *Pneumocystis pneumonia* according to the Revised EORTC/MSGERC Criteria. *J Clin Med*. 2022;12(1). Available at: https://pubmed.ncbi.nlm.nih.gov/36615116.

43. Nijhuis RHT, Godschalk PCR, Smink JHI, van der Zee C, van Hannen EJ. Comparison of the PneumoGenius® and RealStar® *Pneumocystis jirovecii* PCR CE-IVD assays with a lab developed test for the detection of *Pneumocystis jirovecii*. *Med Mycol*. 2022;60(1). Available at: https://pubmed.ncbi.nlm.nih.gov/34894244.

44. Pisculli ML, Sax PE. Use of a serum beta-glucan assay for diagnosis of HIV-related *Pneumocystis jiroveci* pneumonia in patients with negative microscopic examination results. *Clin Infect Dis*. 2008;46(12):1928-1930. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18540807.

45. Sax PE, Komarow L, Finkelman MA, et al. Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related *Pneumocystis jirovecii* pneumonia. *Clin Infect Dis*. 2011;53(2):197-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21690628.

46. Li WJ, Guo YL, Liu TJ, Wang K, Kong JL. Diagnosis of *Pneumocystis pneumonia* using serum (1-3)-beta-D-Glucan: a bivariate meta-analysis and systematic review. *J Thorac Dis*. 2015;7(12):2214-2225. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26793343.

47. Del Corpo O, Butler-Laporte G, Sheppard DC, Cheng MP, McDonald EG, Lee TC. Diagnostic accuracy of serum (1-3)-β-D-glucan for *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2020;26(9):1137-1143. Available at: https://pubmed.ncbi.nlm.nih.gov/32479781.

48. Corsi-Vasquez G, Ostrosky-Zeichner L, Pilkington EF, 3rd, Sax PE. Point-counterpoint: should serum β-d-glucan testing be used for the diagnosis of *Pneumocystis jirovecii* pneumonia? *J Clin Microbiol*. 2019;58(1). Available at: https://pubmed.ncbi.nlm.nih.gov/31434728.

49. Choukri F, Menotti J, Sarfati C, et al. Quantification and spread of *Pneumocystis jirovecii* in the surrounding air of patients with *Pneumocystis* pneumonia. *Clin Infect Dis*. 2010;51(3):259-265. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20572759.

50. Pliquett RU, Asbe-Vollkopf A, Hauser PM, et al. A *Pneumocystis jirovecii* pneumonia outbreak in a single kidney-transplant center: role of cytomegalovirus co-infection. *Eur J Clin Microbiol Infect Dis*. 2012;31(9):2429-2437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22402816.

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

52. Heald A, Flepp M, Chave JP, et al. Treatment for cerebral toxoplasmosis protects against *Pneumocystis carinii* pneumonia in patients with AIDS. The Swiss HIV Cohort Study. *Ann Intern Med*. 1991;115(10):760-763. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1929023.

53. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):693-699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7854375.

54. Schneider MM, Hoepelman AI, Eeftinck Schattenkerk JK, et al. A controlled trial of aerosolized pentamidine or trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. The Dutch AIDS Treatment Group. *N Engl J Med*. 1992;327(26):1836-1841. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1360145.

55. Schneider MM, Nielsen TL, Nelsing S, et al. Efficacy and toxicity of two doses of trimethoprim-sulfamethoxazole as primary prophylaxis against *Pneumocystis carinii*

pneumonia in patients with human immunodeficiency virus. Dutch AIDS Treatment Group. *J Infect Dis*. 1995;171(6):1632-1636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7769306.

56. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected persons. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). *Clin Infect Dis*. 1999;29(4):775-783. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10589887.

57. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. 1992;117(2):106-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1351371.

58. Hardy WD, Feinberg J, Finkelstein DM, et al. A controlled trial of trimethoprim-sulfamethoxazole or aerosolized pentamidine for secondary prophylaxis of *Pneumocystis carinii* pneumonia in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trials Group Protocol 021. *N Engl J Med*. 1992;327(26):1842-1848. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1448121.

59. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) table for grading the severity of adult and pediatric adverse events, corrected version 2.1. July 2017. Available at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.

60. Para MF, Finkelstein D, Becker S, Dohn M, Walawander A, Black JR. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia: AIDS Clinical Trials Group 268. *J Acquir Immune Defic Syndr*. 2000;24(4):337-343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11015150.

61. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11574913.

62. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of *Pneumocystis* pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. 1995;122(10):755-761. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7717598.

63. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1995;20(3):531-541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7756472.

64. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and

toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. 1993;328(21):1514-1520. Available at: https://pubmed.ncbi.nlm.nih.gov/8479488.

65. McCollam S, Lewis JS, 2nd, Bubalo J, Diaz A. *Pneumocystis jirovecii* pneumonia prophylaxis with intravenous pentamidine in adult allogeneic hematopoietic stem cell transplant patients. *Antimicrob Agents Chemother*. 2022;66(11):e0083322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36214573.

66. Awad WB, Asaad A, Al-Yasein N, Najjar R. Effectiveness and tolerability of intravenous pentamidine for *Pneumocystis carinii* pneumonia prophylaxis in adult hematopoietic stem cell transplant patients: a retrospective study. *BMC Infect Dis*. 2020;20(1):400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32503449.

67. Ena J, Amador C, Pasquau F, et al. Once-a-month administration of intravenous pentamidine to patients infected with human immunodeficiency virus as prophylaxis for *Pneumocystis carinii* pneumonia. *Clin Infect Dis*. 1994;18(6):901-904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8086550.

68. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis*. 1999;180(2):369-376. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10395851.

69. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9862944.

70. Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against *Pneumocystis carinii* pneumonia and toxoplasma encephalitis in HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1997;15(2):104-114. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9241108.

71. Antinori A, Murri R, Ammassari A, et al. Aerosolized pentamidine, cotrimoxazole and dapsone-pyrimethamine for primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis. *AIDS*. 1995;9(12):1343-1350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8605054.

72. Youngster I, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf*. 2010;33(9):713-726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20701405.

73. ISSA. Occupational risk prevention in aerosol therapy (pentamidine). 2015. Available at: https://ww1.issa.int/prevention-health/publications?page=2.

74. Pediatric Oncology Group of Ontario. Pentamidine administration. 2022. Available at: https://www.pogo.ca/satellite-manual/4-0-supportive-care-practice-tools/4-2-pentamidine-administration/4-2-1-inhaled-pentamidine.

75. Jacobson MA, Besch CL, Child C, et al. Toxicity of clindamycin as prophylaxis for AIDS-associated toxoplasmic encephalitis. Community Programs for Clinical Research on AIDS. *Lancet*. 1992;339(8789):333-334. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1346413.

76. Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *N Engl J Med*. 1999;340(17):1301-1306. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10219064.

77. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10915098.

78. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. 2000;181(5):1635-1642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10823763.

79. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. *Lancet*. 1999;353(9148):201-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9923876.

80. Weverling GJ, Mocroft A, Ledergerber B, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of highly active antiretroviral therapy in HIV-1 infection. EuroSIDA Study Group. *Lancet*. 1999;353(9161):1293-1298. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10218526.

81. Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD. Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. HIV Outpatient Study (HOPS) Investigators. *Ann Intern Med*. 2000;132(3):201-205. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10651600.

82. Furrer H, Opravil M, Rossi M, et al. Discontinuation of primary prophylaxis in HIV-infected patients at high risk of *Pneumocystis carinii* pneumonia: prospective multicentre study. *AIDS*. 2001;15(4):501-507. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11242147.

83. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. 1999;13(13):1647-1651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10509565.

84. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. *N Engl J Med*. 2001;344(3):159-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11172138.

85. Green H, Hay P, Dunn DT, McCormack S, Investigators S. A prospective multicentre study of discontinuing prophylaxis for opportunistic infections after effective antiretroviral therapy. *HIV Med*. 2004;5(4):278-283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15236617.

86. Opportunistic Infections Project Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE), Mocroft A, Reiss P, et al. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611-619. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20645862.

87. Atkinson A, Zwahlen M, Barger D, et al. Withholding primary *Pneumocystis* pneumonia prophylaxis in virologically suppressed patients with human immunodeficiency virus: an emulation of a pragmatic trial in COHERE. *Clin Infect Dis*. 2021;73(2):195-202. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32448894.

88. Chaiwarith R, Praparattanapan J, Nuntachit N, Kotarathititum W, Supparatpinyo K. Discontinuation of primary and secondary prophylaxis for opportunistic infections in HIV-infected patients who had CD4+ cell count <200 cells/mm(3) but undetectable plasma HIV-1 RNA: an open-label randomized controlled trial. *AIDS Patient Care STDS*. 2013;27(2):71-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23373662.

89. D'Egidio GE, Kravcik S, Cooper CL, Cameron DW, Fergusson DA, Angel JB. *Pneumocystis jiroveci* pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/microl when viral replication is suppressed. *AIDS*. 2007;21(13):1711-1715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17690568.

90. Miro J, Esteve A, Furrer H, Opportunistic Infection Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Safety of stopping primary *T. gondii* prophylaxis with suppressed viremia and CD4>100/mm3. Presented at: CROI; 2016. Boston, MassachusettsAvailable at: https://www.croiconference.org/wp-content/uploads/sites/2/posters/2016/765.pdf.

91. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. *N Engl J Med*. 1993;328(21):1521-1527. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8479489.

92. Safrin S, Finkelstein DM, Feinberg J, et al. Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. *Ann Intern Med*. 1996;124(9):792-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8610948.

93. Butler-Laporte G, Smyth E, Amar-Zifkin A, Cheng MP, McDonald EG, Lee TC. Low-dose TMP-SMX in the treatment of *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Open Forum Infect Dis*. 2020;7(5):ofaa112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32391402.

94. Sattler FR, Cowan R, Nielsen DM, Ruskin J. Trimethoprim-sulfamethoxazole compared with pentamidine for treatment of *Pneumocystis carinii* pneumonia in the acquired

immunodeficiency syndrome. A prospective, noncrossover study. *Ann Intern Med*. 1988;109(4):280-287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3260759.

95. Safrin S, Lee BL, Sande MA. Adjunctive folinic acid with trimethoprim-sulfamethoxazole for *Pneumocystis carinii* pneumonia in AIDS patients is associated with an increased risk of therapeutic failure and death. *J Infect Dis*. 1994;170(4):912-917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7930736.

96. Crothers K, Beard CB, Turner J, et al. Severity and outcome of HIV-associated *Pneumocystis pneumonia* containing Pneumocystis jirovecii dihydropteroate synthase gene mutations. *AIDS*. 2005;19(8):801-805. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15867494.

97. Huang L, Crothers K, Atzori C, et al. Dihydropteroate synthase gene mutations in *Pneumocystis* and sulfa resistance. *Emerg Infect Dis*. 2004;10(10):1721-1728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15504256.

98. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jiroveccii* pneumonia. *Emerg Infect Dis*. 2004;10(10):1760-1765. Available at: https://pubmed.ncbi.nlm.nih.gov/15504261.

99. Alvarez-Martinez MJ, Miro JM, Valls ME, et al. Prevalence of dihydropteroate synthase genotypes before and after the introduction of combined antiretroviral therapy and their influence on the outcome of *Pneumocystis* pneumonia in HIV-1-infected patients. *Diagn Microbiol Infect Dis*. 2010;68(1):60-65. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20727472.

100. Nielsen TL, Eeftinck Schattenkerk JK, Jensen BN, et al. Adjunctive corticosteroid therapy for *Pneumocystis carinii* pneumonia in AIDS: a randomized European multicenter open label study. *J Acquir Immune Defic Syndr*. 1992;5(7):726-731. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1613673.

101. Bozzette SA, Sattler FR, Chiu J, et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. California Collaborative Treatment Group. *N Engl J Med*. 1990;323(21):1451-1457. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2233917.

102. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for *Pneumocystis* Pneumonia. Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. *N Engl J Med*. 1990;323(21):1500-1504. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2136587.

103. Montaner JS, Lawson LM, Levitt N, Belzberg A, Schechter MT, Ruedy J. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med*. 1990;113(1):14-20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2190515.

104. Gallant JE, Chaisson RE, Moore RD. The effect of adjunctive corticosteroids for the treatment of *Pneumocystis carinii* pneumonia on mortality and subsequent complications. *Chest*. 1998;114(5):1258-1263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9823998.

105. Briel M, Bucher HC, Boscacci R, Furrer H. Adjunctive corticosteroids for *Pneumocystis jiroveci* pneumonia in patients with HIV-infection. *Cochrane Database Syst Rev*. 2006;3:CD006150(3):CD006150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16856118.

106. Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med*. 1990;323(12):776-782. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2392131.

107. Black JR, Feinberg J, Murphy RL, et al. Clindamycin and primaquine therapy for mild-to-moderate episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: AIDS Clinical Trials Group 044. *Clin Infect Dis*. 1994;18(6):905-913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8086551.

108. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). CTN-PCP Study Group. *Clin Infect Dis*. 1998;27(3):524-530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9770152.

109. Smego RA, Jr., Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. *Arch Intern Med*. 2001;161(12):1529-1533. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11427101.

110. Dohn MN, Weinberg WG, Torres RA, et al. Oral atovaquone compared with intravenous pentamidine for *Pneumocystis carinii* pneumonia in patients with AIDS. Atovaquone Study Group. *Ann Intern Med*. 1994;121(3):174-180. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7880228.

111. Robin C, Le MP, Melica G, et al. Plasma concentrations of atovaquone given to immunocompromised patients to prevent *Pneumocystis jirovecii*. *J Antimicrob Chemother*. 2017;72(9):2602-2606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28651341.

112. Conte JE, Jr., Chernoff D, Feigal DW, Jr., Joseph P, McDonald C, Golden JA. Intravenous or inhaled pentamidine for treating *Pneumocystis carinii* pneumonia in AIDS. A randomized trial. *Ann Intern Med*. 1990;113(3):203-209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2197911.

113. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A prospective randomized trial. *Ann Intern Med*. 1986;105(1):37-44. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3521428.

114. Kim T, Kim SH, Park KH, et al. Clindamycin-primaquine versus pentamidine for the second-line treatment of *Pneumocystis pneumonia*. *J Infect Chemother*. 2009;15(5):343-346. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19856077.

115. Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. *J*

Antimicrob Chemother. 2009;64(6):1282-1290. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19858161.

116. Benfield T, Atzori C, Miller RF, Helweg-Larsen J. Second-line salvage treatment of AIDS-associated *Pneumocystis jirovecii* pneumonia: a case series and systematic review. *J Acquir Immune Defic Syndr*. 2008;48(1):63-67. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18360286.

117. Soo Hoo GW, Mohsenifar Z, Meyer RD. Inhaled or intravenous pentamidine therapy for *Pneumocystis carinii* pneumonia in AIDS. A randomized trial. *Ann Intern Med*. 1990;113(3):195-202. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2197910.

118. Montgomery AB, Feigal DW, Jr., Sattler F, et al. Pentamidine aerosol versus trimethoprim-sulfamethoxazole for *Pneumocystis carinii* in acquired immune deficiency syndrome. *Am J Respir Crit Care Med*. 1995;151(4):1068-1074. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7697233.

119. McDonald EG, Butler-Laporte G, Del Corpo O, et al. On the treatment of *Pneumocystis jirovecii* pneumonia: current practice based on outdated evidence. *Open Forum Infect Dis*. 2021;8(12):ofab545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34988242.

120. Dworkin MS, Hanson DL, Navin TR. Survival of patients with AIDS, after diagnosis of *Pneumocystis carinii* pneumonia, in the United States. *J Infect Dis*. 2001;183(9):1409-1412. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11294675.

121. Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS*. 2003;17(1):73-80. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12478071.

122. Miller RF, Allen E, Copas A, Singer M, Edwards SG. Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. *Thorax*. 2006;61(8):716-721. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16601092.

123. Powell K, Davis JL, Morris AM, Chi A, Bensley MR, Huang L. Survival for patients with HIV admitted to the ICU continues to improve in the current era of combination antiretroviral therapy. *Chest*. 2009;135(1):11-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18719058.

124. Andrade HB, Shinotsuka CR, da Silva IRF, et al. Highly active antiretroviral therapy for critically ill HIV patients: a systematic review and meta-analysis. *PLoS One*. 2017;12(10):e0186968. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29065165.

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

126. Akgun KM, Miller RF. Critical care in human immunodeficiency virus-infected patients. *Semin Respir Crit Care Med*. 2016;37(2):303-317. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26974306.

127. Grant PM, Komarow L, Andersen J, et al. Risk factor analyses for immune reconstitution inflammatory syndrome in a randomized study of early vs. deferred ART during an opportunistic infection. *PLoS One*. 2010;5(7):e11416. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20617176.

128. Roade Tato L, Burgos Cibrian J, Curran Fabregas A, et al. Immune reconstitution inflammatory syndrome in HIV-infected patients with *Pneumocystis jirovecii* pneumonia. *Enferm Infecc Microbiol Clin*. 2018;36(10):621-626. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29187293.

129. Jagannathan P, Davis E, Jacobson M, Huang L. Life-threatening immune reconstitution inflammatory syndrome after *Pneumocystis* pneumonia: a cautionary case series. *AIDS*. 2009;23(13):1794-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19684486.

130. Eeftinck Schattenkerk JK, Lange JM, van Steenwijk RP, Danner SA. Can the course of high dose cotrimoxazole for *Pneumocystis carinii* pneumonia in AIDS be shorter? A possible solution to the problem of cotrimoxazole toxicity. *J Intern Med*. 1990;227(5):359-362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2341830.

131. Gordin FM, Simon GL, Wofsy CB, Mills J. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. *Ann Intern Med*. 1984;100(4):495-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/6230976.

132. Hughes WT, LaFon SW, Scott JD, Masur H. Adverse events associated with trimethoprim-sulfamethoxazole and atovaquone during the treatment of AIDS-related *Pneumocystis carinii* pneumonia. *J Infect Dis*. 1995;171(5):1295-1301. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7751706.

133. Klein NC, Duncanson FP, Lenox TH, et al. Trimethoprim-sulfamethoxazole versus pentamidine for *Pneumocystis carinii* pneumonia in AIDS patients: results of a large prospective randomized treatment trial. *AIDS*. 1992;6(3):301-305. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1567574.

134. Sattler FR, Frame P, Davis R, et al. Trimetrexate with leucovorin versus trimethoprim-sulfamethoxazole for moderate to severe episodes of *Pneumocystis carinii* pneumonia in patients with AIDS: a prospective, controlled multicenter investigation of the AIDS Clinical Trials Group Protocol 029/031. *J Infect Dis*. 1994;170(1):165-172. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8014493.

135. Masur H, Kaplan JE, Holmes KK, U.S. Public Health Service, Infectious Diseases Society of America. Guidelines for preventing opportunistic infections among HIV-infected persons--2002. Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *Ann Intern Med*. 2002;137(5 Pt 2):435-478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12617574.

136. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2000;14(4):383-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10770540.

137. Zellweger C, Opravil M, Bernasconi E, et al. Long-term safety of discontinuation of secondary prophylaxis against *Pneumocystis* pneumonia: prospective multicentre study. *AIDS*. 2004;18(15):2047-2053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15577626.

138. Mussini C, Pezzotti P, Antinori A, et al. Discontinuation of secondary prophylaxis for *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients: a randomized trial by the CIOP Study Group. *Clin Infect Dis*. 2003;36(5):645-651. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12594647.

139. Furrer H, for the OI working group of COHERE in EuroCoord. HIV replication is a major predictor of primary and recurrent *Pneumocystis* pneumonia - implications for prophylaxis recommendations. Presented at: 15th European AIDS Conference; 2015. Barcelona.

140. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med*. 2001;344(3):168-174. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11188837.

141. Atkinson A, Miro JM, Mocroft A, et al. No need for secondary *Pneumocystis jirovecii* pneumonia prophylaxis in adult people living with HIV from Europe on ART with suppressed viraemia and a CD4 cell count greater than 100 cells/microL. *J Int AIDS Soc*. 2021;24(6):e25726. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34118121.

142. Ahmad H, Mehta NJ, Manikal VM, et al. *Pneumocystis carinii* pneumonia in pregnancy. *Chest*. 2001;120(2):666-671. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11502676.

143. Chen YH, Keller J, Wang IT, Lin CC, Lin HC. Pneumonia and pregnancy outcomes: a nationwide population-based study. *Am J Obstet Gynecol*. 2012;207(4):288 e281-287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23021691.

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

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

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

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

148. Yu PA, Tran EL, Parker CM, et al. Safety of antimicrobials during pregnancy: a systematic review of antimicrobials considered for treatment and postexposure prophylaxis of plague. *Clin Infect Dis*. 2020;70(70 Suppl 1):S37-S50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32435799.

149. Muanda FT, Sheehy O, Berard A. Use of trimethoprim-sulfamethoxazole during pregnancy and risk of spontaneous abortion: a nested case control study. *Br J Clin Pharmacol*. 2018;84(6):1198-1205. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29424001.

150. Santos F, Sheehy O, Perreault S, Ferreira E, Berard A. Exposure to anti-infective drugs during pregnancy and the risk of small-for-gestational-age newborns: a case-control study. *BJOG*. 2011;118(11):1374-1382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21749628.

151. Wen SW, Zhou J, Yang Q, Fraser W, Olatunbosun O, Walker M. Maternal exposure to folic acid antagonists and placenta-mediated adverse pregnancy outcomes. *CMAJ*. 2008;179(12):1263-1268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19047607.

152. Centers for Disease Control and Prevention. Recommendations for the use of folic acid to reduce the number of cases of spina bifida and other neural tube defects. *MMWR Recomm Rep*. 1992;41(RR-14):1-7. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1522835.

153. Darjazini Nahas L, Hmadieh M, Audeh M, Yousfan A, Almasri IA, Martini N. Cleft lip and palate risk factors among otorhinolaryngology: Head and neck surgery patients in two hospitals. *Medicine (Baltimore)*. 2023;102(42):e34419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37861535.

154. Alvestad S, Husebye ESN, Christensen J, et al. Folic acid and risk of preterm birth, preeclampsia, and fetal growth restriction among women with epilepsy: a prospective cohort study. *Neurology*. 2022;99(6):e605-e615. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35577577.

155. Bulloch RE, Wall CR, Thompson JMD, et al. Folic acid supplementation is associated with size at birth in the Screening for Pregnancy Endpoints (SCOPE) international prospective cohort study. *Early Hum Dev*. 2020;147:105058. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32531744.

156. Jonker H, Capelle N, Lanes A, Wen SW, Walker M, Corsi DJ. Maternal folic acid supplementation and infant birthweight in low- and middle-income countries: A systematic review. *Matern Child Nutr*. 2020;16(1):e12895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31680411.

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

158. Czeizel AE, Timar L, Sarkozi A. Dose-dependent effect of folic acid on the prevention of orofacial clefts. *Pediatrics*. 1999;104(6):e66. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10586000.

159. MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *The Lancet*. 1991;338(8760):131-137. Available at: https://www.sciencedirect.com/science/article/pii/014067369190133A?via%3Dihub.

160. Zheng L, Huang J, Kong H, Wang F, Su Y, Xin H. The effect of folic acid throughout pregnancy among pregnant women at high risk of pre-eclampsia: a randomized clinical trial. *Pregnancy Hypertens*. 2020;19:253-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31987769.

161. Razavi B, Lund B, Allen BL, Schlesinger L. Failure of trimethoprim/sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia with concurrent leucovorin use. *Infection*. 2002;30(1):41-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11876516.

162. Forna F, McConnell M, Kitabire FN, et al. Systematic review of the safety of trimethoprim-sulfamethoxazole for prophylaxis in HIV-infected pregnant women: implications for resource-limited settings. *AIDS Rev*. 2006;8(1):24-36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16736949.

163. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17536875.

164. Thyagarajan B, Deshpande SS. Cotrimoxazole and neonatal kernicterus: a review. *Drug Chem Toxicol*. 2014;37(2):121-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24099411.

165. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15230645.

166. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for prevention programmes in *Plasmodium falciparum*-endemic sub-Saharan Africa. *Trop Med Int Health*. 2003;8(6):488-506. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12791054.

167. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. 1989;82(5):668. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2717998.

168. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1(1):1-15. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18690910.

169. Andrejko KL, Mayer RC, Kovacs S, et al. The safety of atovaquone-proguanil for the prevention and treatment of malaria in pregnancy: a systematic review. *Travel Med Infect Dis*. 2019;27:20-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30654041.

170. McGready R, Ashley EA, Moo E, et al. A randomized comparison of artesunate-atovaquone-proguanil versus quinine in treatment for uncomplicated falciparum malaria during pregnancy. *J Infect Dis*. 2005;192(5):846-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16088834.

171. Harstad TW, Little BB, Bawdon RE, Knoll K, Roe D, Gilstrap LC, 3rd. Embryofetal effects of pentamidine isethionate administered to pregnant Sprague-Dawley rats. *Am J Obstet Gynecol*. 1990;163(3):912-916. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2403167.

172. Albino JA, Shapiro JM. Respiratory failure in pregnancy due to *Pneumocystis carinii*: report a successful outcome. *Obstet Gynecol*. 1994;83(5 Pt 2):823-824. Available at: https://pubmed.ncbi.nlm.nih.gov/8159362.

173. Madinger NE, Greenspoon JS, Ellrodt AG. Pneumonia during pregnancy: has modern technology improved maternal and fetal outcome? *Am J Obstet Gynecol*. 1989;161(3):657-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2782348.

174. Koonin LM, Ellerbrock TV, Atrash HK, et al. Pregnancy-associated deaths due to AIDS in the United States. *JAMA*. 1989;261(9):1306-1309. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2783746.

175. Benedetti TJ, Valle R, Ledger WJ. Antepartum pneumonia in pregnancy. *Am J Obstet Gynecol*. 1982;144(4):413-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7124859.

176. Committee on Obstetric Practice, Society for Maternal-Fetal Medicine. ACOG Committee opinion: immune modulating therapies in pregnancy and lactation. *Obstetrics & Gynecology*. 2019;133(4):e287-e295. Available at: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2019/04/immune-modulating-therapies-in-pregnancy-and-lactation.

177. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology*. 2000;62(6):385-392. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11091360.

178. Andersen DH, Blanc WA, Crozier DN, Silverman WA. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics*. 1956;18(4):614-625. Available at: http://www.ncbi.nlm.nih.gov/pubmed/13370229.

179. Skuladottir H, Wilcox AJ, Ma C, et al. Corticosteroid use and risk of orofacial clefts. *Birth Defects Res A Clin Mol Teratol*. 2014;100(6):499-506. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24777675.

180. Gur C, Diav-Citrin O, Shechtman S, Arnon J, Ornoy A. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. *Reprod Toxicol*. 2004;18(1):93-101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15013068.

181. Wei J, Xia F, Miao J, Wang T, Chen L, Yan X. Correction to: The risk of congenital heart defects associated with corticosteroids use during the first trimester of pregnancy: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2023;79(1):13. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36416939.

182. Peltoniemi OM, Kari MA, Hallman M. Repeated antenatal corticosteroid treatment: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand*. 2011;90(7):719-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21426310.

183. Ostensen M, Khamashta M, Lockshin M, et al. Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther*. 2006;8(3):209. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16712713.

184. Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 199: Use of prophylactic antibiotics in labor and delivery. *Obstet Gynecol*. 2018;132(3):e103-e119. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30134425.

185. Prevention of group B streptococcal early-onset disease in newborns: ACOG Committee opinion summary, number 797. *Obstet Gynecol*. 2020;135(2):489-492. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31977793.

186. CLEOCIN HCl [package insert]. Pfizer Pharmacia & Upjohn Company. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/050162s102lbl.pdf.

187. Primaquine phosphate tablets [package insert]. Sanofi-Aventis U.S. LLC. 2017. Available at: https://products.sanofi.us/primaquine/primaquine.pdf.

188. de Azevedo EN, Santos AS, Rocha Mendes ET, Simões MJ, Kulay L. Efeitos do uso crônico do difosfato de primaquina sobre a prenhez da rata. *Rev Bras Ginecol Obstet*. 1998;20(9):505-508. Available at: https://www.scielo.br/j/rbgo/a/kxBPq3JwNx6QgmwDKf694dC/?lang=pt.

189. Pincelli A, Neves PAR, Lourenco BH, et al. The hidden burden of *Plasmodium vivax* malaria in pregnancy in the Amazon: an observational study in northwestern Brazil. *Am J Trop Med Hyg*. 2018;99(1):73-83. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29741155.

190. Tan KR, Abanyie F. Malaria. In: CDC Yellow Book 2024. Centers for Disease Control and Prevention (CDC), ed. New York, NY: Oxford University Press; 2023. https://wwwnc.cdc.gov/travel/yellowbook/2024/infections-diseases/malaria.

191. DeBaun MR. Overview of hemolytic anemias in children. 2022. Available at: https://www.uptodate.com/contents/overview-of-hemolytic-anemias-in-children.

Progressive Multifocal Leukoencephalopathy/JC Virus Infection

Updated: October 19, 2022
Reviewed: October 19, 2022

Epidemiology

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS), caused by the human polyoma virus JC virus (JCV) and characterized by focal demyelination.[1,2] JCV has a worldwide distribution, and 20% to 70% of people exhibit serologic evidence of exposure by their late teens or as adults.[3-7] Primary JCV infection usually occurs asymptomatically in childhood resulting in a chronic carrier state in most individuals. Viral DNA is detected in the urine of 20% to 30% of healthy adults.[4,8-12]

PML is a rare manifestation of JCV reactivation and characteristically manifests as a complication of HIV-1 infection and other immunocompromising diseases or therapies.[13-16] In recent years, PML has been reported in patients treated with immunomodulatory humanized antibodies, including natalizumab[17] and efalizumab.[18] Concern has been raised about a possible increased risk of PML in persons with HIV (PWH) treated with rituximab for non-Hodgkin lymphoma,[19,20] but PML has not been documented in that setting. PML can occur during chronic immunosuppression after organ transplantation and often has a poor prognosis.[21]

Before the advent of combination antiretroviral therapy (ART), PML developed in 3% to 7% of patients with AIDS[22-24] and was almost invariably fatal; spontaneous remissions were rare.[25] With the widespread use of ART, incidence of PML decreased substantially,[26,27] and mortality in PWH who develop the disease has declined.[28-30] Although most CNS opportunistic infections are effectively prevented when CD4 T lymphocyte (CD4) cell counts are maintained above 100 to 200 cells/mm^3, PML still occurs occasionally in patients treated with ART.[2,31,32] PML also can develop in the setting of immune reconstitution after ART initiation, which is discussed below.[2,30,33]

Clinical Manifestations

PML manifests as focal neurological deficits, usually with insidious onset and steady progression. Because the demyelinating lesions can involve different brain regions, specific deficits vary from patient to patient. Although some regions seem to be more favored, any region of the CNS can be involved, including the occipital lobes (hemianopsia), frontal and parietal lobes (aphasia, hemiparesis, and hemisensory deficits), and cerebellar peduncles and deep white matter (dysmetria and ataxia).[13] Spinal cord involvement is rare, and the optic nerves are not involved.[34] Although lesions can be multiple, one lesion is clinically predominant. Initial symptoms and signs usually begin as partial deficits (e.g., weakness in one leg) that worsen over time and involve a larger territory (e.g., evolution to hemiparesis), as individual lesions expand concentrically or along white matter tracts. Less localized clinical syndromes—such as behavioral changes, dementia, or encephalopathy—result from multiple lesions in the setting of PML and are rarely the presenting clinical phenotype.[35]

The time course of evolving demyelination, with clinical progression over several weeks, often provides a clue to diagnosis because the other major opportunistic focal brain disorders (cerebral toxoplasmosis and primary CNS lymphoma) characteristically progress in hours to days and cerebral

infarcts begin even more abruptly. Nonetheless, PML is sometimes mistaken for an evolving stroke, which, like PML, is bright on diffusion-weighted magnetic resonance imaging (MRI). Focal brain lesion can mimic strokes; however, the progressive course should make this diagnosis less likely, and PML must be considered. Headache and fever are not characteristic of PML, and when present may indicate presence of another opportunistic infection. Seizures occur in nearly 20% of PML cases and are associated with lesions immediately adjacent to the cortex.[36,37]

Diagnosis

Initial recognition of PML relies on a combination of clinical and neuroimaging findings: steady progression of focal neurological deficits with MRI almost always demonstrating distinct white matter lesions in areas of the brain corresponding to the clinical deficits. The lesions are hyperintense (white) on T2-weighted and fluid-attenuated inversion recovery sequences and hypointense (dark) on T1-weighted sequences.[2] The T1 findings can be subtle and may help distinguish lesions due to PML from those of other pathologies, including the white matter lesions of HIV encephalitis. A linear, paramagnetic band or rim in the paralesional U-fibers has been described as a common finding in PML and has been proposed to have diagnostic value independent of underlying predisposing disease. Histopathological studies show this band corresponds to iron accumulation within phagocytic cells, although the pathophysiology leading to this remains unclear.[38,39]

Brain imaging with magnetic resonance (MR) or computed tomography is critical to identifying PML and differentiating it from other important treatable diseases that occur in advanced HIV. In contrast to cerebral toxoplasmosis and primary CNS lymphoma, no mass effect or displacement of normal structures is usually evident in PML imaging. Although contrast enhancement is present in 10% to 15% of cases, it is usually sparse with a thin or reticulated appearance adjacent to the edge of the lesions. Exceptions to these characteristic imaging findings can occur when the inflammatory form of PML develops in the setting of immune reconstitution after initiation of ART (see below). Advanced neuroimaging techniques—such as diffusion-weighted imaging (DWI) and MR spectroscopy—may provide additional diagnostic information.[40-42] New PML lesions and the advancing edge of large lesions have a high signal on DWI and a normal-to-low apparent diffusion coefficient, signifying restricted diffusion. These changes relate to regions of active infection and oligodendrocyte swelling. MR spectroscopy can show areas of decreased N-acetylaspartate and increased choline related to axonal loss and cell membrane and myelin breakdown, respectively, with the greatest changes at the center of lesions.[43] Recently, a hyperintense cortical signal seen on MRI scan in non-enhanced T1-weighted cortex images has been associated with seizures complicating inflammatory PML.[37]

In most cases of PML, the combined clinical and radiographic presentations support a presumptive diagnosis. Because the primary treatment method for PML is restoring the patient's immune function, confirming the diagnosis is especially important to ensure ART is initiated rapidly.

JCV DNA is virtually never detected in normal cerebrospinal fluid (CSF) samples. Thus, the usual first step in confirming the diagnosis is to test CSF by polymerase chain reaction (PCR) for the presence of JCV DNA. The assay is positive in approximately 70% to 90% of patients not taking ART, for whom a positive result can be considered diagnostic in the appropriate clinical context—namely, subacute onset of focal neurological abnormalities and suggestive imaging findings.[10,44] JCV may be detectable in the CSF of as few as 60% of ART-treated patients.[45] In patients not taking ART, the number of JCV DNA copies can add additional information for prognosis, although the relationship between copy number and prognosis is less clear in patients taking ART.[46,47] CSF analysis can be repeated if JCV PCR is negative yet suspicion of PML remains high and alternative diagnoses have been excluded. Given that in AIDS patients, multiple opportunistic conditions are sometimes encountered, evaluation of CSF is often indicated to rule out *Cryptococcus*, neurosyphilis,

cytomegalovirus encephalitis, varicella-zoster encephalitis, herpes simplex encephalitis, and tuberculosis. Further, CSF PCR analyses for *Toxoplasma* and consideration of Epstein-Barr virus generally associated with primary CNS lymphoma is often indicated with progressive multifocal brain disease in the setting of AIDS. Because JCV DNA viral load in CSF may be very low even with active PML, highly sensitive PCR performance is desirable. Sensitive assays that detect as few as 50 copies/mL are now available, with some research laboratories exceeding this level of sensitivity; detection of JCV virus in CSF in any amount with the appropriate clinical and imaging findings strongly supports the diagnosis of PML.[48] Analysis of plasma samples for detection of JCV by PCR when positive are relatively specific for PML (~92% in patients with HIV), while the sensitivity is less than 40% in this setting.[49]

In some instances, brain biopsy is required in order to rule out other diagnoses. PML usually can be identified by the characteristic tissue cytopathology—including oligodendrocytes with intranuclear inclusions, bizarre astrocytes, and lipid-laden macrophages—with identification of JCV or cross-reacting polyoma virus by immunohistochemistry, *in situ* nucleic acid hybridization, or electron microscopy.[13,50,51]

Generally, serologic testing is not useful because of high anti-JCV seroprevalence in the general population. Recently, however, antibody testing has been assessed for stratifying risk of PML with natalizumab treatment.[6] Significant increases in JCV-specific antibody titers[52] and detection of intrathecally produced anti-JCV antibodies may prove useful for diagnostic testing[53] but require further prospective study. The value of anti-JCV antibodies in stimulating Fc receptor-bearing effector cell activity contributing to outcome of PML requires further studies.[54]

Preventing Exposure

Currently, no known way exists to prevent exposure to the virus because most individuals are infected in childhood.

Preventing Disease

In many individuals, JCV infection is likely latent and intermittently productive, although clinically silent, in the kidney or other anatomic sites. Systemic infection may increase in the presence of immunosuppression. It remains a subject of debate whether JCV infection is also latent in the CNS or whether PML results from hematogenous dissemination of infection to the brain resulting in subsequent PML lesion development within months of entry to the CNS.[55,56] Therefore, the only known way to prevent disease is to prevent progression of HIV-related immunosuppression with ART **(AII).**

Treating Disease

Recommendations for Treating and Monitoring PML
Treatment
The main approach to treatment is to preserve immune function and reverse HIV-associated immunosuppression with effective ART. • In patients not on ART who are diagnosed with PML, ART should be (re)started immediately (AII). • In patients who are receiving ART but remain viremic because of inadequate adherence or drug resistance, ART should be optimized to achieve HIV suppression (AIII).

• No role for ART intensification in patients with HIV viral suppression (BII). • ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score (BII). • No effective direct-acting antiviral therapy exists for preventing or treating JCV infections or PML. • The following agents are not recommended for the treatment of PML: cytarabine (AII), cidofovir (AII), interferon-alpha (BIII), interleukin-2 (BIII), topotecan (BIII), pembrolizumab (BIII). • The following agents are not recommended due to limited data: 5HT2a receptor antagonist (e.g., olanzapine, ziprasidone, mirtazapine, cyproheptadine, risperidone) (BIII), mefloquine (BIII). Expert consultation is recommended prior to initiation of these agents. • PML-IRIS may require administration of corticosteroid therapy (BIII). The optimal corticosteroid regimen has not been established but should be tailored to individual patients. ART should NOT be discontinued during PML-IRIS (AIII).
Monitoring
• Timing of follow-up assessments (clinical, lumbar puncture, and MRI) should be guided by clinical progress (BIII). • In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation (BIII). • In patients who clinically worsen before or after this 6- to 8-week period, repeat MRI should be obtained as soon as worsening is recognized (BIII).

Key: ART = antiretroviral therapy; CPE = Central Nervous System (CNS) Penetration Effectiveness; IRIS = immune reconstitution inflammatory syndrome; JCV = JC virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

No specific therapy exists for JCV infection or PML. The main approach to treatment involves ART to reverse the immunosuppression that interferes with the normal host response to this virus.[57] In patients with PML who are not on therapy, ART should be started immediately **(AII).** In this setting, more than half of PML patients with HIV experience a remission in which disease progression stops. Although neurological deficits often persist, some patients experience clinical improvement.[28,29,58-63] In one retrospective study of 118 consecutive patients with PML who received ART, 75 patients (63.6%) survived for a median of 114 weeks (2.2 years) after diagnosis of PML.[63] Neurological function in the survivors was categorized as cure or improvement in 33, stabilization or worsening in 40, and unknown in 2. Another retrospective case series reported that 42% of PML survivors on ART had moderate or severe disability.[64] Peripheral blood CD4 count at presentation was the only variable that predicted survival; the odds ratio for death was 2.7 among patients with CD4 counts <100 cells/mm^3 compared with patients who had higher CD4 counts. In other case series, worse prognosis also was associated with high plasma HIV RNA levels at the time of presentation, poor virologic responses to ART, and presence of lesions in the brain stem.[29,32,59,60,62,63,65] Contrast enhancement on imaging may predict better outcomes, as it is indicative of an immune response to the virus.[31] In multiple sclerosis patients with PML, younger age, more restricted unilobar disease, and lower CSF JCV DNA copy numbers are associated with better outcomes; whether these associations are true for PML in PWH is unknown.[66]

ART should be optimized for HIV virologic suppression in patients with PML who have received ART but remain viremic because of inadequate adherence or ARV resistance **(AIII).** More problematic are patients who develop PML despite successful HIV virologic suppression while

taking ART. A preliminary report of PML with patients treated intensively with four classes of ART (including enfuvirtide) suggested that the strategy might offer higher-than-anticipated survival,[67] but it has not yet been followed by structured trial. Therefore, no evidence supports ART intensification for PML **(BII).**

The use of ARV drugs that better penetrate the CNS also has been proposed, with use of the CNS Penetration Effectiveness (CPE) score of drug regimens as a guide. This score is based on the pharmacology of ARV drugs with respect to their chemical characteristics as well as demonstrated entry into the CNS (or, more often, the CSF) and, where available, on their CNS anti-HIV activity.[68] One report found at the beginning of the combination ART era that a high CPE score was associated with longer survival after a PML diagnosis, whereas in the late, more recent ART period, the effect of the CPE score disappeared as more potent ARV regimens led to more effective plasma viral load control.[69] Hence, in the current era, the effectiveness of selecting a treatment regimen with a high CPE score is not established. It seems likely that systemic rather than CNS efficacy is the salient aspect of ART in this setting because ART's most important effect on PML may be restoration of effective anti-JCV immunity that can limit CNS infection.[70,71] ART regimens should be selected based on likelihood of achieving virologic suppression and not CPE score **(BII).**

Several studies have evaluated targeted treatments for PML. However, many anecdotal reports of efficacy have not been confirmed by controlled studies and are therefore not recommended. Based on case reports and demonstration of *in vitro* inhibitory activity against JCV, intravenous (IV) and intrathecal cytarabine (cytosine arabinoside) were tested in a clinical trial, but neither demonstrated clinical benefit.[72] Therefore, treatment with cytarabine is **not recommended (AII).** Similarly, cidofovir initially was reported to have a salutary clinical effect, but several large studies—including retrospective case-control studies, an open-label clinical trial, and a meta-analysis that included patients from five large studies—demonstrated no benefit.[45,61-63,73] Thus, treatment with cidofovir is also **not recommended (AII).**

On the basis of a report indicating that the serotonergic 5HT2a receptor can serve as a cellular receptor for JCV in a glial cell culture system,[74,75] drugs that block the 5HT2a receptor, including olanzapine, ziprasidone, mirtazapine, cyproheptadine, and risperidone, have been suggested as treatment for PML,[76] although the rationale for this practice has been questioned.[77] Again, anecdotes about favorable outcomes[1,78-81] have not been substantiated by reports of genuine benefit in larger case series, cohort studies, or formal clinical trials. Thus, at this time, treatment with serotonergic 5HT2a receptor blockers is **not recommended (BIII).**

After a cell-culture study indicated that JCV replication could be inhibited by a topoisomerase inhibitor,[82] an analogue, topotecan, was studied in a small trial. Results suggested a salutary effect in some patients, although the outcome likely was little different from the natural course in other patients with AIDS, and the main toxicities were hematologic.[83] At this time, topotecan is **not recommended (BIII).**

A Phase I/II clinical trial of the antimalarial drug mefloquine was initiated based on its demonstrated *in vitro* anti-JCV activity. The trial was later halted by the sponsor because demonstration of efficacy was futile.[84] Mefloquine use for PML treatment is **not recommended (BIII).** Immunomodulatory approaches to the treatment of PML in PWH also have been tried, but none has yet been studied in a prospective, controlled clinical trial. Although an initial retrospective analysis suggested that interferon-alpha might improve survival,[85] a subsequent retrospective analysis did not demonstrate benefit beyond that afforded by ART; therefore, interferon-alpha is **not recommended (BIII).**[86] A single report described failure of interferon-beta treatment of HIV-associated PML[87] and natalizumab-related PML developed in patients given interferon-beta for multiple sclerosis.[17] Case

reports have described improvement or recovery in PML-related neurological dysfunction in three patients who were not HIV infected and were treated with IL-2: one with Hodgkin lymphoma treated with autologous bone marrow transplantation, one with low-grade lymphoma and allogeneic stem cell transplantation, and one with myelodysplastic syndrome.[88-90] Like the other reports, these too have not been followed up with more substantial trials; therefore, treatment of PML with IL-2 is **not recommended (BIII).** Recent interest in recombinant IL-7 for treatment of PML when CD4 lymphopenia is persistent, sometimes in combination with VP-1 vaccination strategy, are under consideration as an alternative adjuvant immune therapy to improve PML outcomes.[91-95] Checkpoint inhibitor therapy has been considered recently as a means of enhancing the immune response to JCV most commonly in settings outside of HIV where immune reconstitution may be futile. The outcome of reports is conflicting, and further research is required.[96,97] Use of checkpoint inhibitors for PML in the setting of HIV is **not recommended (BIII).**

Adoptive transfer of autologous or allogeneic virus-specific T cells, either against JCV or the closely related BK virus, have been used for the treatment of PML. Across the several small case series published to date, a single patient with HIV-associated PML was treated with benefit.[98-100] Use of disease-specific T cells is actively being explored, but at present cannot be recommended for HIV-associated PML. In summary, immunomodulatory agents are **not recommended (BIII).**

Special Considerations for ART

ART should be (re)started as soon as possible for all patients, ideally before PML develops. For patients with suspected PML, it is especially imperative to start ART quickly **(AII).** For patients already on treatment who have demonstrated plasma HIV viremia and are adherent to therapy, ART should be adjusted, if possible, based on plasma virus susceptibility **(AII).**

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

Treatment response should be monitored with clinical examination and brain MRI. In patients with detectable JCV DNA in their CSF before initiation of ARV treatment, quantification of CSF JCV DNA may prove useful as an index to follow for assessing treatment response. No clear guidelines exist for the timing of follow-up assessments, but it is reasonable to be guided by clinical progress **(BIII).** Often disease progression occurs before stabilization and improvement occurs.[67] In patients who appear stable or improved, neuroimaging can be obtained 6 to 8 weeks after ART initiation to screen for radiographic signs of progression or of immune response and can serve as a further baseline for subsequent scans should the patient begin to deteriorate **(BIII).** In patients who clinically worsen before or after this 6- to 8-week period, repeat neuroimaging should be obtained as soon as worsening is recognized **(BIII).**

PML-Immune Reconstitution Inflammatory Syndrome

PML has been reported to occur within the first weeks to months after initiating ART[2,32,33,101-103] with clinical and radiographic features that differ from classical PML, including lesions with contrast enhancement, edema and mass effect, and a more rapid clinical course.[38,104] As with other presentations of immune reconstitution inflammatory syndrome (IRIS), it is more likely after advanced HIV with low CD4 counts and greater decline in HIV viral load on initiation of ARV. This presentation has been referred to as inflammatory PML or PML-IRIS. Both unmasking of cryptic PML and paradoxical worsening in a patient with an established PML diagnosis have been observed. Histopathology typically demonstrates perivascular mononuclear inflammatory infiltration.[105-108]

Unmasked PML-IRIS is presumed to represent the effects of a restored immune response to JCV infection in the context of ART, with resultant local immune and inflammatory responses.

Because ART-induced immune reconstitution may be associated with both onset and paradoxical worsening of PML, corticosteroids have been used empirically in this setting with reported benefit.[2,102,109] Further study of corticosteroids for treatment of PML-IRIS is needed to confirm efficacy and refine dosage and duration. At present, however, use of corticosteroids to treat of PML-IRIS may be justified in some PML where edema or mass effect causes serious clinical deterioration **(BIII).** The decision to use steroids can be difficult because it is the immune response to JCV that controls the infection and treatments that blunt that response could be deleterious. Nevertheless, the inflammatory response against PML can, at times, be more damaging than the virus itself, and corticosteroids appear to have a role in treatment of these patients.

The dosage and duration of corticosteroids for PML-IRIS have not been established. In the absence of comparative data, adjuvant corticosteroid therapy should be tailored to individual patients. One approach, modeled on treatment of multiple sclerosis flairs, is to begin with a 3- to 5-day course of IV methylprednisolone dosed at 1 g per day, followed by an oral prednisone taper, dosed according to clinical response. A taper may begin with a dose of 60 mg per day in a single dose, tapered over 1 to 6 weeks. Clinical status should be monitored carefully during this taper in an attempt to minimize systemic and immune effects while avoiding IRIS recrudescence. Contrast-enhanced MRI at 2 to 6 weeks may be helpful in documenting resolution of inflammation and edema and to obtain a new baseline, recognizing that the MRI appearance may worsen despite clinical improvement and that clinical status is likely the best indicator of treatment efficacy. Importantly, ART should be continued **(AIII).**

Several case reports suggest that maraviroc might be beneficial for PML-IRIS,[110] presumably related to the immunomodulatory rather than ARV properties of the CCR5 inhibitor. However, no comparative studies in HIV-associated PML have confirmed benefit of inclusion of maraviroc in HIV therapy in this setting.[110,111] A retrospective cohort study of 27 patients with PML in whom maraviroc was used failed to show utility in preventing PML-IRIS.[112] Maraviroc is not recommended as a component of treatment of PML **(BIII).**

Managing Treatment Failure

PML remission can take several weeks, and no strict criteria exist to define treatment failure. However, a working definition of treatment failure may be continued clinical worsening after 3 months of ART initiation. Changes in plasma HIV RNA levels and blood CD4 count responses provide ancillary predictive information. Failing ART regimens should be changed based on standard guidelines for the use of ART (see Virologic Failure in the Adult and Adolescent Antiretroviral Guidelines). When PML continues to worsen despite fully suppressive ART, one of the unproven therapies described above could be considered after consultation with an expert **(CIII),** although the possibility of toxicity must be balanced against the unproven benefits of these treatments. The search for other potentially treatable comorbid conditions, like hepatitis C virus and associated cirrhosis, also should be considered in this setting.[113]

Preventing Recurrence

Patients who experience remission of PML after ART rarely suffer subsequent recrudescence unless ART is interrupted.[61,114] The main preventive measure, based on its role in reversing the disease, is treatment with an effective ART regimen that suppresses viremia and maintains CD4 counts **(AII).**

Special Considerations During Pregnancy

Diagnostic evaluation of PML should be the same in pregnant or nonpregnant individuals. Therapy during pregnancy should consist of initiating or optimizing the ARV regimen.

References

1. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? *Ann Neurol*. 2006;60(2):162-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16862584.

2. Cinque P, Koralnik IJ, Gerevini S, Miro JM, Price RW. Progressive multifocal leukoencephalopathy in HIV-1 infection. *Lancet Infect Dis*. 2009;9(10):625-636. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19778765.

3. Kean JM, Rao S, Wang M, Garcea RL. Seroepidemiology of human polyomaviruses. *PLoS Pathog*. 2009;5(3):e1000363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19325891.

4. Egli A, Infanti L, Dumoulin A, et al. Prevalence of polyomavirus BK and JC infection and replication in 400 healthy blood donors. *J Infect Dis*. 2009;199(6):837-846. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19434930.

5. Antonsson A, Green AC, Mallitt KA, et al. Prevalence and stability of antibodies to the BK and JC polyomaviruses: a long-term longitudinal study of Australians. *J Gen Virol*. 2010;91(Pt 7):1849-1853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20219899.

6. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: implications for PML risk stratification. *Ann Neurol*. 2010;68(3):295-303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20737510.

7. Knowles WA. Discovery and epidemiology of the human polyomaviruses BK virus (BKV) and JC virus (JCV). *Adv Exp Med Biol*. 2006;577:19-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16626025.

8. Kitamura T, Aso Y, Kuniyoshi N, Hara K, Yogo Y. High incidence of urinary JC virus excretion in nonimmunosuppressed older patients. *J Infect Dis*. 1990;161(6):1128-1133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2161040.

9. Sundsfjord A, Flaegstad T, Flo R, et al. BK and JC viruses in human immunodeficiency virus type 1-infected persons: prevalence, excretion, viremia, and viral regulatory regions. *J Infect Dis*. 1994;169(3):485-490. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8158020.

10. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(2):253-260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9932940.

11. Lednicky JA, Vilchez RA, Keitel WA, et al. Polyomavirus JCV excretion and genotype analysis in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2003;17(6):801-807. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12660526.

12. Kato A, Kitamura T, Takasaka T, et al. Detection of the archetypal regulatory region of JC virus from the tonsil tissue of patients with tonsillitis and tonsilar hypertrophy. *J Neurovirol*. 2004;10(4):244-249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15371154.

13. Richardson EP, Jr., Webster HD. Progressive multifocal leukoencephalopathy: its pathological features. *Prog Clin Biol Res*. 1983;105:191-203. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6304757.

14. Garcia-Suarez J, de Miguel D, Krsnik I, Banas H, Arribas I, Burgaleta C. Changes in the natural history of progressive multifocal leukoencephalopathy in HIV-negative lymphoproliferative disorders: impact of novel therapies. *Am J Hematol*. 2005;80(4):271-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16315252.

15. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. *Neurology*. 2010;75(15):1326-1332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20938025.

16. Anand P, Hotan GC, Vogel A, Venna N, Mateen FJ. Progressive multifocal leukoencephalopathy: a 25-year retrospective cohort study. *Neurol Neuroimmunol Neuroinflamm*. 2019;6(6). Available at: https://www.ncbi.nlm.nih.gov/pubmed/31554669.

17. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol*. 2010;9(4):438-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20298967.

18. Molloy ES, Calabrese LH. Therapy: targeted but not trouble-free: efalizumab and PML. *Nat Rev Rheumatol*. 2009;5(8):418-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19648939.

19. Boue F, Gabarre J, Gisselbrecht C, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol*. 2006;24(25):4123-4128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16896005.

20. Mounier N, Spina M, Gisselbrecht C. Modern management of non-Hodgkin lymphoma in HIV-infected patients. *Br J Haematol*. 2007;136(5):685-698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17229246.

21. Mateen FJ, Muralidharan R, Carone M, et al. Progressive multifocal leukoencephalopathy in transplant recipients. *Ann Neurol*. 2011;70(2):305-322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21823157.

22. Petito CK, Cho ES, Lemann W, Navia BA, Price RW. Neuropathology of acquired immunodeficiency syndrome (AIDS): an autopsy review. *J Neuropathol Exp Neurol*. 1986;45(6):635-646. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3021914.

23. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS. UCLA experience and review. *Am J Pathol*. 1986;124(3):537-558. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2876640.

24. Lang W, Miklossy J, Deruaz JP, et al. Neuropathology of the acquired immune deficiency syndrome (AIDS): a report of 135 consecutive autopsy cases from Switzerland. *Acta Neuropathol*. 1989;77(4):379-390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2540610.

25. Berger JR, Mucke L. Prolonged survival and partial recovery in AIDS-associated progressive multifocal leukoencephalopathy. *Neurology*. 1988;38(7):1060-1065. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3386823.

26. d'Arminio Monforte A, Cinque P, Mocroft A, et al. Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol*. 2004;55(3):320-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14991809.

27. Casado JL, Corral I, Garcia J, et al. Continued declining incidence and improved survival of progressive multifocal leukoencephalopathy in HIV/AIDS patients in the current era. *Eur J Clin Microbiol Infect Dis*. 2014;33(2):179-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23948752.

28. Clifford DB, Yiannoutsos C, Glicksman M, et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(3):623-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10025799.

29. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol*. 2003;9 Suppl 1:47-53. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12709872.

30. Melliez H, Mary-Krause M, Bocket L, et al. Risk of progressive multifocal leukoencephalopathy in the combination antiretroviral therapy era in the French Hospital Database on Human Immunodeficiency Virus (ANRS-C4). *Clin Infect Dis*. 2018;67(2):275-282. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29635465.

31. Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. *Ann Neurol*. 1998;44(3):341-349. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9749600.

32. Cinque P, Bossolasco S, Brambilla AM, et al. The effect of highly active antiretroviral therapy-induced immune reconstitution on development and outcome of progressive multifocal leukoencephalopathy: study of 43 cases with review of the literature. *J Neurovirol*. 2003;9 Suppl 1:73-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12709876.

33. Du Pasquier RA, Koralnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol*. 2003;9 Suppl 1:25-31. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12709868.

34. Bernal-Cano F, Joseph JT, Koralnik IJ. Spinal cord lesions of progressive multifocal leukoencephalopathy in an acquired immunodeficiency syndrome patient. *J Neurovirol*. 2007;13(5):474-476. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17994433.

35. Zunt JR, Tu RK, Anderson DM, Copass MC, Marra CM. Progressive multifocal leukoencephalopathy presenting as human immunodeficiency virus type 1 (HIV)-associated dementia. *Neurology*. 1997;49(1):263-265. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9222204.

36. Lima MA, Drislane FW, Koralnik IJ. Seizures and their outcome in progressive multifocal leukoencephalopathy. *Neurology*. 2006;66(2):262-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16434670.

37. Khoury MN, Alsop DC, Agnihotri SP, et al. Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive

multifocal leukoencephalopathy. *Ann Neurol*. 2014;75(5):659-669. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24752885.

38. Post MJ, Thurnher MM, Clifford DB, et al. CNS-immune reconstitution inflammatory syndrome in the setting of HIV infection, part 2: discussion of neuro-immune reconstitution inflammatory syndrome with and without other pathogens. *AJNR Am J Neuroradiol*. 2013;34(7):1308-1318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22790252.

39. Mahajan KR, Amin M, Poturalski M, et al. Juxtacortical susceptibility changes in progressive multifocal leukoencephalopathy at the gray-white matter junction correlates with iron-enriched macrophages. *Mult Scler*. 2021;27(14):2159-2169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33749379.

40. Chang L, Ernst T, Tornatore C, et al. Metabolite abnormalities in progressive multifocal leukoencephalopathy by proton magnetic resonance spectroscopy. *Neurology*. 1997;48(4):836-845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9109865.

41. Mader I, Herrlinger U, Klose U, Schmidt F, Kuker W. Progressive multifocal leukoencephalopathy: analysis of lesion development with diffusion-weighted MRI. *Neuroradiology*. 2003;45(10):717-721. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12942223.

