Opportunistic Infections: Treatment

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Module 4: Co-Occurring Conditions
Lesson 3: Opportunistic Infections: Treatment

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Background

Overview

The introduction of effective antiretroviral therapy in the mid-1990s has played a major role in the dramatic reduction in opportunistic infection-related morbidity and mortality.[1,2,3] Despite the widespread availability and use of potent antiretroviral therapy, individuals with HIV continue to suffer significant morbidity and mortality from opportunistic infections, defined as infections that are more frequent or severe due to immunosuppression. Most opportunistic infections now occur in people with undiagnosed HIV or in persons diagnosed with HIV who are not engaged in care. Because opportunistic infections continue to occur with potentially devastating consequences, clinicians should have a core understanding of the diagnosis, prevention, and treatment of opportunistic infections. This topic review provides an overview for the treatment of the most common opportunistic infections based on the Adult and Adolescent OI Guidelines.[4]

Immune Reconstitution Syndrome

After initiation of effective antiretroviral therapy and during the early phases of immune reconstitution, a paradoxical worsening of certain clinical conditions can occur; this has been termed immune reconstitution inflammatory syndrome (IRIS).[5,6] Similarly, some patients with profound immunosuppression may have undiagnosed opportunistic infections that may be exposed as a result of an immune upregulation after starting antiretroviral therapy—this has been referred to as “unmasking” IRIS, a process whereby the immune system regains the capacity to recognize antigens and pathogens that previously it was too suppressed to confront. Although IRIS may develop in the context of various infections in a patient with advanced HIV disease, the most commonly observed IRIS events involve disseminated Mycobacterium avium complex disease, cryptococcal meningitis, tuberculosis, progressive multifocal leukoencephalopathy, and cytomegalovirus retinitis.[7,8,9]
**Pneumocystis Pneumonia**

**Background**

*Pneumocystis* pneumonia (PCP) is a leading cause of morbidity and mortality in people with HIV. The causative organism, *Pneumocystis jirovecii*, is classified as a fungus and was previously known as *P. carinii*. Phylogenetic studies led to a name change in 1999 (from *P. carinii* to *P. jirovecii*).[10] Despite the organism name change, the acronym PCP is still widely used to denote *Pneumocystis* pneumonia. Individuals with HIV most often acquire *P. jirovecii* via the airborne route and disease may occur either with newly acquired infection or by reactivation of latent infection.[10] The risk of developing *Pneumocystis* pneumonia increases markedly when the CD4 count drops below 200 cells/mm$^3$.[11,12,13] In the absence of *Pneumocystis* pneumonia prophylaxis or use of effective antiretroviral therapy, *Pneumocystis* pneumonia will develop in approximately 80% of persons with AIDS. After the use of effective antiretroviral therapy became widespread, the incidence of *Pneumocystis* pneumonia among individuals with AIDS in the United States and Western Europe dropped substantially—from approximately 30 cases per 1,000 person-years in the mid-1990s to 3.9 cases per 1,000 person-years in 2008 through 2010 (Figure 1).[1,2]

**Clinical Manifestations**

The most common clinical manifestations in patients with *Pneumocystis* pneumonia are a subacute nonproductive cough, progressive dyspnea (particularly dyspnea on exertion), and fever.[13,14] The pulmonary physical examination is usually normal, but in more advanced disease, rales may be present on auscultation. If untreated, individuals with *Pneumocystis* pneumonia may have progression of clinical disease with worsening dyspnea and hypoxic respiratory failure.

**Diagnosis**

All persons with suspected *Pneumocystis* pneumonia should undergo evaluation to confirm the diagnosis, especially since other bacterial, mycobacterial, and fungal diseases commonly encountered among individuals with advanced immunosuppression, can mimic *Pneumocystis* pneumonia. Nondefinitive tests can be used to support the diagnosis, but all persons with suspected *Pneumocystis* pneumonia should have a definitive diagnosis made.[14,15]

**Nondefinitive Diagnostic Tests**

The diagnosis of *Pneumocystis* pneumonia can be supported by several nonspecific tests.