42. da Pozzo S, Manara R, Tonello S, Carollo C. Conventional and diffusion-weighted MRI in progressive multifocal leukoencephalopathy: new elements for identification and follow-up. *Radiol Med*. 2006;111(7):971-977. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17021685.

43. Shah R, Bag AK, Chapman PR, Cure JK. Imaging manifestations of progressive multifocal leukoencephalopathy. *Clin Radiol*. 2010;65(6):431-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20451009.

44. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997;11(1):1-17. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9110070.

45. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS*. 2008;22(14):1759-1767. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18753934.

46. Yiannoutsos CT, Major EO, Curfman B, et al. Relation of JC virus DNA in the cerebrospinal fluid to survival in acquired immunodeficiency syndrome patients with biopsy-proven progressive multifocal leukoencephalopathy. *Ann Neurol*. 1999;45(6):816-821. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10360779.

47. Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2005;40(5):738-744. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15714422.

48. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. *Neurology*. 2013;80(15):1430-1438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23568998.

49. Ferretti F, Bestetti A, Yiannoutsos CT, et al. Diagnostic and prognostic value of JC virus DNA in plasma in progressive multifocal leukoencephalopathy. *Clin Infect Dis*. 2018;67(1):65-72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29346632.

50. Silver SA, Arthur RR, Erozan YS, Sherman ME, McArthur JC, Uematsu S. Diagnosis of progressive multifocal leukoencephalopathy by stereotactic brain biopsy utilizing immunohistochemistry and the polymerase chain reaction. *Acta Cytol*. 1995;39(1):35-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7847007.

51. Jochum W, Weber T, Frye S, Hunsmann G, Luke W, Aguzzi A. Detection of JC virus by anti-VP1 immunohistochemistry in brains with progressive multifocal leukoencephalopathy. *Acta Neuropathol*. 1997;94(3):226-231. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9292691.

52. Viscidi RP, Khanna N, Tan CS, et al. JC virus antibody and viremia as predictors of progressive multifocal leukoencephalopathy in human immunodeficiency virus-1-infected individuals. *Clin Infect Dis*. 2011;53(7):711-715. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21852452.

53. Knowles WA, Luxton RW, Hand JF, Gardner SD, Brown DW. The JC virus antibody response in serum and cerebrospinal fluid in progressive multifocal leucoencephalopathy. *Clin Diagn Virol*. 1995;4(2):183-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15566839.

54. Tan CS, Ghofrani J, Geiger E, Koralnik IJ, Jost S. Brief report: decreased JC virus-specific antibody-dependent cellular cytotoxicity in HIV-seropositive PML survivors. *J Acquir Immune Defic Syndr*. 2019;82(2):220-224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31513076.

55. Perez-Liz G, Del Valle L, Gentilella A, Croul S, Khalili K. Detection of JC virus DNA fragments but not proteins in normal brain tissue. *Ann Neurol*. 2008;64(4):379-387. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18688812.

56. Tan CS, Ellis LC, Wuthrich C, et al. JC virus latency in the brain and extraneural organs of patients with and without progressive multifocal leukoencephalopathy. *J Virol*. 2010;84(18):9200-9209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20610709.

57. Dunham SR, Schmidt R, Clifford DB. Treatment of progressive multifocal leukoencephalopathy using immune restoration. *Neurotherapeutics*. 2020;17(3):955-965. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32166631.

58. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of human immunodeficiency virus-infected patients in the protease inhibitor era. *J Infect Dis*. 1999;180(3):621-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10438348.

59. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related progressive multifocal leukoencephalopathy on

potent combined antiretroviral therapy. *J Neurovirol*. 1999;5(4):421-429. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10463864.

60. Tassie JM, Gasnault J, Bentata M, et al. Survival improvement of AIDS-related progressive multifocal leukoencephalopathy in the era of protease inhibitors. Clinical Epidemiology Group. French Hospital Database on HIV. *AIDS*. 1999;13(14):1881-1887. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10513646.

61. Cinque P, Pierotti C, Vigano MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. *J Neurovirol*. 2001;7(4):358-363. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11517417.

62. Marra CM, Rajicic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS*. 2002;16(13):1791-1797. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12218391.

63. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis*. 2003;36(8):1047-1052. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12684918.

64. Lima MA, Bernal-Cano F, Clifford DB, Gandhi RT, Koralnik IJ. Clinical outcome of long-term survivors of progressive multifocal leukoencephalopathy. *J Neurol Neurosurg Psychiatry*. 2010;81(11):1288-1291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20710013.

65. Pazzi AL, Galli M, et al. The relationship between outcome of progressive multifocal leukoencephalopathy and type and response to ART in previously HAART-untreated patients. Presented at: 14th Conference on Retroviruses and Opportunistic Infections; 2007. Los Angeles, CA.

66. Dong-Si T, Gheuens S, Gangadharan A, et al. Predictors of survival and functional outcomes in natalizumab-associated progressive multifocal leukoencephalopathy. *J Neurovirol*. 2015;21(6):637-644. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25771865.

67. Gasnault J, Costagliola D, Hendel-Chavez H, et al. Improved survival of HIV-1-infected patients with progressive multifocal leukoencephalopathy receiving early 5-drug combination antiretroviral therapy. *PLoS One*. 2011;6(6):e20967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21738597.

68. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol*. 2008;65(1):65-70. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18195140.

69. Lanoy E, Guiguet M, Bentata M, et al. Survival after neuroAIDS: association with antiretroviral CNS Penetration-Effectiveness score. *Neurology*. 2011;76(7):644-651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21248274.

70. Garvey L, Winston A, Walsh J, et al. Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. *Neurology*. 2011;76(8):693-700. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21339496.

71. Fanjul F, Riveiro-Barciela M, Gonzalez J, et al. Evaluation of progressive multifocal leukoencephalopathy treatments in a Spanish cohort of HIV-infected patients: do protease inhibitors improve survival regardless of central nervous system penetration-effectiveness (CPE) score? *HIV Med*. 2013;14(5):321-325. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23217049.

72. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. *N Engl J Med*. 1998;338(19):1345-1351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9571254.

73. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol*. 2001;7(4):375-381. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11517420.

74. Elphick GF, Querbes W, Jordan JA, et al. The human polyomavirus, JCV, uses serotonin receptors to infect cells. *Science*. 2004;306(5700):1380-1383. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15550673.

75. O'Hara BA, Atwood WJ. Interferon beta1-a and selective anti-5HT(2a) receptor antagonists inhibit infection of human glial cells by JC virus. *Virus Res*. 2008;132(1-2):97-103. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18093678.

76. Altschuler EL, Kast RE. The atypical antipsychotic agents ziprasidone [correction of zisprasidone], risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal leukoencephalopathy. *Med Hypotheses*. 2005;65(3):585-586. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16004936.

77. Santagata S, Kinney HC. Mechanism of JCV entry into oligodendrocytes. *Science*. 2005;309(5733):381-382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16020715.

78. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M. Progressive multifocal leukoencephalopathy in a haploidentical stem cell transplant recipient: a clinical, neuroradiological and virological response after treatment with risperidone. *Antiviral Res*. 2007;74(2):156-158. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17140673.

79. Vulliemoz S, Lurati-Ruiz F, Borruat FX, et al. Favourable outcome of progressive multifocal leucoencephalopathy in two patients with dermatomyositis. *J Neurol Neurosurg Psychiatry*. 2006;77(9):1079-1082. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16914758.

80. Lanzafame M, Ferrari S, Lattuada E, et al. Mirtazapine in an HIV-1 infected patient with progressive multifocal leukoencephalopathy. *Infez Med*. 2009;17(1):35-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19359824.

81. Cettomai D, McArthur JC. Mirtazapine use in human immunodeficiency virus-infected patients with progressive multifocal leukoencephalopathy. *Arch Neurol*. 2009;66(2):255-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19204164.

82. Kerr DA, Chang CF, Gordon J, Bjornsti MA, Khalili K. Inhibition of human neurotropic virus (JCV) DNA replication in glial cells by camptothecin. *Virology*. 1993;196(2):612-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8396804.

83. Royal W, 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol*. 2003;9(3):411-419. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12775425.

84. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. *J Neurovirol*. 2013;19(4):351-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23733308.

85. Huang SS, Skolasky RL, Dal Pan GJ, Royal W, 3rd, McArthur JC. Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol*. 1998;4(3):324-332. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9639075.

86. Geschwind MD, Skolasky RI, Royal WS, McArthur JC. The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol*. 2001;7(4):353-357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11517416.

87. Nath A, Venkataramana A, Reich DS, Cortese I, Major EO. Progression of progressive multifocal leukoencephalopathy despite treatment with beta-interferon. *Neurology*. 2006;66(1):149-150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16401874.

88. Przepiorka D, Jaeckle KA, Birdwell RR, et al. Successful treatment of progressive multifocal leukoencephalopathy with low-dose interleukin-2. *Bone Marrow Transplant*. 1997;20(11):983-987. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9422479.

89. Buckanovich RJ, Liu G, Stricker C, et al. Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin's lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. *Ann Hematol*. 2002;81(7):410-413. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12185517.

90. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. *Neurology*. 2005;65(9):1510. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16275856.

91. Sospedra M, Schippling S, Yousef S, et al. Treating progressive multifocal leukoencephalopathy with interleukin 7 and vaccination with JC virus capsid protein VP1. *Clin Infect Dis*. 2014;59(11):1588-1592. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25214510.

92. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M, Progressive Multifocal Leukeoncephalopathy Consortium. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. *Ther Adv Neurol Disord*. 2015;8(6):255-273. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26600871.

93. Soleimani-Meigooni DN, Schwetye KE, Angeles MR, et al. JC virus granule cell neuronopathy in the setting of chronic lymphopenia treated with recombinant interleukin-7. *J Neurovirol*. 2017;23(1):141-146. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27421731.

94. Miskin DP, Chalkias SG, Dang X, Bord E, Batson S, Koralnik IJ. Interleukin-7 treatment of PML in a patient with idiopathic lymphocytopenia. *Neurol Neuroimmunol Neuroinflamm*. 2016;3(2):e213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27144212.

95. Ray U, Cinque P, Gerevini S, et al. JC polyomavirus mutants escape antibody-mediated neutralization. *Sci Transl Med*. 2015;7(306):306ra151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26400912.

96. Cortese I, Muranski P, Enose-Akahata Y, et al. Pembrolizumab treatment for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2019;380(17):1597-1605. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30969503.

97. Clifford DB. Checkpoint therapy for progressive multifocal leukoencephalopathy: pointless? *Eur J Neurol*. 2020;27(11):2114-2116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32644212.

98. Berzero G, Basso S, Stoppini L, et al. Adoptive transfer of JC virus-specific T lymphocytes for the treatment of progressive multifocal leukoencephalopathy. *Ann Neurol*. 2021;89(4):769-779. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33459417.

99. Muftuoglu M, Olson A, Marin D, et al. Allogeneic BK virus-specific T cells for progressive multifocal leukoencephalopathy. *N Engl J Med*. 2018;379(15):1443-1451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30304652.

100. Cortese I, Beck ES, Al-Louzi O, et al. BK virus-specific T cells for immunotherapy of progressive multifocal leukoencephalopathy: an open-label, single-cohort pilot study. *Lancet Neurol*. 2021;20(8):639-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34302788.

101. Vendrely A, Bienvenu B, Gasnault J, Thiebault JB, Salmon D, Gray F. Fulminant inflammatory leukoencephalopathy associated with HAART-induced immune restoration in AIDS-related progressive multifocal leukoencephalopathy. *Acta Neuropathol*. 2005;109(4):449-455. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15739098.

102. Tan K, Roda R, Ostrow L, McArthur J, Nath A. PML-IRIS in patients with HIV infection: clinical manifestations and treatment with steroids. *Neurology*. 2009;72(17):1458-1464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19129505.

103. Sainz-de-la-Maza S, Casado JL, Perez-Elias MJ, et al. Incidence and prognosis of immune reconstitution inflammatory syndrome in HIV-associated progressive multifocal leucoencephalopathy. *Eur J Neurol*. 2016;23(5):919-925. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26914970.

104. Clifford DB. Neurological immune reconstitution inflammatory response: riding the tide of immune recovery. *Curr Opin Neurol*. 2015;28(3):295-301. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25887769.

105. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after highly active antiretroviral therapy. *AIDS*. 2001;15(14):1900-1902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11579261.

106. Safdar A, Rubocki RJ, Horvath JA, Narayan KK, Waldron RL. Fatal immune restoration disease in human immunodeficiency virus type 1-infected patients with progressive

multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis*. 2002;35(10):1250-1257. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12410486.

107. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry*. 2003;74(8):1142-1144. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12876257.

108. Di Giambenedetto S, Vago G, Pompucci A, et al. Fatal inflammatory AIDS-associated PML with high CD4 counts on HAART: a new clinical entity? *Neurology*. 2004;63(12):2452-2453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15623736.

109. Fournier A, Martin-Blondel G, Lechapt-Zalcman E, et al. Immune reconstitution inflammatory syndrome unmasking or worsening AIDS-related progressive multifocal leukoencephalopathy: a literature review. *Front Immunol*. 2017;8:577. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28588577.

110. Martin-Blondel G, Cuzin L, Delobel P, et al. Is maraviroc beneficial in paradoxical progressive multifocal leukoencephalopathy-immune reconstitution inflammatory syndrome management? *AIDS*. 2009;23(18):2545-2546. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19907215.

111. Januel E, Martin-Blondel G, Lamirel C, et al. Do CCR5 antagonists improve the overall survival of patients with AIDS-related progressive multifocal leucoencephalopathy? *J Neurol Neurosurg Psychiatry*. 2018;89(10):1125-1126. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29305436.

112. Bernard-Valnet R, Moisset X, Maubeuge N, et al. CCR5 blockade in inflammatory PML and PML-IRIS associated with chronic inflammatory diseases' treatments. *Neurol Neuroimmunol Neuroinflamm*. 2022;9(1). Available at: https://www.ncbi.nlm.nih.gov/pubmed/34728496.

113. Hentzien M, Guihot A, de Maindreville D, et al. Progressive multifocal leukoencephalopathy despite immune recovery in a HIV/HCV co-infected patient. *J Neurovirol*. 2020;26(4):607-610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32458280.

114. Crossley KM, Agnihotri S, Chaganti J, et al. Recurrence of progressive multifocal leukoencephalopathy despite immune recovery in two HIV seropositive individuals. *J Neurovirol*. 2016;22(4):541-545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26727910.

Syphilis

Updated: September 25, 2023
Reviewed: January 10, 2024

Epidemiology

Syphilis, caused by *Treponema pallidum*, is associated with an increased risk of sexual acquisition and transmission of HIV.[1-8] In the United States, the national rate of primary and secondary syphilis has increased since 2001.[9-12] Although HIV infection, particularly in the advanced stages, may modify the diagnosis, natural history, or management of *T. pallidum* infection, the principles of syphilis management remain the same for people with and without HIV.[13-18]

Clinical Manifestations

The effects of HIV on the protean manifestations of syphilis have been documented in multiple case reports and small case series, and in a limited number of large studies. In most people with HIV and syphilis, the clinical manifestations of syphilis are similar to those observed in people without HIV. Some studies suggest that infection with HIV may affect the clinical presentation of syphilis, as atypical or multiple genital lesions are more apparent, and accelerated progression of syphilis may be seen in people with advanced immunosuppression.[16,17,19-22] Primary or secondary syphilis also may cause a transient decrease in CD4 T lymphocyte (CD4) cell count and an increase in HIV viral load that improves with recommended syphilis treatment regimens.[13,23-27] Independent of HIV, previous syphilis can attenuate the clinical and laboratory manifestations of incident infection with *T. pallidum*.[28-30]

Primary syphilis commonly presents as a single painless nodule at the site of contact that rapidly ulcerates to form a classic chancre; however, multiple or atypical painful chancres may occur, and primary lesions may be absent or missed in people with HIV.[16,21,31] Progression to secondary syphilis typically follows 2 to 8 weeks after primary syphilis, but an overlap in primary and secondary manifestations can occur, especially in people with HIV. The most common manifestations of secondary syphilis are mucocutaneous lesions that are macular, maculopapular, papulosquamous, or pustular. These lesions can involve the palms and soles and are often accompanied by generalized lymphadenopathy, fever, malaise, anorexia, arthralgias, and headache.[13,17,18] Mpox (formerly known as monkeypox) lesions can have a similar appearance and can occur simultaneously with early syphilis.[32] Condylomata lata (moist, flat papular lesions in warm intertriginous regions) can occur and may resemble condylomata acuminata caused by human papillomavirus. Lues maligna is a rare manifestation of secondary syphilis, characterized by papulopustular skin lesions that can evolve into ulcerative lesions with sharp borders and a dark central crust.[33-35] Manifestations of secondary syphilis involving other locations can occur (e.g., ocular and otic syphilis, meningoencephalitis, hepatitis, nephrotic syndrome, gastritis, pneumonia). In people with secondary syphilis, non-focal central nervous system (CNS) symptoms and cerebrospinal fluid (CSF) abnormalities, such as lymphocytic pleocytosis with a mildly elevated CSF protein, can occur.[19,22,31,36-40] Signs and symptoms of primary and secondary syphilis can overlap or persist from a few days to several weeks before resolving. In some instances, recrudescence of symptoms may occur after secondary infection with subsequent evolution to latent stages.

Latent syphilis is defined as serologic reactivity without clinical signs and symptoms of infection. Latent syphilis can be categorized as early latent syphilis if ≤1 year duration, late latent syphilis if

>1 year duration, or latent syphilis of unknown duration if there is insufficient information to determine the duration of infection. Tertiary syphilis refers to gumma, cardiovascular syphilis, psychiatric manifestations (e.g., memory loss, personality changes), or late neurosyphilis that can develop 10 to 30 years after untreated infection.

Neurosyphilis, similar to ocular and otic syphilis, can occur at any stage of syphilis with different clinical presentations, including cranial nerve dysfunction, meningitis, stroke, acute or chronic change in mental status, and loss of vibration sense. Manifestations of neurosyphilis in people with HIV are similar to those in individuals who do not have HIV. However, clinical manifestations of neurosyphilis, such as concomitant ocular syphilis (including uveitis) or meningitis, may be more common in people with HIV.[19,22,40-46]

Syphilitic uveitis or other ocular syphilis manifestations (e.g., neuroretinitis and optic neuritis) can occur during any stage of syphilis and can manifest as isolated abnormalities or can be associated with neurosyphilis. Syphilis can involve almost any ocular structure, but posterior uveitis and panuveitis are the most common presentations. Other common manifestations can include interstitial keratitis, recurrent anterior uveitis, retinal vasculitis, and optic neuropathy.[47]

All people with ocular symptoms and reactive syphilis serology need a full ocular examination, including cranial nerve evaluation. If cranial nerve dysfunction is present, a CSF evaluation is needed. Among people with isolated ocular symptoms (no cranial nerve dysfunction or other neurologic abnormalities), reactive syphilis serology, and confirmed ocular abnormalities on examination, CSF examination is unnecessary before treatment. CSF analysis might be helpful in evaluating people with ocular symptoms and reactive syphilis serology who do not have ocular findings on examination. If ocular syphilis is suspected, immediate referral to and management in collaboration with an ophthalmologist is crucial. Ocular syphilis should be treated similarly to neurosyphilis, even if a CSF examination is normal.

Isolated hearing loss or other otologic symptoms can occur at any stage of syphilis or can be associated with neurosyphilis. Among people with isolated auditory abnormalities and reactive syphilis serology, CSF evaluation is likely to be normal and is not necessary before treatment.[48]

Diagnosis

Direct Detection

Darkfield microscopy and molecular tests to detect *T. pallidum* in lesion exudates or tissue (e.g., biopsy with silver stain) are definitive for diagnosing early syphilis.[49] Although *T. pallidum* direct antigen detection tests are no longer commercially available, some laboratories provide locally developed and validated polymerase chain reaction (PCR) tests for the direct detection of *T. pallidum*.

Serologic Testing

Serologic diagnosis of syphilis traditionally has involved screening for nontreponemal antibodies with confirmation of reactive tests by treponemal-based assays.[13,50,51] A serologic diagnosis of syphilis is based on nontreponemal tests (i.e., Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR]), followed by confirmation with treponemal tests (i.e., *T. pallidum* particle agglutination [TP-PA], enzyme immunoassays [EIAs], chemiluminescence

immunoassays [CIAs], fluorescent treponemal antibody absorbed [FTA-ABS], or immunoblots). Rapid treponemal assays are also available to screen for syphilis; however, these tests can not differentiate recent or past infection, so testing with a nontreponemal test is indicated to inform further patient management.[50-52] Use of only one type of serologic test (nontreponemal or treponemal) is insufficient for diagnosis and can result in false-negative results among people tested during primary syphilis and false-positive results among people without syphilis or previously treated syphilis.

Traditional Algorithm

False-positive nontreponemal test results can be associated with medical conditions and other factors unrelated to syphilis, including HIV, autoimmune disease, vaccinations, injection drug use, pregnancy, and older age.[50] Individuals with a reactive nontreponemal test should always receive a treponemal test to confirm the syphilis diagnosis. Nontreponemal test antibody titers can correlate with disease activity and are used for monitoring treatment response. Sequential serologic tests should be performed using the same testing method (VDRL or RPR), preferably by the same laboratory. VDRL and RPR are equally valid assays; however, quantitative results from the two tests cannot be compared directly with each other because the methods are different, and RPR titers frequently are slightly higher than VDRL titers.

Nontreponemal test titers usually decrease after treatment and can become nonreactive with time. However, in some instances nontreponemal antibodies might decrease less than fourfold after treatment (i.e., inadequate serologic response) or might decline appropriately but fail to serorevert and persist for a long period. Atypical nontreponemal serologic test results (e.g., unusually high, unusually low, or fluctuating titers) might occur regardless of HIV status. When serologic tests do not correspond with clinical findings indicative of primary, secondary, or latent syphilis, presumptive treatment is recommended for people with risk factors for syphilis, and use of other tests (e.g., biopsy for histology and immunostaining and PCR of lesion) should be considered. For most people with HIV, serologic tests are accurate and reliable for diagnosing syphilis and evaluating response to treatment.[28]

Reverse-Sequence Algorithm

Most people who have reactive treponemal tests will have reactive tests for the remainder of their lives, regardless of adequate treatment or disease activity and do not predict treatment response.

Some laboratories have initiated a reverse-sequence screening algorithm using treponemal EIA or CIA as a screening test, followed by a reflex-quantitative nontreponemal test if the EIA or CIA is positive.

This reverse-sequence algorithm can identify people previously treated for syphilis, those with untreated or incompletely treated syphilis, and those with false-positive results that can occur with a low likelihood of infection.[13,53] People with a positive treponemal screening test should have a standard quantitative nontreponemal test with titer performed reflexively by the laboratory to guide patient management decisions.

In the reverse-sequence screening strategy, having a positive treponemal EIA or CIA and a negative reflex-quantitative nontreponemal test requires a second treponemal test (based on different antigens from the initial test) to confirm the results of the positive initial treponemal test. If a second

treponemal test is positive, people who have been treated appropriately for their stage of syphilis will require no further treatment unless sexual risk history suggests likelihood of re-exposure or there is a sustained fourfold increase in nontreponemal antibody titers. In this instance, a repeat nontreponemal test 2 to 4 weeks after the most recent possible exposure is recommended to evaluate for early infection. Those without a history of treatment for syphilis should be offered treatment. Unless history or results of a physical examination suggest a recent infection (e.g., early-stage syphilis), previously untreated people should be treated for late latent syphilis. If the second treponemal test is negative and the risk of syphilis is low, no treatment is indicated.[13,54] However, if the risk of syphilis is high, treatment should be considered. Multiple studies demonstrate that high quantitative index values or high signal-to-cutoff ratio from treponemal EIA or CIA tests correlate with TP-PA positivity, which might eliminate the need for additional confirmatory testing; however, the range of index values varies among different treponemal immunoassays, and the values that correspond to high levels of reactivity with confirmatory testing might differ by immunoassay.[51,55,56]

In the absence of neurologic signs or symptoms, risk of neurosyphilis is low in people with a reactive treponemal test and a nonreactive nontreponemal test[55,57]; examination of CSF is not recommended.

Early-stage disease (i.e., primary, secondary, and early latent syphilis) is identified using the same diagnostic tests used in people without HIV: standard serologic tests and darkfield microscopy of mucocutaneous lesions, if available. VDRL and RPR titers may be higher, lower (in rare instances), or delayed in people with HIV with early-stage syphilis.[58-62] No data indicate that treponemal tests perform differently among people with HIV[51]; although uncommon, false-negative serologic tests for syphilis can occur with documented *T. pallidum* infection.[61,62] When serologic tests do not correspond with clinical findings indicative of primary or secondary syphilis, presumptive treatment is recommended for people with risk factors for syphilis, and dilution of the sample for prozone phenomenon should be considered. For most people with HIV, serologic tests are accurate and reliable for diagnosing syphilis and for determining response to treatment.

By definition, people with latent syphilis have serological evidence of syphilis (nontreponemal and treponemal testing) in the absence of clinical manifestations. Early latent syphilis may occur in the interval between the primary and secondary stage of infection or following resolution of secondary manifestations and is defined by evidence of infection during the preceding year by—

- A documented seroconversion or fourfold or greater increase in nontreponemal titer; *or*
- Symptoms of primary or secondary syphilis; *or*
- A sex partner with documented primary, secondary, or early latent syphilis.[13]

Late latent syphilis is defined as syphilis in a person who does not have evidence of acquiring infection in the preceding year.

All people with syphilis and signs or symptoms suggesting neurologic disease (e.g., cranial nerve dysfunction, meningitis, stroke, altered mental status) warrant evaluation for neurosyphilis.

CSF abnormalities (i.e., elevated protein and mononuclear pleocytosis) are common in early-stage syphilis[36] and in people with HIV, even those with no neurologic symptoms. The clinical and prognostic significance of CSF laboratory abnormalities with early-stage syphilis in people without neurologic symptoms is unknown. Several studies have demonstrated that in people with syphilis and HIV, CSF laboratory abnormalities are associated with CD4 counts ≤350 cells/mm^3 or in combination with RPR titers ≥1:32.[39,40,63,64] However, unless neurologic signs and symptoms are

present, a CSF examination has not been associated with improved clinical outcomes. Although laboratory testing is helpful in supporting the diagnosis of neurosyphilis, no single test can be used to diagnose neurosyphilis. The diagnosis of neurosyphilis depends on a combination of CSF tests (CSF cell count, CSF protein, and CSF-VDRL) in the setting of reactive serologic test results and neurologic signs and symptoms. CSF examination may indicate mononuclear pleocytosis (6–200 cells/mm^3), mildly elevated protein concentration, or a reactive CSF-VDRL. Among people with HIV, the CSF leukocyte count can be elevated (>5 white blood cell count [WBC]/mm^3); using a higher cutoff (>20 WBC/mm^3) may improve the specificity of neurosyphilis diagnosis.[39] In people with neurologic signs or symptoms, a reactive CSF-VDRL (in a specimen not contaminated with blood) is considered diagnostic of neurosyphilis; however, it is thought to have a very low sensitivity and therefore may miss true disease. Therefore, in people with neurologic signs or symptoms, reactive serologic test results, lymphocytic pleocytosis, or elevated protein, neurosyphilis should be considered even when the CSF-VDRL is negative. In that instance, additional evaluation by using FTA-ABS or TP-PA testing on CSF might be warranted.[13] The CSF FTA-ABS test is less specific for neurosyphilis than the CSF-VDRL but is highly sensitive. Fewer data are available regarding CSF TP-PA; however, the sensitivity and specificity appears similar to the CSF FTA-ABS.[65,66] Neurosyphilis is highly unlikely with a negative CSF FTA-ABS or TP-PA test, especially among people with nonspecific neurologic signs and symptoms.

RPR tests of the CSF have been associated with a high false-negative rate and are not recommended.[67] PCR-based diagnostic methods are not currently recommended as diagnostic tests for neurosyphilis.

Preventing Disease

Recommendations for Preventing Syphilis

Management of Sexual Partners After Exposure to *Treponema pallidum* (Syphilis) to Prevent Disease
Indication for Treatment • Individuals exposed sexually within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner regardless of syphilis serologic status (AII) • Individuals exposed >90 days before syphilis diagnosis in a sex partner, if syphilis serologic test results are not available immediately and the opportunity for follow-up is uncertain (AIII) Treatment • See therapy for early-stage syphilis in the Recommendations for Treating Syphilis table.

Note: Additional logistical information is available from the Centers for Disease Control and Prevention at https://www.cdc.gov/std/treatment/drug-notices.htm.

The resurgence of syphilis and other sexually transmitted infections (STIs), as well as the emergence of mpox, in men who have sex with men (MSM) with HIV underscores the importance of primary prevention of syphilis in this population, which should begin with a behavioral risk assessment and routine discussion of sexual behaviors. Health care providers should discuss patient-centered risk reduction messages and advise specific actions that can reduce the risk of acquiring STIs and of transmitting HIV.[13,68-72] Routine serologic screening for syphilis is recommended at least annually for all people with HIV who are sexually active, with more frequent screening (every 3–6 months) for those who have multiple or anonymous partners.[13,73-75] The occurrence of syphilis or any other STI in a person with HIV is an indication of risk behaviors that should prompt intensified risk assessment

and counseling messages about the manifestations of syphilis, risk of HIV transmission, and prevention strategies with strong consideration for behavioral intervention.[76,77] People undergoing screening or treatment for syphilis also should be evaluated for other STIs, including mpox, chlamydia, and gonorrhea at anatomic sites of exposure in men and chlamydia, gonorrhea, and trichomonas infections in women.[13,78]

Frequent serologic screening can identify people with recent infection and, in some instances, before infectious lesions develop. Treatment can prevent disease progression in the individual and transmission to their partners. Studies in the pre-HIV era demonstrated that approximately one-third of the sexual partners of people who have primary syphilis will develop syphilis within 30 days of exposure; empiric treatment of sexual partners exposed to syphilis will prevent the development of disease and onward syphilis transmission.[79-82] Individuals with recent sexual contact with a person with syphilis in any stage should be evaluated clinically and serologically and treated presumptively. People who have had sexual contact with an individual diagnosed with primary, secondary, or early latent syphilis during the 90 days preceding the diagnosis should be treated presumptively for early syphilis, even if serologic test results are negative **(AII).**

People who have had sexual contact with a person who receives a diagnosis of primary, secondary, or early latent syphilis >90 days before the diagnosis should be treated presumptively for early syphilis if serologic test results are not immediately available and the opportunity for follow-up is uncertain **(AIII).** If serologic tests are negative, no treatment is needed. If serologic tests are positive, treatment should be based on clinical and serologic evaluation and the stage of syphilis. Long-term sexual partners of people who have late latent syphilis should be evaluated clinically and serologically for syphilis and treated on the basis of the evaluation's findings. Sexual partners of people with syphilis should be notified of their exposure and the importance of evaluation for testing and empiric therapy.[13] The following sex partners of people with syphilis are considered at risk for infection and should be confidentially notified of the exposure and need for evaluation: partners who have had sexual contact within (1) 3 months plus the duration of symptoms for people who receive a diagnosis of primary syphilis, (2) 6 months plus the duration of symptoms for those diagnosed with secondary syphilis, and (3) 1 year for people diagnosed with early latent syphilis.

Pre-Exposure Prophylaxis and Post-Exposure Prophylaxis for Prevention

Doxycycline pre-exposure prophylaxis (PrEP) has been examined for prevention of bacterial STIs. In a pilot study, 30 MSM with HIV with previous syphilis were randomly assigned to doxycycline 100 mg daily for 48 weeks versus a financial incentive–based behavioral intervention; doxycycline was associated with a lower incidence of syphilis, but this did not reach statistical significance due to small sample size.[83]

Post-exposure prophylaxis (doxycycline 200 mg after unprotected anal sex) has been studied among MSM and transgender women, with a reduction in incident syphilis by 73%.[84] Several recent randomized open-label clinical trials have found that doxycycline 200 mg after condomless sex among MSM or transgender women with HIV or on HIV PrEP significantly reduced chlamydia, gonorrhea, and syphilis acquisition; a randomized trial of cisgender women on HIV PrEP administered doxycycline 200 mg within 72 hours after sex did not reduce chlamydia, gonorrhea, or syphilis acquisition.[85] There is ongoing evaluation regarding the potential impact of STI postexposure prophylaxis on antimicrobial resistance and the microbiome. Other studies are underway or in development regarding doxycycline prophylaxis for bacterial STIs.[86,87]

Targeted mass treatment of high-risk populations with azithromycin has not been demonstrated to be effective.[88] Azithromycin is not recommended as secondary prevention because of azithromycin treatment failures reported in people with HIV and reports of chromosomal mutations associated with macrolide-resistant *T. pallidum.*[89-93]

Treatment

Recommendations for Treating Syphilis

General Considerations for Treating Syphilis
• Selection of the appropriate penicillin preparation is important because *T. pallidum* can reside in sequestered sites (e.g., the CNS and aqueous humor) that are poorly accessed by certain forms of penicillin. • Combinations of oral benzathine penicillin and procaine penicillin or short-acting benzathine-procaine penicillin (Bicillin C-R) preparations are not appropriate for syphilis treatment. • The efficacy of non-penicillin alternatives has not been well evaluated in people with HIV and should be undertaken only with close clinical and serologic monitoring. • The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache, fever, and myalgias that can occur within the first 24 hours after therapy. It occurs more frequently in people with early syphilis and can induce early labor or cause fetal distress during pregnancy. Patients should be informed about this potential reaction to treatment and that it is not an allergic reaction to penicillin.
Treating *Treponema pallidum* Infections (Syphilis) Depending on Stage of Disease
Primary, Secondary, and Early Latent Syphilis [≤1 year] *Recommended Therapy* • Benzathine penicillin G 2.4 million units IM in a single dose (AII)[a] *Alternative Therapy (For Penicillin-Allergic Patients; See Note Below)* • Doxycycline 100 mg PO twice daily for 14 days (BII),[b] *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days (BII)[b] Note: People with penicillin allergy whose compliance or follow-up cannot be ensured and who have syphilis during pregnancy should undergo penicillin desensitization and treatment with benzathine penicillin. For management of early syphilis during pregnancy, limited evidence indicates a second dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention (BII). **Late Latent (>1 year) or Latent of Unknown Duration** *Recommended Therapy* • Benzathine penicillin G 2.4 million units IM weekly for three doses (AII)[a] *Alternative Therapy (For Penicillin-Allergic Patients)* • Doxycycline 100 mg PO twice daily for 28 days (BIII) Note: People with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (AII).

Tertiary—Cardiovascular or Gummatous Disease

- Perform CSF examination and obtain infectious diseases consultation to guide management.
- People with CSF abnormalities should be treated with a regimen for neurosyphilis (AII).

Recommended Therapy

- Benzathine penicillin G 2.4 million units IM weekly for three doses for people without neurosyphilis (AII)[a]

Neurosyphilis, Otic, or Ocular Syphilis

Recommended Therapy

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or by continuous IV infusion for 10–14 days (AII), *with or without*
- Benzathine penicillin G 2.4 million units IM x 1 after completion of aqueous crystalline penicillin G infusion (CIII)[a]

Alternative Therapy

- Procaine penicillin G 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII). Procaine penicillin has been discontinued by the manufacturer as of June 13, 2023 (see FDA Drug Shortages).

Note: People who are allergic to sulfa-containing medications should not be given probenecid; thus, the procaine penicillin regimen is not recommended (AIII).

For Penicillin-Allergic Patients with Neurosyphilis, Otic, or Ocular Syphilis

Recommended Therapy

- Desensitization to penicillin

Alternative Therapy (If Desensitization Is Not Feasible and Not Pregnant)

- Ceftriaxone 2 g IV daily for 10–14 days (BII)

Note: People who have a history of IgE-mediated penicillin hypersensitivity may lose their sensitivity after 10 years, and a subsequent negative skin test evaluation followed by oral challenge can be considered. Among people for whom the only option is penicillin (e.g., syphilis in pregnancy) and among those with a positive skin test, desensitization to penicillin is the preferred approach.

[a] Benzathine penicillin is currently on the FDA drug shortage webpage due to limited supply. Updates on the expected duration for the shortage are available on the FDA Drug Shortage webpage.

[b] Skin testing for penicillin allergy can be useful in circumstances in which the reagents and expertise are available.

Note: Additional logistical information is available from the Centers for Disease Control and Prevention at https://www.cdc.gov/std/treatment/drug-notices.htm.

Key: CNS = central nervous system; CSF = cerebrospinal fluid; FDA = U.S. Food and Drug Administration; IgE = immunoglobulin E; IM = intramuscular; IV = intravenously; PO = orally

Treatment regimens for syphilis demonstrate that most people with HIV respond appropriately to single dose benzathine penicillin G after exposure to syphilis and for primary, secondary, and early latent syphilis (within the previous 12 months).[13,59,94,95] However, in people with HIV, more frequent clinical and serologic evaluation is recommended—at least every 3 months rather than every 6 months—because serologic nonresponse and neurologic complications may be more frequent.[19,96,97] Use of antiretroviral therapy (ART) in people with syphilis has also been associated with a reduced risk of serologic failure of syphilis treatment[22] and a lower risk of developing neurosyphilis.[22]

Benzathine penicillin G remains the treatment of choice for syphilis. People with HIV with early-stage (primary, secondary, or early latent) syphilis should receive a single intramuscular (IM) injection of 2.4 million units of benzathine penicillin G **(AII).**[13] High-dose amoxicillin given with probenecid in addition to benzathine penicillin G in early syphilis is not associated with improved clinical outcomes.[59] People with a penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin G **(AIII).**

The efficacy of alternative non-penicillin regimens in people with HIV and early syphilis has not been well studied. The use of any alternative penicillin treatment regimen should be undertaken only with close clinical and serologic monitoring. The Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV (the Panel) supports the use of doxycycline, 100 mg orally twice daily for 14 days, to treat early syphilis **(BII).**[98,99] Based on limited clinical studies in people with and without HIV, ceftriaxone (1 g daily either IM or intravenously [IV] for 10–14 days) is also recommended for treating early-stage syphilis **(BII),** but the optimal dose and duration of therapy have not been defined.[100-102] There are limited data suggesting a single 2-g oral dose of oral azithromycin can be effective for treating early syphilis[103-105]; however, *T. pallidum* chromosomal mutations associated with azithromycin resistance and treatment failures have been reported most commonly in MSM.[89-93,106] Azithromycin has not been well studied in people with HIV or among pregnant people. Therefore, azithromycin should not be used as treatment for syphilis **(AII).**

In people with HIV who have late latent syphilis, treatment with three weekly IM injections of 2.4 million units of benzathine penicillin G is recommended **(AII).** Alternative therapy is doxycycline, 100 mg orally twice daily for 28 days; however, it has not been sufficiently evaluated in people with HIV **(BIII).** Limited clinical studies and biologic and pharmacologic evidence suggest that ceftriaxone may be effective, but the optimal dose and duration of therapy have not been determined.[107,108] If the clinical situation requires use of an alternative to penicillin, treatment should be undertaken with close clinical and serologic monitoring.

People with HIV who have clinical evidence of tertiary syphilis (cardiovascular or gummatous disease) should have CSF examination to rule out CSF abnormalities before therapy is initiated. If the CSF evaluation is normal, the recommended treatment of late-stage syphilis is three weekly IM injections of 2.4 million units of benzathine penicillin G **(AII).**[13] However, due to the complexity of tertiary syphilis management, especially cardiovascular syphilis, health care providers are advised to consult an infectious disease specialist.

People with HIV diagnosed with neurosyphilis or ocular or otic syphilis should receive IV aqueous crystalline penicillin G, 18 to 24 million units daily, administered 3 to 4 million units IV every 4 hours or by continuous infusion for 10 to 14 days **(AII),** or procaine penicillin, 2.4 million units IM once daily plus probenecid 500 mg orally four times a day for 10 to 14 days **(BII).**[13] However, procaine penicillin has been recently discontinued by the manufacturer.[109]

People with HIV who are allergic to sulfa-containing medications should not be given probenecid because of potential allergic reaction; therefore, IV penicillin is recommended **(AIII).** Although systemic steroids are used frequently as adjunctive therapy for otic syphilis, such therapy has not been proven beneficial.

Because neurosyphilis treatment regimens are of shorter duration than those used in late latent syphilis, 2.4 million units of benzathine penicillin IM once after completion of IV penicillin G can be considered to provide a comparable duration of therapy **(CIII).**[13]

People who have a history of immunoglobulin E mediated penicillin hypersensitivity may lose their sensitivity after 10 years,[110,111] and a subsequent negative skin test evaluation followed by oral challenge can be considered. Among people for whom the only option is penicillin (e.g., syphilis in pregnancy) and among those with a positive skin test, desensitization to penicillin is the preferred approach. However, based on limited data, ceftriaxone (2 g daily IV for 10–14 days) is recommended as an acceptable alternative regimen **(BII).**[100,101,108] Other alternative regimens for neurosyphilis have not been evaluated adequately. Syphilis treatment recommendations are available in the 2021 Centers for Disease Control and Prevention STI Treatment Guidelines.[13]

Special Considerations with Regard to Starting Antiretroviral Therapy

There are no special considerations regarding the initiation of ART in patients with syphilis. Specifically, there is no evidence that treatment with ART needs to be delayed until treatment for syphilis has been completed. Immune reconstitution inflammatory syndrome in association with syphilis following treatment with ART in people with HIV is uncommon.[112,113]

Monitoring and Adverse Events

Clinical and serologic responses (fourfold decrease from the nontreponemal titer at the time of treatment) to treatment of early-stage (primary, secondary, and early latent) disease should be performed at 3, 6, 9, 12, and 24 months after therapy to ensure resolution of signs and symptoms within 3 to 6 months and seroreversion or a fourfold decline in nontreponemal titers within 24 months. Clinical and serologic responses to treatment are similar in people with HIV; subtle variations can occur, however, including a slower temporal pattern of serologic response in people with HIV.[13,59,79,94,95] Factors associated with the serologic response to treatment in people without HIV include younger age, earlier syphilis stage, and higher RPR titer.[114-116] If clinical signs and symptoms persist, treatment failure should be considered. If clinical signs or symptoms recur or there is a sustained fourfold increase in nontreponemal titers of greater than 2 weeks, treatment failure or reinfection should be considered and managed per recommendations (see Managing Possible Treatment Failure or Reinfection). The potential for reinfection should be based on the sexual history and risk assessment. Clinical trial data have demonstrated that 15% to 20% of people (including people with HIV) treated with recommended therapy for early-stage syphilis will not achieve the fourfold decline in nontreponemal titer used to define treatment response at 1 year.[13,59] Serum nontreponemal test titers may remain reactive, usually ≤1:8, although can be higher, for prolonged periods. In addition, people treated for early-stage syphilis who have a fourfold decline in titer may not serorevert to a negative nontreponemal test, which does not represent treatment failure but an inadequate serologic response.[117]

Response to therapy for late latent syphilis should be monitored using nontreponemal serologic tests at 6, 12, 18, and 24 months to ensure at least a fourfold decline in titer, if initially high (≥1:32), within 24 months of therapy. However, data to define the precise time intervals for adequate serologic responses are limited. Many people with low titers and late latent syphilis do not have a fourfold decline in the initial titer. If clinical symptoms develop or a fourfold increase in nontreponemal titers is sustained over 2 weeks, then treatment failure or reinfection should be considered and managed per recommendations (see Managing Possible Treatment Failure or Reinfection). The potential for reinfection should be based on sexual history and risk assessment.[13]

The earliest CSF indicator of response to neurosyphilis treatment is a decline in CSF lymphocytosis. The CSF-VDRL may respond more slowly. Limited data suggest that changes in CSF parameters

may occur more slowly in people with HIV, especially with advanced immunosuppression.[22,39] Among people with HIV who are on effective ART and people without HIV, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.[118,119] Therefore, repeated CSF examinations are unnecessary for people without HIV or among people with HIV who are on ART and who exhibit serologic and clinical responses to treatment.[13]

The Jarisch-Herxheimer reaction is an acute febrile reaction frequently accompanied by headache, rigors, transient worsening of rash, myalgia, and sometimes even a sepsis-like syndrome, that can occur within the first 24 hours after initiation of treatment for syphilis. Antipyretics can be used to manage symptoms but have not been proven to prevent this reaction. The Jarisch-Herxheimer reaction occurs most frequently in people with early syphilis, high nontreponemal antibody titers, and prior penicillin treatment.[120] People with syphilis should be warned about this reaction, instructed how to manage it, and informed that it is not an allergic reaction to penicillin.

Managing Possible Treatment Failure or Reinfection

Retreatment should be considered for people with early-stage syphilis who have persistent or recurring clinical signs or symptoms of disease, or a sustained fourfold increase in serum nontreponemal titers after an initial fourfold decrease following treatment. The assessment for potential reinfection should be informed by a sexual history and syphilis risk assessment including information about a recent sexual partner with signs or symptoms or recent treatment for syphilis. People who have had syphilis are at increased risk for reinfection. One study showed that 6% of MSM had a repeat early-stage syphilis infection within 2 years of initial infection; HIV infection and multiple sexual partners were associated with increased risk of reinfection.[11] Serologic response should be compared to the titer at the time of treatment. However, assessing serologic response to treatment can be difficult, as definitive criteria for cure or failure have not been well established. People with HIV may be at increased risk of treatment failure, but the magnitude of these risks is not precisely defined and is likely low.[13,38,97]

People who meet the criteria for treatment failure (i.e., signs or symptoms that persist or recur, or a fourfold increase or greater in titer sustained for more than 2 weeks) and who are at low risk for reinfection should be managed for possible treatment failure. If neurologic symptoms or signs are identified, a CSF evaluation is recommended, with findings guiding management. People with nontreponemal titers that do not decrease fourfold within 12 to 24 months of therapy should also be managed as a possible treatment failure. Management should include neurologic examination and retreatment with benzathine penicillin G, 2.4 million units at 1-week intervals for 3 weeks **(BIII).** If titers do not respond appropriately after retreatment, the value of repeated CSF examination or additional therapy is unclear, but it is generally not recommended. The Panel supports benzathine penicillin treatment (2.4 million units IM) without a CSF examination (unless signs or symptoms of neurosyphilis are present) and close clinical follow-up in people with recurrent signs and symptoms of primary or secondary syphilis or a fourfold increase in nontreponemal titers within the past year who are at high risk of syphilis reinfection **(CIII).**

People treated for late latent syphilis should have a CSF examination and be re-treated if they develop clinical signs or symptoms of syphilis or have a sustained fourfold increase in serum nontreponemal test titer and are at low risk for reinfection; this can also be considered if they experience an inadequate serologic response (i.e., less than fourfold decline in an initially high [≥1:32] nontreponemal test titer) within 12 months for early syphilis and 24 months for late latent

syphilis. If CSF examination is consistent with CNS involvement, retreatment should follow the recommendations for treatment of neurosyphilis. People with a normal CSF examination or without ocular or otic symptoms should be treated with benzathine penicillin 2.4 million units IM weekly for three doses **(BIII).** The Panel supports benzathine penicillin treatment (2.4 million units IM) without a CSF examination (unless signs or symptoms of neurosyphilis are present) and close clinical follow-up in people with signs or symptoms of primary or secondary syphilis or a fourfold increase in nontreponemal titers within the past year who are at high risk of reinfection **(CIII)**.

Among people with HIV who are on effective ART and people without HIV, normalization of the serum RPR titer predicts normalization of abnormal CSF parameters after neurosyphilis treatment.[118,119] Therefore, repeated CSF examinations are unnecessary for people with HIV who are on ART and who exhibit serologic and clinical responses after treatment.

Special Considerations During Pregnancy

In recent years, there has been a resurgence in neonatal syphilis in the United States. Syphilis in pregnancy is associated with increased risk of several adverse outcomes, including pregnancy loss, preterm birth, stillbirth, impaired fetal growth, neonatal mortality, and congenital infection, which can cause abnormalities in multiple organ systems. The clinical manifestations of syphilis in pregnancy are similar in people with and without HIV.

Serologic screening for syphilis should be conducted at the first prenatal visit and at 28 weeks. In communities and populations in which the prevalence of syphilis is high and in people at increased risk of infection (i.e., sex with multiple partners or new partner, sex in conjunction with drug use or transactional sex, late entry or no prenatal care, methamphetamine or heroin use, hepatitis C, alcohol misuse,[121] incarceration, STI in pregnancy or partner with STI, unstable housing or homelessness),[122] serologic testing should also be performed at delivery.[13] Providers should consider offering screening for syphilis to sexual partners of pregnant people.

Screening for syphilis during pregnancy should be offered at sites providing episodic care, including emergency departments, jails, and prisons.[123] Antepartum screening with nontreponemal testing is typical, but treponemal screening is being used in some settings. If a treponemal EIA or CIA test is used for antepartum syphilis screening, all positive EIA or CIA tests should be confirmed with a quantitative nontreponemal test (RPR or VDRL), as titers are essential to monitoring treatment response. If the nontreponemal test is negative and the prozone reaction is ruled out (false-negative nontreponemal test that results from high antibody titer) then the results are discordant; a second treponemal test should be performed, preferably on the same specimen (see Diagnosis section above).[124] If the second treponemal test is negative (i.e., EIA positive, RPR negative, and TP-PA negative), the positive EIA or CIA is more likely to represent a false-positive test result for people who are living in communities with low rates of syphilis, have a partner who is uninfected, and have no history of treated syphilis.[55,124] During pregnancy, if there is a low risk for syphilis, there are no signs or symptoms of primary syphilis, the partner has no clinical or serologic evidence of syphilis, and the pregnant person is likely to follow up with clinical care, repeat serologic testing within 4 weeks can be considered to determine whether the EIA or CIA remains positive or whether the RPR, VDRL, or TP-PA result becomes positive. If both the RPR and TP-PA remain negative, no further treatment is necessary. If follow-up is not likely, treatment appropriate for the stage of syphilis is recommended for people with an isolated reactive treponemal test without a history of syphilis treatment.

No postpartum individual or neonate should leave the hospital without documentation of maternal syphilis serologic status determined at least once during pregnancy.[13] All individuals who have a fetal death after 20 weeks of gestation also should be tested for syphilis.

Rates of transmission to the fetus and adverse pregnancy outcomes for untreated syphilis are highest with primary, secondary, and early latent syphilis and decrease with increasing duration of infection. Pregnancy does not appear to alter the clinical course, manifestations, or diagnostic test results for syphilis infection in adults. Concurrent syphilis infection has been associated with increased risk of perinatal transmission of HIV to the infant.[125-131]

Syphilis infection during pregnancy should be considered in those with reactive syphilis serology unless an adequate treatment history is documented clearly in the medical records and sequential serologic antibody titers have declined appropriately for the stage of syphilis. In general, the risk of antepartum fetal infection or congenital syphilis at delivery is related to the quantitative maternal nontreponemal titer, especially if ≥1:8. However, risk for fetal infection is still substantial among pregnant people with late latent syphilis and low titers. All neonates born to people with syphilis should be evaluated for congenital syphilis regardless of maternal treatment or response.

Sustained low nontreponemal titers after documented treatment for the appropriate stage of infection might not require additional treatment; however, rising or persistently high antibody titers may indicate reinfection or treatment failure, and retreatment should be considered.[13]

Benzathine penicillin G is recommended for the treatment of syphilis during pregnancy. Penicillin is the only known effective antimicrobial for preventing transmission to the fetus and for treatment of fetal infection; however, evidence is insufficient to determine the optimal penicillin regimen.[132] For management of early syphilis during pregnancy, limited evidence indicates that a second dose of benzathine penicillin G 2.4 million units IM 1 week after the single dose treatment may be of benefit for congenital syphilis prevention.[13,129,133-135] If a second dose of benzathine penicillin is administered, it should be provided no later than 9 days after the first dose.[13] Sexual partners of pregnant individuals with syphilis should be referred for evaluation and treatment.

Since no alternatives to penicillin have been proven effective and safe for prevention of fetal infection, desensitization and treatment with penicillin should be performed in pregnancy for those who have a history of penicillin allergy **(AIII).**[13] Erythromycin and azithromycin should not be used because these regimens do not reliably cure infection in the pregnant individual or the fetus **(AII)**[132]; tetracyclines should be avoided in the second and third trimesters of pregnancy **(AII).**[129,136] Data are insufficient to recommend ceftriaxone[137,138] for treatment of antenatal infection and prevention of congenital syphilis **(BIII).**

Treatment of syphilis during the second half of pregnancy may precipitate preterm labor or fetal distress if a Jarisch-Herxheimer reaction occurs.[139,140] Obstetric attention is advised if contractions develop or a decrease in fetal movement is noted after treatment. During the second half of pregnancy, syphilis management can be facilitated with sonographic fetal evaluation for congenital syphilis, but this evaluation should not delay therapy. Sonographic signs of fetal or placental syphilis (e.g., hepatomegaly, ascites, fetal hydrops, thickened placenta) indicate a greater risk of fetal treatment failure.[141] Such cases should be managed in consultation with high-risk obstetric specialists. After 20 weeks of gestation, fetal and contraction monitoring for 24 hours after initiation of treatment for early syphilis should be considered when sonographic findings indicate fetal infection.

Coordinated prenatal care and treatment are vital because providers should document that treatment is adequate for the syphilis stage and ensure that the clinical and antibody responses are appropriate for the patient's disease stage. Maternal serologic response during pregnancy after adequate therapy varies by stage of disease and timing of treatment.[142] If syphilis is diagnosed and treated at or before 24 weeks' gestation, serologic titers should not be repeated before 8 weeks after treatment but should be repeated again at delivery. Titers should be repeated sooner if reinfection or treatment failure is suspected. For syphilis diagnosed and treated after 24 weeks' gestation, serologic titers should be repeated at delivery.[13] A majority of women will not achieve a fourfold decrease in titers before delivery, although this does not indicate treatment failure. Inadequate antenatal treatment is likely if delivery occurs within 30 days of therapy, clinical signs of infection are present at delivery, or the maternal nontreponemal titer at delivery is fourfold higher than the pre-treatment titer. There is no evidence that pregnant women with syphilis and HIV are at increased risk for delayed syphilis treatment response compared with women without HIV.[143]

References

1. Dennis AM, Cressman A, Pasquale D, et al. Intersection of syphilis and HIV networks to identify opportunities to enhance HIV prevention. *Clin Infect Dis*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/33978757.

2. Wu MY, Gong HZ, Hu KR, Zheng HY, Wan X, Li J. Effect of syphilis infection on HIV acquisition: a systematic review and meta-analysis. *Sex Transm Infect*. 2021;97(7):525-533. Available at: https://pubmed.ncbi.nlm.nih.gov/33219164.

3. Hart-Malloy R, Rosenthal M, Patterson W, Currenti S, O'Donnell T, Gunn JK. Syphilis among adult males with a history of male-to-male sexual contact living with diagnosed HIV in New York State (excluding New York City): the challenge of intersecting epidemics. *PLoS One*. 2019;14(12):e0226614. Available at: https://pubmed.ncbi.nlm.nih.gov/31851719.

4. Pathela P, Braunstein SL, Schillinger JA, Shepard C, Sweeney M, Blank S. Men who have sex with men have a 140-fold higher risk for newly diagnosed HIV and syphilis compared with heterosexual men in New York City. *J Acquir Immune Defic Syndr*. 2011;58(4):408-416. Available at: https://pubmed.ncbi.nlm.nih.gov/21857351.

5. Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75(1):3-17. Available at: https://pubmed.ncbi.nlm.nih.gov/10448335.

6. Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? *Sex Transm Dis*. 2001;28(10):579-597. Available at: https://pubmed.ncbi.nlm.nih.gov/11689757.

7. Peterman TA, Newman DR, Maddox L, Schmitt K, Shiver S. High risk for HIV following syphilis diagnosis among men in Florida, 2000–2011. *Public Health Rep*. 2014;129(2):164-169. Available at: https://pubmed.ncbi.nlm.nih.gov/24587551.

8. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. *Clin Infect Dis*. 2014;59(7):1020-1026. Available at: https://pubmed.ncbi.nlm.nih.gov/24928295.

9. Centers for Disease Control and Prevention. Outbreak of syphilis among men who have sex with men—Southern California, 2000. *MMWR Morb Mortal Wkly Rep*. 2001;50(7):117-120. Available at: https://pubmed.ncbi.nlm.nih.gov/11393490.

10. Spicknall IH, Kreisel KM, Weinstock HS. Estimates of the prevalence and incidence of syphilis in the United States, 2018. *Sex Transm Dis*. 2021;48(4):247-252. Available at: https://pubmed.ncbi.nlm.nih.gov/33492091.

11. Cohen SE, Chew Ng RA, Katz KA, et al. Repeat syphilis among men who have sex with men in California, 2002–2006: implications for syphilis elimination efforts. *Am J Public Health*. 2012;102(1):e1-8. Available at: https://pubmed.ncbi.nlm.nih.gov/22095364.

12. Centers for Disease Control and Prevention. Syphilis surveillance supplemental slides, 2016–2020. 2022. Available at: https://www.cdc.gov/std/statistics/syphilis-supplement/default.htm.

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

14. Rasoldier V, Gueudry J, Chapuzet C, et al. Early symptomatic neurosyphilis and ocular syphilis: a comparative study between HIV-positive and HIV-negative patients. *Infect Dis Now*. 2021;51(4):351-356. Available at: https://pubmed.ncbi.nlm.nih.gov/33239175.

15. Calza L, Manfredi R, Marinacci G, Tadolini M, Fortunato L, Chiodo F. Efficacy of penicillin G benzathine as antimicrobial treatment of cutaneous secondary syphilis in patients with HIV infection. *J Chemother*. 2002;14(5):533-534. Available at: https://pubmed.ncbi.nlm.nih.gov/12462435.

16. Rompalo AM, Lawlor J, Seaman P, Quinn TC, Zenilman JM, Hook EW, 3rd. Modification of syphilitic genital ulcer manifestations by coexistent HIV infection. *Sex Transm Dis*. 2001;28(8):448-454. Available at: https://pubmed.ncbi.nlm.nih.gov/11473216.

17. Musher DM, Hamill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. *Ann Intern Med*. 1990;113(11):872-881. Available at: https://pubmed.ncbi.nlm.nih.gov/2240901.

18. Radolf JD, Kaplan RP. Unusual manifestations of secondary syphilis and abnormal humoral immune response to Treponema pallidum antigens in a homosexual man with asymptomatic human immunodeficiency virus infection. *J Am Acad Dermatol*. 1988;18(2 Pt 2):423-428. Available at: https://pubmed.ncbi.nlm.nih.gov/2963840.

19. Centers for Disease Control and Prevention. Symptomatic early neurosyphilis among HIV-positive men who have sex with men—four cities, United States, January 2002–June 2004. *MMWR Morb Mortal Wkly Rep*. 2007;56(25):625-628. Available at: https://pubmed.ncbi.nlm.nih.gov/17597693.

20. Nieuwenburg SA, Sprenger RJ, Schim van der Loeff MF, de Vries HJC. Clinical outcomes of syphilis in HIV-negative and HIV-positive MSM: occurrence of repeat syphilis episodes and non-treponemal serology responses. *Sex Transm Infect*. 2021. Available at: https://pubmed.ncbi.nlm.nih.gov/33608479.

21. Towns JM, Leslie DE, Denham I, Azzato F, Fairley CK, Chen M. Painful and multiple anogenital lesions are common in men with Treponema pallidum PCR-positive primary syphilis without herpes simplex virus coinfection: a cross-sectional clinic-based study. *Sex Transm Infect*. 2016;92(2):110-115. Available at: https://pubmed.ncbi.nlm.nih.gov/26378262.

22. Ghanem KG, Moore RD, Rompalo AM, Erbelding EJ, Zenilman JM, Gebo KA. Neurosyphilis in a clinical cohort of HIV-1-infected patients. *AIDS*. 2008;22(10):1145-1151. Available at: https://pubmed.ncbi.nlm.nih.gov/18525260.

23. Muccini C, Crowell TA, Pinyakorn S, et al. Brief report: syphilis incidence and effect on viral load, CD4, and CD4/CD8 ratio in a Thai cohort of predominantly men who have sex with men living with HIV. *J Acquir Immune Defic Syndr*. 2021;86(2):219-223. Available at: https://pubmed.ncbi.nlm.nih.gov/33433124.

24. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS*. 2004;18(15):2075-2079. Available at: https://pubmed.ncbi.nlm.nih.gov/15577629.

25. Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. *Lancet Infect Dis*. 2010;10(7):455-463. Available at: https://pubmed.ncbi.nlm.nih.gov/20610327.

26. Palacios R, Jimenez-Onate F, Aguilar M, et al. Impact of syphilis infection on HIV viral load and CD4 cell counts in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2007;44(3):356-359. Available at: https://pubmed.ncbi.nlm.nih.gov/17159654.

27. Kofoed K, Gerstoft J, Mathiesen LR, Benfield T. Syphilis and human immunodeficiency virus (HIV)-1 coinfection: influence on CD4 T-cell count, HIV-1 viral load, and treatment response. *Sex Transm Dis*. 2006;33(3):143-148. Available at: https://pubmed.ncbi.nlm.nih.gov/16505739.

28. Tuddenham S, Ghanem KG. Management of adult syphilis: key questions to inform the 2021 Centers for Disease Control and Prevention sexually transmitted infections treatment guidelines. *Clin Infect Dis*. 2022;74(Suppl_2):S127-S133. Available at: https://pubmed.ncbi.nlm.nih.gov/35416969.

29. Marra CM, Maxwell CL, Sahi SK, Tantalo LC, Dunaway SB, Lukehart SA. Previous syphilis alters the course of subsequent episodes of syphilis. *Clin Infect Dis*. 2020;71(5):1243-1247. Available at: https://pubmed.ncbi.nlm.nih.gov/31560366.

30. N'Gom PT, Jaffar S, Ricard D, et al. Immune stimulation by syphilis and malaria in HIV-2-infected and uninfected villagers in West Africa. *Br J Biomed Sci*. 1997;54(4):251-255. Available at: https://pubmed.ncbi.nlm.nih.gov/9624734.

31. Rompalo AM, Joesoef MR, O'Donnell JA, et al. Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. *Sex Transm Dis*. 2001;28(3):158-165. Available at: https://pubmed.ncbi.nlm.nih.gov/11289198.

32. Hussain A, Kaler J, Lau G, Maxwell T. Clinical conundrums: differentiating monkeypox from similarly presenting infections. *Cureus*. 2022;14(10):e29929. Available at: https://pubmed.ncbi.nlm.nih.gov/36348880.

33. Tambe S, Zambare U, Nayak C. Nodulo-ulcerative and erythrodermic secondary syphilis in human immunodeficiency virus-infected individuals. *Int J STD AIDS*. 2019;30(5):505-508. Available at: https://pubmed.ncbi.nlm.nih.gov/30630397.

34. Wang H, Wang X, Li S. A case of lues maligna in an AIDS patient. *Int J STD AIDS*. 2012;23(8):599-600. Available at: https://pubmed.ncbi.nlm.nih.gov/22930302.

35. Tucker JD, Shah S, Jarell AD, Tsai KY, Zembowicz A, Kroshinsky D. Lues maligna in early HIV infection case report and review of the literature. *Sex Transm Dis*. 2009;36(8):512-514. Available at: https://pubmed.ncbi.nlm.nih.gov/19455078.

36. Lukehart SA, Hook EW, 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and treatment. *Ann Intern Med*. 1988;109(11):855-862. Available at: https://pubmed.ncbi.nlm.nih.gov/3056164.

37. Bayne LL, Schmidley JW, Goodin DS. Acute syphilitic meningitis. Its occurrence after clinical and serologic cure of secondary syphilis with penicillin G. *Arch Neurol*. 1986;43(2):137-138. Available at: https://pubmed.ncbi.nlm.nih.gov/3947251.

38. Berry CD, Hooton TM, Collier AC, Lukehart SA. Neurologic relapse after benzathine penicillin therapy for secondary syphilis in a patient with HIV infection. *N Engl J Med*. 1987;316(25):1587-1589. Available at: https://pubmed.ncbi.nlm.nih.gov/3587291.

39. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis*. 2004;189(3):369-376. Available at: https://pubmed.ncbi.nlm.nih.gov/14745693.

40. Marra CM, Maxwell CL, Tantalo L, et al. Normalization of cerebrospinal fluid abnormalities after neurosyphilis therapy: does HIV status matter? *Clin Infect Dis*. 2004;38(7):1001-1006. Available at: https://pubmed.ncbi.nlm.nih.gov/15034833.

41. Biotti D, Bidot S, Mahy S, et al. Ocular syphilis and HIV infection. *Sex Transm Dis*. 2010;37(1):41-43. Available at: https://pubmed.ncbi.nlm.nih.gov/20118676.

42. Tucker JD, Li JZ, Robbins GK, et al. Ocular syphilis among HIV-infected patients: a systematic analysis of the literature. *Sex Transm Infect*. 2011;87(1):4-8. Available at: https://pubmed.ncbi.nlm.nih.gov/20798396.

43. Wagner LF, Lanzl I, Rothe K, et al. Clinical and ophthalmological characteristics of ocular syphilis in a retrospective tertiary hospital cohort. *Sex Transm Dis*. 2021;48(6):436-442. Available at: https://pubmed.ncbi.nlm.nih.gov/33156290.

44. Oliver SE, Aubin M, Atwell L, et al. Ocular syphilis – eight jurisdictions, United States, 2014–2015. *MMWR Morb Mortal Wkly Rep*. 2016;65(43):1185-1188. Available at: https://pubmed.ncbi.nlm.nih.gov/27811837.

45. Cope AB, Mobley VL, Oliver SE, et al. Ocular syphilis and human immunodeficiency virus coinfection among syphilis patients in North Carolina, 2014–2016. *Sex Transm Dis*. 2019;46(2):80-85. Available at: https://pubmed.ncbi.nlm.nih.gov/30169474.

46. Woolston S, Cohen SE, Fanfair RN, Lewis SC, Marra CM, Golden MR. A cluster of ocular syphilis cases – Seattle, Washington, and San Francisco, California, 2014–2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(40):1150-1151. Available at: https://pubmed.ncbi.nlm.nih.gov/26469141.

47. Furtado JM, Simoes M, Vasconcelos-Santos D, et al. Ocular syphilis. *Surv Ophthalmol*. 2022;67(2):440-462. Available at: https://pubmed.ncbi.nlm.nih.gov/34147542.

48. Ramchandani MS, Litvack JR, Marra CM. Otosyphilis: a review of the literature. *Sex Transm Dis*. 2020;47(5):296-300. Available at: https://pubmed.ncbi.nlm.nih.gov/32149965.

49. Theel ES, Katz SS, Pillay A. Molecular and direct detection tests for treponema pallidum subspecies pallidum: a review of the literature, 1964–2017. *Clin Infect Dis*. 2020;71(Suppl 1):S4-S12. Available at: https://pubmed.ncbi.nlm.nih.gov/32578865.

50. Tuddenham S, Katz SS, Ghanem KG. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. *Clin Infect Dis*. 2020;71(Suppl 1):S21-S42. Available at: https://pubmed.ncbi.nlm.nih.gov/32578862.

51. Park IU, Tran A, Pereira L, Fakile Y. Sensitivity and specificity of treponemal-specific tests for the diagnosis of syphilis. *Clin Infect Dis*. 2020;71(Suppl 1):S13-S20. Available at: https://pubmed.ncbi.nlm.nih.gov/32578866.

52. Bristow CC, Klausner JD, Tran A. Clinical test performance of a rapid point-of-care syphilis treponemal antibody test: a systematic review and meta-analysis. *Clin Infect Dis*. 2020;71(Suppl 1):S52-S57. Available at: https://pubmed.ncbi.nlm.nih.gov/32578863.

53. Ortiz DA, Shukla MR, Loeffelholz MJ. The traditional or reverse algorithm for diagnosis of syphilis: pros and cons. *Clin Infect Dis*. 2020;71(Suppl 1):S43-S51. Available at: https://pubmed.ncbi.nlm.nih.gov/32578864.

54. Centers for Disease Control and Prevention. Syphilis testing algorithms using treponemal tests for initial screening—four laboratories, New York City, 2005–2006. *MMWR Morb Mortal Wkly Rep*. 2008;57(32):872-875. Available at: https://pubmed.ncbi.nlm.nih.gov/18701877.

55. Park IU, Chow JM, Bolan G, Stanley M, Shieh J, Schapiro JM. Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management. *J Infect Dis*. 2011;204(9):1297-1304. Available at: https://pubmed.ncbi.nlm.nih.gov/21930610.

56. Wong EH, Klausner JD, Caguin-Grygiel G, et al. Evaluation of an IgM/IgG sensitive enzyme immunoassay and the utility of index values for the screening of syphilis infection in a high-risk population. *Sex Transm Dis*. 2011;38(6):528-532. Available at: https://pubmed.ncbi.nlm.nih.gov/21233789.

57. Wohrl S, Geusau A. Neurosyphilis is unlikely in patients with late latent syphilis and a negative blood VDRL-test. *Acta Derm Venereol*. 2006;86(4):335-339. Available at: https://pubmed.ncbi.nlm.nih.gov/16874420.

58. Rompalo AM, Cannon RO, Quinn TC, Hook EW, 3rd. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. *J Infect Dis*. 1992;165(6):1124-1126. Available at: https://pubmed.ncbi.nlm.nih.gov/1583332.

59. Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. *N Engl J Med*. 1997;337(5):307-314. Available at: https://pubmed.ncbi.nlm.nih.gov/9235493.

60. Augenbraun MH, DeHovitz JA, Feldman J, Clarke L, Landesman S, Minkoff HM. Biological false-positive syphilis test results for women infected with human immunodeficiency virus. *Clin Infect Dis*. 1994;19(6):1040-1044. Available at: https://pubmed.ncbi.nlm.nih.gov/7888531.

61. Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma. A diagnostic dilemma. *Ann Intern Med*. 1987;107(4):492-495. Available at: https://pubmed.ncbi.nlm.nih.gov/3307583.

62. Kingston AA, Vujevich J, Shapiro M, et al. Seronegative secondary syphilis in 2 patients coinfected with human immunodeficiency virus. *Arch Dermatol*. 2005;141(4):431-433. Available at: https://pubmed.ncbi.nlm.nih.gov/15837859.

63. Libois A, De Wit S, Poll B, et al. HIV and syphilis: when to perform a lumbar puncture. *Sex Transm Dis*. 2007;34(3):141-144. Available at: https://pubmed.ncbi.nlm.nih.gov/16865051.

64. Ghanem KG. Sensitivity and specificity of lumbar puncture in HIV-infected patients with syphilis and no neurologic symptoms reply. *Clin Infect Dis*. 2009;49:162-163. Available at: https://pubmed.ncbi.nlm.nih.gov/19187028.

65. Jaffe HW, Larsen SA, Peters M, Jove DF, Lopez B, Schroeter AL. Tests for treponemal antibody in CSF. *Arch Intern Med*. 1978;138(2):252-255. Available at: https://pubmed.ncbi.nlm.nih.gov/343742.

66. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. *Sex Transm Dis*. 2012;39(4):291-297. Available at: https://pubmed.ncbi.nlm.nih.gov/22421696.

67. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. *Sex Transm Dis*. 2012;39(6):453-457. Available at: https://pubmed.ncbi.nlm.nih.gov/22592831.

68. Kamb ML, Fishbein M, Douglas JM, Jr., et al. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA*. 1998;280(13):1161-1167. Available at: https://pubmed.ncbi.nlm.nih.gov/9777816.

69. U.S. Preventive Services Task Force, Krist AH, Davidson KW, et al. Behavioral counseling interventions to prevent sexually transmitted infections: U.S. Preventive Services Task Force recommendation statement. *JAMA*. 2020;324(7):674-681. Available at: https://pubmed.ncbi.nlm.nih.gov/32809008.

70. Metsch LR, Feaster DJ, Gooden L, et al. Effect of risk-reduction counseling with rapid HIV testing on risk of acquiring sexually transmitted infections: the AWARE randomized clinical

trial. *JAMA*. 2013;310(16):1701-1710. Available at: https://pubmed.ncbi.nlm.nih.gov/24150466.

71. Brookmeyer KA, Hogben M, Kinsey J. The role of behavioral counseling in sexually transmitted disease prevention program settings. *Sex Transm Dis*. 2016;43(2 Suppl 1):S102-112. Available at: https://pubmed.ncbi.nlm.nih.gov/26779681.

72. Patel P, Bush T, Mayer K, et al. Routine brief risk-reduction counseling with biannual STD testing reduces STD incidence among HIV-infected men who have sex with men in care. *Sex Transm Dis*. 2012;39(6):470-474. Available at: https://pubmed.ncbi.nlm.nih.gov/22592834.

73. Tuite AR, Shaw S, Reimer JN, Ross CP, Fisman DN, Mishra S. Can enhanced screening of men with a history of prior syphilis infection stem the epidemic in men who have sex with men? A mathematical modelling study. *Sex Transm Infect*. 2018;94(2):105-110. Available at: https://pubmed.ncbi.nlm.nih.gov/28705938.

74. de Voux A, Bernstein KT, Bradley H, et al. Syphilis testing among sexually active men who have sex with men and who are receiving medical care for human immunodeficiency virus in the United States: Medical Monitoring Project, 2013–2014. *Clin Infect Dis*. 2019;68(6):934-939. Available at: https://pubmed.ncbi.nlm.nih.gov/29985985.

75. Thompson MA, Horberg MA, Agwu AL, et al. Primary care guidance for persons with human immunodeficiency virus: 2020 update by the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*. 2021;73(11):e3572-e3605. Available at: https://pubmed.ncbi.nlm.nih.gov/33225349.

76. Kidd SE, Grey JA, Torrone EA, Weinstock HS. Increased methamphetamine, injection drug, and heroin use among women and heterosexual men with primary and secondary syphilis - United States, 2013–2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(6):144-148. Available at: https://pubmed.ncbi.nlm.nih.gov/30763294.

77. Copen CE, Brookmeyer KA, Haderxhanaj LT, Hogben M, Torrone EA. Sexual risk behaviors among persons diagnosed with primary and secondary syphilis who reported high-risk substance use: data from the National Notifiable Diseases Surveillance System, 2018. *Sex Transm Dis*. 2022;49(2):99-104. Available at: https://pubmed.ncbi.nlm.nih.gov/34475356.

78. Centers for Disease Control and Prevention. Recommendations for partner services programs for HIV infection, syphilis, gonorrhea, and chlamydial infection. *MMWR Recomm Rep*. 2008;57(RR-9):1-83; quiz CE81-84. Available at: https://pubmed.ncbi.nlm.nih.gov/18987617.

79. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med*. 2020;382(9):845-854. Available at: https://pubmed.ncbi.nlm.nih.gov/32101666.

80. Moore MB, Jr., Price EV, Knox JM, Elgin LW. Epidemiologic treatment of contacts to infectious syphilis. *Public Health Rep*. 1963;78:966-970. Available at: https://pubmed.ncbi.nlm.nih.gov/14084872.

81. Schroeter AL, Turner RH, Lucas JB, Brown WJ. Therapy for incubating syphilis. Effectiveness of gonorrhea treatment. *JAMA*. 1971;218(5):711-713. Available at: https://pubmed.ncbi.nlm.nih.gov/5171497.

82. Schober PC, Gabriel G, White P, Felton WF, Thin RN. How infectious is syphilis? *Br J Vener Dis*. 1983;59(4):217-219. Available at: https://pubmed.ncbi.nlm.nih.gov/6871650.

83. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis*. 2015;42(2):98-103. Available at: https://pubmed.ncbi.nlm.nih.gov/25585069.

84. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis*. 2018;18(3):308-317. Available at: https://pubmed.ncbi.nlm.nih.gov/29229440.

85. Stewart J, Oware K, Donnell D, et al. Doxycycline postexposure prophylaxis for prevention of STIs among cisgender women. Presented at: Conference on Retroviruses and Opportunistic Infections. 2023. Seattle, WA. Available at: https://www.natap.org/2023/CROI/croi_04.htm.

86. Grant JS, Stafylis C, Celum C, et al. Doxycycline prophylaxis for bacterial sexually transmitted infections. *Clin Infect Dis*. 2020;70(6):1247-1253. Available at: https://pubmed.ncbi.nlm.nih.gov/31504345.

87. Luetkemeyer AF, Donnell D, Dombrowski J, et al. Doxy-PEP and antimicrobial resistance in S. aureus, N. gonorrhoeae, and commensal Neisseria. Presented at: Conference on Retroviruses and Opportunistic Infections. 2023. Seattle, WA. Available at: https://www.natap.org/2023/CROI/croi_11.htm.

88. Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. *Lancet*. 2003;361(9354):313-314. Available at: https://pubmed.ncbi.nlm.nih.gov/12559870.

89. Mitchell SJ, Engelman J, Kent CK, Lukehart SA, Godornes C, Klausner JD. Azithromycin-resistant syphilis infection: San Francisco, California, 2000–2004. *Clin Infect Dis*. 2006;42(3):337-345. Available at: https://pubmed.ncbi.nlm.nih.gov/16392078.

90. Wu H, Chang SY, Lee NY, et al. Evaluation of macrolide resistance and enhanced molecular typing of Treponema pallidum in patients with syphilis in Taiwan: a prospective multicenter study. *J Clin Microbiol*. 2012;50(7):2299-2304. Available at: https://pubmed.ncbi.nlm.nih.gov/22518868.

91. Chen CY, Chi KH, Pillay A, Nachamkin E, Su JR, Ballard RC. Detection of the A2058G and A2059G 23S rRNA gene point mutations associated with azithromycin resistance in *Treponema pallidum* by use of a TaqMan real-time multiplex PCR assay. *J Clin Microbiol*. 2013;51(3):908-913. Available at: https://pubmed.ncbi.nlm.nih.gov/23284026.

92. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in Treponema pallidum in the United States and Ireland. *N Engl J Med*. 2004;351(2):154-158. Available at: https://pubmed.ncbi.nlm.nih.gov/15247355.

93. Centers for Disease Control and Prevention. Azithromycin treatment failures in syphilis infections—San Francisco, California, 2002–2003. *MMWR Morb Mortal Wkly Rep*. 2004;53(9):197-198. Available at: https://pubmed.ncbi.nlm.nih.gov/15017376.

94. Ganesan A, Mesner O, Okulicz JF, et al. A single dose of benzathine penicillin G is as effective as multiple doses of benzathine penicillin G for the treatment of HIV-infected persons with early syphilis. *Clin Infect Dis*. 2015;60(4):653-660. Available at: https://pubmed.ncbi.nlm.nih.gov/25389249.

95. Yang CJ, Lee NY, Chen TC, et al. One dose versus three weekly doses of benzathine penicillin G for patients co-infected with HIV and early syphilis: a multicenter, prospective observational study. *PLoS One*. 2014;9(10):e109667. Available at: https://pubmed.ncbi.nlm.nih.gov/25286091.

96. Malone JL, Wallace MR, Hendrick BB, et al. Syphilis and neurosyphilis in a human immunodeficiency virus type-1 seropositive population: evidence for frequent serologic relapse after therapy. *Am J Med*. 1995;99(1):55-63. Available at: https://pubmed.ncbi.nlm.nih.gov/7598143.

97. Walter T, Lebouche B, Miailhes P, et al. Symptomatic relapse of neurologic syphilis after benzathine penicillin G therapy for primary or secondary syphilis in HIV-infected patients. *Clin Infect Dis*. 2006;43(6):787-790. Available at: https://pubmed.ncbi.nlm.nih.gov/16912958.

98. Ghanem KG, Erbelding EJ, Cheng WW, Rompalo AM. Doxycycline compared with benzathine penicillin for the treatment of early syphilis. *Clin Infect Dis*. 2006;42(6):e45-49. Available at: https://pubmed.ncbi.nlm.nih.gov/16477545.

99. Wong T, Singh AE, De P. Primary syphilis: serological treatment response to doxycycline/tetracycline versus benzathine penicillin. *Am J Med*. 2008;121(10):903-908. Available at: https://pubmed.ncbi.nlm.nih.gov/18823862.

100. Bettuzzi T, Jourdes A, Robineau O, et al. Ceftriaxone compared with benzylpenicillin in the treatment of neurosyphilis in France: a retrospective multicentre study. *Lancet Infect Dis*. 2021;21(10):1441-1447. Available at: https://pubmed.ncbi.nlm.nih.gov/34051142.

101. Cao Y, Su X, Wang Q, et al. A multicenter study evaluating ceftriaxone and benzathine penicillin G as treatment agents for early syphilis in Jiangsu, China. *Clin Infect Dis*. 2017;65(10):1683-1688. Available at: https://pubmed.ncbi.nlm.nih.gov/29020150.

102. Hook EW, 3rd, Roddy RE, Handsfield HH. Ceftriaxone therapy for incubating and early syphilis. *J Infect Dis*. 1988;158(4):881-884. Available at: https://pubmed.ncbi.nlm.nih.gov/3171231.

103. Kiddugavu MG, Kiwanuka N, Wawer MJ, et al. Effectiveness of syphilis treatment using azithromycin and/or benzathine penicillin in Rakai, Uganda. *Sex Transm Dis*. 2005;32(1):1-6. Available at: https://pubmed.ncbi.nlm.nih.gov/15614114.

104. Riedner G, Rusizoka M, Todd J, et al. Single-dose azithromycin versus penicillin G benzathine for the treatment of early syphilis. *N Engl J Med*. 2005;353(12):1236-1244. Available at: https://pubmed.ncbi.nlm.nih.gov/16177249.

105. Hook EW, 3rd, Behets F, Van Damme K, et al. A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis. *J Infect Dis*. 2010;201(11):1729-1735. Available at: https://pubmed.ncbi.nlm.nih.gov/20402591.

106. Martin IE, Tsang RS, Sutherland K, et al. Molecular characterization of syphilis in patients in Canada: azithromycin resistance and detection of Treponema pallidum DNA in whole-blood samples versus ulcerative swabs. *J Clin Microbiol*. 2009;47(6):1668-1673. Available at: https://pubmed.ncbi.nlm.nih.gov/19339468.

107. Dowell ME, Ross PG, Musher DM, Cate TR, Baughn RE. Response of latent syphilis or neurosyphilis to ceftriaxone therapy in persons infected with human immunodeficiency virus. *Am J Med*. 1992;93(5):481-488. Available at: https://pubmed.ncbi.nlm.nih.gov/1442850.

108. Smith NH, Musher DM, Huang DB, et al. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. *Int J STD AIDS*. 2004;15(5):328-332. Available at: https://pubmed.ncbi.nlm.nih.gov/15117503.

109. U. S. Food and Drug Administration. Current and resolved drug shortages and discontinuations reported to FDA. 2023. Available at: https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Penicillin%20G%20Procaine%20Injectable%20Suspension&st=d.

110. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and management of penicillin allergy: a review. *JAMA*. 2019;321(2):188-199. Available at: https://pubmed.ncbi.nlm.nih.gov/30644987.

111. Pham MN, Ho HE, Desai M. Penicillin desensitization: treatment of syphilis in pregnancy in penicillin-allergic patients. *Ann Allergy Asthma Immunol*. 2017;118(5):537-541. Available at: https://pubmed.ncbi.nlm.nih.gov/28477786.

112. Frunza-Stefan S, Acharya G, Kazlouskaya V, Vukasinov P, Chiou Y, Thet Z. Immune reconstitution inflammatory syndrome associated with secondary syphilis. *Int J STD AIDS*. 2017;28(3):302-305. Available at: https://pubmed.ncbi.nlm.nih.gov/27566775.

113. Bernal E, Munoz A, Ortiz Mdel M, Cano A. [Syphilitic panuveitis in an HIV-infected patient after immune restoration]. *Enferm Infecc Microbiol Clin*. 2009;27(8):487-489. Available at: https://pubmed.ncbi.nlm.nih.gov/19406524.

114. Sena AC, Wolff M, Behets F, et al. Response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. *Clin Infect Dis*. 2013;56(3):420-422. Available at: https://pubmed.ncbi.nlm.nih.gov/23118269.

115. Sena AC, Wolff M, Martin DH, et al. Predictors of serological cure and Serofast State after treatment in HIV-negative persons with early syphilis. *Clin Infect Dis*. 2011;53(11):1092-1099. Available at: https://pubmed.ncbi.nlm.nih.gov/21998287.

116. Jinno S, Anker B, Kaur P, Bristow CC, Klausner JD. Predictors of serological failure after treatment in HIV-infected patients with early syphilis in the emerging era of universal antiretroviral therapy use. *BMC Infect Dis*. 2013;13:605. Available at: https://pubmed.ncbi.nlm.nih.gov/24369955.

117. Ghanem KG, Hook EW, 3rd. The terms "serofast" and "serological nonresponse" in the modern syphilis era. *Sex Transm Dis*. 2021;48(6):451-452. Available at: https://pubmed.ncbi.nlm.nih.gov/33534408.

118. Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. *Clin Infect Dis*. 2008;47(7):893-899. Available at: https://pubmed.ncbi.nlm.nih.gov/18715154.

119. Xiao Y, Tong ML, Lin LR, et al. Serological response predicts normalization of cerebrospinal fluid abnormalities at six months after treatment in HIV-negative neurosyphilis patients. *Sci Rep*. 2017;7(1):9911. Available at: https://pubmed.ncbi.nlm.nih.gov/28855625.

120. Yang CJ, Lee NY, Lin YH, et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the hiv infection epidemic: incidence and risk factors. *Clin Infect Dis*. 2010;51(8):976-979. Available at: https://pubmed.ncbi.nlm.nih.gov/20825309.

121. Aaron KJ, Brill I, Causey-Pruitt Z, et al. Factors associated with syphilis seroprevalence in women with and at-risk for HIV infection in the Women's Interagency HIV Study (1994–2015). *Sex Transm Infect*. 2022;98(1):4-10. Available at: https://pubmed.ncbi.nlm.nih.gov/33408096.

122. Trivedi S, Williams C, Torrone E, Kidd S. National trends and reported risk factors among pregnant women with syphilis in the United States, 2012–2016. *Obstet Gynecol*. 2019;133(1):27-32. Available at: https://pubmed.ncbi.nlm.nih.gov/30531570.

123. U.S. Preventive Services Task Force, Curry SJ, Krist AH, et al. Screening for syphilis infection in pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. *JAMA*. 2018;320(9):911-917. Available at: https://pubmed.ncbi.nlm.nih.gov/30193283.

124. Mmeje O, Chow JM, Davidson L, Shieh J, Schapiro JM, Park IU. Discordant syphilis immunoassays in pregnancy: perinatal outcomes and implications for clinical management. *Clin Infect Dis*. 2015;61(7):1049-1053. Available at: https://pubmed.ncbi.nlm.nih.gov/26063719.

125. Adachi K, Xu J, Yeganeh N, et al. Combined evaluation of sexually transmitted infections in HIV-infected pregnant women and infant HIV transmission. *PLoS One*. 2018;13(1):e0189851. Available at: https://pubmed.ncbi.nlm.nih.gov/29304083.

126. Berman SM. Maternal syphilis: pathophysiology and treatment. *Bull World Health Organ*. 2004;82(6):433-438. Available at: https://pubmed.ncbi.nlm.nih.gov/15356936.

127. Tess BH, Rodrigues LC, Newell ML, Dunn DT, Lago TD. Breastfeeding, genetic, obstetric and other risk factors associated with mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo Collaborative Study for Vertical Transmission of HIV-1. *AIDS*. 1998;12(5):513-520. Available at: https://pubmed.ncbi.nlm.nih.gov/9543450.

128. Lee MJ, Hallmark RJ, Frenkel LM, Del Priore G. Maternal syphilis and vertical perinatal transmission of human immunodeficiency virus type-1 infection. *Int J Gynaecol Obstet*. 1998;63(3):247-252. Available at: https://pubmed.ncbi.nlm.nih.gov/9989893.

129. Wendel GD, Jr., Sheffield JS, Hollier LM, Hill JB, Ramsey PS, Sanchez PJ. Treatment of syphilis in pregnancy and prevention of congenital syphilis. *Clin Infect Dis*. 2002;35(Suppl 2):S200-209. Available at: https://pubmed.ncbi.nlm.nih.gov/12353207.

130. Kreitchmann R, Fuchs SC, Suffert T, Preussler G. Perinatal HIV-1 transmission among low income women participants in the HIV/AIDS Control Program in Southern Brazil: a cohort study. *BJOG*. 2004;111(6):579-584. Available at: https://pubmed.ncbi.nlm.nih.gov/15198786.

131. Mwapasa V, Rogerson SJ, Kwiek JJ, et al. Maternal syphilis infection is associated with increased risk of mother-to-child transmission of HIV in Malawi. *AIDS*. 2006;20(14):1869-1877. Available at: https://pubmed.ncbi.nlm.nih.gov/16954728.

132. Walker GJ. Antibiotics for syphilis diagnosed during pregnancy. *Cochrane Database Syst Rev*. 2001(3):CD001143. Available at: https://pubmed.ncbi.nlm.nih.gov/11686978.

133. Donders GG, Desmyter J, Hooft P, Dewet GH. Apparent failure of one injection of benzathine penicillin G for syphilis during pregnancy in human immunodeficiency virus-seronegative African women. *Sex Transm Dis*. 1997;24(2):94-101. Available at: https://pubmed.ncbi.nlm.nih.gov/9111755.

134. Sheffield JS, Sanchez PJ, Morris G, et al. Congenital syphilis after maternal treatment for syphilis during pregnancy. *Am J Obstet Gynecol*. 2002;186(3):569-573. Available at: https://pubmed.ncbi.nlm.nih.gov/11904625.

135. Zhu L, Qin M, Du L, Xie RH, Wong T, Wen SW. Maternal and congenital syphilis in Shanghai, China, 2002 to 2006. *Int J Infect Dis*. 2010;14 Suppl 3:e45-48. Available at: https://pubmed.ncbi.nlm.nih.gov/20137991.

136. Ramsey PS, Vaules MB, Vasdev GM, Andrews WW, Ramin KD. Maternal and transplacental pharmacokinetics of azithromycin. *Am J Obstet Gynecol*. 2003;188(3):714-718. Available at: https://pubmed.ncbi.nlm.nih.gov/12634646.

137. Zhou P, Gu Z, Xu J, Wang X, Liao K. A study evaluating ceftriaxone as a treatment agent for primary and secondary syphilis in pregnancy. *Sex Transm Dis*. 2005;32(8):495-498. Available at: https://pubmed.ncbi.nlm.nih.gov/16041252.

138. Katanami Y, Hashimoto T, Takaya S, et al. Amoxicillin and ceftriaxone as treatment alternatives to penicillin for maternal syphilis. *Emerg Infect Dis*. 2017;23(5):827-829. Available at: https://pubmed.ncbi.nlm.nih.gov/28418316.

139. Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch-Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol*. 1990;75(3 Pt 1):375-380. Available at: https://pubmed.ncbi.nlm.nih.gov/2304710.

140. Butler T. The Jarisch-Herxheimer reaction after antibiotic treatment of spirochetal infections: a review of recent cases and our understanding of pathogenesis. *Am J Trop Med Hyg*. 2017;96(1):46-52. Available at: https://pubmed.ncbi.nlm.nih.gov/28077740.

141. Hollier LM, Harstad TW, Sanchez PJ, Twickler DM, Wendel GD, Jr. Fetal syphilis: clinical and laboratory characteristics. *Obstet Gynecol*. 2001;97(6):947-953. Available at: https://pubmed.ncbi.nlm.nih.gov/11384701.

142. Rac MW, Bryant SN, Cantey JB, McIntire DD, Wendel GD, Jr., Sheffield JS. Maternal titers after adequate syphilotherapy during pregnancy. *Clin Infect Dis*. 2015;60(5):686-690. Available at: https://pubmed.ncbi.nlm.nih.gov/25414264.

143. Webster CM, Kasaro MP, Price JT, et al. Seroreduction of syphilis non-treponemal titers during pregnancy for women with and without HIV co-infection. *Int J Gynaecol Obstet*. 2022. Available at: https://pubmed.ncbi.nlm.nih.gov/35122676.

Talaromycosis (formerly Penicilliosis)

Updated: November 21, 2019
Reviewed: January 10, 2024

Epidemiology

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

HIV is a major risk factor for talaromycosis in highly endemic regions, accounting for approximately 88% of disease.[2] The fungus is also a major cause of HIV-associated opportunistic infections in these regions, making up to 16% of hospital admissions due to AIDS,[2,3,6-8] and is a leading cause of HIV-associated blood stream infections and deaths in Vietnam and southern China.[6,9-11] Infection occurs predominantly in individuals[2,3,12] who have very advanced HIV disease with a CD4 T lymphocyte (CD4) cell count of <100 cells/mm^3. Talaromycosis is increasingly diagnosed in immunocompromised individuals who are returning travelers or immigrants from the endemic regions, and it has been reported in Japan, Australia, Belgium, France, Germany, the Netherlands, Sweden, Switzerland, the United Kingdom, Oman (in the Middle East), and the United States.[13,14] Talaromycosis is increasingly recognized in individuals who have a primary immunodeficiency condition (e.g., idiopathic CD4 lymphopenia; anti-interferon-gamma autoantibody-associated immunodeficiency; conditions due to mutations in CYBB or CD40L; or gain-of-function mutation in STAT1/STAT3 pathways) or secondary immunodeficiency conditions (e.g., autoimmune diseases in people on corticosteroids and/or other immunosuppressive therapy; solid and hematological malignancies; solid organ transplantation; hematopoietic stem cell transplantation; and therapy with novel target therapies, such as monoclonal antibodies against CD20 and kinase inhibitors).[15] Talaromycosis-related mortality, despite antifungal therapy in people both with and without HIV, is up to 30%.[2,3,12,16,17]

Similar to other endemic mycoses, talaromycosis is a saprozoonotic infection, meaning the transmissible source has a reservoir both in an abiotic environment and in an animal host. The wild bamboo rat in highland areas in the endemic regions is the known animal reservoir of *T. marneffei*[18,19]; however, case-control studies suggest that human infection results from inhalation of fungal spores released from a soil-related environmental reservoir (plants and farmed animals) rather than from direct bamboo rat–to-human transmission.[20,21] Talaromycosis incidence increased 30% to 50% during the rainy months in southern Vietnam and northern Thailand[3,22] and was associated with increased humidity and not precipitation,[23,24] which suggests that humidity facilitates an expansion of the environmental reservoir, resulting in increased exposure to the fungus. Reactivation of latent infections has been demonstrated in non-autochthonous cases with a history of remote travel to the endemic countries and can occur many years after exposure.[13,14,25] One case of presumed laboratory-acquired talaromycosis was reported in an African man with HIV who was at

the Pasteur Institute in Paris[26]; however, laboratory-acquired infection has never been reported from the endemic regions. Donor-acquired transmission has been reported in a lung-transplant recipient from Belgium.[27]

Clinical Manifestations

Disseminated infection involving multiple organ systems is the most common manifestation of talaromycosis in people with advanced HIV disease. The infection frequently begins as a subacute illness characterized by fever, weight loss, hepatosplenomegaly, lymphadenopathy, and respiratory and gastrointestinal abnormalities.[3,28] These clinical features are nonspecific and are indistinguishable from those of disseminated tuberculosis, other systemic mycoses, or infections due to intracellular pathogens such as *Salmonella* species.

Skin lesions are the most specific but late manifestations of talaromycosis, with central-necrotic papules on the face, trunk, and extremities occurring in 40% to 70% of patients.[1,3,29] Pulmonary involvement manifested as cough or shortness of breath occurs in 40% of patients. Gastrointestinal involvement presenting as diarrhea or abdominal pain occurs in 30% of patients. Significant hepatosplenomegaly is present in 70% of patients and together with intra-abdominal lymphadenopathy cause abdominal distention and pain.[3,7] Meningoencephalitis is a rare manifestation that occurs in <1% of patients and has a rapid disease course with a mortality of 80%.[30] Concurrent infections with other opportunistic pathogens occur in up to 60% of patients, with oropharyngeal candidiasis being the most common.[2]

Tuberculosis coinfection is common (occurring in up to 22% of patients in highly endemic regions) and complicates disease management because of itraconazole and rifampin drug interactions.[3]

Common laboratory findings associated with talaromycosis include anemia and thrombocytopenia due to bone marrow infiltration. Anemia can be profound and may require multiple red cell transfusions. Elevation of aminotransferase is common, with a serum aspartate aminotransferase (AST) over alanine aminotransferase (ALT) ratio of approximately 2.[3]

The median CD4 count in multiple cohorts[2,3] is <50 cells/mm^3.

The chest radiographical findings are broad, ranging from diffuse interstitial disease to reticulonodular infiltrates to alveola infiltrates causing respiratory failure.[31]

Diagnosis

A diagnosis of talaromycosis should be considered in all people with HIV with CD4 count <100 cells/mm^3 who have traveled to or have lived in talaromycosis-endemic areas and present with a systemic infection involving the reticuloendothelial system (i.e., lymph nodes, liver, spleen, and bone marrow).

Skin lesions in talaromycosis have typical central-necrotic appearance and can be a diagnostic sign. However, skin lesions are a late manifestation of talaromycosis and are absent in up to 60% of patients.[1,3,29] The current diagnostic methods for talaromycosis are still based on conventional microscopy, histology, and culture. Culture results usually return within 4 to 5 days but can take up to 28 days. Diagnostic delay, particularly in patients presenting without fever or skin lesions, is

associated with increased mortality.[2,3,15,32] Antigen detection and polymerase chain reaction (PCR)–based methods are promising rapid diagnostics currently being evaluated.

Microscopy, Histology, and Culture Are the Current Gold Standard Diagnostic Methods

A presumptive diagnosis of talaromycosis can be made based on the microscopic examination of Giemsa-, Wright-, or Gomori Methenamine Silver (GMS)–stained samples of skin lesion scrapings, lymph node aspirate, bone marrow aspirate, or tissue sections showing round-to-oval extracellular and intramacrophage yeast-like organisms measuring 3 to 6 µm in diameter. Identification of a clear midline septum in a dividing yeast cell is what distinguishes *T. marneffei* from *Histoplasma* or *Candida* species.[1] In some patients, the fungus can be identified by microscopic examination of a Wright-stained peripheral blood smear.[33]

A definitive diagnosis of talaromycosis can be made by the histopathologic demonstration of the organism in biopsy specimens. There are three histopathological forms. The granulomatous reaction is formed by histiocytes, lymphocytes, and plasma; epithelioid and giant cells and can be seen in reticuloendothelial organs in patients who are HIV-negative or immunocompetent. The suppurative reaction develops with the joining of multiple abscesses seen in the lung and subcutaneous tissues of immunocompetent patients. The anergic and necrotizing reaction is characterized by focal necrosis surrounded by distended histiocytes containing proliferating fungi seen in the lung, liver, and spleen of immunocompromised patients.[34]

Most frequently, a definitive diagnosis of talaromycosis is based on isolation of the organism from cultures of clinical specimens.

Compared to other endemic dimorphic fungi, *T. marneffei* grows more readily in standard BACTEC blood culture media and Sabouraud dextrose agar but takes 5 to 14 days to grow and to demonstrate temperature dimorphism. At 25 °C to 30 °C, the fungus grows as a mold, producing yellow-green colonies with sulcate folds and a red diffusible pigment in the media. Microscopically, filamentous hyphae with characteristic spore-bearing structures called conidiophores and conidia can be seen. At 32 °C to 37 °C, the fungus makes the morphological transition from a mold to a yeast, producing tan-colored colonies without a red diffusible pigment. In laboratory media, only the transitional sausage-shaped cells can be seen microscopically. The round-to-oval yeast cells are only seen in natural tissue.[1]

Culture yield is the highest from bone marrow (100%), followed by skin lesions (90%) and blood (70%).[3,35] Less commonly, talaromycosis has been diagnosed from sputum, pleural fluid, peritoneal fluid, cerebrospinal fluid, pericardium fluid, stool, and urine.

Molecular Diagnosis

Molecular diagnostics for talaromycosis have been based on PCR amplification and sequence identification of specific regions within the fungal ribosome's internally transcribed spacer regions, the 5.8S rRNA, and the 18S rRNA genes of *T. marneffei*.[36-39] These assays have high specificity (100%) but limited sensitivity (60% to 70%). At present, none of the real-time PCR assays have been prospectively validated, standardized, or commercially developed for clinical use.

Antigen Detection

The commercial assay for the detection of *Aspergillus* galactomannan cross-reacts with *T. marneffei* and has a sensitivity of 95.8% (23 of 24 patients with culture-positive talaromycosis were correctly identified) and a specificity of 90.9% (30 of 33 people without talaromycosis were correctly identified) for the detection of talaromycosis (at cutoff index = 1.0).[40] However, the galactomannan test also cross reacts with other endemic fungi, such as *Histoplasma* and *Blastomyces,* and has not been evaluated prospectively.

The Mp1p enzyme-linked immunosorbent assay (ELISA) has been shown to be more sensitive than blood culture (in 372 culture-proven talaromycosis cases, sensitivity was 86.3% for the Mp1p ELISA and 74% for blood culture) and is highly specific (98.1% specificity in 338 healthy controls and 179 people without HIV but with other infections).[41] This assay was used to screen a large serum bank of 8,131 people with HIV in Guangzhou, China, and showed a Mp1p antigenemia prevalence of 9.4%, with prevalence of antigenemia increased from 4.5% to 28.4% as the CD4 count decreased from 200 cells/mm^3 to 50 cells/mm^3, demonstrating a significant burden of disease in southern China.[24] In Vietnam, the Mp1p ELISA identified 4.2% antigenemia in 1,123 asymptomatic people with HIV who had a CD4 count <100 cells/mm^3 initiating antiretroviral therapy (ART) in 22 HIV clinics across Vietnam. Antigenemia was found to be independently associated with 12-month mortality.[42] These data demonstrate that the Mp1p ELISA has the potential to detect infection earlier than culture allows and can potentially be used as a screening tool for subclinical infection, thereby permitting pre-emptive antifungal therapy to prevent disease development. This is an area of active research.

Matrix-Assisted Laser Desorption/Ionization-Time of Flight Method

The matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) method recently has been used for identification of *Talaromyces* to the species level from cultured specimens based on either an in-house database generated from an institution's *T. marneffei* clinical strain collection[43,44] or from the comprehensive National Institutes of Health MDL Mold Library.[45] The MALDI-TOF represents a rapid and reliable tool for downstream fungal identification, eliminating the need to demonstrate thermal dimorphism.

Antifungal Susceptibility Testing

The minimum inhibitory concentrations (MICs) have been consistently low for itraconazole, intermediate for amphotericin B, and high for fluconazole. Thus far, only one retrospective case series from Chiang Mai in Thailand correlated MIC data of 30 clinical isolates with patient outcomes. More recent studies reported low MIC values for the newer generation azole drugs voriconazole (MICs 0.016–0.063 µg/mL) and posaconazole (MICs 0.001–0.002 µg/ml), and intermediate to high MIC values of 2 µg/ml to 8 µg/mL for anidulafungin.[46] A later study utilized a commercial Sensititre YeastOne YO10 assay.[47] These results suggest promising activity of voriconazole and posaconazole for the treatment of talaromycosis and suggest that the echinocandins are less effective against *T. marneffei*.

Preventing Exposure

Two case-controls studies in Thailand and Vietnam demonstrated that people with World Health Organization Stage 4 HIV disease or a CD4 count <100 cells/mm^3 who had an occupational exposure

to plants and farmed animals were at increased risk for infection.[20,21] The risk was higher in the rainy and humid months.[3,22]

Residency or a history of traveling to the highland regions (as short as 3 days) was a risk factor for talaromycosis in people with advanced HIV disease in southern Vietnam.[20] These data suggest that people with advanced HIV should avoid visiting the areas where talaromycosis is highly endemic, particularly highland regions during the rainy and humid months **(BIII).**

Preventing Disease

Preventing First Episode of Talaromycosis (Primary Prophylaxis)

Indication for Primary Prophylaxis
• People with a CD4 count <100 cells/mm^3 who are unable to have ART or have treatment failure without access to effective ART options and who either:
  o Reside in the highly endemic regions in northern Thailand, throughout Vietnam, and in southern China (particularly in highland regions during the rainy humid months) (BI), *or*
  o Are from countries outside of the endemic region and must travel to the region (BIII).
Primary Prophylaxis
• For Individuals Residing in Endemic Areas
  o Preferred Therapy: Itraconazole 200 mg PO once daily (BI)
  o Alternative Therapy: Fluconazole 400 mg PO once weekly (BII)
• For Individuals Traveling to Endemic Areas
  o Preferred Therapy: Begin itraconazole 200 mg PO once daily 3 days before travel and continue for 1 week after leaving the endemic area (BIII).
  o Alternative Therapy: Begin fluconazole 400 mg 3 days before travel, then continue 400 mg once weekly while in the area and take final dose after leaving the endemic area (BIII).
Indication for Discontinuing Primary Prophylaxis for People Who Reside in Endemic Areas
• CD4 count >100 cells/mm^3 for ≥6 months in response to ART (BII)
• Viral load suppression for ≥6 months on ART (BIII)
Indication for Restarting Primary Prophylaxis
• CD4 count decreases to <100 cells/mm^3 (BIII) and the person still resides in or travels to high-risk areas. Primary prophylaxis for travelers may begin 3 days prior to travel to allow serum drug level to reach steady state and may continue for 1 week after travel (BIII).

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

Primary prophylaxis has been shown to reduce the incidence of talaromycosis and other invasive fungal infections. A double-blind, placebo-controlled trial[48] in Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for primary prophylaxis significantly reduced the occurrence of invasive fungal infections (predominantly cryptococcosis and talaromycosis) in people with HIV with a CD4 count <200 cells/mm^3.

In a retrospective study also in Chiang Mai, fluconazole (400 mg weekly) was shown to be as effective as itraconazole (200 mg daily) for primary prophylaxis.[49] However, these studies were conducted prior to the widespread use of ART and had small sample sizes, and a mortality benefit was not observed. Therefore, primary prophylaxis has not been widely adopted given concerns about long-term toxicity, drug–drug interactions, and costs.

Indication for Primary Prophylaxis

Primary prophylaxis is only recommended for people with HIV with CD4 counts <100 cells/mm^3 who reside in the highly endemic regions in northern Thailand, southern China, and northern and southern Vietnam who are unable to have ART for whatever reasons or have treatment failure without access to effective antiretroviral (ARV) options **(BI).** The drug choices for prophylaxis are oral itraconazole 200 mg once daily **(BI)** or oral fluconazole 400 mg once weekly **(BII).**

Primary prophylaxis is not recommended in people with HIV who are on or about to start effective ART and is not recommended in geographic areas outside of the mentioned highly endemic regions **(AIII).**

For people with HIV who are from the United States and from countries outside of the endemic region who are not on effective ART, have a CD4 count <100 cells/mm^3, and must travel to the highly endemic areas mentioned, primary prophylaxis with either itraconazole or fluconazole should begin 3 days prior to travel to allow serum drug level to reach steady state and may continue for 1 week after travel **(BIII).**

Discontinuation of Primary Prophylaxis

Primary prophylaxis for talaromycosis can reasonably be discontinued in people with HIV who are ART adherent and have a sustained CD4 count ≥100 cells/mm^3 for more than 6 months **(BII).** In areas where viral load monitoring has replaced CD4 count monitoring, primary prophylaxis can reasonably be discontinued in people with HIV who achieve sustained virologic suppression at least 6 months **(BIII).**

Treating Disease

Treating Acute Infection in Severely Ill Patients

Preferred Therapy
• Induction Therapy
  o Liposomal amphotericin B 3–5 mg/kg/day IV for 2 weeks, followed by
• Consolidation Therapy
  o Itraconazole 200 mg PO twice daily for 10 weeks (AI), followed by
• Maintenance Therapy or Secondary Prophylaxis
  o Itraconazole 200 mg PO daily (AII)
Alternative Therapy (If Liposomal Amphotericin B Is Not Available)
• Induction Therapy

- Deoxycholate amphotericin B 0.7 mg/kg/day IV for 2 weeks, followed by

- Consolidation Therapy
  - Itraconazole 200 mg PO twice daily for 10 weeks (AI), followed by
- Maintenance Therapy or Secondary Prophylaxis
  - Itraconazole 200 mg PO daily (AII)

Alternative Therapy (If Amphotericin B Is Not Available)

- Induction Therapy
  - Voriconazole 6 mg/kg IV every 12 hours for 1 day (loading dose) and then voriconazole 4 mg/kg IV every 12 hours for 2 weeks, *or*
  - Oral voriconazole 600 mg every 12 hours on day 1 (loading dose) and then voriconazole 400 mg PO every 12 hours for 2 weeks; followed by
- Consolidation Therapy
  - Voriconazole 200 mg PO twice daily, *or*
  - Itraconazole 200 mg PO twice daily for a maximum of 10 weeks (BII); followed by
- Maintenance Therapy or Secondary Prophylaxis
  - Itraconazole 200 mg PO daily (AII)

Note: Itraconazole is not recommended as induction therapy for talaromycosis (AI).

Criteria for Discontinuing Chronic Maintenance Therapy

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

Criteria for Restarting Chronic Maintenance Therapy

- CD4 count decreases to <100 cells/mm^3 (AIII)

Other Considerations

- To improve outcomes, ART can be initiated as early as 1 week after the initiation of treatment for talaromycosis with amphotericin B induction therapy (BII).
- Given erratic absorption of itraconazole, extensive interindividual variability and nonlinear PK of voriconazole, and the potential for drug interactions with ARV drugs, itraconazole and voriconazole concentrations should be monitored, and serum trough concentration should be >0.5 µg/mL for itraconazole and >1 µg/mL for voriconazole (BIII). Both itraconazole and voriconazole can have significant drug–drug interactions with various ARV drugs; dosage adjustment may be necessary, and TDM to guide therapy can be considered (see the Drug–Drug Interactions tables in the Adult and Adolescent Antiretroviral Guidelines for further recommendations).
- Substitution of amphotericin B for high-dose azoles in the first trimester is recommended (BIII). People on secondary prophylaxis with itraconazole or other azoles should postpone pregnancy until their CD4 counts have been restored with ART, such that prophylaxis can be discontinued (BIII).

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; IV = intravenously; PK = pharmacokinetics; PO = orally; TDM = therapeutic drug monitoring

Disseminated talaromycosis is fatal if untreated.[50]

The case fatality rates with antifungal therapy range from 10% to 30%.[2,3,6,16]

Antifungal therapy for talaromycosis is divided into induction, consolidation, and maintenance phases. The treatment recommendations are based on several observational studies in Thailand and China[51-54] and the recent Itraconazole versus Amphotericin B for Penicilliosis (IVAP) randomized, controlled trial in Vietnam.[55]

In an earlier noncomparative prospective study of 74 patients in Thailand, induction therapy with deoxycholate amphotericin B for 2 weeks followed by consolidation therapy with itraconazole for 10 weeks was shown to be highly effective. Treatment success rate (defined by negative blood culture and resolution of fever and skin lesions at the end of a 12-week treatment course) was 97%.[51]

Voriconazole has been used for induction therapy in patients who could not tolerate amphotericin B and was shown to have favorable clinical and microbiological outcomes in 8 of 9 patients in Thailand[53] and 10 of 14 patients in China.[52]

The IVAP trial randomized 440 patients across 5 hospitals in Vietnam and demonstrated that induction therapy with amphotericin B was superior to itraconazole with respect to 6-month mortality (absolute risk of death was 11% and 21%, respectively; hazard ratio of death in the itraconazole arm was 1.88 [95% confidence interval, 1.15–3.09; $P = 0.012$]). Patients in the amphotericin B arm had significantly lower rates of disease complications, including disease relapse and immune reconstitution inflammatory syndrome (IRIS), and had a fourfold faster rate of blood fungal clearance. The difference in mortality between the arms was not dependent on disease severity (based on positive blood culture, blood fungal count, or requirement for oxygen support at presentation) or by a participant's immune status (CD4 count <50 cells/mm^3 or ≥50 cells/mm^3), ART status, or intravenous (IV) drug use.[55]

The recommended induction therapy for all patients, regardless of disease severity, is amphotericin B, preferably liposomal amphotericin B 3 to 5 mg/kg/day where available, or deoxycholate amphotericin B 0.7 mg/kg body weight/day, IV for 2 weeks **(AI).**

Induction therapy should be followed by consolidation therapy with oral itraconazole, 200 mg every 12 hours for a subsequent duration of 10 weeks **(AI).**[55] After this period, maintenance therapy (or secondary prophylaxis) with oral itraconazole 200 mg/day is recommended to prevent recurrence until the CD4 count rises above 100 cells/mm^3 for ≥6 months **(AI).**[56]

For patients who are unable to tolerate any form of amphotericin, induction therapy with IV voriconazole 6 mg/kg every 12 hours on Day 1 (loading dose), then 4 mg/kg every 12 hours or with oral voriconazole 600 mg every 12 hours on Day 1 (loading dose), then 400 mg every 12 hours for 2 weeks is recommended **(BII).**[52,53]

Thereafter, either oral voriconazole or oral itraconazole 200 mg every 12 hours can be used for consolidation therapy for 10 weeks, followed by itraconazole 200 mg/day for secondary prophylaxis. The optimal dose of voriconazole for secondary prophylaxis beyond 12 weeks has not been studied.

Itraconazole is not recommended as an induction therapy for talaromycosis, regardless of disease severity **(AI).**[55]

Special Considerations with Regard to Starting ART

No studies exist regarding the optimal time to start ART in people with HIV who have talaromycosis. In the IVAP trial, the median time to ART initiation, which was similar in both arms, was 3 weeks (range: 1–5 weeks).

Paradoxical IRIS events occurred only in the itraconazole arm (in 11.4% of patients), suggesting that ART can be safely initiated as early as 1 week after starting effective antifungal therapy with amphotericin B **(BIII).**[55]

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

Adverse Event Monitoring

Patients treated with amphotericin B should be monitored for infusion-related adverse reactions (fever, rigors, nausea, vomiting), electrolyte disturbances (particularly hypokalemia and hypomagnesemia), nephrotoxicity (rise in creatinine), and anemia. Hydration with 500 mL to 1,000 mL of normal saline and potassium supplementation before each amphotericin B infusion reduces the risk of nephrotoxicity during treatment **(AII).** Infusion-related adverse reactions can be ameliorated by pre-treatment with acetaminophen and diphenhydramine.

Drug–Drug Interactions and Therapeutic Drug Monitoring

Itraconazole and voriconazole and ARV drugs—such as protease inhibitors, some integrase strand transfer inhibitors, and non-nucleoside reverse transcriptase inhibitors—can have bidirectional interactions with each other, leading to increased or decreased drug concentrations (see Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines). Close monitoring is recommended when using these drugs together.

In settings where therapeutic drug monitoring (TDM) is available, serum itraconazole and voriconazole levels should be obtained in all patients to ensure adequate drug exposure **(BIII).** This is because itraconazole and voriconazole can interact with some ARV drugs and absorption of itraconazole can be erratic, and because of the extensive interindividual variability and nonlinear pharmacokinetics of voriconazole. The target serum trough concentration should be >0.5 μg/mL for itraconazole and >1 μg/mL for voriconazole **(BIII).** Because it is more bioavailable, itraconazole solution is preferred over the capsule formulation.