- **Chest Radiograph**: In patients with *Pneumocystis* pneumonia, the chest radiograph most often shows diffuse bilateral perihilar infiltrates; the appearance of these infiltrates are often described as ground glass and butterfly-shaped (Figure 2).[16,17] Approximately 15 to 20% of persons with *Pneumocystis* pneumonia have a normal chest radiograph, particularly those in the earlier phase of *Pneumocystis* pneumonia.[13,17,18]
- **High Resolution Chest Computed Tomography**: High-resolution chest computed tomography is more sensitive than chest radiography in detecting interstitial abnormalities (Figure 3).[16,19] In some individuals with *Pneumocystis* pneumonia, pneumatoceles or cystic lesions develop; these may result in pneumothorax (Figure 4).[20,21]
- **Exercise Pulse Oximetry**: Oxygen desaturation with exercise as documented with continuous pulse oximetry has been shown to be a feature of most persons with *Pneumocystis* pneumonia.[22]
- **Laboratory Studies**: Nonspecific laboratory findings that may support the diagnosis of *Pneumocystis* pneumonia include lactate dehydrogenase (LDH) greater than 500 mg/dL and a 1,3-beta-D-glucan level of 80 pg/mL or greater; the 1,3-beta-D-glucan is used for testing because it is a major component of the *P. jirovecii* cell wall.[23,24,25] Although the sensitivity of the beta-D-glucan test is high, the specificity is low because persons with HIV who have advanced immunosuppression are at
risk for multiple other fungal pathogens that can also cause elevated beta-D-glucan levels.[25]

Definitive Diagnostic Tests

A definitive diagnosis of *Pneumocystis* pneumonia requires detection of organisms in respiratory secretions or tissue.[13,26] Several tests usually play a role in the definitive diagnosis of *Pneumocystis* pneumonia.

- **Induced Sputum**: An induced sputum sample using an ultrasonic saline nebulizer has a sensitivity for diagnosing *Pneumocystis* pneumonia that ranges from 50 to 90%, assuming the medical facility has experience with performing this test.[13,26] Spontaneously expectorated sputum should not be submitted for diagnosis of *Pneumocystis* pneumonia due to low sensitivity.
- **Bronchoscopy**: A patient with a negative induced sputum should undergo bronchoscopy with bronchoalveolar lavage (BAL), which has a sensitivity of approximately 95%; some centers go directly to BAL as the initial test.[27]
- **Transbronchial or Open-Lung Biopsy**: A transbronchial biopsy or open-lung biopsy can further increase the yield, but is rarely required because of the high yield with BAL.
- **Detection of *P. jiroveci* Organisms in Sample**: Many laboratories now consider the direct immunofluorescent stain as the procedure of choice for identifying *P. jiroveci* organisms; this test has higher sensitivity than stains that can detect *P. jiroveci* (methenamine silver, Giemsa silver, and toluidine blue-O).[13,26,28,29] Although PCR is a highly sensitive test for detecting *P. jirovecii* organisms, it does not accurately distinguish acute infection from colonization.[26,28,30,31]

Treatment of *Pneumocystis* Pneumonia

The prompt and appropriate treatment of *Pneumocystis* pneumonia is essential for having a good outcomes for this potentially fatal opportunistic infection. Accordingly, if the diagnosis of *Pneumocystis* pneumonia is suspected, empiric treatment for *Pneumocystis* pneumonia should be started without delay while the diagnostic evaluation is underway. The Adult and Adolescent OI Guidelines provide treatment regimens and indications for the use of adjunctive corticosteroids based on the severity of the pneumonia.[15] Nontoxic-appearing individuals with suspected or diagnosed *Pneumocystis* pneumonia can receive treatment as an outpatient provided they have a documented PaO2 of 70 mm Hg or greater and a calculated P(A-a O2) gradient less than 35 mm Hg. For all the regimens used to treat *Pneumocystis* pneumonia, the duration of antimicrobial therapy is 21 days, assuming clinical improvement, although the recovery of functional status can often lag behind based on the degree of pulmonary scarring, immunosuppression, comorbidities, and/or development of IRIS.[15]