Prevention and Management of IRIS

Both unmasking and paradoxical IRIS have been described in patients with talaromycosis when ART is initiated.[57-59] In the IVAP trial, 188 of 432 (44%) patients had started ART a median of 3 to 4 months before developing talaromycosis, indicating the role of ART in the unmasking of subclinical infection in a significant proportion of patients.[55] This finding highlights the need for a sensitive assay to screen for subclinical infection and the importance of pre-emptive antifungal therapy to prevent disease and unmasking IRIS. In patients starting ART after a diagnosis of talaromycosis, paradoxical IRIS events only occurred in patients treated with itraconazole induction therapy,[55] demonstrating the role of effective induction therapy with amphotericin B in the prevention of paradoxical IRIS. ART should not be withheld because of concerns for possible development of IRIS **(AIII).**

Patients with paradoxical IRIS typically present with inflammatory manifestations that include erythematous or immunological skin lesions, such as erythema nodosum, as well as large and painful peripheral lymph nodes and synovitis of small joints. Most symptoms can be managed by judicious use of nonsteroid anti-inflammatory medicine. Corticosteroids are reserved for synovitis that interferes with daily function.[59] Although the IRIS events in the IVAP trial were not associated with increased mortality and were managed effectively with continuation of ART and antifungal therapy, they were associated with higher morbidity, including lower quality of life and increased diagnostic testing, duration of hospitalization, and cost.[55]

Managing Treatment Failure and Relapse

Talaromycosis treatment failure and disease relapse were associated with ineffective induction therapy with itraconazole, highlighting the importance of amphotericin B induction therapy.[55] On the basis of case series that included very few patients and on clinical experiences, voriconazole is an alternative therapy for patients who are unable to tolerate amphotericin B treatment **(BII).**

Disease relapse is associated with higher mortality[55] and occurs mainly in patients who are not adherent to ART or have virologic failure, as well as in those who are not adherent to itraconazole consolidation or maintenance therapy. Therapy adherence counseling and TDM for itraconazole and voriconazole, if available, are recommended **(AIII).**

Preventing Recurrence

When to Start Secondary Prophylaxis/Chronic Maintenance Therapy

A study showed that >50% of patients not treated with ART had disease relapse within 6 months after discontinuation of antifungal therapy. A double-blind, placebo-controlled study conducted in Chiang Mai, Thailand, demonstrated that secondary prophylaxis with oral itraconazole 200 mg daily in patients with AIDS reduced the talaromycosis relapse rate from 57% to 0% ($p < 0.001$).[56] All patients who successfully complete induction and consolidation treatment for talaromycosis should receive secondary prophylaxis (maintenance therapy) with oral itraconazole 200 mg/day until they reach criteria for stopping secondary prophylaxis **(AI).**

When to Stop Secondary Prophylaxis/Chronic Maintenance Therapy

No randomized, controlled study has demonstrated the safety of discontinuation of secondary prophylaxis for talaromycosis. However, a retrospective cohort study[60] reported no relapse of talaromycosis after itraconazole was discontinued in patients receiving ART whose CD4 counts were >100 cells/mm^3.

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

Secondary prophylaxis can reasonably be discontinued in patients with sustained virologic suppression for ≥6 months **(BIII).**

Secondary prophylaxis/chronic maintenance therapy should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(BIII).**

Special Considerations During Pregnancy

The diagnosis and treatment of talaromycosis during pregnancy is similar to that in nonpregnant adults, with the following considerations regarding antifungal use in pregnancy. Amphotericin B has not been shown to be teratogenic in animals, and no increase in fetal anomalies has been seen with its use in humans. Neonates born to people on chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia.

Itraconazole at high doses has been shown to be teratogenic in animals, but because humans lack the metabolic mechanism accounting for these defects, the animal teratogenicity data are not applicable to humans. Case series in humans do not suggest an increased risk of birth defects with itraconazole, but experience is very limited.[61]

Voriconazole is Food and Drug Administration Category D because of teratogenicity (cleft palate and renal defects) seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended.

Substitution of amphotericin B for high-dose azoles in the first trimester is recommended **(BIII).** People on secondary prophylaxis with itraconazole or other azoles should postpone pregnancy until their CD4 counts have been restored with ART, such that prophylaxis can be discontinued **(BIII).** If a person becomes pregnant while receiving itraconazole prophylaxis, the decision as to whether to continue should be individualized based on current CD4 count and viral suppression and patient preference.

Figure 1. Geographic Distribution of Talaromycosis

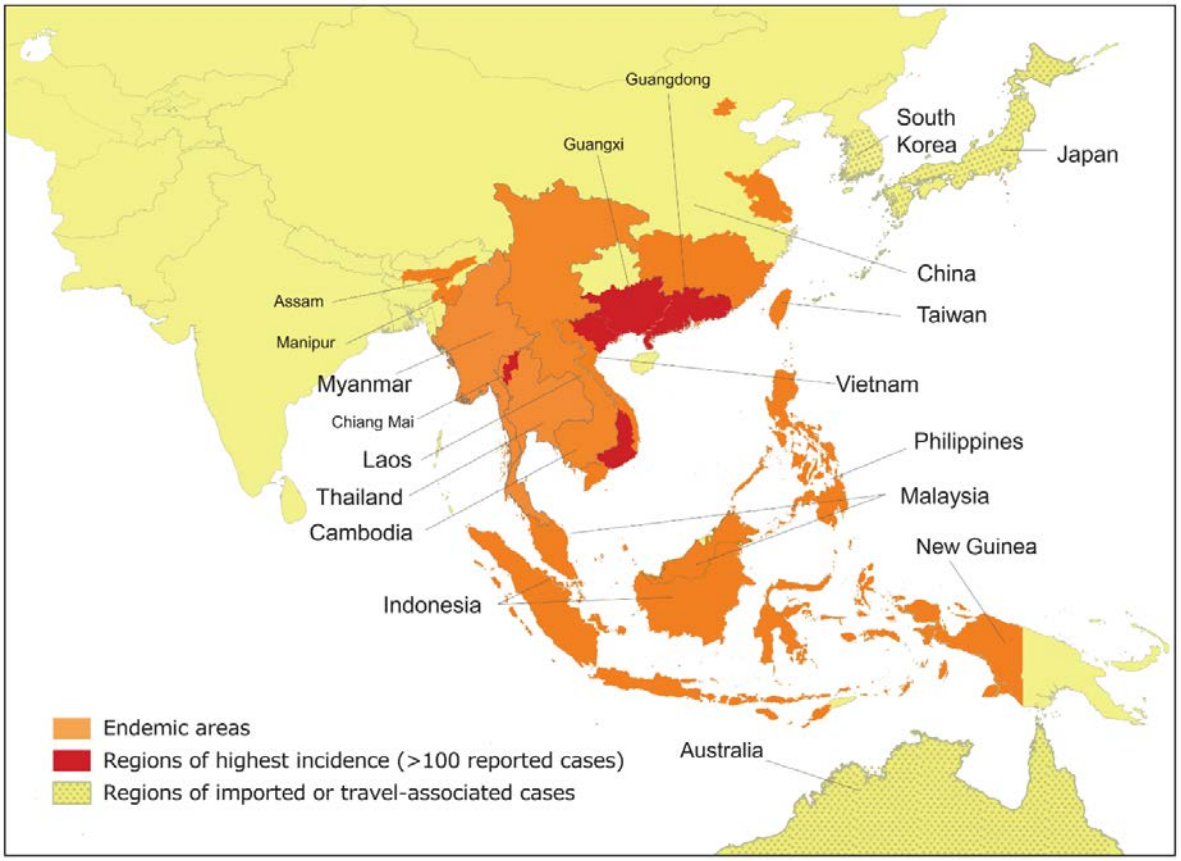

Figure courtesy of Dr. Thuy Le, Division of Infectious Diseases and International Health, Duke University School of Medicine.

References

1. Vanittanakom N, Cooper CR, Jr., Fisher MC, Sirisanthana T. Penicillium marneffei infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. 2006;19(1):95-110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16418525.

2. Hu Y, Zhang J, Li X, et al. Penicillium marneffei infection: an emerging disease in mainland China. *Mycopathologia*. 2013;175(1-2):57-67. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22983901.

3. Le T, Wolbers M, Chi NH, et al. Epidemiology, seasonality, and predictors of outcome of AIDS-associated Penicillium marneffei infection in Ho Chi Minh City, Viet Nam. *Clin Infect Dis*. 2011;52(7):945-952. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21427403.

4. Ranjana KH, Priyokumar K, Singh TJ, et al. Disseminated Penicillium marneffei infection among HIV-infected patients in Manipur state, India. *J Infect*. 2002;45(4):268-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12423616.

5. Samson RA, Yilmaz N, Houbraken J, et al. Phylogeny and nomenclature of the genus Talaromyces and taxa accommodated in Penicillium subgenus Biverticillium. *Stud Mycol*. 2011;70(1):159-183. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22308048.

6. Jiang J, Meng S, Huang S, et al. Effects of Talaromyces marneffei infection on mortality of HIV/AIDS patients in southern China: a retrospective cohort study. *Clin Microbiol Infect*. 2019;25(2):233-241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29698815.

7. Larsson M, Nguyen LH, Wertheim HF, et al. Clinical characteristics and outcome of Penicillium marneffei infection among HIV-infected patients in northern Vietnam. *AIDS Res Ther*. 2012;9(1):24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22897817.

8. Wu TC, Chan JW, Ng CK, Tsang DN, Lee MP, Li PC. Clinical presentations and outcomes of Penicillium marneffei infections: a series from 1994 to 2004. *Hong Kong Med J*. 2008;14(2):103-109. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18382016.

9. Feng RF, Ma Y, Liu ZF, et al. [Specific causes of death among 381 AIDS patients who died in hospitals]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2013;34(12):1237-1241. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24518028.

10. Nga TV, Parry CM, Le T, et al. The decline of typhoid and the rise of non-typhoid salmonellae and fungal infections in a changing HIV landscape: bloodstream infection trends over 15 years in southern Vietnam. *Trans R Soc Trop Med Hyg*. 2012;106(1):26-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22137537.

11. Qi T, Zhang R, Shen Y, et al. Etiology and clinical features of 229 cases of bloodstream infection among Chinese HIV/AIDS patients: a retrospective cross-sectional study. *Eur J Clin Microbiol Infect Dis*. 2016;35(11):1767-1770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27502930.

12. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated Penicillium marneffei infection in southeast Asia. *Lancet*. 1994;344(8915):110-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7912350.

13. Antinori S, Gianelli E, Bonaccorso C, et al. Disseminated Penicillium marneffei infection in an HIV-positive Italian patient and a review of cases reported outside endemic regions. *J Travel Med*. 2006;13(3):181-188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16706952.

14. Cristofaro P, Mileno MD. Penicillium marneffei infection in HIV-infected travelers. *AIDS Alert*. 2006;21(12):140-142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17191362.

15. Chan JF, Lau SK, Yuen KY, Woo PC. Talaromyces (Penicillium) marneffei infection in non-HIV-infected patients. *Emerg Microbes Infect*. 2016;5:e19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26956447.

16. Son VT, Khue PM, Strobel M. Penicilliosis and AIDS in Haiphong, Vietnam: evolution and predictive factors of death. *Med Mal Infect*. 2014;44(11-12):495-501. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25391487.

17. Kawila R, Chaiwarith R, Supparatpinyo K. Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infection in Northern Thailand: a retrospective study. *BMC Infect Dis*. 2013;13:464. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24094273.

18. Cao C, Liang L, Wang W, et al. Common reservoirs for Penicillium marneffei infection in humans and rodents, China. *Emerg Infect Dis*. 2011;17(2):209-214. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21291590.

19. Huang X, He G, Lu S, Liang Y, Xi L. Role of Rhizomys pruinosus as a natural animal host of Penicillium marneffei in Guangdong, China. *Microb Biotechnol*. 2015;8(4):659-664. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25824250.

20. Le T, Jonat B, Kim Cuc N, al E. The exposure and geospatial risk factors for AIDS-associated penicilliosis in Vietnam. Presented at: Conference on Retroviruses and Opportunistic Infections; 2015. Seattle, WA.

21. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Praparattanapan J, Nelson KE. Case-control study of risk factors for Penicillium marneffei infection in human immunodeficiency virus-infected patients in northern Thailand. *Clin Infect Dis*. 1997;24(6):1080-1086. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9195061.

22. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE. Seasonal variation of disseminated Penicillium marneffei infections in northern Thailand: a clue to the reservoir? *J Infect Dis*. 1996;173(6):1490-1493. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8648227.

23. Bulterys PL, Le T, Quang VM, Nelson KE, Lloyd-Smith JO. Environmental predictors and incubation period of AIDS-associated penicillium marneffei infection in Ho Chi Minh City, Vietnam. *Clin Infect Dis*. 2013;56(9):1273-1279. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23386634.

24. Wang YF, Xu HF, Han ZG, et al. Serological surveillance for Penicillium marneffei infection in HIV-infected patients during 2004–2011 in Guangzhou, China. *Clin Microbiol Infect*. 2015;21(5):484-489. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25677258.

25. Castro-Lainez MT, Sierra-Hoffman M, J LL-Z, et al. Talaromyces marneffei infection in a non-HIV non-endemic population. *IDCases*. 2018;12:21-24. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29942740.

26. Hilmarsdottir I, Coutellier A, Elbaz J, et al. A French case of laboratory-acquired disseminated Penicillium marneffei infection in a patient with AIDS. *Clin Infect Dis*. 1994;19(2):357-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7986922.

27. Hermans F, Ombelet S, Degezelle K, et al. First-in-man observation of Talaromyces marneffei-transmission by organ transplantation. *Mycoses*. 2017;60(3):213-217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27687582.

28. Sirisanthana T. Penicillium marneffei infection in patients with AIDS. *Emerg Infect Dis*. 2001;7(3 Suppl):561. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11485672.

29. Chen J, Zhang R, Shen Y, et al. Clinical Characteristics and Prognosis of Penicilliosis Among human immunodeficiency virus-infected patients in eastern China. *Am J Trop Med Hyg*. 2017;96(6):1350-1354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28719279.

30. Le T, Huu Chi N, Kim Cuc NT, et al. AIDS-associated Penicillium marneffei infection of the central nervous system. *Clin Infect Dis*. 2010;51(12):1458-1462. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21054180.

31. Limper AH, Adenis A, Le T, Harrison TS. Fungal infections in HIV/AIDS. *Lancet Infect Dis*. 2017;17(11):e334-e343. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28774701.

32. Zheng J, Gui X, Cao Q, et al. A clinical study of acquired immunodeficiency syndrome associated Penicillium marneffei infection from a non-endemic area in China. *PLoS One*. 2015;10(6):e0130376. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26083736.

33. Supparatpinyo K, Sirisanthana T. Disseminated Penicillium marneffei infection diagnosed on examination of a peripheral blood smear of a patient with human immunodeficiency virus infection. *Clin Infect Dis*. 1994;18(2):246-247. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8161635.

34. Deng Z, Ribas JL, Gibson DW, Connor DH. Infections caused by Penicillium marneffei in China and Southeast Asia: review of eighteen published cases and report of four more Chinese cases. *Rev Infect Dis*. 1988;10(3):640-652. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3293165.

35. Supparatpinyo K, Chiewchanvit S, Hirunsri P, Uthammachai C, Nelson KE, Sirisanthana T. Penicillium marneffei infection in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1992;14(4):871-874. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1315586.

36. LoBuglio KF, Taylor JW. Phylogeny and PCR identification of the human pathogenic fungus Penicillium marneffei. *J Clin Microbiol*. 1995;33(1):85-89. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7699073.

37. Pornprasert S, Praparattanapan J, Khamwan C, et al. Development of TaqMan real-time polymerase chain reaction for the detection and identification of Penicillium marneffei. *Mycoses*. 2009;52(6):487-492. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19207847.

38. Hien HTA, Thanh TT, Thu NTM, et al. Development and evaluation of a real-time polymerase chain reaction assay for the rapid detection of Talaromyces marneffei MP1 gene in human plasma. *Mycoses*. 2016;59(12):773-780. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27453379.

39. Dankai W, Pongpom M, Vanittanakom N. Validation of reference genes for real-time quantitative RT-PCR studies in Talaromyces marneffei. *J Microbiol Methods*. 2015;118:42-50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26327538.

40. Huang YT, Hung CC, Liao CH, Sun HY, Chang SC, Chen YC. Detection of circulating galactomannan in serum samples for diagnosis of Penicillium marneffei infection and cryptococcosis among patients infected with human immunodeficiency virus. *J Clin Microbiol*. 2007;45(9):2858-2862. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17596363.

41. Thu NT, Chan JF, Hien HTA, et al. Clinical performance of the Mp1p immunoassay for rapid diagnosis of Talaromyces marneffei infection. Presented at: Conference on Retroviruses and Opportunistic Infections; 2017. Seattle, WA.

42. Thu N, Dat V, Chan J, et al. Asymptomatic Talaromyces marneffei infection is associated with HIV mortality. Presented at: Asia Pacific AIDS and CoInfection Conference; 2018. Hong Kong, China.

43. Borman AM, Fraser M, Szekely A, Johnson EM. Rapid and robust identification of clinical isolates of Talaromyces marneffei based on MALDI-TOF mass spectrometry or dimorphism in Galleria mellonella. *Med Mycol*. 2019;57(8):969-975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30649411.

44. Lau SK, Lam CS, Ngan AH, et al. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry for rapid identification of mold and yeast cultures of Penicillium marneffei. *BMC Microbiol*. 2016;16:36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26965891.

45. Li L, Chen K, Dhungana N, Jang Y, Chaturvedi V, Desmond E. Characterization of clinical isolates of Talaromyces marneffei and related species, California, USA. *Emerg Infect Dis*. 2019;25(9):1765-1768. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31441765.

46. Lau SK, Lo GC, Lam CS, et al. In vitro activity of posaconazole against Talaromyces marneffei by broth microdilution and Etest methods and comparison to itraconazole, voriconazole, and anidulafungin. *Antimicrob Agents Chemother*. 2017;61(3). Available at: https://www.ncbi.nlm.nih.gov/pubmed/28031205.

47. Lei HL, Li LH, Chen WS, et al. Susceptibility profile of echinocandins, azoles and amphotericin B against yeast phase of Talaromyces marneffei isolated from HIV-infected patients in Guangdong, China. *Eur J Clin Microbiol Infect Dis*. 2018;37(6):1099-1102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29536323.

48. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. *Clin Infect Dis*. 2002;34(2):277-284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11740718.

49. Chaiwarith R, Fakthongyoo A, Praparattanapan J, Boonmee D, Sirisanthana T, Supparatpinyo K. Itraconazole vs fluconazole as a primary prophylaxis for fungal infections in HIV-infected patients in

Thailand. *Curr HIV Res*. 2011;9(5):334-338. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21916838.

50. Supparatpinyo K, Nelson KE, Merz WG, et al. Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated Penicillium marneffei infections and in vitro susceptibilities of isolates from clinical specimens. *Antimicrob Agents Chemother*. 1993;37(11):2407-2411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8285625.

51. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE. Amphotericin B and itraconazole for treatment of disseminated Penicillium marneffei infection in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1998;26(5):1107-1110. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9597237.

52. Ouyang Y, Cai S, Liang H, Cao C. Administration of voriconazole in disseminated Talaromyces (Penicillium) marneffei infection: a retrospective study. *Mycopathologia*. 2017;182(5-6):569-575. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28108867.

53. Supparatpinyo K, Schlamm HT. Voriconazole as therapy for systemic Penicillium marneffei infections in AIDS patients. *Am J Trop Med Hyg*. 2007;77(2):350-353. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17690411.

54. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al. An efficacy study of itraconazole in the treatment of Penicillium marneffei infection. *J Med Assoc Thai*. 1992;75(12):688-691. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1339213.

55. Le T, Kinh NV, Cuc NTK, et al. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. *N Engl J Med*. 2017;376(24):2329-2340. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28614691.

56. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of Penicillium marneffei infection in patients infected with the human immunodeficiency virus. *N Engl J Med*. 1998;339(24):1739-1743. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9845708.

57. Hall C, Hajjawi R, Barlow G, Thaker H, Adams K, Moss P. Penicillium marneffei presenting as an immune reconstitution inflammatory syndrome (IRIS) in a patient with advanced HIV. *BMJ Case Rep*. 2013;2013. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23362074.

58. Liu X, Wu H, Huang X. Disseminated Penicillium marneffei infection with IRIS. *IDCases*. 2015;2(4):92-93. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26793468.

59. Thanh NT, Vinh LD, Liem NT, et al. Clinical features of three patients with paradoxical immune reconstitution inflammatory syndrome associated with Talaromyces marneffei infection. *Med Mycol Case Rep*. 2018;19:33-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29379703.

60. Chaiwarith R, Charoenyos N, Sirisanthana T, Supparatpinyo K. Discontinuation of secondary prophylaxis against penicilliosis marneffei in AIDS patients after HAART. *AIDS*. 2007;21(3):365-367. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17255744.

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

Toxoplasmosis

Updated: September 16, 2024
Reviewed: September 16, 2024

Toxoplasma gondii is a protozoan that can commonly cause asymptomatic infection, a mononucleosis-like syndrome, retinochoroiditis, or congenital infection in immunocompetent individuals, but it presents most often as toxoplasma encephalitis (TE) in people with HIV who are severely immunocompromised.[1-4] Toxoplasmosis in people with HIV appears to occur mainly due to reactivation of latent tissue cysts from a prior infection; primary infection is occasionally associated with acute cerebral or disseminated disease.

Epidemiology

Primary infection occurs most commonly after consumption of undercooked meat, unwashed fruits or vegetables, water, or unpasteurized milk containing viable organisms, or ingesting oocysts that have been shed in cat feces and sporulated in the environment, a process that takes at least 24 hours. In up to 50% of individuals, primary infection can occur in the absence of conventional risk factors.[5] Infection can also be transmitted congenitally, or rarely following organ transplant or blood transfusion.[6-9] The organism is not transmitted through direct person-to-person contact.

Seroprevalence of anti-*Toxoplasma* antibody, indicating prior infection, can vary substantially within the United States based on geography and demographics, with an overall prevalence of approximately 11%, versus 40% to 80% in certain European, Latin American, Asian, and African countries.[10-12] In the era before antiretroviral therapy (ART), the 12-month incidence of TE was approximately 33% in patients with advanced immunodeficiency who were seropositive for *T. gondii* and not receiving prophylaxis with drugs active against the disease. A very low incidence of toxoplasmosis is seen in people with HIV who are seronegative for *T. gondii*. In these individuals, their toxoplasmosis presumably represents primary infection, reactivation of latent disease in individuals who cannot produce detectable antibodies, or the use of insensitive assays.[13,14]

Clinical Manifestations

Clinical disease related to immunodeficiency is rare among people with HIV with CD4 T lymphocyte (CD4) cell counts >200 cells/mm^3. People with CD4 counts <50 cells/mm^3 are at greatest risk.[1,3,14,15] Among people with HIV, the most common clinical presentation of *T. gondii* infection is focal encephalitis, with subacute onset of headache, focal neurologic deficits (e.g., hemiparesis), and sometimes fever.[1,3,15] People with HIV also may present with non-focal encephalitis, with manifestations including isolated headache and generalized seizures.[16] Focal neurological abnormalities may be present on physical examination. In the absence of treatment, disease progression may result in seizures, stupor, coma, and death. Computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain following intravenous contrast administration will typically show multiple contrast-enhancing lesions, with a predilection for the basal ganglia, often with edema and associated mass effect.[1,15,17-19] Toxoplasmosis can more rarely manifest as a single brain lesion or diffuse encephalitis without evidence of focal brain lesions on imaging studies.[16] The latter presentation tends to be rapidly progressive and fatal. Retinochoroiditis, pneumonia, adenopathy, and evidence of other multifocal organ system involvement can occur but are uncommon in people with HIV.

Diagnosis

People with HIV and concomitant TE are usually seropositive for anti-toxoplasma immunoglobulin G (IgG) antibodies.[1,3,15,20] The absence of IgG antibody makes a diagnosis of toxoplasmosis unlikely but not impossible. Anti-toxoplasma immunoglobulin M (IgM) antibodies are usually absent and should not be requested unless primary infection is suspected. Quantitative antibody titers are not useful for diagnosis.

Definitive diagnosis of TE requires a compatible clinical syndrome, identification of one or more mass lesions by CT or MRI, and detection of the organism in a clinical sample. A presumptive diagnosis is based on a consistent clinical and radiographic presentation, presence of anti-*Toxoplasma* IgG antibodies, and response to anti-*Toxoplasma* therapy, but without detection of the organism. Most diagnoses are made either presumptively or based on a positive cerebrospinal fluid (CSF) toxoplasma polymerase chain reaction (PCR).

On imaging studies, toxoplasmosis presents as contrast-enhancing lesions (typically ring-enhancing), with a predilection for the basal ganglia. MRI has sensitivity superior to that of CT and should be obtained in patients with equivocal or negative CT studies. Positron emission tomography[18] or single-photon emission CT scanning[19] may be helpful in distinguishing between TE and primary central nervous system (CNS) lymphoma, but no imaging technique is completely specific. For TE, detection of the organism requires either a brain biopsy, most commonly stereotactic, or a positive CSF PCR test. Hematoxylin and eosin stains can be used for detection of *T. gondii* in biopsies, but sensitivity is significantly increased if immunoperoxidase staining is used and if experienced laboratories process the specimens.[21]

If safe and feasible, a lumbar puncture should be performed for *T. gondii* PCR, as well as for cytology, culture, cryptococcal antigen, and PCR for *Mycobacterium tuberculosis*, Epstein-Barr virus (EBV), and JC virus (JCV) depending on imaging findings. PCR for cytomegalovirus and varicella-zoster virus, as well as testing for syphilis, may also be considered. Detection of *T. gondii* by PCR in CSF has high specificity (96% to 100%), but low sensitivity (50%), especially once specific anti-*Toxoplasma* therapy has been started.[22-25]

The differential diagnosis of CNS lesions with mass effect in patients with AIDS most often includes primary CNS lymphoma, tuberculosis, and endemic fungal infection (e.g., cryptococcosis). Lymphoma can be indistinguishable from TE radiographically, both frequently presenting with ring-enhancing lesions, although lymphoma presents more often with a single lesion.[26] In the absence of immune reconstitution inflammatory syndrome (IRIS), progressive multifocal leukoencephalopathy (PML) can be distinguished based on imaging studies. PML lesions typically involve white matter rather than gray matter, are usually non-contrast-enhancing, and produce no mass effect. There are a large number of less common causes of focal neurologic disease in people with AIDS including Chagas disease, metastatic tumors, and pyogenic brain abscess, particularly in people who inject drugs.

Given the risks associated with a brain biopsy, and the difficulty in obtaining one at many centers, a presumptive diagnosis of TE is established based on an objective response to empiric therapy.[27] Brain biopsy is then reserved for patients who fail to respond to specific therapy, although earlier biopsy should be strongly considered if results from imaging, serology, or CSF PCR do not confirm toxoplasmosis or suggest an etiology other than toxoplasmosis. In patients with contrast-enhancing lesions, detection of EBV in the CSF by PCR should raise concern for CNS lymphoma, especially

when quantitative results show CSF levels above 10,000 EBV copies/mL; however, it is not diagnostic by itself.[28-30] In people with HIV receiving ART, PML-IRIS may also present with contrast-enhancing lesions, in which case JCV by PCR in CSF is highly suggestive of PML.[31]

Preventing Exposure

People with HIV should be counseled regarding sources of *Toxoplasma* infection. Those with CD4 counts <200 cells/mm^3 should be tested for IgG antibody to *Toxoplasma* soon after they are diagnosed with HIV to detect latent infection with *T. gondii* (**BIII).**

To minimize risk of acquiring toxoplasmosis, people with HIV, especially those with CD4 counts <200 cells/mm^3, should be advised not to eat raw or undercooked meat, including undercooked lamb, beef, pork, or venison, and not to eat raw shellfish, including oysters, clams, and mussels **(BIII).** Lamb, beef, venison, and pork should be cooked to an internal temperature of 165 °F to 170 °F;[32] meat cooked until it is no longer pink inside usually has an internal temperature of 165 °F to 170 °F, and therefore, from a more practical perspective, satisfies this requirement. People with HIV should wash their hands after contact with raw meat and after gardening or other contact with soil; they should also wash fruits and vegetables well before eating them raw **(BIII).**

Cat owners with HIV whose CD4 counts are <200 cells/mm^3 and who are seronegative should be advised to have a nonpregnant person without HIV change the litter box daily. If a person with HIV must change the litter box themselves, they should wear gloves and wash their hands thoroughly afterward **(BIII).** They also should be encouraged to keep their cats inside and not to adopt or handle stray cats **(BIII).** Cats should be fed only canned or dried commercial food or well-cooked table food, not raw or undercooked meats **(BIII).** People with HIV do not need to be advised to part with their cats or to have their cats tested for toxoplasmosis **(BIII).**

Preventing Disease

Recommendations for Preventing *Toxoplasma gondii* Encephalitis

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: Listed regimens are also effective against PCP.
Preferred Regimen
• TMP-SMX one DS PO daily (AII)
Alternative Regimens
• TMP-SMX one DS PO three times weekly (BII), *or*
• TMP-SMX one SS PO daily (BIII), *or*
• Dapsone[a] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI), *or*
• (Dapsone[a] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (CI), *or*
• Atovaquone[b] 1,500 mg PO daily (CIII), *or*

• (Atovaquone[b] 1,500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily (CIII) Indication for Discontinuing Primary Prophylaxis • CD4 count >200 cells/mm^3 for >3 months and sustained HIV RNA below limits of detection in response to ARV therapy (AI); *or* • Can consider if CD4 count is 100–200 cells/mm^3 and HIV RNA remains below limits of detection for at least 3–6 months (BII) Indication for Restarting Primary Prophylaxis • CD4 count <100 cells/mm^3 (AIII) • CD4 count 100–200 cells/mm^3 and HIV RNA above detection limits (AIII)
Pregnancy Considerations
Indication, drugs, and doses are the same as for nonpregnant individuals.

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

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

Key: ARV = antiretroviral; CD4 = CD4 T lymphocyte; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IgG = immunoglobulin G; PCP = *Pneumocystis* pneumonia; PO = orally; SS = single-strength; TMP-SMX = trimethoprim-sulfamethoxazole

Indication for Primary Prophylaxis

Toxoplasma-seropositive people who have CD4 counts <100 cells/mm^3 should receive prophylaxis against TE **(AII).**[33,34]

The preferred primary prophylaxis regimen is one double-strength tablet daily of TMP-SMX **(AII).** This is also the preferred prophylaxis regimen for *Pneumocystis jirovecii* pneumonia (PCP), which all people at risk for toxoplasmosis are also at risk for developing. TMP-SMX, one double-strength tablet three times weekly, is an alternative **(BII).** TMP-SMX, one single-strength tablet daily, is also an option **(BIII).** If TMP-SMX cannot be tolerated, the recommended alternative is dapsone plus pyrimethamine plus leucovorin, which also is effective against PCP (see table for rating based on dapsone and pyrimethamine doses).[35-37] Atovaquone with or without pyrimethamine plus leucovorin is active against PCP and can also be considered for toxoplasmosis **(CIII).** For people in whom other alternatives are not possible, pyrimethamine (plus leucovorin) alone may have some efficacy as primary prophylaxis **(CIII).**[14] Aerosolized pentamidine does not protect against TE and **is not recommended** for anti-*Toxoplasma* prophylaxis **(AI).**[33,38]

Discontinuing Primary Prophylaxis

Prophylaxis against TE should be discontinued in adults and adolescents with HIV receiving ARV therapy with sustained suppression of plasma HIV RNA levels below the detection limits of available assays whose CD4 counts increase to >200 cells/mm^3 for more than 3 months **(AI).**[39-43] In this setting primary TE prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, likelihood of development of drug-resistant pathogens, and cost.

A combined analysis of 10 European cohorts found a low incidence of TE in patients with CD4 counts between 100 and 200 cells/mm^3, who were receiving ARVs and had HIV RNA plasma viral loads <400 copies/mL, and who had stopped or never received TE prophylaxis; this suggests that primary TE prophylaxis can be safely discontinued in patients with CD4 counts 100 to 200 cells/mm^3 and HIV plasma RNA levels below limits of detection with commercial assays.[44] Similar observations have been made with regard to stopping primary or secondary prophylaxis for PCP.[44-46] 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).**[44]

Treating Disease

Recommendations for Treating *Toxoplasma gondii* Encephalitis

Treating *Toxoplasma gondii* Encephalitis

Preferred Regimens for Acute Infection
• Pyrimethamine 200 mg PO once, followed by weight-based dosing (AI):
  o Body weight ≤60 kg: pyrimethamine 50 mg PO daily + sulfadiazine 1,000 mg PO every 6 hours + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or twice daily)
  o Body weight >60 kg: pyrimethamine 75 mg PO daily + sulfadiazine 1,500 mg PO every 6 hours + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or twice daily)
or
• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) twice daily (AII)
Note: If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (AII).
Alternative Regimens for Acute Infection
• (Pyrimethamine + leucovorin)[c] plus clindamycin 600 mg IV or PO every 6 hours (AI); preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine[b]-sulfadiazine; must add additional agent for PCP prophylaxis (AII), *or*
• Atovaquone[b] 1,500 mg PO twice daily + (pyrimethamine +leucovorin)[c] (BII), *or*
• Atovaquone[b] 1,500 mg PO twice daily + sulfadiazine[d] (BII), *or*
• Atovaquone[b] 1,500 mg PO twice daily (BII)
• For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies (BI).
• During the desensitization phase, atovaquone 1,500 mg PO should be administered twice daily until therapeutic doses of TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) twice daily are achieved (CIII).
Total Duration for Treating Acute Infection
• At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks
• After completion of the acute therapy, all patients should be continued on chronic maintenance therapy as outlined below.

Chronic Maintenance Therapy for *Toxoplasma gondii* Encephalitis

Preferred Regimens

- Pyrimethamine 25–50 mg PO daily + sulfadiazine 2,000–4,000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily (AI), *or*
- TMP-SMX DS one tablet twice daily (AII)

Alternative Regimens

- (Pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily plus clindamycin 1,800 mg PO daily dose (in 3 or 4 divided doses) (BI); must add additional agent to prevent PCP (AII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily (BII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily + sulfadiazine 2,000–4,000 mg PO daily (in 2 to 4 divided doses) (BII), *or*
- Atovaquone[b] 750–1,500 mg PO twice daily (BII)

Criteria for Discontinuing Chronic Maintenance Therapy (BI)

- Successfully completed initial therapy, *and*
- Asymptomatic of signs and symptoms of TE, *and*
- CD4 count >200 cells/mm^3 for >6 months in response to ARVs

Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance

- CD4 count <200 cells/mm^3 regardless of HIV RNA level (AIII)

Other Considerations

- Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat a mass effect associated with focal lesions or associated edema (BIII) or for control of clinically significant IRIS symptoms in conjunction with ART and anti-toxoplasma therapy (CIII); discontinue as soon as clinically feasible. For patients in whom the diagnosis of TE is presumptive based in part on clinical response, one needs to be careful as CNS lymphoma may also respond to steroids clinically and radiologically.
- Antiseizure medications should be administered to patients with TE and associated seizures (AII) and continued through at least the period of acute treatment (BII); antiseizure medications should not be used as prophylaxis in patients without seizures (BII).

Pregnancy Considerations

Suspected or Confirmed Acute Toxoplasmosis During Pregnancy

Initial Therapy (primary infection during pregnancy or symptomatic reactivation of T. gondii *without encephalitis)*

- Initiation of therapy before 14 weeks of pregnancy: spiramycin administered orally at a dosage of 1.0 g (or 3 million U) every 8 hours (total dosage of 3 g or 9 million U per day) (AII)
- Initiation of therapy on or after 14 weeks of pregnancy: pyrimethamine (50 mg PO twice daily x 2 days, then 50 mg PO daily) + sulfadiazine (75 mg/kg PO x 1 day, then 50 mg/kg PO twice daily) + leucovorin (10–20 mg/day during and 1 week after pyrimethamine use) (AII)

Fetal Assessment

- Amniocentesis for toxoplasmosis PCR to be done at 18 weeks gestation or later (BIII)
- Fetal ultrasonography every 4 weeks until delivery (AIII)
- If no evidence of fetal infection (negative amniotic fluid PCR, no fetal ultrasonographic abnormalities), continue initial therapy.

Treatment of *Toxoplasma gondii* Encephalitis During Pregnancy

- Treatment regimen is the same as for nonpregnant individuals (BIII).
- In general, pyrimethamine should be avoided in the first trimester of pregnancy because of teratogenicity concerns, but in the case of TE, the benefit of using pyrimethamine to the pregnant individual outweighs the risk to the fetus.

Fetal Infection

Criteria for Initiating Treatment for Fetal Infection

- Positive amniotic fluid PCR, *and/or*
- Fetal ultrasonographic findings suggestive of congenital toxoplasmosis

Treatment for Fetal Infection

- Pyrimethamine + sulfadiazine + leucovorin until delivery (AII)

Note: If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX DS one tablet twice daily plus spiramycin 1 g PO three times a day plus leucovorin 4 mg daily should be utilized in place of pyrimethamine-sulfadiazine (BII).

[a] Whenever possible, patients should be tested for G6PD deficiency before administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

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

[c] Pyrimethamine and leucovorin doses: Same doses and frequency as listed in Preferred Regimen for Acute Infection

[d] Sulfadiazine dose: Same as weight-based dose and frequency listed in Preferred Regimen for Acute Infection

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CNS = central nervous system; DS = double-strength; G6PD = glucose-6-phosphate dehydrogenase; IRIS = immune reconstitution inflammatory syndrome; IV = intravenous; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PO = orally; SMX = sulfamethoxazole; TE = toxoplasma encephalitis; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

For many years, the initial therapy of choice for TE has been the combination of pyrimethamine plus sulfadiazine plus leucovorin **(AI).**[2,47-49] Pyrimethamine penetrates the brain parenchyma efficiently even in the absence of inflammation.[50] Leucovorin reduces the likelihood of hematologic toxicities associated with pyrimethamine therapy.[51] Pyrimethamine, however, has become extremely expensive and can be difficult to obtain in the United States.

TMP-SMX has been used with increasing frequency as a preferred regimen **(AII),** although large, randomized trials comparing TMP-SMX to pyrimethamine plus sulfadiazine have not been performed. In a small (77 patients) randomized trial, TMP-SMX was reported to be as effective and better tolerated than pyrimethamine-sulfadiazine.[52] Others have reported similar efficacy of TMP-SMX to pyrimethamine plus sulfadiazine in open-label observational studies.[53,54] A recent meta-analysis found that TMP-SMX was as effective as pyrimethamine plus sulfadiazine, but was associated with less toxicity.[55] If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be utilized **(AII).**

Pyrimethamine plus leucovorin plus clindamycin[47,48] is the preferred alternative regimen for patients with TE who cannot tolerate sulfa drugs or do not respond to first-line therapy **(AI).** This combination, however, does not prevent PCP, therefore additional PCP prophylaxis must be administered when it is used **(AII)** (see discussion under Preventing Recurrence).[56]

For patients with a history of sulfa allergy, rapid sulfa desensitization may be attempted using one of several published strategies **(BI).**[57-62] During the desensitization period, atovaquone with or without pyrimethamine should be administered until therapeutic doses of TMP-SMX are achieved **(CIII).**

No well-studied options exist for patients who cannot take an oral regimen. No parenteral formulation of pyrimethamine exists and the only widely available parenteral sulfonamide is the sulfamethoxazole component of TMP-SMX. Some specialists will use parenteral TMP-SMX **(BII)** or oral pyrimethamine plus parenteral clindamycin **(CIII)** as initial treatment in severely ill patients who require parenteral therapy**.**

Atovaquone (with meals or oral nutritional supplements) plus pyrimethamine plus leucovorin, atovaquone plus sulfadiazine, or (for patients intolerant of both pyrimethamine and sulfadiazine) atovaquone as a single agent also have been shown to be effective in treating TE **(BII).**[63,64,65] However, the relative efficacy of atovaquone-containing regimens compared with other regimens is unknown. Clinicians should be aware that the absorption of the drug varies substantially from patient to patient; plasma levels >18.5 µg/mL are associated with an improved response rate but atovaquone therapeutic drug monitoring is not routinely available.[64-66]

The following regimens have been reported to have activity in treatment of TE in small cohorts of patients or in case reports of one or several patients: azithromycin plus pyrimethamine plus leucovorin **(CII)**[67,68]; clarithromycin plus pyrimethamine plus leucovorin **(CIII)**[69]; 5-fluorouracil plus clindamycin **(CIII)**[70]; dapsone plus pyrimethamine plus leucovorin **(CIII)**[71]; and minocycline or doxycycline combined with either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin **(CIII).**[72,73] There is rarely a reason to use one of these regimens.

Clinical response to acute therapy occurs in ~90% of patients with TE within 14 days of initiating appropriate anti-*Toxoplasma* treatment.[2] The reasons why some patients fail therapy are not clearly proven; whether such failures are due to poor adherence, other host factors, or antimicrobial resistance has not been well delineated. Acute therapy for TE should be continued for 6 weeks, if there is clinical and radiologic improvement **(BII).**[1-4] Longer courses may be necessary if clinical or 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, especially in people with HIV receiving ARVs.[74]

Adjunctive Therapies

Adjunctive corticosteroids such as dexamethasone should only be used for treatment of patients with TE when they are clinically indicated to treat a mass effect associated with focal lesions or associated edema **(BIII).** In those treated with corticosteroids, caution may be needed in diagnosing CNS toxoplasmosis on the basis of treatment response, since primary CNS lymphoma may respond clinically and radiographically to corticosteroids alone; these patients should be monitored carefully as corticosteroids are tapered. In addition, corticosteroids should be discontinued as soon as clinically feasible because of their potential to cause immunosuppression. Patients receiving corticosteroids should be monitored closely for development of other opportunistic infections (OIs), including cytomegalovirus retinitis and tuberculosis.

Antiseizure medications should be administered to patients with TE associated with seizures **(AII)** but **should not be administered** prophylactically to patients **without seizures (BII).** Anticonvulsants, if indicated, should be continued at least through the period of acute therapy **(BII).**

Special Considerations Regarding ART Initiation

There are no data on which to base a recommendation regarding when to start ARV therapy in people with HIV and TE. However, many physicians would initiate ARV therapy within 2 to 3 weeks after the diagnosis of toxoplasmosis, based on the significantly lower incidence of AIDS progression or death (a secondary study endpoint) seen in the early ARV therapy arm of a controlled trial of 282 patients with OIs other than tuberculosis (only 5% of whom had toxoplasmosis) who were randomized to early (median 12 days after initiation of OI therapy) versus deferred (median 45 days) initiation of ARV therapy.[75]

IRIS

IRIS associated with TE has been reported but appears to be rare (~5% in one report).[76-78] Most cases develop as paradoxical worsening with increase in the size and number of lesions, peri-lesional edema, and an increase in contrast enhancement on MRI.[77,79,80] As for IRIS with other infections, corticosteroid therapy, dosed to control symptoms, can be administered in patients with clinically significant symptoms in conjunction with ARVs and anti-*Toxoplasma* therapy **(CIII).**

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

Changes in antibody titers are not useful for monitoring responses to therapy. People with HIV with TE should be monitored routinely for adverse events and clinical and radiologic improvement **(AIII).**

Neurological improvement will occur by 14 days in over 90% of patients[2]; if no improvement is seen by that time, other diagnoses should be considered. Repeat imaging can be considered at 3 and 6 weeks, or sooner for clinical deterioration.[2] After 6 weeks, maintenance therapy at ~50% of treatment doses should be initiated assuming a clinical response has been seen.

Common pyrimethamine toxicities such as rash, nausea, and bone marrow suppression (neutropenia, anemia, and thrombocytopenia) often can be reversed by increasing the leucovorin dose to 10, 25, or 50 mg four times daily **(CIII).** Common sulfadiazine toxicities include rash, fever, leukopenia, hepatitis, nausea, vomiting, diarrhea, renal insufficiency, and crystalluria. Common clindamycin toxicities include fever, rash, nausea, diarrhea (including pseudomembranous colitis or diarrhea related to *Clostridium difficile* toxin), and hepatotoxicity. Common TMP-SMX toxicities include rash, fever, leukopenia, thrombocytopenia, and hepatotoxicity. Common atovaquone toxicities include nausea, vomiting, diarrhea, rash, headache, hepatotoxicity, and fever. Drug interactions between certain anticonvulsants (e.g., phenytoin, phenobarbital, carbamazepine), dexamethasone and antiretroviral (ARV) agents should be evaluated carefully; if necessary, doses should be adjusted, or alternative anticonvulsants or ARV agents should be used.

Managing Treatment Failure

A brain biopsy should be strongly considered in patients who did not have an initial biopsy prior to therapy and who fail to respond to initial therapy for TE **(BII)** as defined by clinical or radiologic deterioration during the first week despite adequate therapy, or who do not show clinical

improvement within 10 to 14 days. A switch to an alternative regimen, as previously described, should be considered for those who undergo brain biopsy and have confirmed histopathologic evidence of TE, or who have a CSF PCR positive for *T. gondii* **(BIII).** In patients who adhere to their regimens, disease recurrence is unusual in the setting of chronic maintenance therapy after an initial clinical and radiographic response.

Preventing Recurrence

When to Start Chronic Maintenance Therapy

Patients who have completed initial therapy for TE should be given chronic maintenance therapy to suppress infection **(AI)**[47,48] until immune reconstitution occurs as a consequence of ARV therapy. The combination of pyrimethamine plus sulfadiazine plus leucovorin is highly effective as suppressive therapy for patients with TE **(AI)** and provides protection against PCP **(AII).** Although sulfadiazine is routinely dosed as a four-times-a-day regimen, a pharmacokinetic study suggests bioequivalence for the same total daily dose when given either twice or four times a day,[81] and limited clinical experience suggests that twice-daily dosing is effective.[82]

For patients being treated with TMP-SMX, this drug should be continued as chronic maintenance at a reduced dose of one double-strength tablet twice daily **(AII).**[52] A small, uncontrolled study in patients who had been receiving ART for a median of 13 months suggested that TMP-SMX could be used as a suppressive regimen in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin to reduce pill burden.[83]

Pyrimethamine plus leucovorin plus clindamycin is commonly used as suppressive therapy for patients with TE who cannot tolerate sulfa drugs **(BI).** Because of the high failure rate observed with lower doses,[47] a dose of 1,800 mg clindamycin daily in 3 or 4 divided doses is recommended. Because this regimen does not provide protection against PCP **(AII),**[56] an additional agent, such as dapsone or aerosol pentamidine, must be used. Atovaquone also is active against both TE[65,66] and PCP[84] and can be used alone, with sulfadiazine, or with pyrimethamine and leucovorin in patients with TE **(BII).**

When to Stop Chronic Maintenance Therapy

Chronic maintenance therapy for TE can be discontinued in adults and adolescents with HIV, if they have successfully completed initial therapy for TE, remain asymptomatic with regard to signs and symptoms of TE, and have an increased CD4 count to >200 cells/mm^3 for >6 months in response to ARV therapy **(BI),** although occasional recurrences have been reported.[40,43,85,86] As part of the evaluation to determine whether discontinuation of therapy is appropriate, some specialists recommend obtaining an MRI of the brain to assess for resolution of brain lesions, although residual contrast-enhancing lesions can be seen for prolonged periods in some ARV-treated patients.

When to Restart Primary Prophylaxis or Maintenance Therapy

Primary prophylaxis should be reintroduced if the CD4 count decreases to <100 cells/mm^3 **(AIII)** regardless of the HIV plasma viral load. Based on results from the COHERE study, an observational study of multiple cohorts, primary prophylaxis may not need to be restarted in patients with CD4 counts of 100 to 200 cells/mm^3 who have had HIV plasma RNA levels below limits of detection for at least 3 to 6 months **(BII).**[44,45] For patients with CD4 counts of 100 to 200 cells/mm^3 with HIV plasma viral load above detection limits of the utilized assay, PCP prophylaxis should be

reintroduced, and most, but not all, regimens will provide prophylaxis for toxoplasmosis as well **(AIII).**

Because there are no published data examining the risk of recurrence in patients stopping chronic maintenance therapy for TE when the CD4 count is between 100 and 200 cells/mm^3, and recurrent TE can be debilitating and potentially life-threatening, maintenance therapy should be reintroduced if the CD4 count decreases to <200 cells/mm^3 **(AIII)** regardless of the HIV plasma viral load.[87]

Special Considerations During Pregnancy

Diagnosis During Pregnancy

Documentation of baseline *T. gondii* serologic status (IgG only) should be obtained in people with HIV 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 pregnant people with HIV with severe immunosuppression.[88,89] Knowing 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.

Toxoplasma infection during pregnancy is usually asymptomatic. Non-specific symptoms may include fever, fatigue, headache, and myalgia after a 5- to 23-day incubation period. In the setting of parasitemia during pregnancy, the placenta may become infected and result in fetal infection. The risk of congenital toxoplasmosis (infection of the fetus) is highest in the setting of a primary infection during pregnancy as compared to reactivation. While the risk of transmission to the fetus increases with gestational age, with the highest risk in the third trimester, the sequelae to the fetus are more severe when toxoplasmosis is acquired early in gestation.[90,91]

Toxoplasmosis diagnostic considerations are not affected by pregnancy. Primary *T. gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, immunoglobulin A, and immunoglobulin E antibodies; IgG avidity; and the differential agglutination tests.[92,93] Because serologic testing is often difficult to interpret and prompt treatment and counseling is particularly important during pregnancy, people with HIV with suspected primary *T. gondii* infection during pregnancy should be managed in consultation with a maternal-fetal medicine specialist where available. The care team may elect to access specialized laboratory testing[93,94] (e.g., the Palo Alto Medical Foundation Toxoplasmosis Serology Laboratory [PAMF-TSL], Palo Alto, CA, at 650-853-4828 and toxolab@pamf.org; and the National Collaborative Chicago-based Congenital Toxoplasmosis Study [NCCCTS], Toxoplasmosis Center, Chicago, IL, 773-834-4130, eFax 773-834 3577 and rmcleod@midway.uchicago.edu).

Screening

The value of routine toxoplasmosis screening programs is debated in the United States but generally accepted in other countries. In countries such as France where pregnant people are universally screened and treated, offspring who acquire toxoplasmosis are reported to have primarily mild disease and rarely severe disease. In contrast, in countries without a universal screening program (e.g., United States), offspring who acquire toxoplasmosis mostly present with severe disease.[95]

Toxoplasmosis is not a nationally notifiable illness, is only reportable in eight states, and case definitions vary.[12]

Preventing Congenital Infection: Initial Therapy and Surveillance

Pregnant people with HIV who have evidence of primary toxoplasmic infection, without TE, should be evaluated and managed during pregnancy in consultation with appropriate specialists **(BIII).** Recent studies support treatment of toxoplasmosis during pregnancy in an effort to decrease congenital transmission and reduce the severity of clinical signs in the offspring.[96-102]

In the setting of primary infection during pregnancy or symptomatic reactivation of *T. gondii*, initial therapy depends on the gestational age at time of acquisition/reactivation.

- For patients presumed to have acquired/reactivated infection at less than 14 weeks gestation, spiramycin is recommended to prevent congenital transmission **(AII).** Spiramycin is not commercially available in the United States. To obtain spiramycin, the provider must call the U.S. Food and Drug Administration directly (301-796-1400) after consultation with PAMF-TSL or NCCCTS (see Diagnosis During Pregnancy for contact information). A clinical pharmacist will assist with the proper paperwork.
- For patients presumed to have acquired/reactivated infection at 14 weeks gestation or beyond, pyrimethamine plus sulfadiazine plus leucovorin is recommended, as the risk of fetal transmission is higher **(AII).** If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, a combination of TMP-SMX, spiramycin, and leucovorin should be utilized in place of pyrimethamine-sulfadiazine **(BII).**[103,104]

For pregnant people with suspected primary or symptomatic reactivation of *T. gondii* during pregnancy, detailed ultrasound examination of the fetus specifically evaluating for hydrocephalus, cerebral calcifications, and growth restriction should be done monthly regardless of gestational age at the time of diagnosis **(AIII).**[93] In addition, patients should undergo an amniocentesis with PCR testing for *T. gondii* DNA in the amniotic fluid.[105] Amniocentesis does not appear to increase the risk of perinatal HIV transmission, particularly in people receiving ARV therapy.[106] Therefore, PCR of amniotic fluid can be considered during gestation in pregnant people on ARV therapy with serologic evidence of recently acquired *Toxoplasma* infection; people suspected to have reactivated their *Toxoplasma* latent infection during pregnancy; and those with ultrasound findings suggestive of fetal *T. gondii* infection **(BIII).**[93] In an effort to minimize false-negative results, amniotic fluid testing for *T. gondii* PCR should be avoided at less than 18-week gestation.[107]

Congenital Infection

For patients whose evaluations do not suggest congenital infection (i.e., no ultrasound findings and negative amniotic fluid PCR), initial therapy should be continued until delivery. For patients started on spiramycin as initial therapy who are found to have a positive PCR in the amniotic fluid and/or ultrasound findings concerning for congenital transmission, therapy should be escalated to pyrimethamine/sulfadiazine/leucovorin **(AII),** or if pyrimethamine is unavailable, TMP-SMX, spiramycin, and leucovorin **(AII).**

Pediatric-care providers should be informed about birthing parents with HIV who have suspected or confirmed *T. gondii* infection to allow evaluation of their neonates for evidence of congenital infection **(AIII).**

Toxoplasma Encephalitis During Pregnancy

Treatment of pregnant people with TE should be the same as in nonpregnant adults **(BIII),** including pyrimethamine plus sulfadiazine plus leucovorin **(AI),** and in consultation with appropriate specialists **(BIII).**[2,47-49] In general pyrimethamine should be avoided in the first trimester of pregnancy because of teratogenicity concerns, but in the case of TE, the benefit of using pyrimethamine to the mother outweighs the risk to the fetus. Of note, this regimen is often used in the treatment of fetuses with toxoplasmosis.[93] The preferred alternative regimen for pregnant patients with TE who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin **(AI).**[47,48] If pyrimethamine is unavailable or cannot be obtained without delay due to costs or other factors, TMP-SMX should be utilized in place of pyrimethamine-sulfadiazine or pyrimethamine-clindamycin **(BI).**

Prophylaxis During Pregnancy

The indications for primary prophylaxis for TE during pregnancy, and the medications and dosages used, are the same as for nonpregnant individuals with HIV. TMP-SMX is the preferred therapy. The risks of TMP-SMX in the first trimester, as discussed for PCP, must be balanced against the risk of TE. Secondary prophylaxis should be provided, using the same indications as for nonpregnant people. Over the past several decades, dapsone (also used for primary prophylaxis) has been used safely in pregnancy to treat leprosy, malaria, and various dermatologic conditions.[108,109] Dapsone appears to cross the placenta.[108,110]

When providing preconception care for people of pregnancy potential with HIV and receiving TE prophylaxis, providers should discuss the option of deferring pregnancy until TE prophylaxis can be safely discontinued **(BIII).**

Pregnancy-Specific Medication Concerns

Spiramycin is recommended to prevent transmission at <14 weeks gestation in the setting of acute primary infection during pregnancy or symptomatic reactivation of *T. gondii* **(AII).**[101,103,111] Spiramycin is not commercially available in the United States. Please see Preventing Congenital Infection: Initial Therapy and Surveillance on how to obtain spiramycin.

Pyrimethamine to prevent transmission should be avoided in the first trimester because of teratogenicity concerns with birth defects in animals, however it is recommended as first-line treatment for maternal TE **(BIII),** where the benefit of using pyrimethamine in a pregnant person outweighs the risk to the fetus. Additionally, pyrimethamine is often used in the setting of a positive fetal diagnosis.[112,113] Pyrimethamine can be administered to pregnant people after the first trimester since human data have not suggested an increased risk of birth defects.[89,114-117]

Sulfadiazine appears safe in pregnancy, without clear evidence of adverse fetal or neonatal outcome.[118,119] Although there are no studies published to date directly linking late third-trimester maternal sulfadiazine to neonatal death or kernicterus, the infant's care provider should be notified of maternal sulfa use in late pregnancy.

Clindamycin, suggested as part of an alternative regimen for patients with TE, is considered safe throughout pregnancy. Atovaquone, used both for prophylaxis and treatment of TE, may be used if indicated. While there are limited data on atovaquone safety in human pregnancy, preclinical studies

have not demonstrated maternal or fetal toxicity.[115] As noted above, dapsone has been used safely in pregnant persons for TE prophylaxis though with long-term therapy, there is a risk of mild hemolysis and a potential—although extremely low—risk of hemolytic anemia in exposed fetuses with glucose-6-phosphate dehydrogenase (or G6PD) deficiency.[108,120]

A detailed discussion of TMP-SMX and pregnancy is reviewed in the PCP chapter.

References

1. Luft BJ, Conley F, Remington JS, et al. Outbreak of central-nervous-system toxoplasmosis in western Europe and North America. *Lancet*. 1983;1(8328):781-784. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6132129.

2. Luft BJ, Hafner R, Korzun AH, et al. Toxoplasmic encephalitis in patients with the acquired immunodeficiency syndrome. Members of the ACTG 077p/ANRS 009 Study Team. *N Engl J Med*. 1993;329(14):995-1000. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8366923.

3. Wong B, Gold JW, Brown AE, et al. Central-nervous-system toxoplasmosis in homosexual men and parenteral drug abusers. *Ann Intern Med*. 1984;100(1):36-42. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6691657.

4. Israelski DM, Chmiel JS, Poggensee L, Phair JP, Remington JS. Prevalence of *Toxoplasma* infection in a cohort of homosexual men at risk of AIDS and toxoplasmic encephalitis. *J Acquir Immune Defic Syndr*. 1993;6(4):414-418. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8455146.

5. Boyer KM, Holfels E, Roizen N, et al. Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening. *Am J Obstet Gynecol*. 2005;192(2):564-571. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15696004.

6. Siegel SE, Lunde MN, Gelderman AH, et al. Transmission of toxoplasmosis by leukocyte transfusion. *Blood*. 1971;37(4):388-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/4927414.

7. Gay J, Gendron N, Verney C, et al. Disseminated toxoplasmosis associated with hemophagocytic syndrome after kidney transplantation: a case report and review. *Transpl Infect Dis*. 2019;21(5):e13154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31373746.

8. Ramanan P, Scherger S, Benamu E, et al. Toxoplasmosis in non-cardiac solid organ transplant recipients: a case series and review of literature. *Transpl Infect Dis*. 2020;22(1):e13218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31769583.

9. Vanjak A, Canoui E, Honsel V, et al. Early primary toxoplasmosis transmitted by liver graft: a case report. *Infect Dis Now*. 2021;51(3):315-316. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33934813.

10. Safarpour H, Cevik M, Zarean M, et al. Global status of *Toxoplasma gondii* infection and associated risk factors in people living with HIV. *AIDS*. 2020;34(3):469-474. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31714356.

11. Jones JL, Kruszon-Moran D, Elder S, et al. *Toxoplasma gondii* infection in the United States, 2011–2014. *Am J Trop Med Hyg*. 2018;98(2):551-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29260660.

12. McCall J, Rothfeldt L, Giesbrecht K, et al. Public health surveillance and reporting for human toxoplasmosis - six states, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71(28):889-893. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35834417.

13. Abgrall S, Rabaud C, Costagliola D, Clinical Epidemiology Group of the French Hospital Database on HIV. Incidence and risk factors for toxoplasmic encephalitis in human immunodeficiency virus-infected patients before and during the highly active antiretroviral therapy era. *Clin Infect Dis*. 2001;33(10):1747-1755. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11595976.

14. Leport C, Chene G, Morlat P, et al. Pyrimethamine for primary prophylaxis of toxoplasmic encephalitis in patients with human immunodeficiency virus infection: a double-blind, randomized trial. ANRS 005-ACTG 154 Group Members. Agence Nationale de Recherche sur le SIDA. AIDS Clinical Trial Group. *J Infect Dis*. 1996;173(1):91-97. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8537688.

15. Luft BJ, Brooks RG, Conley FK, McCabe RE, Remington JS. Toxoplasmic encephalitis in patients with acquired immune deficiency syndrome. *JAMA*. 1984;252(7):913-917. Available at: https://www.pubmed.ncbi.nlm.nih.gov/6748191.

16. Gray F, Gherardi R, Wingate E, et al. Diffuse "encephalitic" cerebral toxoplasmosis in AIDS. Report of four cases. *J Neurol*. 1989;236(5):273-277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2760644.

17. Kupfer MC, Zee CS, Colletti PM, Boswell WD, Rhodes R. MRI evaluation of AIDS-related encephalopathy: toxoplasmosis vs. lymphoma. *Magn Reson Imaging*. 1990;8(1):51-57. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2325518.

18. Pierce MA, Johnson MD, Maciunas RJ, et al. Evaluating contrast-enhancing brain lesions in patients with AIDS by using positron emission tomography. *Ann Intern Med*. 1995;123(8):594-598. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7677300.

19. Ruiz A, Ganz WI, Post MJ, et al. Use of thallium-201 brain SPECT to differentiate cerebral lymphoma from *Toxoplasma* encephalitis in AIDS patients. *AJNR Am J Neuroradiol*. 1994;15(10):1885-1894. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7863938.

20. Derouin F, Leport C, Pueyo S, et al. Predictive value of *Toxoplasma gondii* antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. ANRS 005/ACTG 154 Trial Group. *AIDS*. 1996;10(13):1521-1527. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8931787.

21. Conley FK, Jenkins KA, Remington JS. *Toxoplasma gondii* infection of the central nervous system. Use of the peroxidase-antiperoxidase method to demonstrate *Toxoplasma* in formalin fixed, paraffin embedded tissue sections. *Hum Pathol*. 1981;12(8):690-698. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7026410.

22. Robert-Gangneux F, Darde ML. Epidemiology of and diagnostic strategies for toxoplasmosis. *Clin Microbiol Rev*. 2012;25(2):264-296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22491772.

23. Novati R, Castagna A, Morsica G, et al. Polymerase chain reaction for *Toxoplasma gondii* DNA in the cerebrospinal fluid of AIDS patients with focal brain lesions. *AIDS*. 1994;8(12):1691-1694. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7888118.

24. Cinque P, Scarpellini P, Vago L, Linde A, Lazzarin A. Diagnosis of central nervous system complications in HIV-infected patients: cerebrospinal fluid analysis by the polymerase chain reaction. *AIDS*. 1997;11(1):1-17. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9110070.

25. Mesquita RT, Ziegler AP, Hiramoto RM, Vidal JE, Pereira-Chioccola VL. Real-time quantitative PCR in cerebral toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *J Med Microbiol*. 2010;59(Pt 6):641-647. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20150319.

26. Ciricillo SF, Rosenblum ML. Use of CT and MR imaging to distinguish intracranial lesions and to define the need for biopsy in AIDS patients. *J Neurosurg*. 1990;73(5):720-724. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2213162.

27. Raffi F, Aboulker JP, Michelet C, et al. A prospective study of criteria for the diagnosis of toxoplasmic encephalitis in 186 AIDS patients. The BIOTOXO Study Group. *AIDS*. 1997;11(2):177-184. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9030364.

28. Antinori A, Ammassari A, De Luca A, et al. Diagnosis of AIDS-related focal brain lesions: a decision-making analysis based on clinical and neuroradiologic characteristics combined with polymerase chain reaction assays in CSF. *Neurology*. 1997;48(3):687-694. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9065549.

29. Antinori A, De Rossi G, Ammassari A, et al. Value of combined approach with thallium-201 single-photon emission computed tomography and Epstein-Barr virus DNA polymerase chain reaction in CSF for the diagnosis of AIDS-related primary CNS lymphoma. *J Clin Oncol*. 1999;17(2):554-560. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10080599.

30. Corcoran C, Rebe K, van der Plas H, Myer L, Hardie DR. The predictive value of cerebrospinal fluid Epstein-Barr viral load as a marker of primary central nervous system lymphoma in HIV-infected persons. *J Clin Virol*. 2008;42(4):433-436. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18455472.

31. Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. *Neurology*. 1999;52(2):253-260. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9932940.

32. U.S. Department of Health and Human Services. FoodSafety.gov: your gateway to federal food safety information. Available at: https://www.foodsafety.gov.

33. Carr A, Tindall B, Brew BJ, et al. Low-dose trimethoprim-sulfamethoxazole prophylaxis for toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med*. 1992;117(2):106-111. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1351371.

34. Miro JM, Murray HW, Katlama C. Toxoplasmosis. In: AIDS Therapy. R. Dolin, H. Masur and M. S. Saag, ed Third. New York, New York: Churchill Livingstone. 2008:659-681.

35. Podzamczer D, Salazar A, Jimenez J, et al. Intermittent trimethoprim-sulfamethoxazole compared with dapsone-pyrimethamine for the simultaneous primary prophylaxis of Pneumocystis pneumonia and toxoplasmosis in patients infected with HIV. *Ann Intern Med*. 1995;122(10):755-761. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7717598.

36. Opravil M, Hirschel B, Lazzarin A, et al. Once-weekly administration of dapsone/pyrimethamine vs. aerosolized pentamidine as combined prophylaxis for Pneumocystis carinii pneumonia and toxoplasmic encephalitis in human immunodeficiency virus-infected patients. *Clin Infect Dis*. 1995;20(3):531-541. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7756472.

37. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. The PRIO Study Group. *N Engl J Med*. 1993;328(21):1514-1520. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8479488.

38. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. *N Engl J Med*. 1995;332(11):693-699. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7854375.

39. Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. 2000;182(2):611-615. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10915098.

40. Kirk O, Lundgren JD, Pedersen C, Nielsen H, Gerstoft J. Can chemoprophylaxis against opportunistic infections be discontinued after an increase in CD4 cells induced by highly active antiretroviral therapy? *AIDS*. 1999;13(13):1647-1651. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10509565.

41. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of toxoplasma encephalitis. Swiss HIV Cohort Study. *Lancet*. 2000;355(9222):2217-2218. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10881897.

42. Mussini C, Pezzotti P, Govoni A, et al. Discontinuation of primary prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in human immunodeficiency virus type I-infected patients: the changes in opportunistic prophylaxis study. *J Infect Dis*. 2000;181(5):1635-1642. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10823763.

43. Miro JM, Lopez JC, Podzamczer D, et al. Discontinuation of primary and secondary *Toxoplasma gondii* prophylaxis is safe in HIV-infected patients after immunological restoration with highly active antiretroviral therapy: results of an open, randomized, multicenter clinical trial. *Clin Infect Dis*. 2006;43(1):79-89. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16758422.

44. Miro J, Esteve A, Furrer H, Opportunistic Infection Team of the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord. Safety of stopping primary *T. gondii* prophylaxis with suppressed viremia and CD4>100. Presented at:

Conference on Retroviruses and Opportunistic Infections. 2016. Boston, MA. Available at: https://www.croiconference.org/sessions/safety-stopping-primary-t-gondii-prophylaxis-suppressed-viremia-and-cd4100.

45. Opportunistic Infections Project Team of the Collaboration of Observational HIVERiE, Mocroft A, Reiss P, et al. Is it safe to discontinue primary *Pneumocystis jiroveci* pneumonia prophylaxis in patients with virologically suppressed HIV infection and a CD4 cell count <200 cells/microL? *Clin Infect Dis*. 2010;51(5):611-619. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20645862.

46. Atkinson A, Miro JM, Mocroft A, et al. No need for secondary *Pneumocystis jirovecii* pneumonia prophylaxis in adult people living with HIV from Europe on ART with suppressed viraemia and a CD4 cell count greater than 100 cells/microL. *J Int AIDS Soc*. 2021;24(6):e25726. Available at: https://www.pubmed.ncbi.nlm.nih.gov/34118121.

47. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis*. 1996;22(2):268-275. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8838183.

48. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. The California Collaborative Treatment Group. *Ann Intern Med*. 1992;116(1):33-43. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1727093.

49. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the acquired immunodeficiency syndrome. Efficacy of long-term continuous therapy. *Am J Med*. 1988;84(1):94-100. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3337134.

50. Leport C, Meulemans A, Robine D, Dameron G, Vilde JL. Levels of pyrimethamine in serum and penetration into brain tissue in humans. *AIDS*. 1992;6(9):1040-1041. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1388895.

51. Van Delden C, Hirschel B. Folinic acid supplements to pyrimethamine-sulfadiazine for *Toxoplasma* encephalitis are associated with better outcome. *J Infect Dis*. 1996;173(5):1294-1295. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8627092.

52. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. Italian Collaborative Study Group. *Antimicrob Agents Chemother*. 1998;42(6):1346-1349. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9624473.

53. Pellegrino D, Gryschek R, de Oliveira ACP, Marcusso R, Correia A, Vidal JE. Efficacy and safety of trimethoprim-sulfamethoxazole in HIV-infected patients with cerebral toxoplasmosis in Brazil: a single-arm open-label clinical trial. *Int J STD AIDS*. 2019;30(12):1156-1162. Available at: https://www.pubmed.ncbi.nlm.nih.gov/31558125.

54. Beraud G, Pierre-Francois S, Foltzer A, et al. Cotrimoxazole for treatment of cerebral toxoplasmosis: an observational cohort study during 1994–2006. *Am J Trop Med Hyg*. 2009;80(4):583-587. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19346380.

55. Prosty C, Hanula R, Levin Y, Bogoch, II, McDonald EG, Lee TC. Revisiting the evidence base for modern-day practice of the treatment of toxoplasmic encephalitis: a systematic review and meta-analysis. *Clin Infect Dis*. 2023;76(3):e1302-e1319. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35944134.

56. Girard PM, Lepretre A, Detruchis P, Matheron S, Coulaud JP. Failure of pyrimethamine-clindamycin combination for prophylaxis of *Pneumocystis carinii* pneumonia. *Lancet*. 1989;1(8652):1459. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2567474.

57. Solensky R. Drug desensitization. *Immunol Allergy Clin North Am*. 2004;24(3):425-443, vi. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15242719.

58. Gluckstein D, Ruskin J. Rapid oral desensitization to trimethoprim-sulfamethoxazole (TMP-SMZ): use in prophylaxis for *Pneumocystis carinii* pneumonia in patients with AIDS who were previously intolerant to TMP-SMZ. *Clin Infect Dis*. 1995;20(4):849-853. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7795084.

59. Nguyen MT, Weiss PJ, Wallace MR. Two-day oral desensitization to trimethoprim-sulfamethoxazole in HIV-infected patients. *AIDS*. 1995;9(6):573-575. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7662195.

60. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis*. 2001;184(8):992-997. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11574913.

61. Demoly P, Messaad D, Sahla H, et al. Six-hour trimethoprim-sulfamethoxazole-graded challenge in HIV-infected patients. *J Allergy Clin Immunol*. 1998;102(6 Pt 1):1033-1036. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9847446.

62. Bonfanti P, Pusterla L, Parazzini F, et al. The effectiveness of desensitization versus rechallenge treatment in HIV-positive patients with previous hypersensitivity to TMP-SMX: a randomized multicentric study. C.I.S.A.I. Group. *Biomed Pharmacother*. 2000;54(1):45-49. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10721462.

63. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with acquired immunodeficiency syndrome: ACTG 237/ANRS 039 Study. AIDS Clinical Trials Group 237/Agence Nationale de Recherche sur le SIDA, Essai 039. *Clin Infect Dis*. 2002;34(9):1243-1250. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11941551.

64. Kovacs JA. Efficacy of atovaquone in treatment of toxoplasmosis in patients with AIDS. The NIAID-Clinical Center Intramural AIDS Program. *Lancet*. 1992;340(8820):637-638. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1355212.

65. Torres RA, Weinberg W, Stansell J, et al. Atovaquone for salvage treatment and suppression of toxoplasmic encephalitis in patients with AIDS. Atovaquone/Toxoplasmic Encephalitis Study Group. *Clin Infect Dis*. 1997;24(3):422-429. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9114194.

66. Katlama C, Mouthon B, Gourdon D, Lapierre D, Rousseau F. Atovaquone as long-term suppressive therapy for toxoplasmic encephalitis in patients with AIDS and multiple drug intolerance. Atovaquone Expanded Access Group. *AIDS*. 1996;10(10):1107-1112. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8874627.

67. Saba J, Morlat P, Raffi F, et al. Pyrimethamine plus azithromycin for treatment of acute toxoplasmic encephalitis in patients with AIDS. *Eur J Clin Microbiol Infect Dis*. 1993;12(11):853-856. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8112357.

68. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS*. 2001;15(5):583-589. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11316995.

69. Fernandez-Martin J, Leport C, Morlat P, Meyohas MC, Chauvin JP, Vilde JL. Pyrimethamine-clarithromycin combination for therapy of acute *Toxoplasma* encephalitis in patients with AIDS. *Antimicrob Agents Chemother*. 1991;35(10):2049-2052. Available at: https://www.pubmed.ncbi.nlm.nih.gov/1836943.

70. Dhiver C, Milandre C, Poizot-Martin I, Drogoul MP, Gastaut JL, Gastaut JA. 5-Fluoro-uracil-clindamycin for treatment of cerebral toxoplasmosis. *AIDS*. 1993;7(1):143-144. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8442914.

71. Derouin F, Piketty C, Chastang C, Chau F, Rouveix B, Pocidalo JJ. Anti-*Toxoplasma* effects of dapsone alone and combined with pyrimethamine. *Antimicrob Agents Chemother*. 1991;35(2):252-255. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2024957.

72. Lacassin F, Schaffo D, Perronne C, Longuet P, Leport C, Vilde JL. Clarithromycin-minocycline combination as salvage therapy for toxoplasmosis in patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother*. 1995;39(1):276-277. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7695324.

73. Hagberg L, Palmertz B, Lindberg J. Doxycycline and pyrimethamine for toxoplasmic encephalitis. *Scand J Infect Dis*. 1993;25(1):157-160. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8460343.

74. Coleman B, Smith BR, Kapoor R, et al. Persistence of human immunodeficiency virus-associated cerebral toxoplasmosis lesions in successfully treated patients receiving combination antiretroviral therapy. *Open Forum Infect Dis*. 2023;10(5):ofad208. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37213420.

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

76. Pfeffer G, Prout A, Hooge J, Maguire J. Biopsy-proven immune reconstitution syndrome in a patient with AIDS and cerebral toxoplasmosis. *Neurology*. 2009;73(4):321-322. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19636053.

77. Tremont-Lukats IW, Garciarena P, Juarbe R, El-Abassi RN. The immune inflammatory reconstitution syndrome and central nervous system toxoplasmosis. *Ann Intern Med*. 2009;150(9):656-657. Available at: https://www.pubmed.ncbi.nlm.nih.gov/19414855.

78. Martin-Blondel G, Alvarez M, Delobel P, et al. Toxoplasmic encephalitis IRIS in HIV-infected patients: a case series and review of the literature. *J Neurol Neurosurg Psychiatry*. 2011;82(6):691-693. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20660912.

79. Cabral RF, Valle Bahia PR, Gasparetto EL, Chimelli L. Immune reconstitution inflammatory syndrome and cerebral toxoplasmosis. *AJNR Am J Neuroradiol*. 2010;31(7):E65-66. Available at: https://www.pubmed.ncbi.nlm.nih.gov/20507930.

80. van Bilsen WPH, van den Berg C, Rijnders BJA, et al. Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients. *AIDS*. 2017;31(10):1415-1424. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28375874.

81. Jordan MK, Burstein AH, Rock-Kress D, et al. Plasma pharmacokinetics of sulfadiazine administered twice daily versus four times daily are similar in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2004;48(2):635-637. Available at: https://www.pubmed.ncbi.nlm.nih.gov/14742225.

82. Podzamczer D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. Spanish Toxoplasmosis Study Group. *Eur J Clin Microbiol Infect Dis*. 2000;19(2):89-95. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10746493.

83. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS*. 2004;18(9):1342-1344. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15362670.

84. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med*. 1998;339(26):1889-1895. Available at: https://www.pubmed.ncbi.nlm.nih.gov/9862944.

85. Soriano V, Dona C, Rodriguez-Rosado R, Barreiro P, Gonzalez-Lahoz J. Discontinuation of secondary prophylaxis for opportunistic infections in HIV-infected patients receiving highly active antiretroviral therapy. *AIDS*. 2000;14(4):383-386. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10770540.

86. Bertschy S, Opravil M, Cavassini M, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect*. 2006;12(7):666-671. Available at: https://www.pubmed.ncbi.nlm.nih.gov/16774564.

87. Miro JM. Stopping secondary TE prophylaxis in suppressed patients with CD4 100–200 is not safe. Presented at: Conference on Retroviruses and Opportunistic Infections. 2017. Seattle, WA. Available at: https://www.croiconference.org/sessions/stopping-secondary-te-prophylaxis-suppressed-patients-cd4-100-200-not-safe.

88. Low incidence of congenital toxoplasmosis in children born to women infected with human immunodeficiency virus. European Collaborative Study and Research Network on Congenital Toxoplasmosis. *Eur J Obstet Gynecol Reprod Biol*. 1996;68(1-2):93-96. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8886688.

89. Dunn CS, Beyer C, Kieny MP, et al. High viral load and CD4 lymphopenia in rhesus and cynomolgus macaques infected by a chimeric primate lentivirus constructed using the env, rev, tat, and vpu genes from HIV-1 Lai. *Virology*. 1996;223(2):351-361. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8806570.

90. Li XL, Wei HX, Zhang H, Peng HJ, Lindsay DS. A meta analysis on risks of adverse pregnancy outcomes in *Toxoplasma gondii* infection. *PLoS One*. 2014;9(5):e97775. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24830795.

91. Dunn D, Wallon M, Peyron F, Petersen E, Peckham C, Gilbert R. Mother-to-child transmission of toxoplasmosis: risk estimates for clinical counselling. *Lancet*. 1999;353(9167):1829-1833. Available at: https://www.pubmed.ncbi.nlm.nih.gov/10359407.

92. Montoya JG. Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. *J Infect Dis*. 2002;185 Suppl 1:S73-82. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11865443.

93. Montoya JG, Remington JS. Management of *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2008;47(4):554-566. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18624630.

94. Mitchell CD, Erlich SS, Mastrucci MT, Hutto SC, Parks WP, Scott GB. Congenital toxoplasmosis occurring in infants perinatally infected with human immunodeficiency virus 1. *Pediatr Infect Dis J*. 1990;9(7):512-518. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2371084.

95. Peyron F, Mc Leod R, Ajzenberg D, et al. Congenital toxoplasmosis in France and the United States: one parasite, two diverging approaches. *PLoS Negl Trop Dis*. 2017;11(2):e0005222. Available at: https://www.pubmed.ncbi.nlm.nih.gov/28207736.

96. Cortina-Borja M, Tan HK, Wallon M, et al. Prenatal treatment for serious neurological sequelae of congenital toxoplasmosis: an observational prospective cohort study. *PLoS Med*. 2010;7(10). Available at: https://www.pubmed.ncbi.nlm.nih.gov/20967235.

97. Hotop A, Hlobil H, Gross U. Efficacy of rapid treatment initiation following primary *Toxoplasma gondii* infection during pregnancy. *Clin Infect Dis*. 2012;54(11):1545-1552. Available at: https://www.pubmed.ncbi.nlm.nih.gov/22460980.

98. Kieffer F, Wallon M, Garcia P, Thulliez P, Peyron F, Franck J. Risk factors for retinochoroiditis during the first 2 years of life in infants with treated congenital

toxoplasmosis. *Pediatr Infect Dis J*. 2008;27(1):27-32. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18162934.

99. Prusa AR, Kasper DC, Pollak A, Gleiss A, Waldhoer T, Hayde M. The Austrian Toxoplasmosis Register, 1992–2008. *Clin Infect Dis*. 2015;60(2):e4-e10. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25216688.

100. Syrocot Study Group, Thiebaut R, Leproust S, Chene G, Gilbert R. Effectiveness of prenatal treatment for congenital toxoplasmosis: a meta-analysis of individual patients' data. *Lancet*. 2007;369(9556):115-122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17223474.

101. Mandelbrot L, Kieffer F, Sitta R, et al. Prenatal therapy with pyrimethamine + sulfadiazine vs spiramycin to reduce placental transmission of toxoplasmosis: a multicenter, randomized trial. *Am J Obstet Gynecol*. 2018;219(4):386 e381-386 e389. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29870736.

102. Dunay IR, Gajurel K, Dhakal R, Liesenfeld O, Montoya JG. Treatment of toxoplasmosis: historical perspective, animal models, and current clinical practice. *Clin Microbiol Rev*. 2018;31(4). Available at: https://www.ncbi.nlm.nih.gov/pubmed/30209035.

103. Valentini P, Buonsenso D, Barone G, et al. Spiramycin/cotrimoxazole versus pyrimethamine/sulfonamide and spiramycin alone for the treatment of toxoplasmosis in pregnancy. *J Perinatol*. 2015;35(2):90-94. Available at: https://www.pubmed.ncbi.nlm.nih.gov/25211284.

104. Buonsenso D, Pata D, Turriziani Colonna A, et al. Spyramicine and trimethoprim-sulfamethoxazole combination to prevent mother-to-fetus transmission of *Toxoplasma gondii* infection in pregnant women: a 28-years single-center experience. *Pediatr Infect Dis J*. 2022;41(5):e223-e227. Available at: https://www.pubmed.ncbi.nlm.nih.gov/35175992.

105. de Oliveira Azevedo CT, do Brasil PE, Guida L, Lopes Moreira ME. Performance of polymerase chain reaction analysis of the amniotic fluid of pregnant women for diagnosis of congenital toxoplasmosis: a systematic review and meta-analysis. *PLoS One*. 2016;11(4):e0149938. Available at: https://www.pubmed.ncbi.nlm.nih.gov/27055272.

106. Mandelbrot L, Jasseron C, Ekoukou D, et al. Amniocentesis and mother-to-child human immunodeficiency virus transmission in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales French Perinatal Cohort. *Am J Obstet Gynecol*. 2009;200(2):160 e161-169. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18986640.

107. Romand S, Wallon M, Franck J, Thulliez P, Peyron F, Dumon H. Prenatal diagnosis using polymerase chain reaction on amniotic fluid for congenital toxoplasmosis. *Obstet Gynecol*. 2001;97(2):296-300. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11165598.

108. Brabin BJ, Eggelte TA, Parise M, Verhoeff F. Dapsone therapy for malaria during pregnancy: maternal and fetal outcomes. *Drug Saf*. 2004;27(9):633-648. Available at: https://www.pubmed.ncbi.nlm.nih.gov/15230645.

109. Newman RD, Parise ME, Slutsker L, Nahlen B, Steketee RW. Safety, efficacy and determinants of effectiveness of antimalarial drugs during pregnancy: implications for

prevention programmes in Plasmodium falciparum-endemic sub-Saharan Africa. *Trop Med Int Health*. 2003;8(6):488-506. Available at: https://www.pubmed.ncbi.nlm.nih.gov/12791054.

110. Zuidema J, Hilbers-Modderman ES, Merkus FW. Clinical pharmacokinetics of dapsone. *Clin Pharmacokinet*. 1986;11(4):299-315. Available at: https://www.pubmed.ncbi.nlm.nih.gov/3530584.

111. Schneider MO, Faschingbauer F, Kagan KO, et al. *Toxoplasma gondii* infection in pregnancy - recommendations of the Working Group on Obstetrics and Prenatal Medicine (AGG - Section on Maternal Disorders). *Geburtshilfe Frauenheilkd*. 2023;83(12):1431-1445. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38046526.

112. Remington JS MR, Thulliez P, Desmonts G. Toxoplasmosis. In: Infectious diseases of the fetus and newborn infant. Jack S Remington, Jerome O Klein, Christopher B Wilson and C. J. Baker, ed 6th. Amsterdam: Elsevier; 2007:947. 947. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2675473.

113. Practice bulletin no. 151: cytomegalovirus, parvovirus B19, varicella zoster, and toxoplasmosis in pregnancy. *Obstet Gynecol*. 2015;125(6):1510-1525. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26000539.

114. Peters PJ, Thigpen MC, Parise ME, Newman RD. Safety and toxicity of sulfadoxine/pyrimethamine: implications for malaria prevention in pregnancy using intermittent preventive treatment. *Drug Saf*. 2007;30(6):481-501. Available at: https://www.pubmed.ncbi.nlm.nih.gov/17536875.

115. Nosten F, McGready R, d'Alessandro U, et al. Antimalarial drugs in pregnancy: a review. *Curr Drug Saf*. 2006;1(1):1-15. Available at: https://www.pubmed.ncbi.nlm.nih.gov/18690910.

116. Wong SY, Remington JS. Toxoplasmosis in pregnancy. *Clin Infect Dis*. 1994;18(6):853-861; quiz 862. Available at: https://www.pubmed.ncbi.nlm.nih.gov/8086543.

117. Deen JL, von Seidlein L, Pinder M, Walraven GE, Greenwood BM. The safety of the combination artesunate and pyrimethamine-sulfadoxine given during pregnancy. *Trans R Soc Trop Med Hyg*. 2001;95(4):424-428. Available at: https://www.pubmed.ncbi.nlm.nih.gov/11579889.

118. Baskin CG, Law S, Wenger NK. Sulfadiazine rheumatic fever prophylaxis during pregnancy: does it increase the risk of kernicterus in the newborn? *Cardiology*. 1980;65(4):222-225. Available at: https://www.pubmed.ncbi.nlm.nih.gov/7388849.

119. Yu PA, Tran EL, Parker CM, et al. Safety of antimicrobials during pregnancy: a systematic review of antimicrobials considered for treatment and postexposure prophylaxis of plague. *Clin Infect Dis*. 2020;70(70 Suppl 1):S37-S50. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32435799.

120. Thornton YS, Bowe ET. Neonatal hyperbilirubinemia after treatment of maternal leprosy. *South Med J*. 1989;82(5):668. Available at: https://www.pubmed.ncbi.nlm.nih.gov/2717998.

Varicella-Zoster Virus Diseases

Updated: September 7, 2022
Reviewed: January 10, 2024

Epidemiology

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

Clinical Manifestations

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

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

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

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

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

Acute retinal necrosis (ARN) and progressive outer retinal necrosis (PORN) are variants of necrotizing retinopathy caused by VZV. Although ARN can occur in both immunocompetent and immunocompromised patients, PORN occurs almost exclusively[20] in patients with AIDS with CD4 counts <100 cells/mm^3. In contrast to ARN, PORN is characterized by minimal inflammation in the aqueous and vitreous humor, absence of occlusive retinal vasculitis, and multiple discrete peripheral lesions that manifest initially as yellow foci of retinal opacification in the outer retinal layers.[21] PORN lesions rapidly coalesce, causing full-thickness retinal necrosis and subsequent retinal detachment.[22] Both ARN and PORN are associated with high rates of loss of vision.

People with HIV who have CD4 counts <200 cells/mm^3 are at highest risk of herpes zoster–related complications, including disseminated herpes zoster.[23] The central nervous system (CNS) is a target organ for herpes zoster dissemination in patients coinfected with HIV. Various VZV-related neurologic syndromes occur in people with HIV, including CNS vasculitis, multifocal leukoencephalitis, ventriculitis, myelitis and myeloradiculitis, optic neuritis, cranial nerve palsies and focal brain-stem lesions, and aseptic meningitis.[24]

Diagnosis

Varicella and herpes zoster are typically distinctive in appearance and usually can be diagnosed clinically. Varicella also can be diagnosed retrospectively by documenting seroconversion (i.e., immunoglobulin G [IgG] antibody negative to positive). In immunocompromised persons, varicella may be difficult to distinguish from disseminated herpes zoster (as opposed to dermatomal herpes zoster); a history of VZV exposure, a rash that began with a dermatomal pattern, and VZV serologic testing to assess prior VZV infection may be helpful to distinguish disseminated herpes zoster from varicella. When lesions are atypical or difficult to distinguish from those due to other potential etiologies (including herpes simplex virus [HSV]), swabs of vesicular fluid from a fresh lesion or tissue biopsies can be submitted for viral culture, direct fluorescent antigen testing, or polymerase

chain reaction (PCR). Additionally, scabs may be adequate specimens for PCR testing. PCR of lesions is the most sensitive and specific method for diagnosis of VZV infections. Histopathology and PCR (of blood or fluids, such as cerebrospinal fluid or vitreous humor) can aid with diagnosis of VZV infections of visceral organs (e.g., pneumonitis, encephalitis, retinitis).[25]

Preventing Exposure

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

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

Preventing Disease

Vaccination to Prevent Primary Infection (Varicella)

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

VZV-seronegative adults are potential candidates for varicella vaccination. Some experts would serologically screen adults with HIV without a history of prior varicella or varicella vaccination for VZV IgG. However, the value of this approach may be limited by the lack of sensitivity of commercially available VZV antibody assays (particularly for vaccine-induced antibody).[32,33] No studies have evaluated the vaccine in adolescents or adults with HIV, but many experts recommend varicella vaccination (2 doses, administered 3 months apart) for VZV-susceptible people with HIV aged ≥18 years with CD4 counts ≥200 cells/mm^3 **(BIII).**[34] If varicella vaccination results in disease caused by vaccine virus (a rare event), therapy with acyclovir is recommended **(AIII).** Administration of varicella vaccine to more severely immunocompromised people with HIV (CD4 counts <200 cells/mm^3) is **contraindicated (AIII).** Given the high prevalence of VZV seropositivity in adults, administration of varicella vaccine for adults will be infrequent.

If post-exposure varicella-zoster immune globulin (VariZIG™) has been administered, an interval of at least 5 months is recommended before varicella vaccination **(CIII).**[35] If post-exposure acyclovir has been administered, an interval of at least 3 days is recommended before varicella vaccination **(CIII).**

Pre-Exposure Prophylaxis to Prevent Primary Infection (Varicella)

Long-term prophylaxis with anti-VZV drugs, such as acyclovir or valacyclovir, to prevent varicella **is not recommended (AIII).**

Post-Exposure Prophylaxis to Prevent Primary Infection (Varicella)

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

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

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

Vaccination to Prevent Reactivation Disease (Herpes Zoster)

One U.S. Food and Drug Administration (FDA)-approved vaccine is currently available for the prevention of herpes zoster in immunocompetent adults. In 2017, a subunit vaccine containing recombinant VZV glycoprotein E (gE) and adjuvant AS01B (i.e., recombinant zoster vaccine [RZV] Shingrix) was FDA approved and recommended by the Advisory Committee on Immunization Practices (ACIP) to prevent herpes zoster in immunocompetent adults aged ≥50 years, given on a 2-dose schedule.[39] The approval and recommendation for the vaccine were based on pivotal Phase 3 randomized, placebo-controlled clinical trials involving >30,000 participants aged ≥50 years in which the vaccine efficacy against herpes zoster in vaccinated participants was 97.2% overall and 91.3% in those aged ≥70 years.[40,41] The most common solicited adverse reactions in vaccine recipients were pain (78% of recipients), myalgia (45%), and fatigue (45%), with Grade 3 injection site reactions (pain, redness, and swelling) reported in 9.4% of vaccine recipients and Grade 3 solicited systemic events (myalgia, fatigue, headache, fever, and gastrointestinal symptoms) reported

by 10.8% of vaccine recipients.[39,42] Systemic Grade 3 reactions were reported more frequently after Dose 2 than after Dose 1.[42]

Data on use of RZV in people with HIV are limited. A Phase 1/2 randomized, placebo-controlled study enrolled 94 adults with HIV receiving ART[43] with CD4 count ≥200 cells/mm^3, 14 adults receiving ART with CD4 count <200 cells/mm^3, and 15 ART-naive adults with CD4 count ≥500 cells/mm^3. The participants' median age was 46 years. Participants received the vaccine in three doses administered at 0, 2, and 6 months. The vaccine increased humoral and cell-mediated immunity to VZV gE after two doses, including among people with CD4 counts <200 cells/mm^3. The most common side effects included pain at the injection sites (98.6% of participants, 16.4% Grade 3), fatigue (75.3%, 16.4% Grade 3), myalgia (74.0%, 13.7% Grade 3), and headache (64.4%, 8.2% Grade 3). No vaccine-related severe adverse events occurred during follow-up. Based on these very limited data in people with HIV, the vaccine appears safe and immunogenic. No efficacy data are available for the RZV among people with HIV.

Given that the risk of herpes zoster is high among people with HIV, and the vaccine appears safe, administration of RZV to people with HIV 18 years of age and older is recommended following the FDA-approved schedule for persons without HIV (intramuscular [IM] dose at 0 and 2–6 months) **(AIII).**

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

RZV is not a treatment of herpes zoster and should not be given during acute episodes **(AIII).** It also should not be given to individuals with VZV-related inflammatory eye disease (keratitis or anterior uveitis) during episodes of active inflammation **(AIII).**

A 1-dose attenuated live-zoster virus vaccine (i.e., zoster vaccine live [ZVL], Zostavax®) for prevention of herpes zoster was FDA approved for use in immunocompetent adults aged ≥50 years. However, as of November 18, 2020, it is no longer available for use in the United States, and recommendations for its use have been removed from these guidelines. Those who previously received ZVL should be revaccinated with RZV.

Treating Disease

Varicella

No controlled prospective studies of antiviral therapy for varicella in adults with HIV have been reported. For uncomplicated varicella, the preferred treatment options are valacyclovir (1 g PO three times daily) or famciclovir (500 mg PO three times daily), initiated as early as possible after lesion onset and continued for 5 to 7 days **(AII).** Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) is an alternative **(BII).** Intravenous (IV) acyclovir 10 mg/kg every 8 hours for 7 to 10 days is the recommended initial treatment for people with HIV with severe or complicated varicella **(AIII).**[15,44,45] If no evidence of visceral involvement with VZV is apparent, many experts recommend switching from IV to oral antiviral therapy after the patient has defervesced **(BIII).**[46]

Herpes Zoster

Antiviral therapy should be instituted as soon as possible for all people with HIV with herpes zoster diagnosed within 1 week of rash onset (or any time prior to full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in people with HIV are oral valacyclovir **(AII),** famciclovir **(AII),** or acyclovir **(BII)** (doses as above) for 7 to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. If cutaneous lesions are extensive or if visceral involvement is suspected, IV acyclovir should be initiated and continued until clinical improvement is evident **(AII).**[47] A switch from IV acyclovir to oral antiviral therapy (to complete a 10- to 14-day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral VZV infection are improving **(BIII).** Adjunctive corticosteroid therapy for herpes zoster in people with HIV **is not recommended** because no data support its benefit in this population **(AIII).**

In patients with HZO, both stromal keratitis and anterior uveitis require treatment with topical corticosteroids; in many cases, chronic, low-dose topical corticosteroid therapy is necessary to maintain suppression of inflammation. Recurrences or exacerbations of inflammation are common. A role for antiviral agents in the management of chronic keratitis and uveitis has not been established.

ARN should be treated promptly with antiviral therapy. One treatment recommended by some experts is high-dose IV acyclovir (10 mg/kg every 8 hours for 10 to 14 days), followed by prolonged high-dose oral valacyclovir (1 g three times daily) **(AIII).** High-dose oral antiviral treatment for at least 14 weeks has been shown to decrease the risk of second eye involvement among those who present with unilateral ARN syndrome;[48,49] **(AIII)** however, many ophthalmologists and infectious disease specialists will continue oral antiviral therapy for much longer. Many experts would also include an intravitreous injection of ganciclovir as part of the initial induction therapy. Additional intravitreous injections can be given if there is concern for lack of treatment response, but injections should not be more frequent than twice weekly **(BIII).** Use of oral valaciclovir instead of IV acyclovir for initial treatment has been reported. This approach should be used with caution because serum drug levels with oral treatment will not be as high as those achieved with IV administration **(CIII).** Involvement of an experienced ophthalmologist in the management of patients with VZV ocular disease is strongly recommended **(AIII).**

Optimal antiviral therapy for PORN remains undefined and should be managed in consultation with an experienced ophthalmologist **(AIII).**[50-52] Outcomes with IV acyclovir or ganciclovir monotherapy were poor. Better results were obtained with IV ganciclovir (or the combination of ganciclovir plus foscarnet), along with intravitreal antiviral drug injections.[22,51,53] Specific treatment should include systemic therapy with at least one IV drug (either acyclovir or ganciclovir) **(AIII)** coupled with injections of at least one intravitreal drug (ganciclovir or foscarnet) **(BIII).**[53,54] Intravitreal cidofovir should not be used because such injections may be associated with loss of intraocular pressure and other adverse effects. Ganciclovir ocular implants previously recommended by some experts are no longer manufactured. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

When to Start Antiretroviral Therapy

All people with HIV should receive ART as soon as possible after diagnosis of HIV infection. The presence of disease caused by VZV is not an indication to defer or discontinue ART **(AIII).**

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

For monitoring and adverse event recommendations related to anti-herpesvirus drugs, see preceding guideline sections on Herpes Simplex Virus and Cytomegalovirus.

Initiation of ART appears to be associated with an increased frequency of VZV reactivation, peaking at about 3 months after ART initiation.[7,13,14,55,56] Observational studies have shown the risk of herpes zoster to increase twofold to fourfold between 4 and 16 weeks after initiating ART. The clinical presentation and natural history of herpes zoster in the setting of immune reconstitution is similar to that observed in other people with HIV, and episodes of herpes zoster in either setting should be managed in the same manner.

Managing Treatment Failure

Treatment failure caused by resistance of VZV to acyclovir and related drugs (e.g., famciclovir, ganciclovir) is rare, but should be suspected when clinical findings do not improve within 7 days of initiation of therapy or when skin lesions have an atypical (e.g., verrucous) appearance. A viral culture should be obtained, and if VZV is isolated, susceptibility testing performed to establish antiviral drug susceptibility and to document the need for alternative therapy. Among patients with suspected or proven acyclovir-resistant VZV infections, treatment with IV foscarnet is recommended **(AII).**[57] IV cidofovir is a potential alternative **(CIII).** Both foscarnet and cidofovir are nephrotoxic agents and should be given in consultation with an expert in infectious diseases.

Special Considerations During Pregnancy

Pregnant women with HIV who are susceptible to VZV and are in close contact with a person with active varicella or herpes zoster should receive VariZIG as soon as possible (within 10 days)[36] after exposure to VZV **(AIII).** If oral acyclovir is used for post-exposure prophylaxis, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV **(CIII).** Pregnant women should not receive varicella vaccine **(AIII).**

For pregnant women without HIV with varicella, the risk of transmitting VZV to the infant resulting in congenital varicella syndrome is 0.4% when varicella infection occurs at or before 12 weeks gestation, 2.2% with infection at 13 to 20 weeks, and negligible with infection after 20 weeks.[58] Women with varicella during the first half of pregnancy should be counseled about the risks to the fetus and offered detailed ultrasound surveillance for findings indicative of fetal congenital varicella syndrome.[58] Administration of VariZIG is recommended primarily to prevent complications in the mother; whether it has any benefit in prevention of congenital varicella syndrome is unknown. VariZIG should be administered to infants born to women who have varicella from 5 days before delivery to 2 days after delivery to reduce the severity and mortality of neonatal varicella acquired by exposure to maternal viremia **(AIII).**

Oral acyclovir or valacyclovir are the preferred treatments for pregnant women with HIV who have uncomplicated varicella during pregnancy **(BIII).** Pregnant women with HIV who have severe varicella or who exhibit signs or symptoms of VZV pneumonitis should be hospitalized and treated with IV acyclovir (10 mg/kg every 8 hours) **(AII).**

No controlled studies of antiviral therapy of herpes zoster during pregnancy have been reported. Recommended therapy for uncomplicated herpes zoster in pregnant women with HIV is oral

acyclovir or valacyclovir **(BIII).** Pregnant women should not receive the herpes zoster vaccine **(AIII).**

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

Pre-Exposure Prevention of VZV Primary Infection

Indications

- Adults and adolescents with HIV who have CD4 counts ≥200 cells/mm^3 and who do not have documentation of varicella vaccination, a history or diagnosis of varicella or herpes zoster confirmed by a health care provider, or laboratory confirmation of VZV disease; and anyone with HIV who is VZV seronegative should avoid exposure to persons with varicella or herpes zoster (CIII).

Vaccination

- Household contacts who are VZV-susceptible should be vaccinated to prevent potential transmission of VZV to at-risk people with HIV (BIII).
- In VZV-seronegative persons aged ≥18 years with CD4 counts ≥200 cells/mm^3, administer primary varicella vaccination (Varivax™) in two doses (0.5 mL SQ) 3 months apart (BIII).
- If vaccination results in disease due to live-attenuated vaccine virus, treatment with acyclovir is recommended (AIII).
- If post-exposure VariZIG™ has been administered, wait ≥5 months before varicella vaccination (CIII).
- If post-exposure acyclovir has been administered, wait ≥3 days before varicella vaccination (CIII).
- Administration of varicella vaccine to severely immunocompromised people with HIV (CD4 counts <200 cells/mm3) is contraindicated (AIII).

Post-Exposure Prophylaxis of VZV Primary Infection

Indications

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

Preferred Prophylaxis

- VariZIG 125 IU/10 kg (maximum of 625 IU) IM, administered as soon as possible and within 10 days after exposure to a person with active varicella or herpes zoster (AIII)
- If post-exposure VariZIG has been administered, wait ≥5 months before varicella vaccination (CIII).

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

Alternative Prophylaxis (Begin 7-10 Days After Exposure)

- Acyclovir 800 mg PO 5 times daily for 5 to 7 days (BIII), *or*
- Valacyclovir 1 gm PO 3 times daily for 5 to 7 days (BIII)

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

Recommendations for Preventing and Treating Varicella-Zoster Virus Infections

Preventing Herpes Zoster (Shingles)

Vaccination

Recombinant zoster vaccine (RZV, Shingrix) is the only available vaccine for prevention of shingles in the United States. As of November 18, 2020, attenuated zoster vaccine live (ZVL, Zostavax) is no longer available for use in the United States.

RZV

Recommended in adults with HIV aged ≥18 years, regardless of CD4 count:

- RZV 0.5 mL IM injection—2-dose series at 0 and then at 2 to 6 months (AIII).
- RZV should not be given during an acute episode of herpes zoster (AIII).
- Following initiation of ART, some experts would delay RZV vaccination until patients are suppressed virologically on ART (CIII) or until CD4 count recovery (CIII) to maximize immunologic response to the vaccine.

Treating Varicella Infections

Primary Varicella Infection (Chickenpox)

Uncomplicated Cases

Preferred Therapy

- Valacyclovir 1 g PO 3 times a day (AII), *or*
- Famciclovir 500 mg PO 3 times a day (AII)

Alternative Therapy

- Acyclovir 800 mg PO 5 times daily (BII)

Duration

- 5 to 7 days

Severe or Complicated Cases

- Acyclovir 10 mg/kg IV every 8 hours for 7 to 10 days (AIII)
- May switch to oral famciclovir, valacyclovir, or acyclovir after defervescence if there is no evidence of visceral involvement (BIII)

Herpes Zoster (Shingles)

Acute, Localized, Dermatomal

Preferred Therapy

- Valacyclovir 1,000 mg PO 3 times a day (AII), *or*
- Famciclovir 500 mg PO 3 times a day (AII)

Alternative Therapy

- Acyclovir 800 mg PO 5 times daily (BII)

Duration

- 7 to 10 days; longer duration should be considered if lesions resolve slowly

Herpes Zoster Ophthalmitis (HZO)

Late dendriform lesions of the corneal epithelium should be treated with systemic or topical anti-herpetic medications (AIII).

Extensive Cutaneous Lesion or Visceral Involvement

- Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident (AII).
- Switch to oral therapy (valacyclovir 1 g 3 times a day, famciclovir 500 mg 3 times a day, or acyclovir 800 mg PO 5 times daily to complete a 10- to 14-day course) when formation of new lesions has ceased and signs and symptoms of visceral VZV infection are improving (BIII).

Acute Retinal Necrosis (ARN)

- Acyclovir 10 mg/kg IV every 8 hours for 10 to 14 days, followed by valacyclovir 1 g PO 3 times a day for ≥14 weeks (AIII). In addition, an intravitreous injection of ganciclovir (2 mg/0.05 mL) can be given as a part of initial treatment, and injections can be repeated at a frequency of twice weekly until there is evidence of a treatment response (BIII). Involvement of an experienced ophthalmologist is recommended (AIII).
- Use of oral valaciclovir instead of IV acyclovir for initial treatment has been reported, but this approach should be used with caution, because serum drug levels with oral treatment will not be as high as those achieved with IV administration (CIII).

Progressive Outer Retinal Necrosis (PORN)

- Involvement of an experienced ophthalmologist is strongly recommended (AIII).
- Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg every 12 hours plus ganciclovir 2 mg/0.05 mL and/or foscarnet 1.2 mg/0.05 mL intravitreal twice weekly (AIII)
- Optimize ARV regimen (AIII).
- Duration of therapy is not well defined and should be determined based on clinical, virologic, and immunologic responses in consultation with an ophthalmologist.

Note: Ganciclovir ocular implants are no longer commercially available.

Key: ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; HZO = herpes zoster ophthalmicus; IM = intramuscular; IU = international unit; IV = intravenous; IVIG = intravenous immunoglobulin; PO = orally; PORN = progressive outer retinal necrosis; RZV = recombinant zoster vaccine; SQ = subcutaneous; VariZIG = varicella zoster immune globulin; VZV = varicella zoster virus; ZVL = zoster vaccine live

References

1. Reynolds MA, Kruszon-Moran D, Jumaan A, Schmid DS, McQuillan GM. Varicella seroprevalence in the U.S.: data from the National Health and Nutrition Examination Survey, 1999-2004. *Public Health Rep*. 2010;125(6):860-869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21121231.

2. Guris D, Jumaan AO, Mascola L, et al. Changing varicella epidemiology in active surveillance sites—United States, 1995-2005. *J Infect Dis*. 2008;197 Suppl 2:S71-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18419413.

3. Buchbinder SP, Katz MH, Hessol NA, et al. Herpes zoster and human immunodeficiency virus infection. *J Infect Dis*. 1992;166(5):1153-1156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1308664.

4. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med*. 1995;155(15):1605-1609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7618983.

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

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

7. Grabar S, Tattevin P, Selinger-Leneman H, et al. Incidence of herpes zoster in HIV-infected adults in the combined antiretroviral therapy era: results from the FHDH-ANRS CO4 cohort. *Clin Infect Dis*. 2015;60(8):1269-1277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25601456.

8. Shearer K, Maskew M, Ajayi T, et al. Incidence and predictors of herpes zoster among antiretroviral therapy-naive patients initiating HIV treatment in Johannesburg, South Africa. *Int J Infect Dis*. 2014;23:56-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24680820.

9. Erdmann NB, Prentice HA, Bansal A, et al. Herpes zoster in persons living with HIV-1 infection: viremia and immunological defects are strong risk factors in the era of combination antiretroviral Therapy. *Front Public Health*. 2018;6:70. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29594092.

10. Jansen K, Haastert B, Michalik C, et al. Incidence and risk factors of herpes zoster among HIV-positive patients in the German Competence Network for HIV/AIDS (KompNet): a cohort study analysis. *BMC Infect Dis*. 2013;13:372. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23937603.

11. Blank LJ, Polydefkis MJ, Moore RD, Gebo KA. Herpes zoster among persons living with HIV in the current antiretroviral therapy era. *J Acquir Immune Defic Syndr*. 2012;61(2):203-207. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22766968.

12. Moanna A, Rimland D. Decreasing incidence of herpes zoster in the highly active antiretroviral therapy era. *Clin Infect Dis*. 2013;57(1):122-125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23487391.

13. Nacher M, Basurko C, Adenis A, et al. Predictive factors of herpes zoster HIV-infected patients: another adverse effect of crack cocaine. *PLoS One*. 2013;8(11):e80187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24244647.

14. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med*. 2001;110(8):605-609. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11382367.

15. Wallace MR, Hooper DG, Pyne JM, Graves SJ, Malone JL. Varicella immunity and clinical disease in HIV-infected adults. *South Med J*. 1994;87(1):74-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8284723.

16. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *J Pain*. 2008;9(1 Suppl 1):S3-9. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18166460.

17. Gnann JW, Jr., Crumpacker CS, Lalezari JP, et al. Sorivudine versus acyclovir for treatment of dermatomal herpes zoster in human immunodeficiency virus-infected patients: results from a randomized, controlled clinical trial. Collaborative Antiviral Study Group/AIDS Clinical Trials Group, Herpes Zoster Study Group. *Antimicrob Agents Chemother*. 1998;42(5):1139-1145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9593141.

18. Harrison RA, Soong S, Weiss HL, Gnann JW, Jr., Whitley RJ. A mixed model for factors predictive of pain in AIDS patients with herpes zoster. *J Pain Symptom Manage*. 1999;17(6):410-417. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10388246.

19. Hu AY, Strauss EC, Holland GN, Chan MF, Yu F, Margolis TP. Late varicella-zoster virus dendriform keratitis in patients with histories of herpes zoster ophthalmicus. *Am J Ophthalmol*. 2010;149(2):214-220 e213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19909942.

20. Engstrom RE, Jr., Holland GN, Margolis TP, et al. The progressive outer retinal necrosis syndrome. A variant of necrotizing herpetic retinopathy in patients with AIDS. *Ophthalmology*. 1994;101(9):1488-1502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8090452.

21. Ormerod LD, Larkin JA, Margo CA, et al. Rapidly progressive herpetic retinal necrosis: a blinding disease characteristic of advanced AIDS. *Clin Infect Dis*. 1998;26(1):34-45; discussion 46-37. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9455507.

22. Yin PD, Kurup SK, Fischer SH, et al. Progressive outer retinal necrosis in the era of highly active antiretroviral therapy: successful management with intravitreal injections and

monitoring with quantitative PCR. *J Clin Virol*. 2007;38(3):254-259. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17280866.

23. Veenstra J, van Praag RM, Krol A, et al. Complications of varicella zoster virus reactivation in HIV-infected homosexual men. *AIDS*. 1996;10(4):393-399. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8728043.

24. Gray F, Belec L, Lescs MC, et al. Varicella-zoster virus infection of the central nervous system in the acquired immune deficiency syndrome. *Brain*. 1994;117 (Pt 5):987-999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7953606.

25. Leung J, Harpaz R, Baughman AL, et al. Evaluation of laboratory methods for diagnosis of varicella. *Clin Infect Dis*. 2010;51(1):23-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20504232.

26. Levin MJ, Gershon AA, Weinberg A, et al. Administration of live varicella vaccine to HIV-infected children with current or past significant depression of CD4(+) T cells. *J Infect Dis*. 2006;194(2):247-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16779732.

27. Armenian SH, Han JY, Dunaway TM, Church JA. Safety and immunogenicity of live varicella virus vaccine in children with human immunodeficiency virus type 1. *Pediatr Infect Dis J*. 2006;25(4):368-370. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16567993.

28. Bekker V, Westerlaken GH, Scherpbier H, et al. Varicella vaccination in HIV-1-infected children after immune reconstitution. *AIDS*. 2006;20(18):2321-2329. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17117018.

29. Son M, Shapiro ED, LaRussa P, et al. Effectiveness of varicella vaccine in children infected with HIV. *J Infect Dis*. 2010;201(12):1806-1810. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20441519.

30. Marin M, Guris D, Chaves SS, et al. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2007;56(RR-4):1-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17585291.

31. Wood SM, Shah SS, Steenhoff AP, Rutstein RM. Primary varicella and herpes zoster among HIV-infected children from 1989 to 2006. *Pediatrics*. 2008;121(1):e150-156. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18086820.

32. Breuer J, Schmid DS, Gershon AA. Use and limitations of varicella-zoster virus-specific serological testing to evaluate breakthrough disease in vaccinees and to screen for susceptibility to varicella. *J Infect Dis*. 2008;197 Suppl 2:S147-151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18419389.

33. Ludwig B, Kraus FB, Allwinn R, Keim S, Doerr HW, Buxbaum S. Loss of varicella zoster virus antibodies despite detectable cell mediated immunity after vaccination. *Infection*. 2006;34(4):222-226. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16896582.

34. Centers for Disease Control and Prevention. Recommended adult immunization schedule: United States, 2010. *Ann Intern Med*. 2010;152(1):36-39. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20048270.

35. Centers for Disease Control and Prevention. A new product (VariZIG) for postexposure prophylaxis of varicella available under an investigational new drug application expanded access protocol. *MMWR Morb Mortal Wkly Rep*. 2006;55(8):209-210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16511443.

36. Centers for Disease C, Prevention. FDA approval of an extended period for administering VariZIG for postexposure prophylaxis of varicella. *MMWR Morb Mortal Wkly Rep*. 2012;61(12):212. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22456121.

37. American Academy of Pediatrics. Varicella-zoster virus infections. *In: Red Book: 2018–2021 Report of the Committee on Infectious Diseases*. 31st ed. 2018:869-883. Available at: https://redbook.solutions.aap.org/chapter.aspx?sectionid=189640215&bookid=2205.

38. Barnabas RV, Baeten JM, Lingappa JR, et al. Acyclovir prophylaxis reduces the incidence of herpes zoster among HIV-infected individuals: results of a randomized clinical trial. *J Infect Dis*. 2016;213(4):551-555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26142452.

39. Dooling KL, Guo A, Patel M, et al. Recommendations of the Advisory Committee on Immunization Practices for use of herpes zoster vaccines. *MMWR Morb Mortal Wkly Rep*. 2018;67(3):103-108. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29370152.

40. Lal H, Cunningham AL, Godeaux O, et al. Efficacy of an adjuvanted herpes zoster subunit vaccine in older adults. *N Engl J Med*. 2015;372(22):2087-2096. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25916341.

41. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the herpes zoster subunit vaccine in adults 70 years of age or older. *N Engl J Med*. 2016;375(11):1019-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27626517.

42. U.S. Food and Drug Administration. Shingrix [package insert]. 2017. Available at: https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM581605.pdf.

43. Berkowitz EM, Moyle G, Stellbrink HJ, et al. Safety and immunogenicity of an adjuvanted herpes zoster subunit candidate vaccine in HIV-infected adults: a phase 1/2a randomized, placebo-controlled study. *J Infect Dis*. 2015;211(8):1279-1287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25371534.

44. Prober CG, Kirk LE, Keeney RE. Acyclovir therapy of chickenpox in immunosuppressed children—a collaborative study. *J Pediatr*. 1982;101(4):622-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6750068.

45. Arvin AM. Antiviral therapy for varicella and herpes zoster. *Semin Pediatr Infect Dis*. 2002;13(1):12-21. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12118839.

46. Carcao MD, Lau RC, Gupta A, Huerter H, Koren G, King SM. Sequential use of intravenous and oral acyclovir in the therapy of varicella in immunocompromised children. *Pediatr Infect Dis J*. 1998;17(7):626-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9686730.

47. Balfour HH, Jr., Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med*. 1983;308(24):1448-1453. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6343861.

48. Palay DA, Sternberg P, Jr., Davis J, et al. Decrease in the risk of bilateral acute retinal necrosis by acyclovir therapy. *Am J Ophthalmol*. 1991;112(3):250-255. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1882936.

49. Jeon S, Kakizaki H, Lee WK, Jee D. Effect of prolonged oral acyclovir treatment in acute retinal necrosis. *Ocul Immunol Inflamm*. 2012;20(4):288-292. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22621210.

50. Scott IU, Luu KM, Davis JL. Intravitreal antivirals in the management of patients with acquired immunodeficiency syndrome with progressive outer retinal necrosis. *Arch Ophthalmol*. 2002;120(9):1219-1222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12215102.

51. Moorthy RS, Weinberg DV, Teich SA, et al. Management of varicella zoster virus retinitis in AIDS. *Br J Ophthalmol*. 1997;81(3):189-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9135381.

52. Austin RB. Progressive outer retinal necrosis syndrome: a comprehensive review of its clinical presentation, relationship to immune system status, and management. *Clin Eye Vis Care*. 2000;12(3-4):119-129. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11137426.

53. Kim SJ, Equi R, Belair ML, Fine HF, Dunn JP. Long-term preservation of vision in progressive outer retinal necrosis treated with combination antiviral drugs and highly active antiretroviral therapy. *Ocul Immunol Inflamm*. 2007;15(6):425-427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18085485.

54. Gore DM, Gore SK, Visser L. Progressive outer retinal necrosis: outcomes in the intravitreal era. *Arch Ophthalmol*. 2012;130(6):700-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22801826.

55. Dunic I, Djurkovic-Djakovic O, Vesic S, Zerjav S, Jevtovic D. Herpes zoster as an immune restoration disease in AIDS patients during therapy including protease inhibitors. *Int J STD AIDS*. 2005;16(7):475-478. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16004625.

56. Espinosa E, Pena-Jimenez A, Ormsby CE, Vega-Barrientos R, Reyes-Teran G. Later onset of herpes zoster-associated immune reconstitution inflammatory syndrome. *HIV Med*. 2009;10(7):454-457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19490175.

57. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in human immunodeficiency virus-infected patients: results of foscarnet therapy. *Clin Infect Dis*. 1998;27(6):1525-1527. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9868672.

58. Pastuszak AL, Levy M, Schick B, et al. Outcome after maternal varicella infection in the first 20 weeks of pregnancy. *N Engl J Med*. 1994;330(13):901-905. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8114861.