Mild-to-Moderate *Pneumocystis* Pneumonia

Mild-to-moderate *Pneumocystis* pneumonia is defined as having a PaO2 of 70 mm Hg or greater and a calculated P(A-a O2) gradient less than 35 (Table 1).[15] Individuals who are being considered for treatment as an outpatient should appear nontoxic and meet the criteria for mild-to-moderate *Pneumocystis* pneumonia.

- **Preferred Therapy**: The recommended treatment for mild-to-moderate *Pneumocystis* pneumonia is oral trimethoprim-sulfamethoxazole, given in three divided daily doses.
- **Alternative Therapy**: For patients who cannot take trimethoprim-sulfamethoxazole, alternative regimens include trimethoprim plus dapsone, primaquine plus clindamycin, or atovaquone. Prior to starting dapsone or primaquine, it is advisable to check a glucose-6-phosphate dehydrogenase (G6PD) level, since both drugs may induce hemolytic anemia in patients with G6PD deficiency. Compared to trimethoprim-sulfamethoxazole, trimethoprim plus dapsone has fewer side effects but is less convenient due to a high pill burden. Atovaquone causes few side effects, but it is only available in liquid form. In addition, it is less effective (and more expensive) than trimethoprim-sulfamethoxazole and the bad taste of atovaquone can impact adherence to a full course of treatment.
Moderate-to-Severe PCP

Moderate-to-severe *Pneumocystis* pneumonia is defined by room air PaO$_2$ less than 70 mm Hg or alveolar-arterial O2 gradient greater than or equal to 35 mm Hg (Table 2).[15]

- **Preferred Therapy:** The recommended treatment is trimethoprim-sulfamethoxazole. The oral dosage is the same as with mild-to-moderate disease, but therapy for moderate-to-severe is usually started intravenously and then switched to oral therapy after clinical improvement.

- **Alternative Therapy:** If a person has a mild allergy to trimethoprim-sulfamethoxazole, rapid desensitization should be considered. In cases of life-threatening allergy or in cases where desensitization is not possible, alternative agents include intravenous pentamidine or intravenous clindamycin plus oral primaquine. A G6PD level should be checked for persons who will receive primaquine.

- **Use of Adjunctive Corticosteroids:** For moderate-to-severe *Pneumocystis* pneumonia, adjunctive corticosteroids improve survival and should be started as soon as antimicrobial treatment is started for *Pneumocystis* pneumonia (and at the latest within 72 hours of initiating antimicrobial therapy).[13,15,32] The recommended regimen for the corticosteroids is prednisone 40 mg twice daily for days 1 to 5, prednisone 40 mg once daily for days 6 to 10, and prednisone 20 mg once daily for days 11 to 21. The dose of intravenous methylprednisolone, if parenteral therapy is needed, is 80% of the oral prednisone dosage (i.e., 32 mg methylprednisolone = 40 mg prednisone).

**Timing of Starting Antiretroviral Therapy**

Individuals not on antiretroviral therapy who develop *Pneumocystis* pneumonia should start antiretroviral therapy within 2 weeks of the diagnosis of *Pneumocystis* pneumonia, if possible.[15] The recommendation to start antiretroviral therapy early is primarily based on data from a randomized, controlled trial that evaluated the timing of initiating antiretroviral therapy in 282 adults with acute opportunistic infections, including 177 (63%) with *Pneumocystis* pneumonia; participants randomized to early initiation of antiretroviral therapy (median 12 days after start of acute opportunistic infection treatment) experienced a lower incidence of progression to AIDS or death, as compared to those randomized to deferred initiation (median 45 days after start of acute opportunistic infection treatment).[33]

**Preventing Recurrence (Secondary Prophylaxis)**

**Secondary Prophylaxis**

All persons with HIV who are diagnosed with *Pneumocystis* pneumonia should receive secondary prophylaxis beginning immediately after completion of the 21-day treatment course (Table 3).[15] Individuals who do not receive secondary prophylaxis have a high risk for developing another episode of *Pneumocystis* pneumonia.