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Updated: October 29, 2024
Reviewed: October 29, 2024

This table provides recommendations for the use of chemoprophylaxis to prevent the first episode of opportunistic disease. For the use of immunizations to prevent certain infections in people with HIV, please refer to the Immunizations for Preventable Diseases in Adults and Adolescents With HIV section.

Opportunistic Infections	Indication	Preferred	Alternative
Coccidioidomycosis	A new positive *Coccidioides* IgM or IgG test in patients who previously tested negative; do not have signs, symptoms, or laboratory abnormalities compatible with active disease; and have CD4 count <250 cells/mm^3 (AIII)	Fluconazole 400 mg PO daily (AIII)	None
Histoplasma capsulatum Infection	CD4 count <150 cells/mm^3 and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases per 100 person-years) (BI)	Itraconazole 200 mg PO daily (BI)	None
Malaria	Travel to disease-endemic area	Recommendations are the same for HIV-infected and HIV-uninfected patients. Recommendations are based on the region of travel, malaria risks, and drug susceptibility in the region. Refer to the Centers for Disease Control and Prevention webpage for the most recent recommendations based on region and drug susceptibility: Malaria.	
Mycobacterium avium Complex (MAC) Disease	CD4 count <50 cells/mm^3 AND not receiving ART or remains viremic on ART or has no options for a fully suppressive ART regimen (AI) Not recommended for those who immediately initiate ART after HIV diagnosis (AII) Disseminated MAC disease should be ruled out before starting primary prophylaxis. See the MAC section for more information.	Azithromycin 1,200 mg PO once weekly (AI), *or* Clarithromycin 500 mg PO twice daily (AI), *or* Azithromycin 600 mg PO twice weekly (BIII)	Rifabutin (dose adjustment may be necessary with some ARV drugs, and rifabutin is not recommended if used with certain ARV drugs)[a] (BI); rule out active TB before starting rifabutin to avoid monotherapy in the setting of TB.

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
Mycobacterium tuberculosis Infection (TB) (i.e., treatment of latent TB infection [LTBI])	Positive screening test for LTBI,[b] no evidence of active TB, and no prior treatment for active TB or LTBI (AI), *or* Close contact with a person with infectious TB (with no evidence of active TB), regardless of screening test results and CD4 count (AII) For recommendations on management of drug interactions with ARVs, see the Dosing Recommendations for Use of ARV and Anti-TB Drugs When Treating Latent TB Infection table in the *Mycobacterium tuberculosis* Infection and Disease section and the Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines.	3HP Rifapentine (see weight-based dosing below) plus INH 15 mg/kg (900 mg maximum) plus pyridoxine 50 mg PO once weekly for 12 weeks (AI) *Weight-Based Rifapentine Dose* • Weighing 25.1–32 kg: 600 mg PO once weekly • Weighing 32.1–49.9 kg: 750 mg PO once weekly • Weighing >50 kg: 900 mg PO once weekly Note: 3HP is recommended only for virally suppressed persons receiving EFV, RAL, or once daily DTG-based ARV regimen (AII). *or* 3HR INH 300 mg plus rifampin 600 mg plus pyridoxine 25–50 mg PO daily for 3 months (AI)	INH 300 mg plus pyridoxine 25–50 mg PO daily for 6–9 months (AII), *or* 4R: Rifampin 600 mg PO daily for 4 months (BI), *or* 1HP: Rifapentine (see weight-based dosing below) plus INH 300 mg plus pyridoxine 25–50 mg) PO once daily for 4 weeks (BI) Weight-Based Rifapentine Dose • *Weighing* <35 kg: 300 mg PO once daily • *Weighing* 35–45 kg: 450 mg PO once daily • *Weighing* >45 kg: 600 mg PO once daily Note: 1HP is recommended only for patients receiving an efavirenz-based ARV regimen (AI). For persons exposed to drug-resistant TB, select anti-TB drugs after consultation with experts and public health authorities (AIII).
Pneumocystis Pneumonia (PCP)	CD4 count 100–200 cells/mm^3, if plasma HIV RNA level is above detection limits (AI), *or* CD4 count <100 cells/mm^3, regardless of plasma HIV RNA level (AIII) Note: Patients who are receiving pyrimethamine/ sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII).	TMP-SMX 1 DS tablet PO daily (AI), *or* TMP-SMX 1 SS tablet PO daily (AI) Note: TMP-SMX also confers protection against toxoplasmosis and some protection against many respiratory bacterial infections.	The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*: • TMP-SMX 1 DS PO three times weekly (BI), *or* • Dapsone[c] 50 mg PO daily with pyrimethamine[d] 50 mg plus leucovorin 25 mg PO weekly (BI), *or* • Dapsone[c] 200 mg plus pyrimethamine[d] 75 mg plus leucovorin 25 mg PO weekly (BI), *or* • Atovaquone 1,500 mg PO daily with food (BI) The following regimens should only be used if the person is seronegative for *Toxoplasma gondii*: • Dapsone[c] 100 mg PO daily or 50 mg PO twice daily (BI), *or*

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
			• Aerosolized pentamidine 300 mg via Respigard II nebulizer every month (BI), *or* • Intravenous pentamidine 300 mg every 28 days (CIII)
Syphilis	Individuals exposed sexually within ≤90 days of the diagnosis of primary, secondary, or early latent syphilis in a sex partner, regardless of serologic status (AII), *or* Individuals exposed >90 days before syphilis diagnosis in a sex partner, if serologic test results are not available immediately and the opportunity for follow-up is uncertain (AIII)	Benzathine penicillin G 2.4 million units IM for one dose (AII)	For penicillin-allergic patients: • Doxycycline 100 mg PO twice daily for 14 days (BII), *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days (BII)
Talaromycosis (Penicilliosis)	Persons with HIV and CD4 cell counts <100 cells/mm^3, who are unable to have ART, or have treatment failure without access to effective ART options, and— Who reside in the highly endemic regions* in northern Thailand, northern or southern Vietnam, or southern China (BI), *or* Who are from countries outside of the endemic region, and must travel to the region (BIII) * Particularly in highland regions during the rainy and humid months	For persons who reside in endemic areas, itraconazole 200 mg PO once daily (BI) For those traveling to the highly endemic regions, begin itraconazole 200 mg PO once daily 3 days before travel, and continue for 1 week after leaving the endemic area (BIII).	For persons who reside in endemic areas, fluconazole 400 mg PO once weekly (BII) For those traveling to the highly endemic regions, take the first dose of fluconazole 400 mg 3 days before travel, continue 400 mg once weekly, and take the final dose after leaving the endemic area (BIII).
Toxoplasma gondii Encephalitis	*Toxoplasma* IgG-positive patients with CD4 count <100 cells/mm^3 (AII) Note: All regimens recommended for primary prophylaxis against toxoplasmosis also are effective as PCP prophylaxis.	TMP-SMX 1 DS PO daily (AII)	TMP-SMX 1 DS PO three times weekly (BII), *or* TMP-SMX 1 SS PO daily (BIII), *or* Dapsone[c] 50 mg PO daily plus (pyrimethamine[d] 50 mg plus leucovorin 25 mg) PO weekly (BI), *or* (Dapsone[c] 200 mg plus pyrimethamine[d] 75 mg plus leucovorin 25 mg) PO weekly (CI), *or*

Table 1. Chemoprophylaxis to Prevent First Episode of Opportunistic Disease

Opportunistic Infections	Indication	Preferred	Alternative
			Atovaquone 1,500 mg PO daily (CIII), *or* (Atovaquone 1,500 mg plus pyrimethamine[d] 25 mg plus leucovorin 10 mg) PO daily (CIII)

[a] Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for dosing recommendations.

[b] Screening tests for latent tuberculosis infection include tuberculin skin tests and interferon-gamma release assays.

[c] Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) before administration of dapsone. An alternative agent should be used in patients found to have G6PD deficiency.

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

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Opportunistic Infection Guidelines.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; DS = double strength; DTG = dolutegravir; EFV = efavirenz; IgG = immunoglobulin G; IgM = immunoglobulin M; IM = intramuscular; INH = isoniazid; IV = intravenously; LTBI = latent tuberculosis infection; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis* pneumonia; PO = orally; RAL= raltegravir; SS = single strength; TB = tuberculosis; TMP-SMX = trimethoprim-sulfamethoxazole

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

Updated: December 16, 2024
Reviewed: December 16, 2024

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
Bacterial Enteric Infections	Empiric Therapy Pending Definitive Diagnosis	For People With HIV and CD4 >500 cells/mm^3, 1–2 Days of Loose Stool Without Fever or Blood in Stool • Oral hydration, no further workup, and no antibiotics For People With HIV and CD4 200–500 cells/mm^3 With Diarrhea Severe Enough to Compromise Quality of Life or the Ability to Work • Azithromycin 500 mg PO daily for 5 days (BIII), *or* • Ciprofloxacin 500–750 mg PO every 12 hours for 5 days (BIII) For People With HIV and Severe Disease (e.g., CD4 <200 cells/mm^3 or Concomitant AIDS-Defining Illness and With Clinically Severe Diarrhea [≥6 Liquid Stools Per Day or Bloody Stool and/or Accompanying Fever or Chills]) • Hospitalization for diagnostic evaluation and IV antibiotics • Ceftriaxone IV 1–2 g every 24 hours (BIII) Note: If *Campylobacter* or *Shigella* bacteremia is suspected, a carbapenem is preferred (BIII). Therapy and duration should be adjusted based on microbiology and antibiotic sensitivity results. If no pathogen is identified and the patient recovers quickly, 5 days of therapy is recommended.		Diagnostic fecal specimens should be obtained before initiation of empiric antimicrobial therapy. If a pathogen is identified, antibiotic susceptibilities should be performed to confirm and inform antibiotic choices, given increased reports of antibiotic resistance. Oral or IV rehydration (if indicated) should be given to patients with diarrhea (AIII). Antimotility agents should be avoided if there is concern about inflammatory diarrhea, including CDI (BIII). Risk of bacteremia increases with decreasing CD4 count. If no clinical response is observed after 3–4 days, consider a follow-up stool culture with antibiotic susceptibility testing or alternative diagnostic tests (e.g., toxin assays, molecular testing) to evaluate alternative diagnoses, antibiotic resistance, or drug–drug interaction (BIII). MSM may be at increased risk for antibiotic resistant enteric infections.

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

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
		For patients with persistent diarrhea (>14 days) without severe clinical signs, antibiotics therapy can be withheld until a diagnosis is made.		
	Campylobacteriosis	For Mild Disease If CD4 Count >200 cells/mm^3 • No therapy unless symptoms persist for more than several days (CIII) For Mild to Moderate Disease (If Susceptible) • Azithromycin 500 mg PO daily for 5 days (BIII) (not recommended for patients with bacteremia [AIII]), *or* • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for 7–10 days (BIII) For *Campylobacter* Bacteremia • Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours for ≥14 days if the isolate is sensitive (BIII) plus an aminoglycoside (BIII) to limit the emergence of antibiotic resistance For Recurrent Infections • Duration of therapy may be extended to 2–6 weeks (BIII).	For Mild to Moderate Disease (If Susceptible) • Levofloxacin 750 mg (PO or IV) every 24 hours (BIII) • Add an aminoglycoside to fluoroquinolone in bacteremic patients (BIII) to limit the emergence of antibiotic resistance.	Oral or IV rehydration if indicated (AIII) Antimotility agents should be avoided (BIII). Third-generation cephalosporins are not reliably active and use of alternative cell wall–active agents, such as carbapenems, may be necessary in severely ill people who require empiric IV therapy until antimicrobial susceptibilities return. In the United States in 2018, 29% of *C. jejuni* isolates were resistant to ciprofloxacin and 2% were resistant to azithromycin; among *C. coli* isolates, 40.5% were resistant to fluoroquinolone and 13.3% were resistant to azithromycin. Effective ART may reduce the frequency, severity, and recurrence of *Campylobacter* infections.
	Clostridium difficile Infection (CDI)	For Severe or Nonsevere CDI • Fidaxomicin 200 mg PO twice daily for 10 days (AI) Recurrent CDI • 2021 IDSA CDI Guidelines suggest use of fidaxomicin over oral vancomycin because it has a greater likelihood for a sustained clinical response at 30 days (AI).	For Severe or Nonsevere CDI • Vancomycin 125 mg PO four times daily for 10 days (AI) For Nonsevere CDI *If Neither Fidaxomicin nor Vancomycin Is Available* • Metronidazole 500 mg (PO) three times daily for 10 days (CI)	Severe CDI: white blood cell count ≥15,000 cells/mL or serum creatinine concentrations >1.5 mg/dL; nonsevere CDI: white blood cell count <15,000 cells/mL and serum creatinine concentrations <1.5 mg/dL

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

<table>
<tr><th colspan="2">Opportunistic Infection</th><th>Preferred Therapy</th><th>Alternative Therapy</th><th>Other Comments</th></tr>
<tr><td></td><td></td><td></td><td>Recurrent CDI
Vancomycin is an acceptable option (see IDSA Guideline for tapered and pulsed regimens) (AI).
FMT may be considered after three CDI episodes (i.e., an initial and two recurrent episodes) (CIII).</td><td></td></tr>
<tr><td></td><td>Salmonellosis</td><td colspan="2">All people with HIV and salmonellosis should receive antimicrobial treatment due to an increase of bacteremia (by 20-fold to 100-fold) and mortality (by up to sevenfold) compared to individuals without HIV (AIII).</td><td rowspan="2">Oral or IV rehydration if indicated (AIII)

Antimotility agents should be avoided (BIII).

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

Effective ART may reduce the frequency, severity, and recurrence of salmonella infections.</td></tr>
<tr><td></td><td></td><td>For Invasive Disease (Suspected or Confirmed)
Ceftriaxone IV 1–2 g every 24 hours pending susceptibilities (BIII)
For Nontyphoidal Salmonella Gastroenteritis (With or Without Bacteremia) (If Susceptible)
Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (AIII)
Duration of Therapy
For Gastroenteritis Without Bacteremia
If CD4 count ≥200 cells/mm^3: 7–14 days (BIII)
If CD4 count <200 cells/mm^3: minimum of 2 weeks (may extend to up to 6 weeks if with severe disease) (BIII)
For Gastroenteritis With Bacteremia
If CD4 count ≥200/mm^3: 14 days or longer duration if bacteremia persists or if the infection is complicated (e.g., if metastatic foci of infection are present) (BIII)
If CD4 count <200 cells/mm^3: 2–6 weeks (BIII)</td><td>For Nontyphoidal Salmonella Gastroenteritis (With or Without Bacteremia) (If Susceptible)
Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), or
Moxifloxacin 400 mg (PO or IV) every 24 hours (BIII), or
TMP-SMX (160 mg/800 mg) PO (or IV) every 12 hours (BIII), or
Ceftriaxone 1–2 g IV every 24 hours (BIII)</td></tr>
</table>

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

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
		Secondary Prophylaxis Should Be Considered for Patients With • Recurrent *Salmonella* bacteremia (BIII), *or* • Recurrent gastroenteritis (with or without bacteremia) with CD4 count <200 cells/mm^3 with severe diarrhea (BIII)		
	Shigellosis	• Ciprofloxacin 500–750 mg PO (or 400 mg IV) every 12 hours (if MIC <0.12 μg/mL) (AIII) Duration of Therapy • Gastroenteritis: 5–7 days (AIII) (except ciprofloxacin [5–10 days] and azithromycin [5 days]) • Bacteremia: ≥14 days (BIII) • Recurrent infections: Up to 6 weeks (BIII) *In Severely Ill Patients Requiring Empiric Parenteral Therapy While Awaiting Susceptibility* • Consider initiating a carbapenem until antimicrobial susceptibilities are available (BIII). Note: Increased resistance of *Shigella* to fluoroquinolones in the United States. Alternative antibiotics should be considered if ciprofloxacin MIC is ≥0.12 μg/mL (BIII).	• Levofloxacin 750 mg (PO or IV) every 24 hours (BIII), *or* • Trimethoprim 160 mg/sulfamethoxazole 800 mg PO or IV every 12 hours for 5–7 days (BIII), or • Azithromycin 500 mg PO daily for 5 days (BIII), or • Ceftriaxone 1–2 g IV every 24 hours (BIII) Note: Azithromycin and TMP-SMX are not recommended for treatment of bacteremia. Note: Azithromycin-resistant *Shigella* spp. have been reported in MSM with HIV.	Therapy may slightly shorten the duration of illness and/or prevent the spread of infection (AIII). Oral or IV rehydration if indicated (AIII) Antimotility agents should be avoided (BIII). Many *Shigella* strains that are resistant to fluoroquinolones exhibit resistance to other commonly used antibiotics. Antibiotic sensitivity testing of *Shigella* isolates from individuals with HIV should be performed routinely. Given increasing antimicrobial resistance and limited data showing that antibiotic therapy limits transmission, antibiotic treatment may be withheld in patients with CD4 count >500 cells/mm^3 whose diarrhea resolves prior to culture confirmation of *Shigella* infection (CIII). Effective ART may decrease the risk of recurrence of *Shigella* infections.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Bartonellosis	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis • Doxycycline 100 mg PO or IV every 12 hours (AII), *or* • Erythromycin 500 mg PO or IV every 6 hours (AII) CNS Infections • (Doxycycline 100 mg +/- RIF 300 mg) PO or IV every 12 hours (AIII) Confirmed *Bartonella* Endocarditis • (Doxycycline 100 mg IV plus RIF 300 mg PO or IV) every 12 hours for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours (BII) Other Severe Infections • (Doxycycline 100 mg PO or IV +/- RIF 300 mg PO or IV) every 12 hours (BIII), *or* • (Erythromycin 500 mg PO or IV every 6 hours) +/- RIF 300 mg PO or IV every 12 hours (BIII) Duration of Therapy • At least 3 months (AII)	For Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, Osteomyelitis, and Other Severe Infection • Azithromycin 500 mg PO daily (BIII) • Clarithromycin 500 mg PO twice a day (BIII) Confirmed *Bartonella* Endocarditis • (Doxycycline 100 mg IV every 12 hours plus gentamicin 1 mg/kg IV every 8 hours) for 2 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours (BII)	When RIF is used, take into consideration the potential for significant interaction with ARV drugs and other medications (see Table 4 for dosing recommendations). If relapse occurs after initial (>3 month) course of therapy, long-term suppression with doxycycline or a macrolide is recommended as long as the CD4 count is <200 cells/mm^3 (AIII).
Candidiasis (Mucocutaneous)	For Oropharyngeal Candidiasis—Initial Episodes (For 7–14 Days) • Fluconazole 200 mg PO loading dose, followed by 100–200 mg PO daily (AI) For Esophageal Candidiasis (For 14–21 Days) • Fluconazole 200-mg loading dose, followed by 100–200 mg (up to 400 mg) PO or IV daily (AI). (Consider oral suspension for people with difficulty swallowing.)	For Oropharyngeal Candidiasis—Initial Episodes (For 7–14 Days) *Oral Therapy* • Itraconazole oral solution 200 mg PO daily (BI), *or*	Chronic or prolonged use of azoles may promote the development of resistance. Systemic azoles may have significant drug–drug interactions with ARV drugs. A higher relapse rate for esophageal candidiasis is seen with echinocandins use than with fluconazole.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	For Uncomplicated Vulvovaginal Candidiasis • Fluconazole 150 mg PO for one dose (AII), *or* • Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (AII), *or* • Ibrexafungerp 300 mg PO twice daily for 1 day (BI) For Severe or Recurrent Vulvovaginal Candidiasis • Fluconazole 100–200 mg PO daily for ≥7 days (AII), *or* • Topical antifungal ≥7 days (AII) For Recurrent Vulvovaginal Candidiasis Only *(the following regimens include treatment for the acute episode plus treatment to reduce recurrence)* • Oteseconazole 600 mg PO at Day 1, 450 mg at Day 2, followed by once-weekly 150-mg dosing starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or* • Fluconazole 150 mg PO at Days 1, 4, and 7, followed by oteseconazole 150 mg PO daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for those who are not of reproductive potential); *or* • Fluconazole 150 mg PO every 72 hours for three doses, followed by ibrexafungerp 300 mg PO twice daily 1 day per month for 6 months (BI). (Use an effective form of contraception during treatment and for 4 days after the last dose.)	• Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily (BI), *or* • Posaconazole tablet 300 mg PO twice a day for 1 day, then 300 mg daily (BI) *Topical Therapy* • Miconazole mucoadhesive buccal 50-mg tablet once daily; apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet.) (BI), *or* • Clotrimazole troches 10 mg PO five times daily (BI), *or* • Nystatin suspension 4–6 mL four times a day (BII) For Esophageal Candidiasis (For 14–21 Days) • Itraconazole oral solution 200 mg PO daily (AI), *or* • Isavuconazole 400 mg PO loading dose, followed by 100 mg PO daily (BI), *or* • Isavuconazole 400 mg PO once weekly (BI), *or* • Voriconazole 200 mg PO or IV twice a day (BI), *or* • Posaconazole oral suspension 400 mg PO twice a day for 1 day, then 400 mg daily (BI), *or* • Posaconazole tablet 300 mg PO twice a day for 1 day, then 300 mg daily (BI), *or* • Lipid formulation of amphotericin B 3–4 mg/kg IV daily (BI), *or* • Caspofungin 70 mg IV loading dose, followed by 50 mg IV daily (BI), *or*	Suppressive therapy is usually not recommended (CIII) unless patients have frequent or severe recurrences. If the Decision Is to Use Suppressive Therapy *Oropharyngeal Candidiasis* • Fluconazole 100 mg PO once daily or three times weekly (BI) *Esophageal Candidiasis* • Fluconazole 100–200 mg PO daily (BI), *or* • Posaconazole oral suspension 400 mg PO twice a day (BII), *or* • Posaconazole tablet 300 mg PO daily (BII) *Vulvovaginal Candidiasis* • Fluconazole 150 mg PO once weekly (BII), *or* • Oteseconazole 600 mg at Day 1 and 450 mg at Day 2 for treatment of the acute episode, followed by once-weekly 150-mg doses starting at Day 14 for 11 weeks (AI) (for those who are not of reproductive potential); *or* • Fluconazole 150 mg at Days 1, 4, and 7 for treatment of the acute episode, followed by oteseconazole 150 mg daily at Days 14–20, followed by oteseconazole 150 mg once weekly starting at Day 28 for 11 weeks (Weeks 4–14) (AI) (for

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		• Micafungin 150 mg IV daily (BI), *or* • Anidulafungin 100 mg IV once, then 50 mg IV daily (BI) For Azole-Refractory *Candida glabrata* Vaginitis • Boric acid vaginal suppository 600 mg once daily for 14 days (BII)	those who are not of reproductive potential); *or* • Ibrexafungerp 300 mg twice daily 1 day per month for 6 months (BI). (Use an effective form of contraception during treatment and for 4 days after the last dose.)
Chagas Disease (American Trypanosomiasis)	For Acute or Reactivated Disease • Benznidazole 5–8 mg/kg/day PO in two divided doses for 60 days (BIII) (commercially available at https://www.benznidazoletablets.com/en; most experts recommend a daily maximum of 300 mg), *or* • Nifurtimox (Lampit®) 8–10 mg/kg/day PO in three divided doses for 60 days (BIII) (commercially available through retail sources)	None	Treatment is effective in reducing parasitemia and preventing clinical symptoms or slowing disease progression; however, these drugs have limited efficacy in achieving parasitological cure. Treatment is not recommended for patients with advanced chagasic cardiomyopathy. Duration of therapy has not been studied in patients with HIV. Initiation or optimization of ART is recommended for all people with HIV with concomitant *Trypanosoma cruzi* (AIII).
Coccidioidomycosis	Mild-to-Moderate Pulmonary Infection • Fluconazole 400 mg PO daily (AII), *or* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) • Duration of therapy: clinical response to 3–6 months of therapy, CD4 count ≥250 cells/mm^3, and viral suppression on ART (AII)	Mild-to-Moderate Pulmonary Infection *For Patients Who Failed to Respond to Fluconazole or Itraconazole* • Voriconazole 400 mg PO twice daily on Day 1, then 200 mg PO twice a day (BIII) • Posaconazole delayed release tablet 300 mg PO twice a day on Day 1, then 300 mg PO once daily (BIII), *or*	Some patients with meningitis may develop hydrocephalus and require CSF shunting. Therapy should be lifelong in patients with meningeal infections because relapse occurs in 80% of patients with HIV after discontinuation of triazole therapy (AII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Severe Pulmonary or Extrapulmonary Infection (Except Meningitis) • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII), *or* • Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII) • Continue until clinical improvement, then switch to an azole (fluconazole 400 mg PO daily or itraconazole 200 mg PO twice daily) (BIII). Therapy should be continued for at least 12 months and usually much longer, and should be continued in patients with HIV viremia or with CD4 count <250 cells/mm^3 (BIII). Meningeal Infections • Fluconazole 800–1,200 mg PO daily (AII) • Duration of therapy: lifelong (AII)	• Isavuconazole sulfate 372 mg PO every 8 hours for six doses, then 372 mg once daily (BIII) Severe Pulmonary or Extrapulmonary Infection (Except Meningitis) • Some specialists will combine amphotericin B with a triazole (fluconazole or itraconazole, with itraconazole preferred for bone disease) as initial therapy and continue triazole once amphotericin B is stopped (CIII). Meningeal Infections • Itraconazole 200 mg PO two or three times daily (BII), *or* • Voriconazole 200–400 mg PO twice daily (BIII), *or* • Posaconazole delayed release tablet 300 mg PO twice on Day 1, then 300 mg PO once daily (CIII), *or* • Isavuconazole sulfate 372 mg PO every 8 hours for six doses, then 372 mg once daily (CIII) • Intrathecal amphotericin B deoxycholate when triazole antifungals are ineffective (AIII)	See Table 4 for drug–drug interactions or triazole antifungal drugs and other drugs for treatment or prevention of OIs. Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and antiretroviral efficacy and reduce concentration-related toxicities. Intrathecal amphotericin B should only be given in consultation with a specialist and administered by an individual with experience with the technique.

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

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

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• Levofloxacin 750 mg IV once daily (AI), *or* moxifloxacin, 400 mg IV once daily (AI), especially for patients with penicillin allergies. Empiric Therapy for Hospitalized Patients With Severe CAP • An IV beta-lactam plus IV azithromycin (AI), *or* • An IV beta-lactam plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) (AI) *Preferred Beta-Lactams* • Ceftriaxone, cefotaxime, or ampicillin-sulbactam Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia • An IV antipneumococcal, antipseudomonal beta-lactam plus (ciprofloxacin 400 mg IV every 8–12 hours or levofloxacin 750 mg IV once daily) (AI) *Preferred Beta-Lactams* • Piperacillin-tazobactam, cefepime, imipenem, or meropenem Empiric Therapy for Patients at Risk for Methicillin-Resistant *Staphylococcus aureus* Pneumonia • Add vancomycin IV or linezolid (IV or PO) to the baseline regimen (AII). • Addition of clindamycin to vancomycin (but not to linezolid) can be considered for severe necrotizing pneumonia to minimize bacterial toxin production (CII).	Empiric Therapy for Patients at Risk of *Pseudomonas* Pneumonia • An IV antipneumococcal, antipseudomonal beta-lactam plus an IV aminoglycoside plus azithromycin (BII), *or* • An IV antipneumococcal, antipseudomonal beta-lactam plus an aminoglycoside plus (levofloxacin 750 mg IV once daily or moxifloxacin 400 mg IV once daily) (BIII) *For Penicillin-Allergic Patients* • Replace the beta-lactam with aztreonam (BIII).	

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptococcosis	For CNS and/or Disseminated Disease *Induction Therapy (for ≥2 weeks, followed by consolidation therapy)* • In the United States and other settings where daily electrolytes and kidney function monitoring and electrolyte and IV fluid administration is possible o Liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (AII) (Note: Flucytosine dose should be adjusted in patients with renal dysfunction.) • In resource-limited settings, as recommended by WHO: o Liposomal amphotericin B 10 mg/kg IV as a single dose on Day 1, followed by flucytosine 25 mg/kg four times a day plus fluconazole 1,200 mg daily for 2 weeks (AI) • If not improved clinically or remain clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative (BIII). *Consolidation Therapy (for ≥8 weeks, followed by maintenance therapy)* • Fluconazole 800 mg PO daily (AI) • For clinically stable patients with negative CSF cultures and ART has been started, dose can be reduced to 400 mg PO daily (AII) • If CSF remains positive (but clinically stable) after 2 weeks of induction therapy, use one of the following two options for an additional 2 weeks before reducing the dose of fluconazole to 800 mg PO daily:	For CNS and/or Disseminated Disease *Induction Therapy (for ≥2 weeks, followed by consolidation therapy)* • Amphotericin B lipid complex 5 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 2 weeks (BII), *or* • Amphotericin B deoxycholate 1 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day for 1 week, followed by fluconazole 1,200 mg PO daily for an additional week (BI) *Additional Studied Induction Regimens (for 2 weeks)* • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus flucytosine 25 mg/kg PO four times a day (BI) • Liposomal amphotericin B 3–4 mg/kg IV daily plus fluconazole 800–1,200 mg PO daily (BIII) • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily plus fluconazole 800–1,200 mg PO or IV daily (BI) • Fluconazole 1,200 mg PO or IV daily plus flucytosine 25 mg/kg PO four times a day (BII) *Consolidation Therapy (for ≥8 weeks, followed by maintenance therapy)* • If fluconazole is not available or not well tolerated: Itraconazole 200 mg PO twice a day for 8 weeks (CI)	Addition of flucytosine to amphotericin B has been associated with more rapid sterilization of CSF and decreased risk for subsequent relapse. Patients receiving flucytosine should have either blood levels monitored (peak level 2 hours after dose should be 25–100 μg/mL) or at least twice weekly monitoring of complete blood counts for cytopenia. Dosage should be adjusted in patients with renal insufficiency (BII). Irrespective of which regimen is used, patients must be followed carefully in hospital for at least 7 days and ideally 14 days (AII). For patients with CNS disease, LP should be performed at Day 7 and Day 14 to ensure an appropriate clinical response and culture sterility. If increased ICP is documented, daily LP should be performed until the pressure is decreased into the normal range and symptoms have abated (AII). Opening pressure should always be measured when an LP is performed. Repeated LPs or CSF shunting are essential to effectively managing increased intracranial pressure.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	o Fluconazole 1,200 mg PO daily with flucytosine 25 mg/kg PO four times a day for 2 weeks (BIII) o Fluconazole 1,200 mg PO daily for 2 weeks (BIII), *or* Note: Duration of consolidation therapy should be at least 8 weeks from the time of negative CSF culture (AII). *Maintenance Therapy* • Fluconazole 200 mg PO daily for ≥1 year from initiation of antifungal therapy (AI) For Non-CNS Extrapulmonary (BIII) or Diffuse Pulmonary Disease (BIII) or People With Non-CNS Symptoms With Normal CSF and Serum CrAg **≥1:640 by LFA (or ≥1:160 by EIA** or Latex Agglutination) (BII) • Treatment is the same as for CNS cryptococcosis. For Non-CNS Focal Pulmonary Infiltrates (With Mild Symptoms) • Fluconazole 400 mg daily for 6 to 12 months (duration guided by symptom resolution) (BIII) For Asymptomatic Antigenemia Without Meningitis and Serum **CrAg <1:640 by LFA (or <1:160** by EIA or Latex Agglutination) • Fluconazole: 800–1,200 mg PO daily for 2 weeks, followed by 400–800 mg PO daily for a total of 10 weeks, then fluconazole 200 mg PO daily for a total of 6 months plus effective ART (BIII)	*Maintenance Therapy* • If fluconazole is not available or not well tolerated: Itraconazole 200 mg PO twice a day (CI) • If susceptibility studies have been performed and the fluconazole MIC is ≥16 μg/mL, the fluconazole dose may be increased to 400 mg daily (BIII). For Non-CNS Extrapulmonary (BIII) or Diffuse Pulmonary Disease (BIII) or People With Non-CNS Symptoms With Normal **CSF and Serum CrAg ≥1:640 by LFA (or ≥1:160 by EIA or** Latex Agglutination) (BII) • Alternative treatment options are the same as for CNS cryptococcosis.	Corticosteroids and mannitol are ineffective in reducing ICP and are not recommended (AIII). Some specialists recommend a brief course of tapering dose of corticosteroid for management of severe IRIS symptoms (BIII). All people with non-CNS extrapulmonary symptoms and cryptococcal antigenemia should have their CSF sampled to rule out CNS disease. People with asymptomatic cryptococcal antigenemia, lower risk, and serum CrAg titer <1:80 by LFA (or <1:20 by EIA or latex agglutination) can be safely treated without lumbar puncture (AI). All others with asymptomatic cryptococcal antigenemia should undergo CSF sampling to rule out CNS disease.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Cryptosporidiosis	• Aggressive oral and/or IV rehydration and replacement of electrolyte loss (AIII), *and* • Symptomatic treatment of diarrhea with antimotility agents (AIII), *and* • ART initiation to achieve immune restoration to CD4 count >100 cells/mm^3 (AII).	No therapy has been shown to be effective without ART. Consider trial of these agents in conjunction with ART, rehydration, and symptomatic treatment: • Nitazoxanide 500–1,000 mg PO twice a day with food for at least 14 days (CIII), *or* • Paromomycin 500 mg PO four times daily for 14–21 days (CIII)	Tincture of opium may be more effective than loperamide in management of diarrhea (CIII). Because diarrhea can cause lactase deficiency, patients should avoid milk products (CIII).
Cytomegalovirus (CMV) Disease	CMV Retinitis Induction Therapy (Followed by Chronic Maintenance Therapy) *For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea)* • Ganciclovir 5 mg/kg every 12 hours IV or valganciclovir 900 mg PO twice a day or for 14–21 days (AI) (some prefer IV ganciclovir initially and transition to PO valganciclovir when there is evidence of clinical response) with or without • Intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) to rapidly achieve high intraocular concentration, continued weekly until lesion inactivity is achieved (AIII); *plus* *For Peripheral Lesions* • Valganciclovir 900 mg PO twice a day for 14–21 days, then 900 mg once daily (AI) *Maintenance Therapy* • Valganciclovir 900 mg PO daily (AI) for 3–6 months until ART-induced immune recovery	CMV Retinitis *For Immediate Sight-Threatening Lesions (within 1,500 microns of the fovea): Intravitreal therapy as listed in the Preferred section, plus one of the following:* *Alternative Systemic Induction Therapy (Followed by Chronic Maintenance Therapy)* • Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours for 14–21 days (BI), *or* • Cidofovir 5 mg/kg/week IV for 2 weeks; saline hydration before and after therapy and probenecid, 2 g PO 3 hours before dose, followed by 1 g PO 2 hours and 8 hours after the dose (total of 4 g) (CI) (Note: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid.)	The choice of therapy for CMV retinitis should be individualized, based on tolerance of systemic medications, prior exposure to anti-CMV drugs, and location of the lesion (AIII). Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include initiation or optimization of ART (BIII). 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.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	CMV Esophagitis or Colitis • Ganciclovir 5 mg/kg IV every 12 hours; may switch to valganciclovir 900 mg PO every 12 hours once the patient can tolerate oral therapy (BI) • Valganciclovir 900 mg PO every 12 hours may be considered as initial therapy in mild diseases (CIII). • Duration: 21–42 days or until symptoms have resolved (CII) • Maintenance therapy is usually not necessary but should be considered after relapses (BII). Well-Documented, Histologically Confirmed CMV Pneumonia • Experience for treating CMV pneumonitis in HIV patients is limited. Use of IV ganciclovir or IV foscarnet is reasonable (doses same as for CMV retinitis) (CIII). • The optimal duration of therapy and the role of oral valganciclovir have not been established. CMV Neurological Disease *Note: Treatment should be initiated promptly.* • Ganciclovir 5 mg/kg IV every 12 hours plus (foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg IV every 8 hours) to stabilize disease and maximize response. Continue until there is symptomatic improvement and resolution of neurologic symptoms (CIII). • The optimal duration of therapy and the role of oral valganciclovir have not been established.	*Chronic Maintenance (For 3–6 Months Until ART-Induced Immune Recovery)* • Foscarnet 90–120 mg/kg IV once daily (AI), *or* • Cidofovir 5 mg/kg IV every other week with saline hydration and probenecid as above (BI) CMV Esophagitis or Colitis • Foscarnet 90 mg/kg IV every 12 hours or 60 mg/kg every 8 hours (BI) for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance, *or* • Valganciclovir 900 mg PO every 12 hours in milder disease and if able to tolerate PO therapy (BII), *or* • Duration: 21–42 days or until symptoms have resolved (CII) • For mild disease, if ART can be initiated without delay, consider withholding CMV therapy (CIII).	Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping chronic maintenance therapy for early detection of relapse or IRU, and then periodically after sustained immune reconstitution (AIII). IRU may develop in the setting of immune reconstitution. Treatment of IRU • Periocular, intravitreal, or short courses of systemic steroid (BIII)

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Hepatitis B Virus (HBV) Disease	ART is recommended for all patients with HIV/HBV coinfection regardless of CD4 cell count and HBV DNA level (AII). The ART regimen must include drugs that are active against both HBV and HIV (AII). If CrCl ≥60 mL/min: • (TAF [10 or 25 mg][a] plus FTC 200 mg) or (TAF 25 mg plus 3TC 300 mg) PO once daily (AII), *or* • (TDF 300 mg plus [FTC 200 mg or 3TC 300 mg]) once daily (AII) If CrCl 30–59 mL/min: • TAF (10 or 25 mg)[a] plus FTC 200 mg PO once daily (AII) If CrCl <30 mL/min, not on HD: • Renally dosed entecavir (in place of TDF/[FTC or 3TC] or TAF/FTC) with a fully suppressive ART regimen (AIII), *or* • ART with renally dose-adjusted TDF and (FTC or 3TC) can be used (AIII) if recovery of renal function is unlikely. • If CrCl ≥15 to 29 mL/min, then ART with TAF (10 or 25 mg)[a] once daily plus renally dose-adjusted FTC or 3TC is an option (AIII). - Some clinicians may continue full-dose FTC or 3TC to allow for people to remain on fixed-dose TAF/FTC products. If on HD: • Renally dose-adjusted TDF plus [FTC 200 mg or 3TC 300 mg once daily] (see Table 6) (AII) • TAF [10 or 25 mg][a] plus FTC 200 mg PO once daily (given after HD on dialysis days) (AII)	For People on NRTI-Sparing ART • Entecavir 0.5 mg once daily may be used in place of (TAF or TDF) plus (3TC or FTC) (AIII)	Directly acting HBV drugs—such as emtricitabine, entecavir, lamivudine, or tenofovir—**must not be given** in the absence of a fully suppressive ART regimen to avoid selection of drug-resistant HIV (AI). Chronic administration of 3TC or FTC as the only HBV-active drug **should be avoided** because of the high rate of selection of HBV drug-resistance mutations (AI). People with 3TC-resistant HBV will have cross-resistance to FTC and partial resistance to entecavir, these agents **should not be used** (AI). If 3TC resistance is suspected or documented, TDF or TAF should be added to the ART regimen (AIII). When changing ART regimens, continue agents with anti-HBV activity (AIII). If anti-HBV therapy is discontinued and a flare occurs, therapy should be reinstituted because it can be potentially lifesaving (AIII). Because HBV reactivation can occur during treatment for HCV with direct-acting antivirals in the absence of anti-HBV therapy, all people with HIV/HBV coinfection who will be treated for HCV infection should be on HBV-active ART at the time of HCV treatment initiation (AIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Duration • Continue treatment indefinitely (AIII).		If immunosuppressive therapy is given, HBV reactivation can occur. For people who are HBsAg-positive, treatment for HBV infection should be administered (AII). For detailed recommendations, see Hepatitis B Virus Infection.
Hepatitis C Virus (HCV) Disease	For Treatment-Naive Patients Without Cirrhosis (Any Genotype or No Pre-treatment Genotype) • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AI), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AI) Characteristics that exclude patients from receiving simplified approach to therapy are outlined in Box 1 of the Hepatitis C Virus section. For Treatment-Naive Patients With Compensated Cirrhosis (Recommendations Based on Genotypes) *Genotypes 1, 2, 4–6* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AIII), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AI) *Genotype 3* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 8 weeks (AIII) For Treatment of Acute HCV Infection • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet),	For Treatment-Naive Patients With Compensated Cirrhosis (Recommendations Based on Genotypes) *Genotypes 1, 2, 4–6* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 12 weeks (CI) *Genotype 3* • Glecaprevir/pibrentasvir FDC (100 mg/40 mg per tablet), three tablets daily for 12 weeks (CI), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily with or without ribavirin for 12 weeks, pending results of NS5A RAS testing (CI)	A simplified approach to HCV treatment can be used in treatment-naive patients with any genotype and without cirrhosis. This approach includes standardized treatment with no on-treatment testing or in-person follow-up and limited follow-up to confirm SVR. See Hepatitis C Virus section to review a summary of drug–drug interactions between HCV therapy and ARV drugs. HCV treatment should not be withheld solely due to perceived lack of adherence to ART or untreated HIV (BIII). Effort should be made to document SVR (HCV RNA less than lower limits of quantification) at least 12 weeks after completion of therapy (AI). Patients without cirrhosis who achieve SVR do not require continued liver disease monitoring. Recommendations for treatment after DAA failure are not provided. The reader is referred to the corresponding section

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	three tablets daily for 8 weeks (AII), *or* • Sofosbuvir/velpatasvir FDC (400 mg/100 mg per tablet), one tablet daily for 12 weeks (AII)		in the AASLD/IDSA HCV treatment guidance.
Herpes Simplex Virus (HSV) Disease	Orolabial Lesions (for 5–10 days) • Valacyclovir 1 g PO twice a day (AIII), *or* • Famciclovir 500 mg PO twice a day (AIII), *or* • Acyclovir 400 mg PO three times a day (AIII) Initial or Recurrent Genital HSV (for 5–14 days) • Valacyclovir 1 g PO twice a day (AI), *or* • Famciclovir 500 mg PO twice a day (AI), *or* • Acyclovir 400 mg PO three times a day (AI) Severe Mucocutaneous HSV • Initial therapy acyclovir 5 mg/kg IV every 8 hours (AIII) • After lesions begin to regress, change to PO therapy as above. Continue until lesions are completely healed. Chronic Suppressive Therapy *For Patients With Severe Recurrences of Genital Herpes (AI) or Patients Who Want to Minimize Frequency of Recurrences (AI)* • Valacyclovir 500 mg PO twice a day (AI), *or* • Famciclovir 500 mg PO twice a day (AI), *or* • Acyclovir 400 mg PO twice a day (AI) • Continue indefinitely, regardless of CD4 count.	For Acyclovir-Resistant HSV *Preferred Therapy* • Foscarnet 80–120 mg/kg/day IV in two to three divided doses until clinical response (AI) *Alternative Therapy (CIII)* • IV cidofovir (dosage as in CMV retinitis), *or* • Topical trifluridine 1% three times a day, *or* • Topical cidofovir 1% once daily, *or* • Topical imiquimod 5% three times weekly, *or* • Topical foscarnet 1% five times daily Duration of Therapy • 21–28 days or longer	Patients with HSV infection can be treated with episodic therapy when symptomatic lesions occur, or with daily suppressive therapy to prevent recurrences. Extemporaneous compounding of topical products can be prepared using trifluridine ophthalmic solution and the IV formulation of cidofovir and foscarnet. An expanded access program of oral pritelivir is now available for immunocompromised patients with acyclovir-resistant HSV infection. For more information, see the AiCuris Pritelivir website.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Histoplasmosis	Severe Disseminated Disease *Induction Therapy (for ≥2 weeks or until clinically improved)* • Liposomal amphotericin B 3 mg/kg IV daily (AI) *Maintenance Therapy (for ≥12 months)* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) Mild-to-Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in Persons With CD4 <300 cells/mm^3 *Both Induction and Maintenance Therapy (for ≥12 months)* • Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO twice a day (AII) Meningitis *Induction Therapy (4–6 weeks depending on symptom resolution and improvement of CSF findings)* • Liposomal amphotericin B 5 mg/kg IV daily (AIII) *Maintenance Therapy (for ≥12 months and until resolution of abnormal CSF findings)* • Itraconazole 200 mg PO two to three times a day (AIII), with dose adjustment based on serum itraconazole concentration Long-Term Suppression Therapy *For patients with severe disseminated or CNS infection after completion of ≥12 months of therapy (AIII) or who relapse despite appropriate therapy (after reinduction therapy) (BIII)* • Itraconazole 200 mg PO daily (AIII)	Severe Disseminated Disease *Induction Therapy* • Amphotericin B lipid complex 5 mg/kg IV daily (AIII) *Maintenance Therapy (for ≥12 months)* • Posaconazole extended-release tablet 300 mg PO twice a day for 1 day, then 300 mg PO once daily (BIII) • Voriconazole 400 mg PO twice a day for 1 day, then 200 mg PO twice a day (BIII), *or* • Fluconazole 800 mg PO daily (CII) Mild-to-Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in Persons With CD4 <300 cells/mm^3 *Both Induction and Maintenance Therapy (for ≥12 months)* • Posaconazole extended-release tabet 300 mg PO twice a day for 1 day, then 300 mg PO once daily (BIII) • Voriconazole 400 mg PO twice a day for 1 day, then 200 mg PO twice a day (BIII), *or* • Fluconazole 800 mg PO daily (CII) Meningitis *Induction Therapy (4–6 weeks depending on symptom resolution and improvement of CSF findings)* • Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (BIII)	Itraconazole, posaconazole, and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities. Random serum concentration of itraconazole between 1–2 μg/mL is recommended. Frequency and severity of toxicities increase when concentration is ≥5 μg/mL. The recommendations for posaconazole, voriconazole, and fluconazole are based on very limited clinical data and for people who are only moderately ill.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		Maintenance Therapy (for ≥12 months and until resolution of abnormal CSF findings) • Voriconazole 400 mg PO twice a day for 1 day, then 200 mg twice a day (BIII), *or* • For people who cannot tolerate itraconazole and voriconazole: Fluconazole 800 mg PO daily (CII) Long-Term Suppression Therapy • Fluconazole 400 mg PO once daily (CII) • Voriconazole 200 mg PO twice daily (BIII) • Posaconazole 300 mg extended-release tablet PO once daily (BIII)	

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Human Herpesvirus-8 (HHV-8) 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) plus ART • Liposomal doxorubicin first-line chemotherapy (AI) Primary Effusion Lymphoma • Chemotherapy (per oncology consult) plus 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 twice a day for 3 weeks (CII), *or* • Ganciclovir 5 mg/kg IV every 12 hours for 3 weeks (CII), *or* • Valganciclovir PO or Ganciclovir IV plus zidovudine 600 mg PO every 6 hours for 7–21 days (CII) • Rituximab +/- Prednisone (CII) • Monoclonal antibody targeting IL-6 or IL-6 receptor (BII) Concurrent KS and MCD • Rituximab plus 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, especially in patients with concurrent KS. Patients who received rituximab for MCD may experience subsequent exacerbation or emergence of KS.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Human Papillomavirus (HPV) Disease	Treatment of Genital Warts		Patients with HIV may have larger or more numerous warts and may not respond as well to therapy for genital warts when compared to individuals without HIV. Intralesional interferon is usually not recommended because of high cost, difficult administration, and potential for systemic side effects (CIII). In patients with HIV, the rate of recurrence of genital warts despite treatment is high. There is no consensus on the treatment of oral warts. Many treatments for anogenital warts cannot be used in the oral mucosa. Surgery is the most common treatment for oral warts that interfere with function or for aesthetic reasons.
	Patient-Applied Treatment Options for Uncomplicated External Warts That Can Be Easily Identified by Patients • Topical imiquimod 5% cream: Apply to genital warts at bedtime on 3 nonconsecutive nights per week for up to 16 weeks, until lesions are no longer visible. Each treatment should be washed with soap and water 6–10 hours after application (BII); *or* • Topical podophyllotoxin (e.g., podofilox 0.5% solution or 0.5% gel): Apply to genital warts twice a day for 3 days, followed by 4 days of no therapy. Can be repeated weekly for up to 4 cycles (BIII); *or* • Topical sinecatechins 15% ointment: Apply to affected areas three times a day for up to 16 weeks, until warts are completely cleared and not visible (BIII); *or* • Topical cidofovir 1%: Daily for 5 days per week for 8 weeks (CIII). Topical formulation is not commercially available but may be compounded.	Provider-Applied Therapy for Complex or Multicentric Lesions, or Lesions Inaccessible to Patient, or Due to Patient or Provider Preference • Cryotherapy (liquid nitrogen or cryoprobe): Apply until each lesion is thoroughly frozen. Repeat every 1–2 weeks for up to 4 weeks, until lesions are no longer visible (BIII). Some specialists allow the lesion to thaw, then freeze a second time in each session (BIII); *or* • Trichloroacetic acid or bichloroacetic acid cauterization (80% to 90% aqueous solution): Apply to warts only and allow to dry until a white frost develops. Repeat weekly for up to 6 weeks, until lesions are no longer visible (BIII); *or* • Intralesional cidofovir (15 mg/mL solution) injected directly into the wart (maximum 1 mL per session). May be repeated every 4 weeks for total of 3–4 treatments (CIII). • Surgical excision (BIII) or laser surgery (CIII) for external or anal warts	
Isosporiasis *(Cystoisosporiasis)*	For Acute Infection • TMP-SMX (160 mg/800 mg) PO (or IV) four times a day for 10 days (AII), *or* • TMP-SMX (160 mg/800 mg) PO (or IV) twice a day for 7–10 days (BI)	For Acute Infection • Pyrimethamine[b] 50–75 mg PO daily plus leucovorin 10–25 mg PO daily (BIII), *or* • Ciprofloxacin 500 mg PO twice a day for 7 days (CI) as a second-line alternative	Fluid and electrolyte management in patients with dehydration (AIII). Nutritional supplementation for malnourished patients (AIII). Immune reconstitution with ART may result in fewer relapses (AIII).

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

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
		• Can start with twice a day dosing first and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist (BIII) • IV therapy may be used for patients with potential or documented malabsorption. Chronic Maintenance Therapy (Secondary Prophylaxis) • In patients with CD4 count <200 cells/mm^3, TMP-SMX (160 mg/800 mg) PO three times weekly (AI)	Chronic Maintenance Therapy (Secondary Prophylaxis) • TMP-SMX (160 mg/800 mg) PO daily or (320 mg/1,600 mg) three times weekly (BIII) • Pyrimethamine[b] 25 mg PO daily plus leucovorin 5–10 mg PO daily (BIII) • Ciprofloxacin 500 mg three times weekly (CI) as a second-line alternative	
Leishmaniasis	Visceral	For *Leishmania infantum/chagasi* • Liposomal amphotericin B 3–5 mg/kg IV daily (AII), *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, 38) (AII) • To achieve total dose of 20–60 mg/kg (AII) For *Leishmania donovani* • Liposomal amphotericin B 5 mg/kg on Days 1, 3, 5, 7, 9, and 11 plus miltefosine 50 mg PO twice daily (for 28 days if from East Africa or 14 days if from Southeast Asia) (BI) Chronic Maintenance Therapy *For Patients With CD4 Count <200 cells/mm^3 (AII)* • Liposomal amphotericin B 4 mg/kg IV every 2–4 weeks (AII)	For *Leishmania infantum/chagasi or donovani* • Amphotericin B deoxycholate 0.5–1.0 mg/kg IV daily for total dose of 1.5–2.0 g (BII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BII) For *Leishmania donovani* • Liposomal amphotericin B 3–5 mg/kg IV daily to achieve total dose of 20–60 mg/kg (AII), *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg (AII), *or* • For Indian *L. donovani*: Miltefosine ~2.5–3.0 mg/kg PO daily in 2–3 divided doses (maximum 150 mg daily) for 28 days (BII)	ART should be initiated or optimized as soon as possible (AIII). Pentavalent antimony is for investigational use only. For miltefosine, visit www.profounda.com.

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

Opportunistic Infection		Preferred Therapy	Alternative Therapy	Other Comments
			Chronic Maintenance Therapy (Secondary Prophylaxis) • Amphotericin B lipid complex 3 mg/kg IV every 21 days (BII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM every 4 weeks (BII), *or* • Pentamidine 4 mg/kg (maximum 300 mg) IV every 2–4 weeks (BII)	
	Cutaneous	For Initial Infection • Liposomal amphotericin B 4 mg/kg IV daily for 10 days (BIII) to achieve total dose of 20–60 mg/kg, *or* • Liposomal amphotericin B interrupted schedule (e.g., 4 mg/kg on Days 1–5, 10, 17, 24, 31, 38) to achieve total dose of 20–60 mg/kg (BIII), *or* • Miltefosine 2.5 mg/kg/day PO in 2–3 divided doses for 28 days (maximum 150 mg per day) (BIII), *or* • Pentavalent antimony (meglumine antimoniate) 20 mg/kg IV or IM daily for 28 days (BIII) Chronic Maintenance Therapy • May be indicated in immunocompromised patients with multiple relapses (CIII) • Drugs and doses same as for visceral leishmaniasis	Possible Options • Cryotherapy, *or* • Topical paromomycin, *or* • Intralesional pentavalent antimony (meglumine antimoniate) or pentamidine, *or* • PO or IV fluconazole (*L. major & L. mexicana)* • IV pentamidine • Local heat therapy No data exist for any of these agents in patients with HIV; choice and efficacy are dependent on species of *Leishmania.*	ART should be initiated or optimized as soon as possible (AIII). Pentavalent antimony is for investigational use only. For miltefosine, visit www.profounda.com.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Malaria	Because *Plasmodium falciparum* malaria can progress within hours from mild symptoms or low-grade fever to severe disease or death, all patients with HIV with confirmed or suspected *P. falciparum* infection should be hospitalized for evaluation, initiation of treatment, and observation (AIII). Treatment recommendations for patients with HIV are the same as for patients without HIV (AIII). Choice of therapy is guided by the degree of parasitemia, the species of *Plasmodium*, the patient's clinical status, region of infection, and the likely drug susceptibility of the infected species, and can be found at https://www.cdc.gov/malaria.	When suspicion for malaria is low, antimalarial treatment should not be initiated until the diagnosis is confirmed.	For treatment recommendations for specific regions, clinicians should refer to https://www.cdc.gov/malaria or call the CDC Malaria Hotline: 770-488-7788, Monday–Friday, 8 a.m.–4:30 p.m. ET, or 770-488-7100 after hours.
Microsporidiosis	For GI Infections Caused by *Enterocytozoon bienuesi* • Initiate or optimize ART with immune restoration to CD4 count >100 cells/mm^3 (AII), *plus* • Manage dehydration and diarrhea with fluid support (AII) and malnutrition and wasting with nutritional supplements (AIII). For Intestinal and Disseminated (Not Ocular) Infections Caused by Microsporidia Other Than *E. bienuesi* and *Vittaforma corneae* • Albendazole 400 mg PO twice daily (AII), continue until CD4 count >200 cells/mm^3 for >6 months after initiation of ART (BIII) For Disseminated Disease Caused by *Trachipleistophora* or *Anncaliia* • Itraconazole 400 mg PO daily plus albendazole 400 mg PO twice daily (CIII)	For GI Infections Caused by *E. bienuesi* • Fumagillin 60 mg/day (BII) and TNP-470 (a synthetic analog of fumagillin) (BIII) may be effective, but neither is available in the United States. • Nitazoxanide (1,000 mg twice daily) may have some effect, but response may be minimal in patients with low CD4 counts (CIII).	Antimotility agents can be used for diarrhea control if required (BIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	For Ocular Infection • Topical fumagillin bicylohexylammonium (Fumidil B) eyedrops 3 mg/mL in saline (fumagillin 70 µg/mL): two eyedrops every 2 hours for 4 days, then two eyedrops four times daily (investigational use only in United States) (BII) plus albendazole 400 mg PO twice daily, for management of systemic infection (BIII) *If CD4 Count >200 Cells/mm³* • Continue until symptoms resolve (CIII). *If CD4 Count ≤200 Cells/mm³* • Continue until resolution of ocular symptoms and CD4 count increases to >200 cells/mm³ for >6 months in response to ART (BIII).		
Mpox	For Severe Disease or at Risk for Severe Disease (See Other Comments for Definition) • Tecovirimat 600 mg PO every 12 hours (<120 kg) or every 8 hours (≥120 kg) for 14 days (BIII) within 30 minutes of a fatty meal, *or* • Tecovirimat 200 mg IV every 12 hours for 14 days (<120 kg) or 300 mg IV every 12 hours (≥120 kg) if concern exists regarding altered GI absorption capacity, inability to take PO, or extent of organ systems affected by mpox (BIII)		ART should be initiated as soon as possible (AIII). For severe disease, consider early intervention by adding one of the adjunctive therapies at the time of first medical encounter, in consultation with CDC or an expert in mpox treatment (CIII). Patients with severe immunocompromise might benefit from extended treatment (i.e., >14 days) of preferred and/or adjunctive therapies if new confirmed mpox lesions occur or existing lesions worsen despite treatment. Vaccination with any live virus vaccines should be delayed until 3 months after VIGIV administration (CIII). People who received VIGIV shortly after a live virus vaccination should be

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Adjunctive Therapy for Severe Disease or at Risk for Severe Disease • Cidofovir 5 mg/kg/week IV for two doses with saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose and 1 g PO 8 hours after the dose (total of 4 g) (BIII), *or* • Brincidofovir 200 mg PO once weekly for two doses (BIII), *or* • VIGIV 6,000–9,000 units/kg IV single dose (BIII) *Preferred Therapy for Ocular Mpox* • Tecovirimat 600 mg PO every 12 hours (<120 kg) or every 8 hours (≥120 kg) for 14 days (CIII) within 30 minutes of a fatty meal, *and* • Trifluridine (Viroptic) 1 drop into affected eye(s) every 2 hours when awake (max: 9 drops/day) until reepithelialization, then every 4 hours (min: 5 drops/day) for 7 days, or until all periocular lesions have healed (CIII) o Prolonged use of trifluridine beyond 21 days might cause corneal epithelial toxicity and should be avoided (AII).		revaccinated 3 months after administration of the immune globulin (CIII). Definition for Severe Disease or at Risk for Severe Disease: People with HIV who are not virologically suppressed or who have CD4 counts <350 cells/mm^3 are considered at high risk for severe mpox. Severe mpox might manifest as hemorrhagic disease; large number of lesions, such that they are confluent; sepsis; encephalitis; ocular or periorbital infections; or other conditions requiring hospitalization.
Mycobacterium avium Complex (MAC) Disease	At Least Two Drugs as Initial Therapy to Prevent or Delay Emergence of Resistance (AII) • Clarithromycin 500 mg PO twice daily (AI) plus ethambutol 15 mg/kg PO daily (AI), *or* • Azithromycin 500–600 mg plus ethambutol 15 mg/kg PO daily (AII) if drug interaction or intolerance precludes the use of clarithromycin.	Some experts would add a third drug if more severe disease is present. • Rifabutin 300 mg PO daily (dose adjustment may be necessary based on drug interactions) (CI)	Testing of susceptibility to clarithromycin and azithromycin is recommended. NSAIDs can be used for moderate to severe symptoms attributed to IRIS (BIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Duration • At least 12 months (AII) • Shorter duration may be considered. CD4 count should be >100 cells/mm^3 for ≥6 months in response to ART before discontinuation of MAC therapy (CIII).	• Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table of the *Mycobacterium tuberculosis* section for dosing recommendations. Some experts would add a fourth drug if the risk of mortality is high, emergence of drug resistance is likely, CD4 count <50 cells/mm^3, high mycobacterial loads (>2 $\log_{10}$ CFU/mL of blood) are present, or effective ART is absent (CIII). • A fluoroquinolone (CIII) (e.g., moxifloxacin 400 mg PO daily or levofloxacin 500 mg PO daily), *or* • An injectable aminoglycoside (CIII) (e.g., amikacin 10–15 mg/kg IV daily or streptomycin 1 g IV or IM daily).	If IRIS symptoms persist, a short course (i.e., 4–8 weeks) of a systemic corticosteroid (equivalent to 20–40 mg of prednisone daily) can be used (BII). Bedaquiline, tedizolid, linezolid, and omadacycline have demonstrated *in vitro* activity against clinical isolates of MAC; these might also be considered in people with refractory MAC disease.
Mycobacterium tuberculosis (TB) Disease: Drug-Susceptible TB	Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for dosing recommendations. Intensive Phase (8 Weeks) • INH (plus pyridoxine) plus (RIF or RFB) plus PZA plus EMB PO daily (AI) • If drug susceptibility report shows sensitivity to INH and RIF, then EMB may be discontinued before the end of 2 months (AI). Continuation Phase (Duration Depends on Site and Severity of Infection as noted below) • INH (plus pyridoxine) plus (RIF or RFB) PO daily (AII)	Only for Patients Receiving an Efavirenz-based ARV Regimen; Not Recommended for Extrapulmonary TB *Intensive Phase (8 Weeks)* INH plus RPT 1200 mg plus moxifloxacin 400 mg plus PZA plus pyridoxine 25–50mg PO daily (AI)[c] *Continuation Phase (9 Weeks)* • INH plus RPT 1200 mg plus moxifloxacin 400 mg plus pyridoxine 25–50mg PO daily (AI)	DOT is recommended for all patients (AII). All rifamycins may have significant pharmacokinetic interactions with ARV drugs; please refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for dosing recommendations.