- **Preferred Therapy:** For secondary prophylaxis, trimethoprim-sulfamethoxazole (one single-strength or double-strength tablet daily) is the drug of choice.

- **Alternative Therapies:** For secondary prophylaxis, alternative therapies include dapsone, dapsone plus pyrimethamine plus leucovorin, aerosolized pentamidine, or atovaquone.

**Indications for Discontinuing Secondary Prophylaxis**

Secondary prophylaxis against *Pneumocystis* pneumonia should be discontinued in persons who respond to antiretroviral therapy with an increase in CD4 count to greater than 200 cells/mm$^3$ for longer than 3 months.[15] In addition, clinicians can consider discontinuing secondary prophylaxis for *Pneumocystis* pneumonia if the individual has a CD4 count of 100 to 200 cells/mm$^3$ and the HIV RNA levels remain below the limit of detection for at least 3 to 6 months.[15,34,35] If an episode of *Pneumocystis* pneumonia occurs at a CD4 count greater than 200 cells/mm$^3$ in a person already on antiretroviral therapy, most experts would recommend continuing *Pneumocystis* pneumonia prophylaxis for life, regardless of how high the CD4 rises.
Restarting Secondary Prophylaxis Therapy

If the CD4 count decreases to less than 100 cells/mm$^3$, prophylaxis should be reinitiated, regardless of HIV RNA levels.[15] In addition, persons with a CD4 count in the 100 to 200 cells/mm$^3$ range should restart secondary prophylaxis if HIV plasma RNA levels are detectable.[15] Note that for Pneumocystis pneumonia, the criteria for discontinuing and restarting secondary prophylaxis is the same as for discontinuing and restarting primary prophylaxis.
Toxoplasma gondii Encephalitis

Background

*Toxoplasma gondii* is a protozoan parasite that can infect humans and cause focal encephalitis and more rarely, retinitis, pneumonitis, and disseminated disease. Most *Toxoplasma* disease in persons with HIV occurs from reactivation of latent organisms in patients who have a CD4 count less than 100 cells/mm\(^3\).[36,37] In the United States, prior to the availability of effective antiretroviral therapy, the incidence of *Toxoplasma* encephalitis among AIDS patients with a CD4 count less than 100 cells/mm\(^3\) was 40 per 1000 person-years;[38] this rate has decreased significantly with widespread use of antiretroviral therapy and trimethoprim-sulfamethoxazole for prophylaxis.[1,2] All individuals diagnosed with HIV should be tested for IgG antibody to *T. gondii* at their initial medical visit.[39]

Clinical Manifestations

The central nervous system is by far the most common site for the development of toxoplasmosis. Extracerebral disease, such as pulmonary or ocular involvement, occurs in about 1 to 2% of individuals with AIDS and toxoplasmosis.[40] Individuals with AIDS and *Toxoplasma* encephalitis characteristically present with headache, confusion, fever, and focal neurologic deficits (Figure 5) and (Figure 6).[37,39] Approximately 30% of persons with HIV and *Toxoplasma* encephalitis develop seizures, and those with severe disease may present with more profound changes in mental status. Abnormal findings on physical examination may include fever, hemiparesis, ataxia, altered consciousness, and cranial nerve palsy.

Diagnosis

*Toxoplasma* encephalitis is usually a presumptive diagnosis based on a combination of clinical manifestations, a positive serum anti-*Toxoplasma* antibody, and characteristic neuroradiographic findings.

- **Anti-*Toxoplasma* Antibody**: Among persons with acute *Toxoplasma* encephalitis, approximately 95% have detectable anti-*Toxoplasma* IgG antibodies using an enzyme-linked immunosorbent assay (ELISA), and approximately 85% have detectable antibodies using an indirect immunofluorescence assay (IFA) with a cutoff of greater than or equal to 1:16.[37]
- **Brain Imaging**: Contrast brain computed tomography (CT) scan shows enhancing lesions in approximately 90% of adults with HIV who have acute *Toxoplasma* encephalitis.[37] Individuals with AIDS and *Toxoplasma* encephalitis generally have multiple ring-enhancing lesions that often involve the basal ganglia (Figure 7) and (Figure 8).[37] Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for identifying *Toxoplasma* brain lesions, and often shows multiple lesions when CT scan has demonstrated only a solitary lesion. Since MRI is the more sensitive test, it is ideal to perform an MRI at the time the initial diagnosis is made and use this test to follow response to therapy.
- **Analysis of Cerebrospinal Fluid**: Ideally, a lumbar puncture should also be performed for *T. gondii* PCR testing on the cerebrospinal fluid (CSF) sample to help support the diagnosis; PCR for *T. gondii* in this setting has a high specificity but low sensitivity, particularly once anti-*toxoplasma* therapy has been initiated.[41,42] In addition, CSF studies can help to investigate other conditions in the differential diagnosis and CSF should be sent for cytology, culture (bacterial and fungal), cryptococcal antigen; and PCR for *Mycobacterium tuberculosis*, Epstein-Barr Virus (EBV), and John Cunningham (JC) Virus.[43,44]
- **Brain Biopsy**: In some circumstances, such as an acute life-threatening presentation or failure to respond to therapy for toxoplasmosis, a definitive diagnosis is needed; this requires detection of *T. gondii* organism in a clinical sample usually obtained via a stereotactic CT-guided brain biopsy (with hematoxylin and eosin staining, or ideally immunoperoxidase staining).

Treatment of *Toxoplasma* Encephalitis
Individuals with suspected *Toxoplasma* encephalitis should immediately receive intensive high-dose initial anti-*Toxoplasma* therapy. The Adult and Adolescent OI Guidelines provides recommendations for preferred and alternative regimens for the initial treatment (Table 4).[39]

**Initial Therapy for Toxoplasma Encephalitis**

The initial treatment is for at least 6 weeks; longer duration for acute treatment may be required if clinical manifestations or neuroradiographic findings indicate extensive disease, or if the response to treatment is incomplete at 6 weeks. Following the initial treatment course, persons with HIV and toxoplasmosis should transition to chronic maintenance therapy.

- **Preferred Therapy:** Based on the highest quality data and treatment experience, the preferred first-line therapy for *Toxoplasma* encephalitis is pyrimethamine plus sulfadiazine plus leucovorin (if pyrimethamine is available).[36,45,46] Leucovorin is used in this regimen to prevent hematologic toxicity secondary to pyrimethamine. Further, in recent years the cost of pyrimethamine has skyrocketed, which has limited or even precluded its use in some settings.[47] If pyrimethamine is not available, the alternative therapy, trimethoprim-sulfamethoxazole, should be used for initial therapy, assuming the patient does not have a sulfa allergy.[39]

- **Alternative Therapy:** For persons who cannot take a preferred regimen, there are multiple alternative regimens: pyrimethamine plus clindamycin plus leucovorin; trimethoprim-sulfamethoxazole; atovaquone plus pyrimethamine plus leucovorin; atovaquone plus sulfadiazine; or atovaquone alone.[45,46,48,49]

**Timing of Starting Antiretroviral Therapy**

For persons with HIV who develop *Toxoplasma* encephalitis while not taking antiretroviral therapy, the optimal timing for initiating antiretroviral therapy remains unknown. Based on available data, most experts recommend starting antiretroviral therapy within 2 to 3 weeks of the diagnosis of *Toxoplasma* encephalitis.[39] This recommendation is primarily based on extrapolation of findings that showed early antiretroviral therapy reduces AIDS progression and death in individuals with acute opportunistic infections.[33]