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Total Duration of Therapy for Drug-Susceptible TB • Pulmonary, Uncomplicated TB: 6 months (BII) • Pulmonary TB with Positive Culture at 8 Weeks of TB Treatment, or Severe Cavitary or Disseminated Extrapulmonary TB: 9 months (BII) • TB Meningitis: 9–12 months (BII) • Extrapulmonary TB in Other Sites: 6 months (BII)		Therapeutic drug monitoring should be considered in patients receiving rifamycin and interacting ART. Adjunctive corticosteroids for TB meningitis (AII): Dexamethasone 0.3–0.4mg/kg/day for 2–4 weeks, then taper by 0.1 mg/kg per week until 0.1 mg/kg, then 4 mg per day, and taper by 1 mg/week for total of 12 weeks. At doses above 16 mg, dexamethasone is a CYP3A4 inducer and can decrease certain ARVs that are substrates of CYP3A4 (e.g., DOR, RPV, and protease inhibitors). Consultation with a pharmacist is recommended. Adjunctive corticosteroid is not recommended for patients with TB pericarditis (AI). See text for recommendations on preventing and managing paradoxical TB-IRIS, including prednisone dosing recommendations.
Mycobacterium tuberculosis (TB) Disease: Drug-Resistant TB	Refer to the Dosing Recommendations for Use of ARV and Anti-TB Drugs for Treatment of Active Drug Sensitive TB table in the *Mycobacterium tuberculosis* section for dosing recommendations. Empiric Therapy for Suspected Resistance to Rifamycin[d] +/- Resistance to Other Drugs • INH (plus pyridoxine) plus PZA plus EMB plus (moxifloxacin or levofloxacin) plus (linezolid or amikacin[e]) (BII) Confirmed Resistance to INH • (Moxifloxacin or levofloxacin) plus (RIF or RFB) plus EMB plus PZA for 6 months (BII) Confirmed Resistance to Rifamycin +/- Other Drugs (AI) *For 14 Days* • Pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily plus bedaquiline 400 PO daily, *followed by*	*Confirmed Resistance to Rifamycin +/- Other Drugs* • Therapy should be individualized based on drug-susceptibility results and clinical and microbiologic responses, to include ≥5 active drugs, and with close consultation with experienced specialists (BIII).	

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	For 24 Weeks • Pretomanid 200 mg plus linezolid 600 mg plus moxifloxacin 400 mg daily, *and* • Bedaquiline 200 mg PO three times per week Omit moxifloxacin if resistant to fluoroquinolones (AI). Duration • 6–24 months (see Managing Drug-Resistant TB in the *Mycobacterium tuberculosis* section for discussion)		
Pneumocystis Pneumonia (PCP)	People with HIV who develop PCP despite TMP-SMX prophylaxis can usually be treated with standard doses of TMP-SMX (BIII). Duration of PCP treatment: 21 days (AII) For Moderate to Severe PCP • TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) IV given in divided doses every 6 or 8 hours (AI); may switch to PO formulations after clinical improvement (AI) For Mild to Moderate PCP • TMP-SMX: (TMP 15–20 mg/kg/day and SMX 75–100 mg/kg/day) PO given in three divided doses (AI), *or* • TMP-SMX: (160 mg/800 mg or DS) two tablets PO three times daily (AI) Secondary Prophylaxis, After Completion of PCP Treatment • TMP-SMX DS: one tablet PO daily (AI), *or* • TMP-SMX (80 mg/400 mg or SS): one tablet PO daily (AI)	For Moderate to Severe PCP • Primaquine 30 mg (base) PO daily plus (clindamycin 600 mg IV every 6 hours or 900 mg IV every 8 hours) or (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) (AI) (some clinicians prefer this option because it is more effective and less toxic than pentamidine), *or* • Pentamidine 4 mg/kg IV daily infused over ≥60 minutes (AI); can reduce dose to 3 mg/kg IV daily in the event of toxicities (BI) For Mild to Moderate PCP • Dapsone 100 mg PO daily plus TMP 15 mg/kg/day PO given in three divided doses (BI), *or* • Primaquine 30 mg (base) PO daily plus (clindamycin 450 mg PO every 6 hours or 600 mg PO every 8 hours) (BI), *or* • Atovaquone 750 mg PO twice daily with food (BI)	Indications for Adjunctive Corticosteroids for Moderate to Severe PCP (AI) • PaO_2 <70 mmHg at room air, *or* • A-a gradient ≥35 mmHg Prednisone Doses (Beginning as Early as Possible and Within 72 Hours of PCP Therapy) (AI) • Days 1–5: 40 mg PO twice daily • Days 6–10: 40 mg PO daily • Days 11–21: 20 mg PO daily IV methylprednisolone can be administered as 80% of prednisone dose. Benefit of using a corticosteroid if started after 72 hours of treatment is unknown, but some clinicians will use it for moderate to severe PCP (BIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
		Secondary Prophylaxis, After Completion of PCP Treatment The following regimens can be used for people who are seropositive or seronegative for *Toxoplasma gondii*: • TMP-SMX DS: one tablet PO three times weekly (BI), *or* • Dapsone 50 mg PO daily with pyrimethamine[b] 50 mg plus leucovorin 25 mg PO weekly (BI), *or* • Dapsone 200 mg plus pyrimethamine[b] 75 mg plus leucovorin 25 mg PO weekly (BI), *or* • Atovaquone 1,500 mg PO daily with food (BI) The following regimens should only be used if the person is seronegative for *Toxoplasma gondii*: • Dapsone 100 mg PO daily (BI), *or* • Aerosolized pentamidine 300 mg monthly via Respirgard II nebulizer (BI), *or* • Intravenous pentamidine 300 mg every 28 days (CIII)	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[b]/sulfadiazine for the treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis (AII). If TMP-SMX is discontinued because of a mild adverse reaction, reinstitution should be considered after the reaction resolves (AII). The dose can be increased gradually (desensitization) (BI) or the drug can be given at a reduced dose or frequency (CIII). TMP-SMX should be permanently discontinued in patients with possible or definite Stevens-Johnson syndrome or toxic epidermal necrosis (AIII). See alternative options.
Progressive Multifocal Leukoencephalopathy (PML)/JC Virus Infections	There is no specific antiviral therapy for JC virus infection. The main treatment approach is to reverse the immunosuppression caused by HIV. Initiate ART immediately in ART-naive patients (AII). Optimize ART to achieve viral suppression in patients who develop PML and receive ART but remain viremic (AIII).	None	Corticosteroids may be used for PML-IRIS (BIII). The optimal corticosteroid regimen has not been established but should be tailored to individual patients. ART should not be discontinued during PML-IRIS (AIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
Syphilis (*Treponema pallidum* Infection)	Early-Stage (Primary, Secondary, and Early-Latent Syphilis) • Benzathine penicillin G 2.4 million units IM for one dose (AII) Late-Latent Disease (>1 Year) or of Unknown Duration • Benzathine penicillin G 2.4 million units IM weekly for three doses (AII) Late-Stage (Tertiary–Cardiovascular or Gummatous Disease) • Benzathine penicillin G 2.4 million units IM weekly for three doses (AII) Note: Rule out neurosyphilis before initiation of benzathine penicillin. People with CSF abnormalities should be treated with a regimen for neurosyphilis [AII]. Neurosyphilis, Otic, or Ocular Syphilis • Aqueous crystalline penicillin G 18–24 million units per day (administered as 3–4 million units IV every 4 hours or by continuous IV infusion) for 10–14 days (AII) +/- benzathine penicillin G 2.4 million units IM x 1 dose after completion of IV therapy (CIII)	Early-Stage (Primary, Secondary, and Early-Latent Syphilis) *For Penicillin-Allergic Patients* • Doxycycline 100 mg PO twice daily for 14 days (BII), *or* • Ceftriaxone 1 g IM or IV daily for 10–14 days (BII) Late-Latent Disease (>1 Year) or of Unknown Duration *For Penicillin-Allergic Patients* • Doxycycline 100 mg PO twice a day for 28 days (BIII) Neurosyphilis • Procaine penicillin 2.4 million units IM daily plus probenecid 500 mg PO four times a day for 10–14 days (BII), *or* • For penicillin-allergic patients, desensitization to penicillin is the preferred approach (BIII); if not feasible and the patient is not pregnant, ceftriaxone 2 g IV daily for 10–14 days (BII).	The efficacy of non-penicillin alternatives has not been evaluated in patients with HIV, and they should be used only with close clinical and serologic monitoring. People with penicillin allergy whose compliance or follow-up cannot be ensured should be desensitized and treated with benzathine penicillin (AII). For management of early syphilis during pregnancy, limited evidence indicates a second dose of benzathine penicillin G 2.4 million units IM one week after the single dose treatment may be of benefit for congenital syphilis prevention (BII). The Jarisch-Herxheimer reaction is an acute febrile reaction accompanied by headache and myalgia that can occur within the first 24 hours after therapy for syphilis. This reaction occurs most frequently in patients with early syphilis, high non-treponemal titers, and prior penicillin treatment. Procaine penicillin has been discontinued by the manufacturer as of June 13, 2023 (see FDA Drug Shortages).
Talaromycosis (Penicilliosis)	Induction Therapy • Liposomal amphotericin B 3–5 mg/kg/day IV (AI) *Duration* • 2 weeks (AI), followed by consolidation therapy	Induction Therapy • Amphotericin B deoxycholate 0.7 mg/kg/day IV for 2 weeks (if liposomal amphotericin B is not available) (AI)	Itraconazole is not recommended as induction therapy for talaromycosis (AI).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Consolidation Therapy • Itraconazole 200 mg PO twice daily for 10 weeks (AI), followed by chronic maintenance therapy Chronic Maintenance Therapy • Itraconazole 200 mg PO once daily, until CD4 count >100 cells/mm^3 for ≥6 months (AII)	*If Amphotericin B Is Not Available* • Voriconazole 6 mg/kg IV every 12 hours for 1 day (loading dose), then 4 mg/kg IV every 12 hours (BII), *or* • Voriconazole 600 mg PO twice daily for 1 day (loading dose), then 400 mg PO twice daily (BII) *Duration* • 2 weeks (BII), followed by consolidation therapy with itraconazole (preferred) or voriconazole Consolidation Therapy • Voriconazole 200 mg PO twice daily for 10 weeks (BII), followed by chronic maintenance therapy Chronic Maintenance Therapy • Itraconazole should be used (AII). Chronic maintenance therapy with voriconazole has not been studied.	ART can be initiated as early as 1 week after initiation of treatment for talaromycosis (BIII). Itraconazole and voriconazole may have significant interactions with certain ARV agents. These interactions are complex and can be bidirectional. Refer to Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage recommendations. Therapeutic drug monitoring and dosage adjustment may be necessary to ensure triazole antifungal and ARV efficacy and reduce concentration-related toxicities. The goals of itraconazole and voriconazole trough concentrations are >0.5 mcg/mL and >1.0 mcg/mL, respectively.
Toxoplasma gondii Encephalitis	Treatment of Acute Infection • Pyrimethamine[b] 200 mg PO one time, followed by weight-based therapy (AI): o If ≤60 kg: Pyrimethamine[b] 50 mg PO once daily plus sulfadiazine 1,000 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily o If >60 kg: Pyrimethamine[b] 75 mg PO once daily plus sulfadiazine 1,500 mg PO every 6 hours plus leucovorin 10–25 mg PO once daily Note: Leucovorin dose can be increased to 50 mg daily or twice a day.	Treatment of Acute Infection • Pyrimethamine[b] (leucovorin)* plus clindamycin 600 mg IV or PO every 6 hours (AI), *or* • Atovaquone 1,500 mg PO twice a day with food plus pyrimethamine[b] (leucovorin)* (BII), *or* • Atovaquone 1,500 mg PO twice a day with food plus sulfadiazine 1,000–1,500 mg PO every 6 hours (weight-based dosing, as in preferred therapy) (BII), *or* • Atovaquone 1,500 mg PO twice a day with food (BII)	If pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (AII). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI). Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	• TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO twice a day (AII) Duration for Acute Therapy • At least 6 weeks (BII); longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks • After completion of acute therapy, all patients should be initiated on chronic maintenance therapy. Chronic Maintenance Therapy • Pyrimethamine[b] 25–50 mg PO daily plus sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) plus leucovorin 10–25 mg PO daily (AI), *or* • TMP-SMX DS one tablet twice a day (AII)	Chronic Maintenance Therapy • (Pyrimethamine[b] 25–50 mg plus leucovorin 10–25 mg) PO daily plus clindamycin 600 mg PO every 8 hours plus (BI), *or* • Atovaquone 750–1,500 mg PO twice a day plus (pyrimethamine[b] 25 mg plus leucovorin 10 mg) PO daily (BII), *or* • Atovaquone 750–1,500 mg PO twice a day plus sulfadiazine 2,000–4,000 mg PO daily (in two to four divided doses) (BII), *or* • Atovaquone 750–1,500 mg PO twice a day with food (BII) * Pyrimethamine[b] and leucovorin doses are the same as for preferred therapy.	Adjunctive corticosteroids (e.g., dexamethasone) should only be administered when clinically indicated to treat mass effect associated with focal lesions or associated edema (BIII); discontinue as soon as clinically feasible. Antiseizure medications should be administered to patients with a history of seizures (AII) and continued through acute treatment (BII) but should not be used as seizure prophylaxis (BII). If clindamycin is used in place of sulfadiazine, additional therapy must be added to prevent PCP (AII).
Varicella Zoster Virus (VZV) Disease	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases* • Initiate as soon as possible after symptom onset and continue for 5–7 days: o Valacyclovir 1 g PO three times a day (AII), *or* o Famciclovir 500 mg PO three times a day (AII) *Severe or Complicated Cases* • Acyclovir 10 mg/kg IV every 8 hours for 7–10 days (AIII) • May switch to oral valacyclovir, famciclovir, or acyclovir after defervescence if no evidence of visceral involvement (BIII).	Primary Varicella Infection (Chickenpox) *Uncomplicated Cases (for 5–7 Days)* • Acyclovir 800 mg PO five times a day (BII) Herpes Zoster (Shingles) *Acute Localized Dermatomal* • For 7–10 days; consider longer duration if lesions are slow to resolve • Acyclovir 800 mg PO five times a day (BII)	In managing VZV of the eyes, consultation with an ophthalmologist experienced in management of VZV retinitis is strongly recommended (AIII). Duration of therapy for VZV retinitis is not well defined and should be determined based on clinical, virologic, and immunologic responses and ophthalmologic responses. Optimization of ART is recommended for serious and difficult-to-treat VZV infections (e.g., retinitis, encephalitis) (AIII).

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

Opportunistic Infection	Preferred Therapy	Alternative Therapy	Other Comments
	Herpes Zoster (Shingles) *Acute Localized Dermatomal* • For 7–10 days; consider longer duration if lesions are slow to resolve. • Valacyclovir 1 g PO three times a day (AII), *or* • Famciclovir 500 mg three times a day (AII) Extensive Cutaneous Lesion or Visceral Involvement • Acyclovir 10 mg/kg IV every 8 hours until clinical improvement is evident (AII) • May switch to PO therapy (valacyclovir, famciclovir, or acyclovir) after clinical improvement (i.e., when no new vesicle formation or improvement of signs and symptoms of visceral VZV) to complete a 10- to 14-day course (BIII). ARN • Acyclovir 10 mg/kg IV every 8 hours for 10–14 days, followed by valacyclovir 1 g PO three times a day for >14 weeks (AIII), *plus* • Intravitreal ganciclovir 2 mg/0.05 mL twice weekly for 1–2 doses (BIII) PORN • Acyclovir 10 mg/kg IV every 8 hours or ganciclovir 5 mg/kg IV every 12 hours (AIII), *plus* • ≥1 intravitreal antiviral injection: ganciclovir 2 mg/0.05 mL or foscarnet 1.2 mg/0.05 mL twice weekly (AIII) • Initiate or optimize ART (AIII).		In patients with herpes zoster ophthalmicus who have stromal keratitis and anterior uveitis, topical corticosteroids to reduce inflammation may be necessary. The role of ART has not been established in these cases.

[a] TAF 10-mg dose is in the FDC tablets of EVG/c/TAF/FTC and DRV/c/TAF/FTC; when TAF is used with other antiretrovirals, the dose is 25 mg.

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

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

[c] This regimen was not studied and is not recommended for people who are pregnant, breastfeeding, <40 kg, or who have most types of extrapulmonary TB (other than pleural TB or lymphadenitis).

[d] Many patients with RIF resistance also have resistance to isoniazid. Susceptibility should be confirmed in any patient with RIF resistance to determine if isoniazid can be included in the treatment regimen.

[e] Given the risk of ototoxicity and nephrotoxicity with aminoglycosides, use of amikacin should generally be restricted to bridging regimens, while awaiting availability of less toxic medications and/or results of drug-susceptibility testing.

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Opportunistic Infection Guidelines.

Key: +/- = with or without; 3TC = lamivudine; A-a = alveolar-arterial; AASLD = American Association for the Study of Liver Diseases; ARN = acute retinal necrosis; ART = antiretroviral therapy; ARV = antiretroviral; CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; CDI = *Clostridium difficile* infection; CFU = colony-forming unit; CNS = central nervous system; COBI = cobicistat; CrCl = creatinine clearance; CSF = cerebrospinal fluid; DAA = direct-acting antiviral; DOT = directly observed therapy; DRV = darunavir; DS = double strength; EIA = enzyme immunoassay; EMB = ethambutol; EVG = elvitegravir; FDA = U.S. Food and Drug Administration; FDC = fixed-dose combination; FMT = fecal microbiota therapy; FTC = emtricitabine; G6PD = glucose-6-phosphate dehydrogenase; GI = gastrointestinal; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HD = hemodialysis; ICP = intracranial pressure; IDSA = Infectious Diseases Society of America; IL-6 = interleukin-6; IM = intramuscular; INH = isoniazid; IRIS = immune reconstitution inflammatory syndrome; IRU = immune reconstitution uveitis; IV = intravenous; LFA = lateral flow assay; LP = lumbar puncture; MIC = minimum inhibitory concentration; MSM = men who have sex with men; NSAID = nonsteroidal anti-inflammatory drugs; OI = opportunistic infection; PaO_2 = partial pressure of oxygen; PCP = *Pneumocystis* pneumonia; PCR = polymerase chain reaction; PO = oral; PORN = progressive outer retinal necrosis; PZA = pyrazinamide; RFB = rifabutin; RIF = rifampin; RPT = rifapentine; SMX = sulfamethoxazole; SQ = subcutaneous; SS = single strength; STR = single-tablet regimen; SVR = sustained virologic response; TAF = tenofovir alafenamide; TB = tuberculosis; TDF = tenofovir disoproxil fumarate; TMP = trimethoprim; VIGIV = vaccinia immune globulin intravenous; WHO = World Health Organization

Table 3. Indications for Discontinuing and Restarting Primary and Secondary Prophylaxis (or Chronic Maintenance Therapy) for Selected Opportunistic Infections in Adults and Adolescents With HIV

Updated: October 29, 2024
Reviewed: October 29, 2024

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/mm^3 (CII)	No recommendation
Bartonellosis	Not applicable	Not applicable	• Received at least 3–4 months of treatment, *and* • CD4 count >200 cells/mm^3 for ≥6 months (CIII) Some specialists would only discontinue therapy if *Bartonella* titers have also decreased by fourfold (CIII).	No recommendation
Candidiasis (Mucocutaneous)	Not applicable	Not applicable	If used, reasonable to discontinue when CD4 count >200 cells/mm^3 (AIII)	No recommendation
Coccidioidomycosis	CD4 count ≥250 cells/mm^3 with virologic suppression on ART (BIII)	No recommendation	Focal Coccidioidal Pneumonia (AII) • Clinically responded to 3–6 months of antifungal therapy, with CD4 count ≥250 cells/mm^3, and achieved viral suppression on ART • Continue monitoring for recurrence after treatment discontinuation by using serial chest radiographs and coccidioidal serology. Diffuse Pulmonary or Disseminated Non-Meningeal Disease (BIII) • Clinical and serological response to ≥12 months of therapy, *and* • Consultation with experts	No recommendation

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance
			• For diffuse pulmonary disease, continue monitoring for recurrence after treatment discontinuation by using serial chest radiographs and coccidioidal serology. Coccidioidal Meningitis (AII) • Suppressive therapy should be continued indefinitely, even with an increase in CD4 count on ART.	
Cryptococcal Meningitis	Not applicable	Not applicable	If the following criteria are fulfilled (BII): • Completed initial (induction and consolidation) therapy, *and* • Received at least 1 year of antifungal therapy, *and* • Remain asymptomatic of cryptococcal infection, *and* • CD4 count ≥100 cells/mm^3 and with suppressed plasma HIV RNA in response to ART	CD4 count <100 cells/mm^3 (AIII)
Cytomegalovirus Retinitis	Not applicable	Not applicable	• CMV treatment for at least 3–6 months 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 anatomic location of lesions, vision in the contralateral eye, and feasibility of regular ophthalmologic monitoring. • Routine (i.e., every 3 months) ophthalmologic follow-up is recommended after stopping therapy for early detection of relapse or immune restoration uveitis, and then periodically after sustained immune reconstitution (AIII).	CD4 count <100 cells/mm^3 (AIII)

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance
Histoplasma capsulatum Infection	On ART with CD4 count ≥150 cells/mm^3 for 6 months and with viral suppression on ART (BIII)	For patients at high risk of acquiring histoplasmosis (as noted in Table 1), restart if CD4 count decreases to <150 cells/mm^3 (BIII).	If the following criteria (AI) are fulfilled: • Received azole therapy for >1 year, *and* • Negative fungal blood cultures, *and* • Serum or urine *Histoplasma* antigen below the level of quantification, *and* • Viral suppression on ART, *and* • CD4 count ≥150 cells/mm^3 for ≥6 months in response to ART	CD4 count <150 cells/mm^3 (BIII)
Isospora belli Infection	Not applicable	Not applicable	Sustained increase in CD4 count to >200 cells/mm^3 for >6 months in response to ART and without evidence of *I. belli* infection (BIII)	No recommendation
Leishmaniasis: Visceral (and possibly cutaneous leishmaniasis in immunocompromised patients with multiple relapses)	Not applicable	Not applicable	If CD4 count increases to >350 cells/mm^3 and HIV viral load is suppressed for 6 months in response to ART and there is no evidence of clinical relapse of visceral leishmaniasis (CIII)	No recommendation
Microsporidiosis	Not applicable	Not applicable	If there are no signs or symptoms of non-ocular (BIII) or ocular (CIII) microsporidiosis and CD4 count is >200 cells/mm^3 for >6 months in response to ART	No recommendation
Mycobacterium avium Complex Disease	Continuing a fully suppressive ART regimen (AI)	CD4 count <50 cells/mm^3 and not on fully suppressive ART (AIII)	If the following criteria are fulfilled (AI): • Completed ≥12 months of therapy, *and* • No signs and symptoms of MAC disease, *and* • Have sustained (>6 months) CD4 count >100 cells/mm^3 in response to ART	If a fully suppressive ART regimen is not possible and CD4 count is consistently <100 cells/mm^3 (BIII)
Pneumocystis Pneumonia	CD4 count increased from <200 to	CD4 count <100 cells/mm^3	CD4 count increased from <200 cells/mm^3 to ≥200 cells/mm^3	CD4 count <100 cells/mm^3

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

Opportunistic Infection	Indication for Discontinuing Primary Prophylaxis	Indication for Restarting Primary Prophylaxis	Indication for Discontinuing Secondary Prophylaxis/Chronic Maintenance Therapy	Indication for Restarting Secondary Prophylaxis/Chronic Maintenance
	≥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 to 6 months (BII)	regardless of HIV RNA level (AIII) CD4 count 100–200 cells/mm^3 and HIV RNA above detection limit of the assay (AIII)	for ≥3 months in response to ART (AII) Can consider when CD4 count is 100–200 cells/mm^3 if HIV RNA remains below limits of detection for 3–6 months (BII) If PCP occurs at a CD4 count >200 cells/mm^3 while on ART, continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART (BIII). If PCP occurs at a CD4 count >200 cells/mm^3 while not on ART, discontinuation of prophylaxis can be considered when HIV RNA levels are suppressed to below limits of detection for ≥3 to 6 months (CIII).	regardless of HIV RNA level (AIII) CD4 count 100–200 cells/mm^3 and with HIV RNA above detection limit of the assay (AIII)
Talaromycosis (Penicilliosis)	CD4 count >100 cells/mm^3 for >6 months in response to ART (BII) *or* If achieved sustained HIV viral suppression for >6 months (BIII)	CD4 count <100 cells/mm^3 (BIII)—if patient is unable to have ART, or has treatment failure without access to effective ART options, and still resides in or travels to the endemic area	CD4 count >100 cells/mm^3 for ≥6 months in response to ART (BII) *or* If achieved sustained HIV viral suppression for >6 months (BIII)	CD4 count <100 cells/mm^3 (BIII)
Toxoplasma gondii Encephalitis	CD4 count increased to >200 cells/mm^3 for >3 months and sustained HIV RNA below limits of detection in response to ART (AI) Can consider when CD4 count is 100–200 cells/mm^3 if HIV RNA remains below limits of detection for at least 3–6 months (BII)	CD4 count <100 cells/mm^3 (AIII) CD4 count 100–200 cells/mm^3 and with HIV RNA above detection limit of the assay (AIII)	If the following criteria are fulfilled (BI): • Successfully completed initial therapy • Receiving maintenance therapy and remaining free of signs and symptoms of TE, *and* • CD4 count >200 cells/mm^3 for >6 months in response to ART	CD4 count <200 cells/mm^3 (AIII)

Table 3. Indications for Discontinuing and Restarting Opportunistic Infection Secondary Prophylaxis or Chronic Maintenance in Adults and Adolescents With HIV

For information regarding the evidence ratings, refer to the Rating System for Prevention and Treatment Recommendations in the Introduction section of the Adult and Adolescent Antiretroviral Guidelines.

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

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

Updated: September 25, 2023
Reviewed: January 10, 2024

This table lists the known, predicted, or suspected pharmacokinetic (PK) interactions between drugs used for the treatment or prevention of HIV-associated opportunistic infections (OIs). Many of the drugs listed in this table may also interact with antiretroviral (ARV) drugs. Clinicians should see the Drug–Drug Interactions tables in the most current Adult and Adolescent Antiretroviral Guidelines to assess interaction potentials between OI drugs and ARV drugs.

Throughout the table, three recommendations are commonly used when concomitant administration of two drugs may lead to untoward consequences. The rationales for these recommendations are summarized below:

Do not coadminister.

There is either strong evidence or strong likelihood that the PK interaction cannot be managed with a dose modification of one or both drugs and will or may result in either—

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

Coadministration should be avoided, if possible.

There is a potential for significant PK interactions. If other more favorable options exist, clinicians are advised to consider changing components of the regimen to accommodate a safer or more effective regimen. However, coadministration of the drugs may be necessary when there are no other acceptable therapeutic options that provide a more favorable benefit-to-risk ratio. Therapeutic drug monitoring, if available, may facilitate any necessary dose adjustments.

Use with caution.

Drug combinations are recommended to be used with caution when—

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

Rifamycin-Related Induction Interactions

Rifamycin antibiotics are potent inducers of Phase 1 and Phase 2 drug metabolizing reactions. They also affect various transporters. When a rifamycin antibiotic must be combined with an interacting drug, close monitoring for clinical efficacy of the coadministered agent is advised. Therapeutic drug monitoring, if available, may facilitate any necessary dose adjustments.

- *Rifampin (also known as rifampicin):* Interactions may not be apparent in the first several days of rifampin therapy. However, with daily doses of rifampin, enzyme induction increases over a week or more. Based on

limited data, larger daily doses of rifampin (e.g., 1,200 mg or more) appear to produce the same maximum induction as lower doses, but the induction effect occurs more rapidly.

- *Rifabutin:* In general, rifabutin as a cytochrome P450 3A4 (CYP3A4) inducer is about 40% of the potency of rifampin, but this can vary by substrate and enzymatic reaction. Rifabutin is also a substrate of CYP3A4 and may be subject to changes in drug exposure when given concomitantly with 3A4 inhibitors or inducers. Rifabutin dosage modification, therapeutic drug monitoring, and/or more frequent monitoring for rifabutin-related toxicities may be needed.
- *Rifapentine:* In general, daily rifapentine is at least as potent an inducer as rifampin. However, the potential for drug interactions with once-weekly rifapentine is not well studied. Reduced exposure of concurrent drugs that are CYP3A4 substrates is likely to occur with once-weekly rifapentine, with the extent varying by drug.

Azole- and Macrolide-Related Inhibition Interactions

Azole antifungals, including fluconazole, isavuconazole, itraconazole, posaconazole, and voriconazole, are substrates and potent inhibitors of metabolic pathways, including cytochrome P450 enzymes and/or drug transporters (e.g., p-glycoprotein). Interactions involving azole antifungals are common. When an azole antifungal must be combined with an interacting drug, close monitoring for clinical toxicity and efficacy of the azole and/or the coadministered agent may be needed. Therapeutic drug monitoring, if available, may facilitate any necessary dose adjustments.

Macrolides have been shown to form complexes with drug-oxidizing enzymes, including cytochrome P450 enzymes, which render an inhibitory effect. In general, erythromycin and clarithromycin are moderate to strong inhibitors, while azithromycin's propensity for causing clinically relevant drug interactions is lowest, as it does not form complexes with cytochrome P450 enzymes that lead to enzyme inactivation.

Pharmacodynamic Interactions

Pharmacodynamic interactions are not addressed in this table. For example, many of the drug classes listed below independently possess a risk for QTc prolongation, including azoles, macrolides, and certain anti-tuberculosis and antimalarial medications. Coadministration of drugs in these classes may require monitoring for QTc prolongation, particularly in patients with predisposing risk factors.

Therapeutic Drug Monitoring

Drug interactions can alter oral absorption or systemic clearance of drugs. More than one interaction can occur at the same time, with potentially opposing effects. Therapeutic drug monitoring (TDM), if available, may facilitate any necessary dose adjustments in these complicated patients. TDM allows the clinician to make informed, individualized decisions about dose adjustments that are more precise than standardized dose adjustments based upon anticipated, average effects.

Drugs that are marked with an asterisk (*) in the table below are known to have assays (for clinical and/or research purposes) available within the United States and typically in Europe as well. When TDM is appropriate, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution.

Note: To avoid redundancy, drug–drug interactions are listed only once by primary drug (listed alphabetically). Subsequently, when an interacting agent becomes the primary drug, guideline users are referred to the entry for the initial primary drug. See the Clarithromycin row for the first example of this format.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Artemether/ Lumefantrine	Clarithromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ lumefantrine expected	Coadministration should be avoided, if possible. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ lumefantrine possible	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Isavuconazole	↑ lumefantrine possible	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Itraconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Mefloquine	↓ lumefantrine possible	If mefloquine is administered immediately before artemether/lumefantrine, monitor for decreased efficacy of artemether/lumefantrine and encourage food intake.
	Posaconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.
	Rifabutin[a]	↓ artemether, DHA, and lumefantrine expected	Use with caution. Monitor for antimalarial efficacy.
	Rifampin[a]	Artemether AUC ↓ 89% DHA AUC ↓ 85% Lumefantrine AUC ↓ 68%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ artemether, DHA, and lumefantrine expected	Do not coadminister.
	Voriconazole	↑ lumefantrine expected	Coadministration should be avoided, if possible. If coadministered, monitor for lumefantrine toxicities.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Atovaquone*	Doxycycline	Atovaquone concentration ↓ approximately equal to 40% with tetracycline No interaction study with doxycycline	Dose adjustment not established; if coadministered, instruct patient to take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifabutin[a]	Atovaquone C_{ss} ↓ 34% Rifabutin C_{ss} ↓ 19%	Dose adjustment not established; if coadministered, instruct patient to take atovaquone with fatty meal and monitor for decreased atovaquone efficacy.
	Rifampin[a]	Atovaquone C_{ss} ↓ 52% Rifampin C_{ss} ↑ 37%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ atovaquone expected	Do not coadminister.
Bedaquiline*	Clarithromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ bedaquiline expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ bedaquiline possible	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Isavuconazole	↑ bedaquiline possible	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Itraconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities. If coadministration is required for >14 days, weigh the benefits of therapy against the risks of bedaquiline toxicities.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Posaconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
	Rifabutin[a]	↔ bedaquiline ↓ rifabutin possible	If coadministered, separate time of administration; perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	Bedaquiline AUC ↓ 53%	Do not coadminister.
	Rifapentine[a]	Daily Rifapentine Bedaquiline AUC ↓ 55% Weekly Rifapentine ↓ bedaquiline expected	Do not coadminister.
	Voriconazole	↑ bedaquiline expected	Coadministration should be avoided, if possible. If coadministered, monitor for bedaquiline toxicities.
Brincidofovir	Clarithromycin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone clarithromycin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone erythromycin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities. Consider azithromycin in place of erythromycin.
	Rifampin	↑ brincidofovir expected	Coadministration should be avoided, if possible. If coadministered, postpone rifampin for at least 3 hours after brincidofovir and monitor for brincidofovir toxicities.
Caspofungin	Rifabutin[a]	↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).
	Rifampin[a]	Caspofungin C_{min} ↓ 30%	If coadministered, caspofungin dose should be increased to 70 mg/day.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
			Consider alternative echinocandin (e.g., micafungin or anidulafungin).
	Rifapentine[a]	Daily Rifapentine ↓ caspofungin expected Weekly Rifapentine ↓ caspofungin possible	Monitor for antifungal efficacy. Dose not established. Consider increasing caspofungin dose to 70 mg/day or switch to another echinocandin (e.g., micafungin or anidulafungin).
Chloroquine*	Clarithromycin	↑ chloroquine expected	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Erythromycin	↑ chloroquine expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Fluconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Isavuconazole	↑ chloroquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Itraconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Posaconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
	Rifabutin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifampin[a]	↓ chloroquine expected	Monitor for chloroquine efficacy.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ chloroquine expected	Monitor for chloroquine efficacy.
	Voriconazole	↑ chloroquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for chloroquine toxicities.
Clarithromycin*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Fluconazole	Clarithromycin AUC ↑ 18% and C_{min}↑ 33%	No dose adjustment necessary in patients with normal renal function. Monitor for clarithromycin toxicity.
	Isavuconazole	↑ isavuconazole and clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of both isavuconazole and clarithromycin. Role of isavuconazole TDM has not been established.
	Itraconazole	↑ itraconazole and clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of both itraconazole and clarithromycin; perform itraconazole and clarithromycin TDM and adjust dose accordingly.
	Mefloquine	↑ mefloquine expected	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for mefloquine toxicity.
	Posaconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of clarithromycin; perform clarithromycin TDM and adjust dose accordingly.
	Quinine	↑ quinine expected ↑ clarithromycin possible	Do not coadminister. Consider azithromycin in place of clarithromycin.
	Rifabutin[a]	Clarithromycin AUC ↓ 44% 14-OH clarithromycin AUC ↑ 57% Rifabutin AUC ↑ 76% to 99% des-Rbt AUC ↑ 375%	Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, consider reducing rifabutin dose, perform clarithromycin and rifabutin TDM and adjust dose accordingly. Monitor for rifabutin toxicities.
	Rifampin[a]	Clarithromycin concentration ↓ 87% Rifampin AUC ↑ 60%	Do not coadminister. Use azithromycin in place of clarithromycin.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ clarithromycin expected ↑ 14-OH clarithromycin and rifapentine expected	Daily Rifapentine Do not coadminister. Use azithromycin in place of clarithromycin. Weekly Rifapentine Use with caution. Consider azithromycin in place of clarithromycin. If coadministered, monitor for rifapentine toxicities and clarithromycin efficacy; perform clarithromycin and rifapentine TDM and adjust doses accordingly.
	Voriconazole	↑ clarithromycin expected	Coadministration should be avoided, if possible. Consider azithromycin in place of clarithromycin. If coadministered, monitor for toxicities of clarithromycin; perform clarithromycin TDM and adjust dose accordingly.
Dapsone*	Rifabutin[a]	Dapsone AUC ↓ 27% to 40%	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
	Rifampin[a]	Dapsone concentration ↓ 7-fold to 10-fold and $t_{1/2}$ ↓ from 24 hours to 11 hours	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ dapsone expected	Coadministration should be avoided, if possible. Consider alternatives for dapsone.
Doxycycline	Atovaquone	See Atovaquone.	See Atovaquone.
	Rifabutin[a]	↓ doxycycline possible	Monitor closely for doxycycline efficacy or consider alternative therapy.
	Rifampin[a]	Doxycycline AUC ↓ 59%	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifapentine[a]	Daily Rifapentine ↓ doxycycline expected Weekly Rifapentine ↓ doxycycline possible	Use with caution. Monitor closely for doxycycline efficacy or consider alternative therapy.
Erythromycin	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Fluconazole	↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Isavuconazole	↑ erythromycin and isavuconazole possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Itraconazole	Itraconazole AUC ↑ 36% ↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Mefloquine	↑ mefloquine possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Posaconazole	↑ erythromycin expected	Do not coadminister. Consider azithromycin in place of erythromycin.
	Quinine	↑ quinine expected ↑ erythromycin possible	Do not coadminister. Consider azithromycin in place of erythromycin.
	Rifabutin[a]	↓ erythromycin possible ↑ rifabutin possible	Use with caution. Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy and rifabutin toxicities; perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	↓ erythromycin expected	Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ erythromycin expected	Consider azithromycin in place of erythromycin. If coadministered, monitor for erythromycin efficacy.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Voriconazole	↑ erythromycin expected	Do not coadminister. Consider azithromycin in place of erythromycin.
Fluconazole*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine possible	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ fluconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and fluconazole toxicity.
	Rifabutin[a]	Rifabutin AUC ↑ 80% ↔ fluconazole expected	Use with caution. Monitor for rifabutin toxicities. Perform rifabutin TDM; may need to decrease rifabutin dose to 150 mg/day.
	Rifampin[a]	Fluconazole AUC ↓ 23% to 56%	Monitor for antifungal efficacy; may need to increase fluconazole dose.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ fluconazole expected	Monitor for antifungal efficacy; may need to increase fluconazole dose.
Glecaprevir/ Pibrentasvir	Rifabutin[a]	↓ glecaprevir and pibrentasvir possible	Coadministration should be avoided, if possible. Consider alternative agents.
	Rifampin[a]	Glecaprevir AUC ↓ 88% Pibrentasvir AUC ↓ 87%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ glecaprevir and pibrentasvir expected	Do not coadminister. Consider alternative agents.
	TDF	TFV AUC ↑ 29% when coadministered as EFV/TDF/FTC	Use usual dose. Monitor renal function or consider TAF.
	TAF	↔ TFV concentration when coadministered as EVG/c/TAF/FTC	No dose adjustment necessary

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
Isavuconazole*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ isavuconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and isavuconazole toxicities.
	Rifabutin[a]	↓ isavuconazole expected ↑ rifabutin expected	Consider alternative agent(s). If alternative agents are not available, use with close monitoring for isavuconazole antifungal activity and rifabutin toxicity. Perform rifabutin TDM and adjust dose accordingly.
	Rifampin[a]	Isavuconazole AUC ↓ 97%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ isavuconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Itraconazole*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Quinine	↑ quinine expected ↑ itraconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine and itraconazole toxicities; perform itraconazole TDM and adjust dose accordingly.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifabutin[a]	Itraconazole AUC ↓ 70% ↑ rifabutin expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifampin[a]	Itraconazole AUC ↓ 64% to 88%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ itraconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Linezolid*	Rifabutin[a]	↓ linezolid possible	Monitor for linezolid efficacy.
	Rifampin[a]	Linezolid AUC ↓ 32%	Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly.
	Rifapentine[a]	Daily Rifapentine ↓ linezolid expected Weekly Rifapentine ↓ linezolid possible	Daily Rifapentine Monitor for linezolid efficacy. Perform linezolid TDM and adjust dose accordingly. Weekly Rifapentine Monitor for linezolid efficacy.
Mefloquine*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Posaconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
	Rifabutin[a]	↓ mefloquine possible	Monitor for mefloquine efficacy.
	Rifampin[a]	Mefloquine AUC ↓ 68%	Do not coadminister. Use alternative antimalarial drug or rifabutin.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ mefloquine expected	Do not coadminister. Use alternative antimalarial drug or rifabutin.
	Voriconazole	↑ mefloquine expected	Coadministration should be avoided, if possible. If coadministered, monitor for mefloquine toxicities.
Posaconazole*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	↑ quinine expected ↑ posaconazole possible	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.
	Rifabutin[a]	Posaconazole AUC ↓ 49% Rifabutin AUC ↑ 72%	Coadministration should be avoided, if possible. If coadministered, perform posaconazole and rifabutin TDM and adjust doses accordingly; monitor for clinical response to posaconazole and rifabutin toxicities.
	Rifampin[a]	↓ posaconazole expected	Do not coadminister when treating invasive fungal infections. If coadministered for treatment of noninvasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response.
	Rifapentine[a]	Daily and Weekly Rifapentine: ↓ posaconazole expected	Daily Rifapentine Do not coadminister when treating invasive fungal infections. If coadministered for treatment of noninvasive fungal infections, perform posaconazole TDM and adjust dose accordingly; monitor for clinical response. Weekly Rifapentine Coadministration should be avoided, if possible. If coadministered, perform posaconazole TDM and

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
			adjust dose accordingly; monitor clinical response.
Quinine*	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Rifabutin[a]	↓ quinine possible ↑ rifabutin possible	Monitor for quinine efficacy. Monitor for rifabutin toxicity.
	Rifampin[a]	Quinine AUC ↓ 75% to 85%	Do not coadminister.
	Rifapentine[a]	Daily and Weekly Rifapentine ↓ quinine expected	Do not coadminister.
	Voriconazole	↑ quinine expected	Coadministration should be avoided, if possible. If coadministered, monitor for quinine toxicities.
Rifabutin[a]*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Sofosbuvir/Velpatasvir	↓ velpatasvir, sofosbuvir expected	Do not coadminister.
	TAF	↓ TAF, TFV, TFV-DP expected ↑ TFV-DP expected versus TDF alone	If coadministered, monitor for HIV and HBV treatment efficacy. Note: Interpretation extrapolated from TAF and rifampin (see Rifampin). FDA labeling recommends not to coadminister.
	TDF	↔ TDF, TFV, TFV-DP expected	No dosage adjustment necessary.
	Voriconazole	Voriconazole AUC ↓ 79% Rifabutin AUC ↑ 4-fold	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s). Coadministration may be considered if both voriconazole and rifabutin TDM is available to guide therapy.
Rifampin[a]*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	Sofosbuvir/Velpatasvir	Sofosbuvir AUC ↓ 72% Velpatasvir AUC ↓ 82%	Do not coadminister.
	TAF	TAF Plus Rifampin • TAF AUC ↓ 56% • TFV AUC ↓ 53% • TFV-DP AUC ↓ 36% Intracellular TFV-DP concentration is 4.2-fold greater than with TDF alone.	If coadministered, monitor for HIV and HBV treatment efficacy. Note: FDA labeling recommends not to coadminister.
	TDF	TDF Plus Rifampin 600 mg Daily ↔ TFV	No dosage adjustment necessary
	Voriconazole	Voriconazole AUC ↓ 96%	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Rifapentine[a]*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Atovaquone	See Atovaquone.	See Atovaquone.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Caspofungin	See Caspofungin.	See Caspofungin.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Dapsone	See Dapsone.	See Dapsone.
	Doxycycline	See Doxycycline.	See Doxycycline.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Fluconazole	See Fluconazole.	See Fluconazole.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Isavuconazole	See Isavuconazole.	See Isavuconazole.
	Itraconazole	See Itraconazole.	See Itraconazole.
	Linezolid	See Linezolid.	See Linezolid.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Mefloquine	See Mefloquine.	See Mefloquine.
	Posaconazole	See Posaconazole.	See Posaconazole.
	Quinine	See Quinine.	See Quinine.
	TAF	Daily and Weekly Rifapentine ↓ TAF, TFV, TFV-DP possible	If coadministered, monitor for HIV and HBV treatment efficacy. Note: FDA labeling recommends not to coadminister.
	TDF	↔ TDF, TFV, TFV-DP expected	No dosage adjustment necessary
	Sofosbuvir/Velpatasvir	↓ sofosbuvir, velpatasvir expected	Do not coadminister.
	Voriconazole	↓ voriconazole expected	Do not coadminister. Consider alternative antifungal and/or antimycobacterial agent(s).
Sofosbuvir*/ Velpatasvir	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	TAF	TFV AUC ↑ 52% (when RPV/TAF/FTC given with SOF/VEL/VOX)	No dosage adjustment necessary
	TDF	TFV AUC ↑ 35% to 40% (when given with EVG/c/FTC or RPV/FTC) TFV AUC ↑ 81% (when given with EFV/FTC and SOF/VEL) TFV AUC ↑ 39% (when given with DRV/r/FTC and SOF/VEL/VOX)	Monitor for TDF toxicities. Consider TAF in place of TDF.
Tenofovir* Alafenamide	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
Tenofovir* Disoproxil Fumarate	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.

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

Primary Drug	Interacting Agent	Effect on Primary and/or Concomitant Drug Concentrations	Recommendations
	Rifapentine[a]	See Rifapentine.	See Rifapentine.
	Glecaprevir/Pibrentasvir	See Glecaprevir/Pibrentasvir.	See Glecaprevir/Pibrentasvir.
	Sofosbuvir/Velpatasvir	See Sofosbuvir/Velpatasvir.	See Sofosbuvir/Velpatasvir.
Voriconazole*	Artemether/Lumefantrine	See Artemether/Lumefantrine.	See Artemether/Lumefantrine.
	Bedaquiline	See Bedaquiline.	See Bedaquiline.
	Chloroquine	See Chloroquine.	See Chloroquine.
	Clarithromycin	See Clarithromycin.	See Clarithromycin.
	Erythromycin	See Erythromycin.	See Erythromycin.
	Mefloquine	See Mefloquine.	See Mefloquine.
	Quinine	See Quinine.	See Quinine.
	Rifabutin[a]	See Rifabutin.	See Rifabutin.
	Rifampin[a]	See Rifampin.	See Rifampin.
	Rifapentine[a]	See Rifapentine.	See Rifapentine.

[a] Refer to the subsection Rifamycin-Related Induction Interactions in the Table 4 introduction above.

* Drugs marked with asterisk (*) are those which are known to have assays available (for clinical and/or research purposes) within the United States and typically in Europe. When TDM is appropriate, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution.

Key to Symbols

↑ = increase
↓ = decrease
↔ = no substantial change

Key: 14-OH = active metabolite of clarithromycin; AUC = area under the curve; C_{min} = minimum concentration; C_{ss} = concentration at steady state; des-Rbt = desacetyl rifabutin; DHA = dihydroartemisinin; DRV/r = darunavir/ritonavir; EFV = efavirenz; EVG/c = elvitegravir/cobicistat; FDA = U.S. Food and Drug Administration; FTC = emtricitabine; HBV = hepatitis B virus; RPV = rilpivirine; SOF = sofosbuvir; $t_{1/2}$ = half-life; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TFV= tenofovir; TFV-DP = tenofovir diphosphate; VEL = velpatasvir; VOX = voxilaprevir

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Updated: December 31, 2024
Reviewed: December 31, 2024

This table should not be considered a comprehensive list of all possible adverse reactions to each medication. For additional information, clinicians should consult other appropriate resources, such as the U.S. Food and Drug Administration prescribing information. The most serious or common adverse reactions for each drug in the table are generally listed first. For information regarding the effects of these medications on a pregnant individual and the fetus, please refer to the Special Considerations During Pregnancy section of the individual chapter in the guidelines (e.g., see Special Considerations During Pregnancy in the Herpes Simplex Virus chapter for information on the use of acyclovir during pregnancy).