**Response to Initial Therapy**

More than 70% of individuals with AIDS and *Toxoplasma* encephalitis have clinical and radiographic improvement within 14 days of receiving appropriate therapy for *Toxoplasma* encephalitis.[36,37,50] In one retrospective study, among patients with *Toxoplasma* encephalitis who eventually responded to anti-*Toxoplasma* therapy, 86% had improvement by day 7 and 91% had improvement (with respect to at least half of baseline abnormalities) by day 14 (Figure 9).[50] Thus, if by day 14 the person has not responded to therapy, the clinician should strongly consider a diagnosis other than *Toxoplasma* encephalitis and obtain further studies, typically including a brain biopsy, in an attempt to make a definitive or alternative diagnosis.[50]

**Use of Adjunctive Corticosteroids**

For patients with *Toxoplasma* encephalitis, the use of corticosteroids (e.g., dexamethasone) should be used only if clinically indicated for treatment of mass effect or edema from a focal lesion, with the goal to discontinue the corticosteroids as soon as it is clinically feasible.[39] Note that primary central nervous system lymphoma will likely respond to corticosteroids and this may confound the diagnosis.

**Use of Anticonvulsants**

For patients with *Toxoplasma* encephalitis, the routine use of prophylactic anticonvulsants is not recommended. If, however, a person with *Toxoplasma* encephalitis has a history of seizures, then
anticonvulsants should be administered at least through the acute treatment phase. Note that significant drug interactions potentially exist with anticonvulsants and antiretroviral medications.

**Preventing Recurrence (Chronic Maintenance Therapy)**

**Chronic Maintenance Therapy**

If the patient with *Toxoplasma* encephalitis has successfully completed at least 6 weeks of acute therapy, then a transition to chronic maintenance therapy should take place (Table 5).[39]

- **Preferred Regimen:** The preferred chronic maintenance regimen is pyrimethamine plus sulfadiazine plus leucovorin (if pyrimethamine is available), but at a lower dose than used for acute *Toxoplasma* encephalitis. This regimen is also considered adequate for *Pneumocystis* pneumonia prophylaxis. In the United States, the high cost of pyrimethamine resulting from an extraordinary price increase in recent years may warrant using alternative regimens.[51]

- **Alternative Regimen:** Multiple options are available as alternative regimens for chronic maintenance therapy in patients with *Toxoplasma* encephalitis, including pyrimethamine plus clindamycin, trimethoprim-sulfamethoxazole, atovaquone plus pyrimethamine plus leucovorin, atovaquone plus sulfadiazine, or atovaquone alone. Trimethoprim-sulfamethoxazole, in particular, offers a suppressive regimen with a reduced pill burden.[39,52] Of note, the regimen of pyrimethamine plus clindamycin does not provide adequate prophylaxis for *Pneumocystis* pneumonia and thus an additional agent, such as aerosolized pentamidine, is needed to address *Pneumocystis* pneumonia prophylaxis.

**Discontinuing Chronic Maintenance Therapy**

In the absence of chronic maintenance therapy for *Toxoplasma* encephalitis in persons not taking antiretroviral therapy, the rate of relapse after an initial episode of *Toxoplasma* encephalitis is high, with an incidence of 50 to 80% among persons surviving more than 6 to 12 months.[53] Discontinuation of chronic maintenance therapy requires meeting the following three criteria:[39]

- Successful completion of initial therapy for *Toxoplasma* encephalitis, and
- No signs or symptoms of *Toxoplasma* encephalitis, and
- A sustained increase in the CD4 count to a level above 200 cells/mm$^3$ for longer than 6 months in response to antiretroviral therapy

Note: Some experts recommend performing a brain MRI performed prior to discontinuing chronic maintenance therapy to assess for resolution of brain lesions; in this situation, failure to have resolution of the lesions would warrant continued chronic maintenance therapy.

**Restarting Chronic Maintenance Therapy**

Secondary prophylaxis for *Toxoplasma* encephalitis should be restarted if the CD4 count decreases to less than 200 cells/mm$^3$.[39]
Disseminated *Mycobacterium avium* Complex Disease

**Background**

In the era prior to effective antiretroviral therapy, *Mycobacterium avium* complex (MAC) infection was a common complication of advanced HIV disease.[54] *Mycobacterium avium* complex represents a group of nontuberculous mycobacteria that are ubiquitous in the environment; the mode of transmission is thought to occur via the lungs or gastrointestinal tract, but preventing environmental exposure is not realistic.[55] Most persons who develop disseminated MAC have a CD4 count of less than 50 cells/mm$^3$ (Figure 10).[56] The incidence of disseminated MAC infection has declined dramatically since the early 1990s and the incidence rate is now very low.[1, 2, 57, 58] When cases of disseminated MAC occur, they typically involve individuals with HIV who have advanced immunosuppression and are unaware of their HIV diagnosis, or persons with HIV aware of their HIV diagnosis, but who are not engaged in medical care.

**Clinical Manifestations**

Persons with HIV at risk for MAC have a weak immune response to the mycobacterial organisms and thus experience minimal tissue destruction; the MAC-related clinical manifestations result from the huge burden of organisms, which interfere with tissue function and alter cytokine production.[59] Persons with disseminated MAC typically have CD4 counts of less than 50 cells/mm$^3$ and present with nonspecific symptoms, including fatigue, fever, weight loss, diarrhea, and abdominal pain (Figure 11).[60] Physical examination findings may reveal hepatomegaly, splenomegaly, or lymphadenopathy. Common abnormal laboratory studies include anemia, increased alkaline phosphatase (often with normal bilirubin and hepatic aminotransferase levels), and an increased serum lactate dehydrogenase level.[59, 60, 61] Abdominal CT scan abnormalities may include multiple large retroperitoneal and mesenteric lymph nodes, hepatomegaly, splenomegaly, and a thickened small bowel wall.[62]

**Diagnosis**

The definitive diagnosis of disseminated MAC is usually made by isolating the organism from a normally sterile body site.[55] Use of mycobacterial blood cultures to isolate MAC has become the preferred method of diagnosis: among persons with untreated disseminated MAC, obtaining two sets of blood cultures has a sensitivity of greater than 90%.[63, 64] In persons with positive MAC blood cultures, the laboratory will usually detect mycobacterial growth by day 14, at which point the *Mycobacterium* species can be identified using DNA probes. The diagnosis of disseminated MAC is sometimes made from a lymph node biopsy or a bone marrow biopsy.

**Treatment of Disseminated MAC**

**Initial Therapy for Disseminated MAC**

The Adult and Adolescent OI Guidelines recommended initial treatment for disseminated MAC consists of at least two active drugs—typically a macrolide plus ethambutol.[55] Although macrolide therapy alone will usually cause an initial marked decline in MAC organism burden, resistance is likely to develop unless at least one additional medication active against MAC is included in the regimen (Table 6).[55] In general, the treatment regimen for disseminated MAC should be continued for a minimum of 12 months.[55]

- **Preferred Therapy:** Based on data from multiple studies, the preferred initial two-drug therapy consists of a macrolide, either clarithromycin or azithromycin, in combination with ethambutol.[65, 66, 67, 68] When choosing the macrolide, most clinicians prefer azithromycin due to better tolerance and fewer problematic drug interactions. Ethambutol is recommended as the second drug in the MAC treatment regimen in combination with the macrolide, primarily to prevent the development of drug resistance that occurs with macrolide monotherapy.[69] Persons taking
ethambutol require regular ophthalmologic examinations due to the risk of optic neuritis.