Drug(s)	Adverse Reactions
Acyclovir	• Crystalluria and nephrotoxicity secondary to obstructive urolithiasis, particularly after rapid high-dose IV infusion. Risk is increased with dehydration or pre-existing renal impairment. o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Neurotoxicity with high doses (agitation, confusion, hallucination, seizure, coma), especially in people with renal impairment and/or older adults • Thrombophlebitis at peripheral IV infusion site • Nausea, vomiting, and headache
Adefovir	• Nephrotoxicity, especially in people with underlying renal insufficiency, predisposing comorbidities, or taking concomitant nephrotoxic drugs • Nausea and asthenia
Albendazole	• Rash, pruritus, and fever • Elevated transaminases • Alopecia • Nausea, vomiting, abdominal pain, headache, and dizziness • Bone marrow suppression (i.e., pancytopenia, aplastic anemia, agranulocytosis, and leukopenia) (rare) o Individuals with liver disease, including hepatic echinococcosis, appear to be at higher risk.
Amikacin	• Nephrotoxicity o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Ototoxicity, both hearing loss and vestibular toxicity, is possible. • Neuromuscular blockade, especially with myasthenia or Parkinson's disease and rapid infusion of large doses (rare)

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Amphotericin B Deoxycholate and Lipid Formulations	• Nephrotoxicity (lower incidence with liposomal formulations); irreversible nephrotoxicity is related to cumulative dose. o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Hypokalemia, hypomagnesemia, and hypocalcemia • Infusion-related reactions, including fever, chills, rigors, flank or back pain, and hypotension (lower incidence with liposomal formulations and slower infusion rates) • Thrombophlebitis • Elevated transaminases and bilirubin • Headache, nausea, vomiting, and diarrhea • Heart failure (rarely reported) • Anemia (rare)
Anidulafungin	• Refer to Echinocandins below.
Artemether/Lumefantrine	• QTc prolongation • Anemia, including delayed hemolytic anemia (rare) • Fever, chills, fatigue, arthralgia, and myalgia • Headache, dizziness, asthenia, and insomnia • Nausea, vomiting, diarrhea, abdominal pain, and anorexia • Rash and pruritus
Artesunate	• Acute renal failure requiring dialysis • Hemoglobinuria and jaundice, anemia, thrombocytopenia, neutropenia • Delayed hemolysis and immune hemolytic anemia • QTc prolongation and bradycardia • Hypersensitivity reactions (anaphylaxis) • Dizziness, nausea, and vomiting
Atovaquone	• Elevated transaminases • Rash, nausea, vomiting, abdominal pain, and diarrhea • Fever, headache, and insomnia
Atovaquone/Proguanil	• Abdominal pain, nausea, vomiting, anorexia, diarrhea, headache, asthenia, dizziness, and rash • Elevated transaminases
Azithromycin	• Ototoxicity with prolonged use or high concentrations • Elevated transaminases • Hypersensitivity reactions

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Nausea, vomiting, metallic taste, diarrhea, and abdominal pain • QTc prolongation
Benznidazole	• Photosensitivity and hypersensitivity reactions (including maculopapular rash, allergic dermatitis, TEN, and DRESS) • Paresthesia and peripheral neuropathy, headache, and insomnia • Bone marrow suppression • Nausea, vomiting, abdominal pain, anorexia, and weight loss
Bedaquiline	• QTc prolongation • Elevated transaminases • Nausea, vomiting, anorexia, diarrhea, elevated amylase, arthralgia, headache, and skin rash Note: Due to long medication half-life, adverse effects may persist even after discontinuation.
Bezlotoxumab	• Exacerbation of congestive heart failure • Nausea, fever, and headache • Infusion-related reactions
Brincidofovir	• Elevated transaminases and bilirubin • Nausea, vomiting, and diarrhea • Male infertility
Caspofungin	• Refer to Echinocandins below.
Chloroquine and Hydroxychloroquine	• Auditory and visual disturbances, including blurry vision. Retinal toxicity may occur with long-term use. • QTc prolongation and cardiac arrhythmias • Cardiomyopathy • Bone marrow suppression and hemolysis • Neuropsychiatric changes, including extrapyramidal reactions, suicidal behavior, and convulsive seizures • Hypersensitivity reactions (including TEN, SJS, and EM) • Severe hypoglycemia which may require adjustment of antidiabetic medications • Photosensitivity, pruritus, skin pigmentation, and exacerbation of psoriasis • Dizziness, headache, nausea, vomiting, diarrhea, anorexia, abdominal pain, and hepatitis • Neuromyopathy (may occur with long-term use) (rare)
Cidofovir	• Nephrotoxicity, proteinuria, azotemia, proximal tubular dysfunction (normoglycemic glycosuria, hypophosphatemia), and metabolic acidosis (including Fanconi's syndrome) o Administer IV fluid hydration and oral probenecid to reduce the risk for nephrotoxicity.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Neutropenia and anemia • Ocular hypotony and anterior uveitis/iritis • Nausea, vomiting, abdominal pain, anorexia, and diarrhea • Asthenia, fever, headache, and alopecia • Side effects most likely related to coadministration with probenecid: rash, nausea, vomiting, anorexia, and gout exacerbation.
Ciprofloxacin	• Refer to Fluoroquinolones below.
Clarithromycin	• Elevated transaminases and hepatotoxicity (rare) • Ototoxicity, including hearing loss and tinnitus, with high doses or prolonged use • QTc prolongation • Increased risk of cardiac complications or death in people with heart disease • Diarrhea • Headache, nausea, vomiting, diarrhea, abdominal cramps, and dysgeusia
Clindamycin	• Diarrhea, including *C. difficile*–associated diarrhea and pseudomembranous colitis • Metallic taste (with IV infusion), thrombophlebitis, and arrhythmia with rapid IV infusion • Hypersensitivity reactions (including SJS and TEN) • Nausea, vomiting, and abdominal pain • Elevated transaminases
Clotrimazole (Troche)	• Nausea, vomiting, anorexia, and metallic taste
Cycloserine	• Neuropsychiatric toxicities, including convulsions, psychosis, somnolence, confusion, inability to concentrate, hyperreflexia, headache, tremor, vertigo, paresis, dysarthria, depression (with suicidal ideation), peripheral neuropathy, and seizures (particularly with higher doses and in people with history of chronic alcoholism) o Administer with pyridoxine. • Hypersensitivity reactions (including SJS), allergic dermatitis, and rash
Dapsone	• Methemoglobinemia, hemolytic anemia, neutropenia, and agranulocytosis o Do not use in people with G6PD deficiency. o Risk may be increased with concomitant use of folic acid antagonists (e.g., pyrimethamine). • Rash, fever • Sulfone syndrome (fever, exfoliative dermatitis, lymphadenopathy, hepatic necrosis, and hemolysis) • Phototoxicity and severe cutaneous reactions (including SJS and TEN) • Drug-induced lupus erythematosus

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Hepatotoxicity and nephrotic syndrome • Peripheral neuropathy • Nausea and anorexia
Doxycycline	• Pill-induced esophagitis/esophageal ulceration • Intracranial hypertension • Photosensitivity and skin hyperpigmentation • Thrombophlebitis (with IV infusion) • Nausea and vomiting
Echinocandins (anidulafungin, caspofungin, micafungin)	• Histamine-related infusion reactions (flushing, rash, pruritus, hypotension, and dyspnea) and thrombophlebitis • Elevated transaminases and hepatotoxicity • Diarrhea, nausea, vomiting, fever, and headache • Hemolysis (micafungin) (rare)
Emtricitabine	• Headache, nausea, and diarrhea • Skin hyperpigmentation and rash (palms and soles)
Entecavir	• Headache, fatigue, dizziness, and nausea • Lactic acidosis
Ethambutol	• Optic neuritis (dose- and duration-dependent) and peripheral neuropathy • Headache, nausea, vomiting, anorexia, abdominal pain, and hyperuricemia/gout flare • Hypersensitivity reactions
Ethionamide	• Dose-dependent GI side effects, including nausea, vomiting, anorexia, diarrhea, abdominal pain, and metallic taste (dose titration may alleviate some symptoms) • Hepatotoxicity • Dizziness, drowsiness, confusion, clumsiness, visual disturbances, depression, peripheral neuropathy, and postural hypotension o Administer with pyridoxine. • Photosensitivity and severe cutaneous reactions (including SJS, TEN, and DRESS) • Endocrine side effects, including hypothyroidism (with or without goiter), gynecomastia, acne, alopecia, menstrual irregularities, impotence, and hypoglycemia
Famciclovir	• Nephrotoxicity (in people with underlying renal disease) • Headache, nausea, vomiting, and diarrhea
Fidaxomicin	• Nausea, vomiting, and abdominal pain

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Flucytosine	• Concentration-dependent (>100 mcg/mL) bone marrow suppression (anemia, neutropenia, agranulocytosis, and thrombocytopenia) • Elevated transaminases • Diarrhea, nausea, vomiting, and headache • Rash, pruritus, and photosensitivity
Fluconazole	• Hepatotoxicity • QTc prolongation • Alopecia (with doses ≥400 mg/day for ≥2 months) and dry skin • Nausea, vomiting, diarrhea, and abdominal pain
Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin)	• Restlessness, insomnia, nightmares, confusion, anxiety, paranoia, tremors, seizures, hallucinations, depression, suicidal thoughts, and attempted and completed suicide • Tendonitis and tendon rupture (associated with age over 60, concurrent corticosteroids, diabetes, and kidney, heart, and lung transplant) • Diarrhea, including *C. difficile*–associated diarrhea and colitis • QTc prolongation • Photosensitivity/phototoxicity • Anemia, thrombocytopenia, and leukopenia • Arthralgia and myalgia • Peripheral neuropathy and retinal detachment • Hyper- and hypoglycemia, including hypoglycemic coma • Nausea, diarrhea, bloating, headache, dizziness, and malaise • Vasculitis • Aortic dissection (rare) • Elevated transaminases • Interstitial nephritis (rare) • Severe cutaneous reactions (including SJS and TEN) (rare)
Foscarnet	• Nephrotoxicity and electrolyte imbalances (e.g., hypocalcemia, hypomagnesemia, hypophosphatemia, hyperphosphatemia, hypokalemia) o Administer IV fluid hydration to reduce the risk of nephrotoxicity. • Paresthesia and seizure (associated with electrolyte imbalances) • Anemia • Nausea, vomiting, anorexia, and headache • Genital ulceration • Thrombophlebitis

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Fumagillin (Investigational)	• Nausea, vomiting, diarrhea, anorexia, and abdominal cramps • Thrombocytopenia, anemia, and neutropenia • Vertigo
Ganciclovir	• Neutropenia, thrombocytopenia, anemia, and pancytopenia • Nephrotoxicity • Thrombophlebitis • Nausea, vomiting, fever, asthenia, and hyperhidrosis
Glecaprevir/Pibrentasvir	• Risk of hepatitis B virus reactivation • Hepatic decompensation/failure in people with advanced liver disease • Mild headache, fatigue, nausea, and diarrhea • Altered glucose tolerance in diabetic patients
Ibrexafungerp	• Diarrhea, nausea, abdominal pain, vomiting, and headache
Isavuconazonium Sulfate (Isavuconazole)	• Hepatotoxicity and cholelithiasis • Infusion-related reactions (hypotension, dyspnea, chills, dizziness, paresthesia, and hypoesthesia) • Hypersensitivity reactions (including SJS) • Shortening of QT interval • Nausea, vomiting, diarrhea, headache, dyspnea, and cough • Hypokalemia
Isoniazid	• Hepatotoxicity or asymptomatic elevation in aminotransferase enzymes • Peripheral neuropathy, paresthesia, seizures, psychosis (rare), and optic neuritis o Administering with pyridoxine may prevent or reduce these adverse effects. • Nausea, diarrhea, and flushing • Arthralgia and lupus-like syndrome • Hypersensitivity reactions (including TEN and DRESS) (rare)
Itraconazole	• New-onset or worsening heart failure, edema, adrenal insufficiency, and hypokalemia • QTc prolongation • Elevated transaminases and hepatotoxicity
Lamivudine	• Nausea and vomiting
Levofloxacin	• Refer to Fluoroquinolones above.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Linezolid	• Anemia, neutropenia, and thrombocytopenia (especially with treatment lasting longer than 2–4 weeks, renal insufficiency, or elevated trough concentrations) • Peripheral neuropathy and optic neuritis with long-term therapy • Nausea, vomiting, diarrhea, and headache • Serotonin syndrome (rare) • Seizure (in people with a history of seizure or with risk factors for seizure) (rare) • Lactic acidosis, hypoglycemia, and hyponatremia (rare) • Rhabdomyolysis
Mefloquine	• Depression, psychosis, anxiety, agitation, dizziness, headache, insomnia, and abnormal dreams • QTc prolongation and arrhythmias (extrasystole and sinus bradycardia) • Agranulocytosis and aplastic anemia • Nausea, vomiting, diarrhea, and epigastric pain Note: Due to long medication half-life, side effects may persist even after discontinuation.
Micafungin	• Refer to Echinocandins above.
Miconazole Buccal Tablets	• Dysgeusia, diarrhea, nausea, vomiting, upper abdominal pain, and headache • Local reactions (e.g., oral discomfort, burning, pain, tongue/mouth ulceration, gingival pruritus, swelling, and dry mouth) • Hypersensitivity reactions (may occur in people with known hypersensitivity reaction to milk product concentrate)
Miltefosine	• Nephrotoxicity and elevated transaminases and bilirubin • Retinal degeneration • Leukocytosis and thrombocytopenia • Impaired fertility, scrotal pain, and impaired ejaculation • Nausea, vomiting, diarrhea, anorexia, headache, and motion sickness • Severe cutaneous reactions (including SJS)
Moxifloxacin	• Refer to Fluoroquinolones above.
Nifurtimox	• People with a history of brain injury, seizures, psychiatric disease, and serious behavioral alterations may experience worsening of their conditions. • Vomiting, nausea, decreased appetite, weight loss, abdominal pain, headache, fever, polyneuropathy, insomnia, restlessness, tremors, dizziness, and vertigo • Carcinogenic and teratogenic potential and impaired fertility • Hypersensitivity reactions with hypotension, angioedema, dyspnea, pruritus, rash, or other severe skin reactions

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Nitazoxanide	• Nausea, vomiting, diarrhea, abdominal pain, headache, and chromaturia
Nystatin (Oral Preparations)	• Unpleasant taste, nausea, vomiting, anorexia, and diarrhea
Omadacycline	• Nausea, vomiting, and diarrhea • Elevated transaminases • Infusion site reactions
Oteseconazole	• Nausea, diarrhea, and headache
Paromomycin	• Nausea, vomiting, abdominal cramps, anorexia, rash, and headache • Nephrotoxicity (rare) o Inflammatory bowel disease and renal insufficiency may increase risk.
Penicillin G	All Penicillin G Preparations • Hypersensitivity (immediate or delayed reactions, including anaphylaxis), bone marrow suppression, nausea, vomiting, diarrhea, and drug fever • Jarisch-Herxheimer reaction when used for syphilis (occurs most frequently in persons with early syphilis, high non-treponemal antibody titers, and prior penicillin treatment) Benzathine Penicillin G • IM injection-site reactions (pain and erythema), procaine neuropsychiatric reactions (with high dose), and neurovascular damage (due to inadvertent intravascular instead of IM injection) Aqueous Crystalline Penicillin G (IV) • Thrombophlebitis • Neurotoxicity at high doses—especially in people with renal dysfunction—and hyperkalemia or hypernatremia at high doses (depending on formulation)
Pentamidine	IV Administration • Nephrotoxicity, azotemia • Infusion-related hypotension and thrombophlebitis • QTc prolongation, arrhythmias (including Torsades de pointes), and electrolyte abnormalities • Hypoglycemia, hyperglycemia, and diabetes mellitus • Hepatotoxicity and GI intolerance • Leukopenia and thrombocytopenia • Rash • Pancreatitis (rare) Aerosolized Therapy • Bronchospasm, cough, dyspnea, tachypnea, and metallic taste

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
Posaconazole	IV or PO Administration • Hepatotoxicity • QTc prolongation and hypokalemia • Pseudohyperaldosteronism (hypokalemia and hypertension) • Nausea, vomiting, diarrhea, abdominal pain, and headache IV Infusion • Thrombophlebitis, SBECD accumulation, and worsening renal function with IV formulation (especially in people with eGFR <50 mL/min per package labeling, but observational studies with IV voriconazole suggest that this may not be a concern)
Pretomanid	Adverse Events Reported When Used in Combination With Other Antituberculosis Medications • Nausea, vomiting, headache, and diarrhea • Elevated transaminases • Peripheral and optic neuropathy, myelosuppression, and lactic acidosis (with linezolid) • QTc prolongation (with bedaquiline) Other • Dose-related increase in serum creatinine without change in GFR
Primaquine	• Methemoglobinemia, hemolytic anemia (use with caution in people with mild-moderate G6PD deficiency; do not use if severe G6PD deficiency), leukopenia, and neutropenia • QTc prolongation • Abdominal cramps, nausea, vomiting, and dizziness
Pyrazinamide	• Hepatotoxicity • Polyarthralgia and myalgia • Hyperuricemia/gout flare • Thrombocytopenia and sideroblastic anemia • Nausea, vomiting, flushing, rash, and photosensitivity
Pyrimethamine	• Neutropenia, anemia, thrombocytopenia, and megaloblastic anemia o Administer with leucovorin to reduce the risk of bone marrow suppression. • Anorexia, nausea, vomiting, and rash
Quinine	• QTc prolongation and cardiac arrhythmias • Cinchonism (tinnitus, vertigo, and blurred vision) • Hemolytic anemia (especially in patients with G6PD deficiency), thrombocytopenia, and agranulocytosis • Vision abnormalities (e.g., photophobia, altered color perception, and blindness)

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Hypersensitivity reactions (including SJS and TEN) • Hypoglycemia • Headache, nausea, vomiting, and diarrhea
Rifabutin	• Concentration-dependent uveitis, neutropenia, and thrombocytopenia • Arthralgia • Hepatotoxicity • Rash • Nausea, vomiting, abdominal pain, diarrhea, and anorexia • Red-orange discoloration of body fluids (e.g., urine, sweat, saliva)
Rifampin	• Hepatotoxicity (cholestatic hepatitis) • Thrombocytopenia and hemolytic anemia • Renal failure • Hypersensitivity reactions with flu-like syndrome • Interstitial pulmonary disease • Nausea, vomiting, anorexia, abdominal pain, flatulence, diarrhea, headache, confusion, flushing, and rash • Red-orange discoloration of body fluids
Rifapentine	• Hepatotoxicity • Anemia, neutropenia, and lymphopenia • Hypersensitivity reactions, including flu-like symptoms • Arthralgia • Rash and pruritis • Nausea, vomiting, diarrhea, and anorexia • Red-orange discoloration of body fluids
Sofosbuvir/Velpatasvir	• Risk of hepatitis B virus reactivation • Headache, fatigue, and anemia (associated with ribavirin coadministration) • Altered glucose tolerance in diabetic persons
Streptomycin	• Neurotoxicity, including irreversible ototoxicity (both hearing loss and vestibular toxicity) • Nephrotoxicity • Neuromuscular blockade and respiratory paralysis (associated with rapid infusion of large aminoglycoside doses)
Sulfadiazine	• Severe cutaneous reactions (including SJS, EM, and TEN) and photosensitivity • Anemia, neutropenia, agranulocytosis, and thrombocytopenia

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Crystalluria (nephrolithiasis, urolithiasis) and nephrotoxicity o Administer oral or IV fluid hydration to reduce the risk of nephrotoxicity. • Hepatotoxicity • Drug fever • Peripheral neuritis, tinnitus, hallucinations, seizures (rare), vertigo, and insomnia • Nausea, vomiting, diarrhea, and headache
Tafenoquine	• Decreased hemoglobin as a result of methemoglobinemia and hemolytic anemia o Do not use in people with G6PD deficiency; may cause harm to fetuses and breastfeeding infants who are G6PD-deficient. • Psychiatric adverse reactions (in people with history of psychiatric illness) • Hypersensitivity reactions (angioedema and urticaria) • Visual disturbances • Dizziness, nausea, vomiting, and headache
Tecovirimat	IV or PO Administration • Headache, nausea, abdominal pain, and vomiting IV Infusion • Infusion site pain, swelling, erythema, and extravasation • Contains hydroxypropyl-β-cyclodextrin, which may accumulate in people with renal impairment and has the potential to cause renal toxicity
Tedizolid	• Nausea, vomiting, and diarrhea • Headache and dizziness • Infusion- or injection-related reactions • Thrombocytopenia
Tenofovir Disoproxil Fumarate	• Renal insufficiency and Fanconi syndrome (proximal renal tubulopathy with hypophosphatemia, hypouricemia, proteinuria, and normoglycemic glycosuria) • Decreased bone mineral density • Nausea and vomiting
Tenofovir Alafenamide	• Lower incidence of renal or bone toxicities than with tenofovir disoproxil fumarate
Trimethoprim-Sulfamethoxazole	• Cutaneous reactions (in some cases SJS, EM, and TEN) and photosensitivity • Anemia, neutropenia, agranulocytosis, and thrombocytopenia • Hepatotoxicity • Dose-dependent increase in serum creatinine (without change in eGFR), interstitial nephritis, crystalluria (in people with inadequate hydration), and hyperkalemia (with high-dose TMP) o Encourage oral hydration when using oral TMP-SMX.

Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections

Drug(s)	Adverse Reactions
	• Hypoglycemia and hyponatremia • Drug fever • Nausea and vomiting • Aseptic meningitis and pancreatitis (rare)
Valacyclovir	• Neurotoxicity (e.g., agitation, confusion, hallucination, seizure, coma) with high doses, especially in people with renal impairment • Nephrotoxicity o Encourage oral fluid hydration to reduce the risk of nephrotoxicity. • Nausea, vomiting, abdominal pain, and headache
Valganciclovir	• Bone marrow suppression • Confusion, fever, and tremor • Nephrotoxicity o Encourage oral fluid hydration to reduce the risk of nephrotoxicity. • Carcinogenic and teratogenic potential and impaired fertility • Nausea, vomiting, and diarrhea
Voriconazole	• Visual disturbances (e.g., abnormal vision, color vision change, and/or photophobia) • Optic neuritis (associated with >28 days treatment) • Headache, delirium, hallucination, peripheral neuropathy (rare), and encephalopathy (associated with trough >5.5 mcg/mL) • Hepatotoxicity • QTc prolongation • Photosensitivity • Voriconazole-associated cutaneous squamous cell carcinoma (with long-term use) • Fluorosis and periostitis with high dose and/or prolonged use • Fever, nausea, vomiting, chills, tachycardia, and peripheral edema • Nail changes and alopecia (with long-term use) • SBECD accumulation with IV formulation and worsening renal function (especially in people with eGFR <50 mL/min per package labeling, but observational studies suggest that this may not be a concern)

Key: DRESS = drug reaction with eosinophilia and systemic symptoms; eGFR = estimated glomerular filtration rate; EM = erythema multiforme; G6PD = glucose-6-phosphate dehydrogenase; GFR = glomerular filtration rate; GI = gastrointestinal; IM = intramuscular; IV = intravenous; PO = oral; QTc = QT corrected for heart rate; SBECD = sulfobutylether cyclodextrin; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections that Require Dosage Adjustment in Patients with Renal Insufficiency

Updated: September 25, 2023
Reviewed: January 10, 2024

When renally cleared drugs are administered to patients with reduced renal function, drug accumulation leading to supratherapeutic concentrations and drug toxicities is a primary concern. However, clearance is only one of the pharmacokinetic parameters that affect a drug's disposition. The volume of distribution of a drug also can be altered in patients with reduced renal function. Furthermore, some patients with HIV or diabetes mellitus can have reduced oral absorption of certain drugs. Therefore, although a drug may require a dose reduction in renal failure based on reduced clearance (i.e., increased concentrations), other factors—such as an increased volume of distribution or reduced oral absorption—may decrease concentrations.

Therapeutic drug monitoring (TDM), if available and appropriate, may facilitate dose adjustments in these complicated patients. TDM allows the clinician to make informed, individualized decisions about dose adjustments that are more precise than standardized dose adjustments based on estimated creatinine clearance. Drugs that are marked with an asterisk (*) in the table below are known to have assays (for clinical and/or research purposes) available within the United States and typically in Europe as well. When TDM is appropriate, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution.

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Acyclovir*	IV Dose *Serious HSV* • 5 mg/kg IV every 8 hours *VZV Infections or HSV encephalitis* • 10 mg/kg IV every 8 hours	26–50	100% of dose IV every 12 hours
		10–25	100% of dose IV every 24 hours
		<10	50% of dose IV every 24 hours
		HD	50% of dose every 24 hours; administer dose after HD on days of dialysis.
	PO Dose for Herpes Zoster: 800 mg PO five times per day	10–25	800 mg PO every 8 hours
		<10	800 mg PO every 12 hours
		HD	800 mg PO every 12 hours; administer dose after HD on days of dialysis
Adefovir	10 mg PO every 24 hours	30–49	10 mg PO every 48 hours
		10–29	10 mg PO every 72 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
		HD	10 mg PO weekly; administer dose after HD
Amikacin* For mycobacterial infections	IV 15 mg/kg per day *or* 25 mg/kg three times per week	Use with caution in patients with renal insufficiency and family history of ototoxicity.	15 mg/kg two to three times per week Perform TDM to adjust dose, with target peak concentration 35–45 mcg/mL and trough concentration <4 mcg/mL. Administer dose after HD on days of dialysis.
Amphotericin B*	3–6 mg/kg IV per day (lipid formulation) or 0.7–1.0 mg/kg IV per day (amphotericin B deoxycholate)	N/A	No dosage adjustment necessary; consider alternative antifungals if renal insufficiency occurs during therapy despite adequate hydration.
Cidofovir	5 mg/kg IV on Day 0, repeat 5 mg/kg IV dose on Day 7, then 5 mg/kg IV every 2 weeks Give each dose with probenecid and saline hydration (see Table 2 for dosing instructions).	Pretreatment SCr >1.5 mg/dL *or* CrCl ≤55 mL/min *or* Proteinuria ≥100 mg/dL (≥2 +)	Cidofovir is not recommended unless benefits outweigh risks. See "Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis" for recommendations on renal dose adjustments.
		If SCr increases by 0.3–0.4 mg/dL above baseline	Decrease to 3 mg/kg IV per dose.
		If SCr increases >0.5 mg/dL above baseline *or* Proteinuria ≥3 +	Discontinue therapy.
Ciprofloxacin*	500–750 mg PO every 12 hours *or* 400 mg IV every 8–12 hours	30–50	500–750 mg PO every 12 hours *or* 400 mg IV every 12 hours
		<30	250–500 mg PO every 24 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
			or 400 mg IV every 24 hours	
		HD or PD	250–500 mg PO every 24 hours *or* 200–400 mg IV every 24 hours; administer after HD or PD on days of dialysis.	
Clarithromycin*	500 mg PO every 12 hours	30–60	Usual dose unless used with an HIV PI or with COBI, then reduce dose by 50%.	
		<30	250 mg PO twice daily *or* 500 mg PO once daily If used with an HIV PI or COBI, reduce dose by 75% (or consider using azithromycin as alternative).	
Cycloserine*	10–15 mg/kg/day PO in two divided doses (maximum 1,000 mg/day); start at 250 mg once daily and increase dose per tolerability. Target peak concentration 20–35 mcg/mL	30–80	Usual dose; consider TDM and monitor for toxicities.	
		<30 (not on HD) or HD	250 mg once daily or 500 mg three times per week Perform TDM and adjust dose accordingly. Monitor for toxicities. Use with caution in patients with ESRD who are not on dialysis.	
Emtricitabine*[a] (FTC)	One 200-mg capsule PO once daily *or* 240-mg solution PO once daily	CrCl^ or eGFR# (mL/min)	Oral Capsules	Oral Solution
		15–29	200 mg every 72 hours	80 mg every 24 hours
		<15 and not on HD	200 mg every 96 hours	60 mg every 24 hours
		HD (administer dose after HD on days of dialysis)	200 mg every 24 hours	240 mg every 24 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
Emtricitabine*/ Tenofovir* Alafenamide (FTC/TAF) (FDC Trade Name: Descovy) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing FTC/TAF.	One tablet (FTC 200 mg/TAF 25 mg) PO once daily	<30 and not on HD	Coformulated tablet **is not recommended.**	
		HD	One tablet daily. Administer dose after HD on days of dialysis.	
Emtricitabine*/ Tenofovir* Disoproxil Fumarate (FTC/TDF) (FDC Trade Name: Truvada) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing FTC/TDF.	One (FTC 200 mg/TDF 300 mg) tablet PO daily	30–49	One tablet PO every 48 hours (monitor for worsening renal function or consider switching to TAF)	
		<30 or HD	**Do not use** coformulated tablet. Use formulation for each component drug and adjust dose according to recommendations for the individual drugs.	
Entecavir	Usual Dose: 0.5 mg PO once daily For Treatment of 3TC-Refractory HBV or for Patients with Decompensated Liver Disease: 1 mg PO once daily	CrCl^ or eGFR# (mL/min)	Usual Renal Dose Adjustment	3TC-Refractory or Decompensated Liver Disease
		30 to <50	• 0.25 mg PO every 24 hours, *or* • 0.5 mg PO every 48 hours	• 0.5 mg PO every 24 hours, *or* • 1 mg PO every 48 hours
		10 to <30	• 0.15 mg PO every 24 hours, *or* • 0.5 mg PO every 72 hours	• 0.3 mg PO every 24 hours, *or* • 1 mg PO every 72 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
		<10 or HD or CAPD (administer after HD on days of dialysis)	• 0.05 mg PO every 24 hours, *or* • 0.5 mg PO once every 7 days	• 0.1 mg PO every 24 hours, *or* • 1 mg PO once every 7 days
Ethambutol*	For MAI: 15 mg/kg PO daily For MTB: 15–25 mg/kg PO daily (See the Dosing Recommendations table in the *Mycobacterium tuberculosis* section for additional MTB dosing recommendations.)	<30 or HD	Usual dose PO three times weekly (in patients on HD, give dose after dialysis).	
		PD	Do not use in patients on PD. Consider alternative MAI or MTB treatment (e.g., moxifloxacin). Perform TDM to guide optimal dosing.	
Ethionamide*	15–20 mg/kg PO daily (usually 250–500 mg PO once or twice daily)	<30 or HD	250–500 mg PO once daily Consider TDM.	
Famciclovir*	For Herpes Zoster: 500 mg PO every 8 hours For HSV: 500 mg PO every 12 hours	40–59	500 mg PO every 12 hours	
		20–39	500 mg PO every 24 hours	
		<20	250 mg PO every 24 hours	
		HD	250 mg PO only on HD days, administer after HD	
Fluconazole*	200–1,200 mg PO or IV every 24 hours (dose and route of administration depends on type of OI)	≤50	Administer 100% of the indication-specific initial dose, then adjust maintenance doses to 50% of dose every 24 hours.	
		HD	Administer 100% of the indication-specific initial dose, then adjust maintenance doses to full dose three times per week after HD.	
Flucytosine*	25 mg/kg PO every 6 hours TDM is recommended for patients to guide optimal dosing (target peak serum concentration 2 hours after dose: 25-100 mcg/mL). If TDM is not possible, monitor CBC twice weekly.	21–40	25 mg/kg PO every 12 hours	
		10–20	25 mg/kg PO every 24 hours	
		<10	25 mg/kg PO every 48 hours	
		HD	25–50 mg/kg PO every 48–72 hours; administer dose after HD.	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
Foscarnet	Induction Therapy for CMV Infection: 180 mg/kg/day IV in two divided doses Maintenance Therapy for CMV Infection or for Treatment of HSV Infections: 90–120 mg/kg IV once daily	Dosage adjustment needed according to calculated CrCl/kg; consult product label for dosing table.	Dosage adjustment needed according to calculated CrCl/kg; consult product label for dosing table.
Ganciclovir*	Induction Therapy: 5 mg/kg IV every 12 hours	50–69	2.5 mg/kg IV every 12 hours
		25–49	2.5 mg/kg IV every 24 hours
		10–24	1.25 mg/kg IV every 24 hours
		<10 or HD	1.25 mg/kg IV three times per week; administer dose after HD.
	Maintenance Therapy: 5 mg/kg IV every 24 hours	50–69	2.5 mg/kg IV every 24 hours
		25–49	1.25 mg/kg IV every 24 hours
		10–24	0.625 mg/kg IV every 24 hours
		<10 or HD	0.625 mg/kg IV three times per week; administer dose after HD.
Lamivudine[b] (3TC)	300 mg PO every 24 hours	15–29	150 mg PO once, then 100 mg PO every 24 hours
		5–14	150 mg PO once, then 50 mg PO every 24 hours
		<5 or HD	50 mg PO once, then 25 mg PO every 24 hours; administer dose after HD on days of dialysis.
Lamivudine/ Tenofovir Disoproxil Fumarate (3TC/TDF) (FDC Trade Names: Cimduo or Temixys) Note: Please refer to product information for dosing recommendations for other ARV FDC	One (3TC 300 mg/TDF 300 mg) tablet PO every 24 hours	<50	Coformulated tablet is not recommended.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
products containing 3TC/TDF.				
Levofloxacin*	500 mg (low dose) or 750–1,000 mg (high dose) IV or PO daily	CrCl^ or eGFR# (mL/min)	Low Dose	High Dose
		20–49	500 mg once, then 250 mg every 24 hours, IV or PO	750 mg every 48 hours IV or PO
		<20 or CAPD or HD (administer dose after HD on days of dialysis)	500 mg once, then 250 mg every 48 hours, IV or PO Dose can be adjusted based on serum concentrations.	750 mg once, then 500 mg every 48 hours, IV or PO
Paromomycin	500 mg PO every 6 hours	<10	Minimal systemic absorption. No dosage adjustment necessary but monitor for worsening renal function and ototoxicity in patients with ESRD.	
Peginterferon Alfa-2a	180 mcg SQ once weekly	<30	135 mcg SQ once weekly	
		HD	135 mcg SQ once weekly May reduce to 90 mcg once weekly if severe adverse effects or laboratory abnormalities occur.	
Penicillin G (Potassium or Sodium)	Neurosyphilis, Ocular Syphilis, or Otosyphilis • 3–4 million units IV every 4 hours, *or* • 18–24 million units IV daily as continuous infusion	10–50	2–3 million units every 4 hours *or* 12–18 million units as continuous infusion	
		<10	2 million units every 4–6 hours, *or* 8–12 million units as continuous infusion	
		HD or CAPD	2 million units every 4–6 hours, *or* 8 million units as continuous infusion	
Pentamidine	4 mg/kg IV every 24 hours May reduce dose to 3 mg/kg IV daily in the event of toxicities	<10	4 mg/kg IV every 48 hours	
Posaconazole*	IV: 300 mg twice daily on Day 1; then 300 mg once daily Delayed-Release Tablet: 300 mg PO once daily	<50	No dosage adjustment of oral dose in patients with renal insufficiency. Higher variability in serum concentrations observed in patients with CrCl <20 mL/min. Perform posaconazole TDM (target trough concentration at least >1.25 mcg/mL for treatment).	

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
	Oral Suspension: 400 mg PO twice daily		IV posaconazole is not recommended by the manufacturer because of potential toxicity due to accumulation of SBCD (vehicle of IV product). However, an observational study did not find worsening in renal function in patients with CrCl <50 ml/min given SBCD. Switch patients with CrCl <50 mL/min to oral posaconazole when feasible.
Pyrazinamide*	See the *Mycobacterium tuberculosis* section for weight-based dosing guidelines.	<30 or HD	25–35 mg/kg/dose three times per week; administer dose after HD.
Quinine Sulfate*	650 mg salt (524 mg base) PO every 8 hours	<10 or HD	650 mg once, then 325 mg PO every 12 hours
Rifabutin*	5 mg/kg PO daily (usually 300 mg PO daily) See the *Mycobacterium tuberculosis* section and Drug–Drug Interactions in the Adult and Adolescent Antiretroviral Guidelines for dosage adjustment based on interactions with ARVs.	<30	If toxicity is suspected, consider 50% of dose once daily and perform rifabutin TDM.
Sofosbuvir*	400 mg PO daily	<30	Not recommended. Up to 20-fold higher sofosbuvir metabolite observed in patients with this level of renal impairment.
Streptomycin	15 mg/kg IM or IV every 24 hours *or* 25 mg/kg IM or IV three times per week	Use with caution in patients with renal insufficiency.	TDM is no longer available. Consider an alternative aminoglycoside, as clinically appropriate. If used: 15 mg/kg two to three times weekly. Administer dose after HD.
Sulfadiazine	1,000–1,500 mg PO every 6 hours (1,500 mg every 6 hours for patients >60 kg)	≤ 50	No data. Use alternative anti-toxoplasma therapy.
Tecovirimat	IV: *35 to <120 kg*: 200 mg every 12 hours	30–89	No dosage adjustment necessary Use with caution due to potential accumulation of hydroxypropyl-β-cyclodextrin.

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
	≥*120 kg:* 300 mg every 12 hours	<30	Contraindicated due to potential accumulation of hydroxypropyl-β-cyclodextrin. Note: IV formulation may be considered in patients with CrCl <30 only if drug absorption via enteral administration is expected to be problematic based on an individual risk-benefit assessment in consultation with CDC. In these circumstances, use with caution and monitor renal function continuously. Switch to the oral formulation as soon as possible.
	PO: *40 to <120 kg:* 600 mg every 12 hours ≥*120 kg:* 600 mg every 8 hours	Any eGFR	No dosage adjustment necessary
Tenofovir* Alafenamide (TAF) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing FTC/TAF.	25 mg PO daily	<15	Not recommended
		<15 on HD	No dosage adjustment required. Administer dose after HD on days of dialysis.
Tenofovir* Disoproxil Fumarate (TDF) Note: Please refer to product labels for dosing recommendations for other ARV FDC products containing TDF.	300 mg PO daily	30–49	300 mg PO every 48 hours (consider switching to TAF for treatment of HBV)
		10–29	300 mg PO every 72–96 hours (consider switching to alternative agent for treatment of HBV)
		<10 and not on dialysis	Not recommended
		HD	300 mg PO once weekly; administer dose after dialysis
Trimethoprim* / Sulfamethoxazole (TMP-SMX)	For PCP Treatment • 5 mg/kg (of TMP component) IV every 6–8 hours, *or*	15–30	5 mg/kg (TMP) IV every 12 hours, or two TMP-SMX DS tablets PO every 12 hours
		<15	5 mg/kg (TMP) IV every 24 hours, or one TMP-SMX DS tablet PO every 12 hours (or two TMP-SMX DS tablets every 24 hours)

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR# (mL/min)	Dose
	• Two TMP-SMX DS tablets PO every 8 hours	HD	5 mg/kg/day (TMP) IV, or two TMP-SMX DS tablets PO daily; administer dose after HD on days of dialysis. Consider TDM to optimize therapy (target TMP concentrations: 5–8 mcg/mL).
	For PCP Prophylaxis • One TMP-SMX DS tablet PO daily, • One TMP-SMX DS tablet PO three times per week, *or* • One TMP-SMX SS tablet PO daily	15–30	Reduce dose by 50% (e.g., 1 SS tablet PO daily).
		<15	Reduce dose by 50% or use alternative agent.
	For Toxoplasmosis Encephalitis (TE) Treatment: 5 mg/kg (TMP component) IV or PO every 12 hours	15–30	5 mg/kg (TMP component) IV or PO every 24 hours
		<15	5 mg/kg (TMP component) IV or PO every 24 hours or use alternative agent
	For TE Chronic Maintenance Therapy • One TMP-SMX DS tablet twice daily, *or* • One TMP-SMX DS tablet daily	15–30	Reduce dose by 50%.
		<15	Reduce dose by 50% or use alternative agent.
	For Toxoplasmosis Primary Prophylaxis: One TMP-SMX DS tablet PO daily	15–30	Reduce dose by 50%.
		<15	Reduce dose by 50% or use alternative agent.
Valacyclovir*	For Herpes Zoster: 1 g PO three times daily	30–49	1 g PO every 12 hours
		10–29	1 g PO every 24 hours
		<10	500 mg PO every 24 hours
		HD	500 mg PO every 24 hours; administer dose after HD on days of dialysis.
		30–49	No dosage adjustment
		10–29	For Treatment: 1 g PO every 24 hours

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl^ or eGFR# (mL/min)	Dose	
	For Herpes Simplex Virus Treatment: 1 g PO twice daily For Herpes Simplex Chronic Suppressive Therapy: 500 mg PO twice daily		For Suppressive Therapy: 500 mg PO every 24 hours	
		<10	500 mg PO every 24 hours	
		HD	500 mg PO every 24 hours; administer dose after HD on days of dialysis.	
Valganciclovir	Induction Therapy: 900 mg PO twice daily Maintenance Therapy: 900 mg PO once daily	CrCl^ or eGFR# (mL/min)	Induction	Maintenance
		40–59	450 mg PO twice daily	450 mg PO daily
		26–39	450 mg PO daily	450 mg PO every 48 hours
		10–25	450 mg PO every 48 hours	450 mg PO twice weekly
		<10 and not on dialysis	Not recommended Use IV ganciclovir. May consider: • 200 mg (oral powder for solution) PO three times per week If oral powder formulation is not available, consider: • 450 mg (tablet) PO three times weekly	Not recommended Use IV ganciclovir. May consider: • 100 mg (oral powder for solution) PO three times per week If oral powder formulation is not available, consider: • 450 mg (tablet) PO twice weekly
		HD	Not recommended Use IV ganciclovir. May consider: • 200 mg (oral powder for solution) PO three times per week after HD If oral powder formulation is not available, may consider: • 450 mg (tablet) PO three times per week after HD	Not recommended Use IV ganciclovir. May consider: • 100 mg (oral powder for solution) PO three times per week after HD If oral powder formulation is not available, may consider: • 450 mg (tablet) PO twice per week after HD

Table 6. Dosing Recommendations for Drugs Used to Treat or Prevent Opportunistic Infections That Require Dosage Adjustment in Patients with Renal Insufficiency

Drug(s)	Usual Dose	Dosage Adjustment in Renal Insufficiency	
		CrCl^ or eGFR[#] (mL/min)	Dose
Voriconazole*	6 mg/kg IV every 12 hours for two doses, then 4 mg/kg IV every 12 hours *or* 200–300 mg PO every 12 hours	<50	IV voriconazole **is not recommended** by the manufacturer because of potential toxicity due to accumulation of SBCD (vehicle of IV product). An observational study did not find worsening in renal function in patients with CrCl <50 ml/min. Switch patients with CrCl <50 ml/min to oral voriconazole when feasible. No need for dosage adjustment when the oral dose is used. Perform TDM to adjust dose.

* Drugs marked with asterisk (*) are those known to have assays available (for clinical and/or research purposes) within the United States and typically in Europe. When TDM is appropriate, clinicians should contact their clinical laboratory to determine assay availability and turnaround time for their institution.

[a] The prescribing information for emtricitabine (Emtriva) recommends adjusting doses for patients with CrCl 30-49 and for patients on hemodialysis. However, the prescribing information for several FDC products that contain emtricitabine (including Descovy, Biktaryy, Genvoya, and Odefsey) recommends that the standard dose (emtricitabine 200 mg) can be given once daily in these patients (on days of hemodialysis, give after completion of dialysis). The recommendations in this table incorporate the dosing guidance from the FDC products.

[b] The prescribing information for lamivudine (Epivir) recommends dosage adjustment from 300 mg once daily to 150 mg once daily for patients with CrCl 30–49 mL/min. However, the prescribing information for several FDC products that contain lamivudine (including Epzicom, Dovato, and Triumeq) recommends no dose adjustment for CrCl 30–49 mL/min. The recommendation in this table incorporates the dosing guidance from the FDC products.

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

[#]When estimating kidney function to facilitate drug dosing in patients with renal insufficiency, please refer to the drug's prescribing information and to the National Institute of Diabetes and Digestive and Kidney Diseases' Determining Drug Dosing in Adults with Chronic Kidney Disease page for a discussion on using CrCl based on the Cockcroft-Gault equation versus eGFR.

Key: 3TC = lamivudine; ARV = antiretroviral; CAPD = continuous ambulatory peritoneal dialysis; CBC = complete blood count; CMV = cytomegalovirus; COBI = cobicistat; CrCl = creatinine clearance; DS = double strength; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; FDC = fixed-dose combination; FTC = emtricitabine; HBV = hepatitis B virus; HD = hemodialysis; HSV = herpes simplex virus; IM = intramuscular; IV = intravenous; MAI = *Mycobacterium avium intracellulare;* MTB = *Mycobacterium tuberculosis*; N/A = not applicable; OI = opportunistic infection; PCP = *Pneumocystis* pneumonia; PD = peritoneal dialysis; PI = protease inhibitor; PO = orally; SCr = serum creatinine; SQ = subcutaneous; SBCD = sulfobutylether cyclodextrin; SS = single strength; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TDM = therapeutic drug monitoring; TMP-SMX = trimethoprim-sulfamethoxazole; VZV = varicella zoster virus

Appendix A. List of Abbreviations (Last updated May 7, 2013; last reviewed January 10, 2024)

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

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

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

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

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

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

Appendix B. Panel Roster and Financial Disclosures

Leadership

Member	Institution	Financial Disclosure	
		Company	Relationship
Constance Benson	*University of California, San Diego School of Medicine*	Gilead Sciences	Research Support (paid to institution)
John Brooks	*Atlanta, GA*	None	N/A
Shireesha Dhanireddy	*University of Washington Medicine*	None	N/A
Henry Masur	*National Institutes of Health*	None	N/A
Alice Pau	*National Institutes of Health*	None	N/A

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

Appendix B. Panel Roster and Financial Disclosures

Section Review Group

Member	Institution	Financial Disclosure	
		Company	Relationship
Lydia Aoun Barakat	*Yale University School of Medicine*	None	N/A
Rodrigo Burgos	*University of Illinois Chicago College of Pharmacy*	OptumRx	Consultant
		Merck Janssen Vaccines & Prevention Moderna	Research Support (paid to institution)
Thomas Campbell*	*University of Colorado School of Medicine*	None	N/A
Catherine Decker	*Walter Reed National Military Medical Center*	None	N/A
Ellen Kitchell	*The University of Texas Southwestern Medical Center*	None	N/A
Susana Lazarte	*The University of Texas Southwestern Medical Center*	Gilead Sciences	Research Support (paid to institution)
Paul Pham	*The Johns Hopkins University School of Medicine; Westview Urgent Care Medi Center*	Novo Nordisk	Stockholder
Gregory Robbins	*Massachusetts General Hospital*	Leonard-Meron Biosciences Seed Health/LUCA Biologics Teradyne	Consultant
		Emergent BioSolutions Pfizer	Research Support
Anandi Sheth	*Emory University School of Medicine*	None	N/A
William Short	*Perelman School of Medicine at the University of Pennsylvania*	ViiV Healthcare	Advisory Board
		Gilead Sciences	Research Support

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Bacterial Enteric Infections

Member	Institution	Financial Disclosure	
		Company	Relationship
Carolyn Alonso	*Harvard Medical School; Beth Israel Deaconess Medical Center*	ClinicalCare	Honoraria
Anna Bowen	*Centers for Disease Control and Prevention*	None	N/A
Paul Pham	*The Johns Hopkins University School of Medicine*	Novo Nordisk	Stockholder
Jennifer Spicer	*Emory University School of Medicine*	None	N/A
Brian Zanoni*	*Emory University School of Medicine*	Accordant Health Services	Consultant

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Bartonellosis

Member	Institution	Financial Disclosure	
		Company	Relationship
Nesli Basgoz	*Harvard Medical School*	Allergen	Equity Interest
Carl Boodman	*University of Manitoba, Canada*	Research Foundation – Flanders, Fonds de recherche du Québec	Research Support
		European Society of Clinical Microbiology and Infectious Diseases	Research Support
		Clinical Investigator Program (University of Manitoba)	Research Support
		European Union (doctoral mobility grant)	Travel Support
		International Diagnostics Network/Global Health CPD	Consultant
James Kirby	*Harvard Medical School; Beth Israel Deaconess Medical Center*	None	N/A
Jane Koehler	*University of California, San Francisco School of Medicine*	None	N/A
Grace Marx	*Centers for Disease Control and Prevention*	None	N/A
Stacey Rose*	*Baylor College of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Candidiasis

Member	Institution	Financial Disclosure	
		Company	Relationship
Melissa Johnson	*Duke University School of Medicine*	Scynexis	Research Support
		Biomeme	Patent
Michail Lionakis	*National Institutes of Health*	None	N/A
Jeniel Nett*	*University of Wisconsin–Madison School of Medicine and Public Health*	National Institutes of Health	Research Support
		Burroughs Wellcome Fund	Research Support
		Doris Duke Charitable Foundation	Research Support
			Honoraria
Jack Sobel	*Wayne State University School of Medicine*	Mycovia Pharmaceuticals	Advisory Board
			Speakers Bureau
			Consultant
		Scynexis	Advisory Board
			Speakers Bureau
			Consultant
		UpToDate	Honoraria
			Author

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Community-Acquired Pneumonia

Member	Institution	Financial Disclosure	
		Company	Relationship
Engi Attia		None	N/A
Miwako Kobayashi	*Centers for Disease Control and Prevention*	None	N/A
Ionnis Konstantinidis	*University of Pittsburgh Medical Center*	None	N/A
Michael Niederman	*NewYork-Presbyterian/Weill Cornell Medical Center*	Merck & Co.	Advisory Board
		Gilead Sciences	
		Bayer	
		IQVIA	DSMB Chair/Member
Maria Rodriguez-Barradas*	*Michael E. DeBakey Department of Veterans Affairs Medical Center; Baylor College of Medicine*	None	N/A
Jerry Zifodya	*Tulane School of Medicine*	Firland Foundation	Research Support
		Wetmore Foundation	Research Support

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Cryptosporidiosis/Microsporidiosis

Member	Institution	Financial Disclosure	
		Company	Relationship
Mahalia Desruisseaux	*Yale School of Medicine*	None	N/A
Timothy Hatlen	*University of California, Los Angeles David Geffen School of Medicine*	None	N/A
Michele Hlavsa	*Centers for Disease Control and Prevention*	None	N/A
Nagalingeswaran Kumarasamy	*The Warren Alpert Medical School of Brown University*	None	N/A
Honorine Ward	*Tufts University School of Medicine*	None	N/A
Louis Weiss*	*Albert Einstein College of Medicine*	National Institutes of Health/National Institute of Allergy and Infectious Diseases	Research Support
Clinton White	*The University of Texas Medical Branch*	None	N/A
Lihua Xiao	*Centers for Disease Control and Prevention*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Geographic Opportunistic Infections

Member	Institution	Financial Disclosure	
		Company	Relationship
Naomi Aronson	*Uniformed Services University of the Health Sciences, F. Edward Hébert School of Medicine*	Wellcome Trust	Scientific Advisory Board
Johanna Daily	*Albert Einstein College of Medicine, Weiler Hospital*	None	N/A
Mahalia Desruisseaux	*Yale School of Medicine*	None	N/A
Thuy Le	*Duke University School of Medicine*	Gilead Sciences	Research Support (paid to institution)
Rogelio López-Vélez	*Ramón y Cajal Health Research Institute, Ramón y Cajal University Hospital*	None	N/A
Rojelio Mejia	*Baylor College of Medicine*	Romark, L.C.	Research Support (paid to institution)
Edward Mitre*	*Uniformed Services University of the Health Sciences, F. Edward Hébert School of Medicine*	None	N/A
Susan Montgomery	*Centers for Disease Control and Prevention*	None	N/A
Sunil Parikh	*Yale School of Public Health*	Medincell	Scientific Advisory Board
		Kainomyx	Consultant
Adrienne Showler	*National Institute of Allergy and Infectious Diseases*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Hepatitis B Virus

Member	Institution	Financial Disclosure	
		Company	Relationship
Debika Bhattacharya	*University of California, Los Angeles David Geffen School of Medicine*	Gilead Sciences	Research Support (paid to institution)
Claudia Hawkins	*Northwestern University Feinberg School of Medicine*	None	N/A
Min Kim	*Centers for Disease Control and Prevention*	None	N/A
Kristen Marks	*Weill Cornell Medicine*	Gilead Sciences	Consultant
		Immorna	DSMB member
		Novo Nordisk	DSMB member
		Viiv Healthcare	Research Support (paid to institution)
Chloe Thio*	*The Johns Hopkins University School of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Hepatitis C Virus

Member	Institution	Financial Disclosure	
		Company	Relationship
Meena Bansal	*Icahn School of Medicine at Mount Sinai*	None	N/A
Greer Burkholder	*The University of Alabama at Birmingham Heersink School of Medicine*	Merck Foundation Cepheid	Research Support
Emily Cartwright	*Centers for Disease Control and Prevention*	None	N/A
Arthur Kim	*Harvard Medical School*	Kintor Pharmaceuticals	Data Monitoring Committee
Nina Kim	*University of Washington School of Medicine and School of Public Health*	Gilead Sciences (FOCUS Grant)	Research Support (paid to institution)
Kristen Marks	*Weill Cornell Medicine*	Gilead Sciences	Consultant
		Immorna	Data Safety Monitoring Board Member
		Novo Norodisk	Data Safety Monitoring Board Member
		Viiv	Research Support (paid to institution)
Susanna Naggie	*Duke University School of Medicine*	Bristol Myers Squibb	Adjudication Committee
		Pardes Biosciences, Inc.	Consultant
		National Institutes of Health	Research Support
		Vir Biotechnology	Advisory Board
		Gilead Sciences	Research Support
		Personal Health Insights, Inc.	Data Safety Monitoring Board Chair/Member
			Research Support
		FHI 360	Event Adjudication
Merceditas Villanueva*	*Yale School of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Herpes (HHV-8/CMV)

Member	Institution	Financial Disclosure	
		Company	Relationship
Gary Holland	*David Geffen School of Medicine at the University of California, Los Angeles*	None	N/A
Christine Johnston	*University of Washington School of Medicine*	Gilead Sciences AbbVie	Consultant
Warren Phipps*	*University of Washington School of Medicine*	None	N/A
Ramya Ramaswami	*National Institutes of Health*	Celgene/Bristol-Myers Squibb	Cooperative Research and Development Agreement
		EMD Serono	
		Merck	
		CTI BioPharma	
Shannon Ross	*The University of Alabama at Birmingham Heersink School of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Herpes (HSV/VZV)

Member	Institution	Financial Disclosure	
		Company	Relationship
Gary Holland	*David Geffen School of Medicine at the University of California, Los Angeles*	None	N/A
Christine Johnston	*University of Washington School of Medicine*	Gilead Sciences AbbVie	Consultant
Andrew Karaba	*The Johns Hopkins University School of Medicine*	Hologic, Inc.	Consultant
Poonam Mathur	*University of Washington School of Medicine*	None	N/A
Shannon Ross	*The University of Alabama at Birmingham Heersink School of Medicine*	None	N/A
Sarah Schmalzle*	*University of Maryland, Institute of Human Virology*	Thera Technologies Gilead Sciences	Research Support (paid to institution)

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Human Papillomavirus

Member	Institution	Financial Disclosure	
		Company	Relationship
Susan Cu-Uvin	*The Warren Alpert Medical School of Brown University*	AIDS Malignancy Consortium	Data Safety Monitoring Board Chair/Member
		International Antiviral Society–USA	Honoraria
			Speaker
		UpToDate	Honoraria
			Author
Grant Ellsworth*	*Weill Cornell Medical College*	Merck	Research Support (paid to institution)
Andrea Lisco	*National Institutes of Health*	Merck	Other—Resource Support (no grant, salary, or other funds provided)
		NeoImmuneTech	Research Support (paid to institution)
Lauri Markowitz	*Centers for Disease Control and Prevention*	None	N/A
L. Stewart Massad	*Washington University School of Medicine in St. Louis*	None	N/A
Anna-Barbara Moscicki	*David Geffen School of Medicine at the University of California, Los Angeles*	Merck	Advisory Board
Joel Palefsky	*University of California, San Francisco School of Medicine*	Merck	Research Support (paid to institution)
Elizabeth Stier	*Boston University Medical Campus*	None	N/A
John Weiser	*Centers for Disease Control and Prevention*	None	N/A
John Winters	*Icahn School of Medicine at Mount Sinai*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Immunizations

Member	Institution	Financial Disclosure	
		Company	Relationship
Meagan Deming	*University of Maryland School of Medicine*	None	N/A
Shireesha Dhanireddy	*University of Washington School of Medicine*	None	N/A
Philip Peters	*Centers for Disease Control and Prevention*	None	N/A
Daniel Solomon*	*Harvard Medical School*	None	N/A
Jennifer Whitaker	*Baylor College of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Invasive Mycoses

Member	Institution	Financial Disclosure	
		Company	Relationship
John Baddley	*University of Maryland School of Medicine*	Synexis	Research Support (paid to institution)
David Boulware	*University of Minnesota Medical School*	Appili Therapeutics Matinas BioPharma	Research Support (paid to institution)
Marisa Miceli	*University of Michigan Medical School*	SCYNEXIS F2G Mayne Pharma	Research Support (paid to institution)
		SCYNEXIS	Data Safety Monitoring Board
		Astellas Pharma	Consulting
John Perfect*	*Duke University School of Medicine*	Pfizer	Advisory Board
George R. Thompson	*University of California, Davis Medical Center*	Amplyx Pharmaceuticals Astellas Pharma Cidara Therapeutics F2G Mayne Pharma	Scientific Advisory Board

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Mpox

Member	Institution	Financial Disclosure	
		Company	Relationship
John Brooks	*Atlanta, GA*	None	N/A
Chase Cannon	*University of Washington*	Roche Diagnostics	Consultant
Emily Heil	*University of Maryland School of Pharmacy*	Wolters Kluwer	Consultant
Jesse O'Shea*	*Centers for Disease Control and Prevention*	None	N/A
Agam Rao	*Centers for Disease Control and Prevention*	None	N/A
Boghuma Kabisen Titanji	*Emory University School of Medicine*	Critica ICMEC	Advisory Board
		GSK Mediq	Honoraria
		Critica	Consultant
Jason Zucker	*Columbia University Vagelos College of Physicians and Surgeons*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Mycobacterium avium Complex

Member	Institution	Financial Disclosure	
		Company	Relationship
Constance Benson*	*University of California, San Diego School of Medicine*	Gilead Sciences	Research Support (paid to institution)
Lauren Collins	*Emory University School of Medicine*		
Timothy Hatlen	*Harbor-UCLA Medical Center*		
Maura Manion	*National Institutes of Health*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Mycobacterium tuberculosis

Member	Institution	Financial Disclosure	
		Company	Relationship
James Brust*	*Albert Einstein College of Medicine*	None	N/A
Kelly Dooley	*Vanderbilt University School of Medicine*	None	N/A
Neela Goswami	*Centers for Disease Control and Prevention*	None	N/A
Scott Heysell	*University of Virginia School of Medicine*	None	N/A
Jyoti Mathad	*NewYork-Presbyterian/Weill Cornell Medicine*	None	N/A
Graeme Meintjes	*University of Cape Town, South Africa, Faculty of Health Sciences*	Gilead Sciences	Honoraria
		Otsuka	Data and Safety Monitoring Board
Sarita Shah	*Emory University School of Medicine*	None	N/A
Timothy Sterling	*Vanderbilt University Medical Center*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Pharmacology

Member	Institution	Financial Disclosure	
		Company	Relationship
Rodrigo Burgos	*University of Illinois Chicago, Retzky College of Pharmacy*	ViiV Healthcare, GSK	Advisory Board
		Gilead Sciences Janssen Vaccines & Prevention Merck Shionogi, Inc. ViiV Healthcare, GSK	Research Support
		OptumRx, Inc.	Consultant
Daniel Chastain	*The University of Georgia College of Pharmacy*	None	N/A
Jomy George	*U.S. Food and Drug Administration*	None	N/A
Emily Heil	*University of Maryland School of Pharmacy*	Wolters Kluwer (Lexicomp)	Consultant
Rupali Jain	*University of Washington School of Pharmacy*	Wolters Kluwer	Consultant
Bernadette Jakeman	*The University of New Mexico College of Pharmacy*	American College of Clinical Pharmacy (Infectious Diseases Self-Assessment Program Chapter) ASHP Continuing Education CEimpact Education Pharmacy Times Continuing Education ViiV Healthcare, GSK	Honoraria
		Merck	Research Support
		Wolters Kluwer	Consultant
Safia Kuriakose*	*National Institutes of Health*	None	N/A
Alice Pau	*National Institutes of Health*	None	N/A
Charles Peloquin	*University of Florida College of Pharmacy and Emerging Pathogens Institute*	Sun Pharmaceutical Industries Ltd.	Consultant

Member	Institution	Financial Disclosure	
		Company	Relationship
Anthony Podany	*University of Nebraska Medical Center*	None	N/A
Katherine Yang	*University of California, San Francisco School of Pharmacy*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Progressive Multifocal Leukoencephalopathy

Member	Institution	Financial Disclosure	
		Company	Relationship
Shruti Agnihotri	*The University of Alabama at Birmingham Heersink School of Medicine*	Moderna Pfizer Gilead Sciences Johnson & Johnson	Equity Interest
Paola Cinque	*San Raffaele Scientific Institute, Milan, Italy*	Pfizer Takeda Pharmaceuticals ShirePharma Polpharma	Data and Safety Monitoring Board
		Cellevolve Sobi	Advisory Board
		Excision BioTherapeutics Janssen	Consultant
David Clifford*	*Washington University School of Medicine in St. Louis*	Wave Life Sciences Atara Biotherapeutics Cellevolve Takeda Pharmaceuticals	Data and Safety Monitoring Board
		Arena Pharmaceuticals Roche Seagen (Seattle Genetics)	Consultant
		National Institutes of Health	Research Support
Irene Cortese	*National Institutes of Health*	Nouscom PDC*line Pharma Life Sciences Partners V Cv	Equity Interest
Jose M. Miro	*Hospital Clínic de Barcelona–IDIBAPS, University of Barcelona, Spain*	None	N/A
C. Sabrina Tan	*The University of Iowa Carver College of Medicine*	Cellevolve	Advisory Board

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Pneumocystis Pneumonia

Member	Institution	Financial Disclosure	
		Company	Relationship
Kristina Crothers	*University of Washington School of Medicine*	None	N/A
Jannik Helweg-Larsen	*Rigshospitalet, Copenhagen University, Denmark*	None	N/A
Aley Kalapila	*Emory University School of Medicine*	None	N/A
Joseph Kovacs*	*National Institutes of Health*	Matinas BioPharma	Research Support
		Merck	
Alison Morris	*University of Pittsburgh School of Medicine*	None	N/A
Sean Wasserman	*University of Cape Town, South Africa, Faculty of Health Sciences*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Pregnancy

Member	Institution	Financial Disclosure	
		Company	Relationship
Jean Anderson	*The Johns Hopkins University School of Medicine*	DKBmed	Research Support (paid to institution)
Katherine Bunge	*UPMC Magee-Womens Hospital*	None	N/A
Karley Dutra	*Medical University of South Carolina*	None	N/A
Oluwatosin Goje	*Cleveland Clinic Lerner College of Medicine*	UpToDate	Honoraria
			Topic Contributor
		Merck	Honoraria
			Topic Contributor
		ClinicalKey	Honoraria
		Evvy	Advisory Board
		Scynexis	Consultant
Erica Hardy	*Warren Alpert Medical School of Brown University*	None	N/A
Sylvia LaCourse*	*University of Washington School of Medicine and School of Public Health*	Merck	Research Support (paid to institution)
Gweneth Lazenby	*Medical University of South Carolina*	Sanaria	Data and Safety Monitoring Board
Anna Powell	*The Johns Hopkins University School of Medicine*	Cepheid	Consultant
		UpToDate	Honoraria
Rodney Wright	*Albert Einstein College of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Syphilis

Member	Institution	Financial Disclosure	
		Company	Relationship
Laura Bachmann	*Centers for Disease Control and Prevention*	None	N/A
Khalil Ghanem	*The Johns Hopkins University School of Medicine*	None	N/A
Matthew Hamill	*The Johns Hopkins University School of Medicine*	Chembio Diagnostics, Inc.	Honoraria
		Cepheid Chembio Diagnostics, Inc. Roche Diagnostics	Other
Edward W. Hook	*University of Alabama at Birmingham Marnix E. Heersink School of Medicine*	Visby Medical	Scientific Advisory Board
Arlene Sena	*University of North Carolina at Chapel Hill School of Medicine*	None	N/A
Irene Stafford	*The University of Texas Health Science Center at Houston, McGovern Medical School*	None	N/A
Susan Tuddenham*	*The Johns Hopkins University School of Medicine*	None	N/A
Kimberly Workowski	*Emory University School of Medicine*	None	N/A

* Section Group Lead

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

Appendix B. Panel Roster and Financial Disclosures

Toxoplasma gondii

Member	Institution	Financial Disclosure	
		Company	Relationship
Sarita Boyd	*U.S. Food and Drug Administration*	None	N/A
Joseph Kovacs*	*National Institutes of Health*	None	N/A
Janaki Kuruppu	*National Institutes of Health*	None	N/A
Leon Lai	*MedStar Washington Hospital Center*	None	N/A
Jose M. Miro	*Hospital Clínic de Barcelona–IDIBAPS, University of Barcelona, Spain*	None	N/A
Daniel Podzamczer	*Fight AIDS and Infectious Diseases Foundation, Hospital Germans Trias i Pujol, Badalona, Spain*	Gilead Sciences	Consultant
		MSD	
		Janssen	
		ViiV Healthcare	
Bryan R. Smith	*National Institutes of Health*	None	N/A

* Section Group Lead

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