- **Alternative Therapy**: The alternative approach is to use a three- or four-drug regimen; this alternative approach can be considered if the CD4 count less than 50 cells/mm$^3$, the mycobacterial load is high (greater than 2 log CFU/mL of blood), or the individual is not taking effective antiretroviral therapy.[55] In the current antiretroviral therapy era, most experts would use a two-drug regimen against MAC and initiate antiretroviral therapy, reserving a three- or four-drug regimen for situations with documented macrolide-resistant MAC. When three- or four-drug regimens are used, the two medications in the preferred regimen (macrolide plus ethambutol) are combined with one or more additional agents, including rifabutin, an aminoglycoside, or a fluoroquinolone.[70,71] Clofazimine is not recommended for the treatment of MAC as it does not add any benefit and may increase mortality.[72,73]

**Timing of Initiating Antiretroviral Therapy**

Individuals newly diagnosed with disseminated MAC who are not on antiretroviral therapy should promptly start treatment for disseminated MAC and preferably start antiretroviral therapy at the same time.[55] The recommendation to start antiretroviral therapy at the same time as starting MAC treatment is for two reasons: (1) to improve the treatment response to antimycobacterial therapy and, (2) to lower the risk of developing other serious opportunistic infections.

**MAC and Immune Reconstitution Inflammatory Syndrome (IRIS)**

*Mycobacterium avium* complex IRIS is a well-documented complication following initiation of antiretroviral therapy in patients with significant immunosuppression.[74] Persons with MAC-related IRIS usually present with intraabdominal or peripheral lymphadenopathy, or pulmonary-thoracic disease; the risk of death from MAC IRIS appears to be low, and the long-term prognosis is favorable.[74] The management of moderate-to-severe MAC IRIS-related symptoms should start with a nonsteroidal, antiinflammatory drug, but if there is no clinical improvement or initial symptoms are severe, then more aggressive treatment of IRIS is warranted using systemic corticosteroid therapy; the corticosteroids are typically given for 4 to 8 weeks in doses equivalent to 20 to 40 mg of oral prednisone daily.[55] With severe MAC IRIS, some experts recommend repeated courses of corticosteroids or longer treatment courses. Antiretroviral therapy should typically be continued if MAC IRIS develops.

**Preventing Recurrence (Chronic Maintenance Therapy)**

**Chronic Maintenance Therapy**

The regimens for chronic maintenance therapy (secondary prophylaxis) in patients with MAC are exactly the same as those used for initial therapy.[55]

**Discontinuing Chronic Maintenance Therapy**

Discontinuing secondary prophylaxis (chronic maintenance therapy) requires meeting all the following criteria:[55]

- Successful completion of at least 12 months of MAC therapy, and
- No signs or symptoms of MAC disease, and
- Sustained increase in CD4 count to greater than 100 cells/mm$^3$ for longer than 6 months in response to antiretroviral therapy

**Restarting Chronic Maintenance Therapy**

Secondary prophylaxis should be restarted if the CD4 count declines to less than 100 cells/mm$^3$.[55]
Cryptococciosis

Background

Cryptococciosis is an opportunistic fungal infection that causes significant morbidity and mortality in persons with HIV who have advanced immunosuppression. In the United States, the incidence of cryptococcal antigenemia is 2.9% in adults with a CD4 count less than 100 cells/mm$^3$ and 4.3% in those with less than 50 cells/mm$^3$.\[75\] Most cryptococcal infections in persons with HIV are caused by Cryptococcus neoformans, though Cryptococcus gattii is increasingly recognized as a causative agent in the United States, particularly in the Pacific Northwest.\[76, 77, 78, 79\] As with other opportunistic infections, the widespread use of highly active antiretroviral therapy has led to a decrease in the incidence of cryptococcal meningitis, and most cases are identified in persons with recently diagnosed HIV who have advanced immunosuppression, or in persons with established HIV who are not engaged in health care and thus are not taking antiretroviral therapy.\[80\]

Clinical Manifestations

Cryptococcal meningitis occurs as a result of disseminated infection and typically manifests with a more indolent presentation than acute bacterial meningitis.\[81\] Most patients with early cryptococcal meningitis develop nonspecific symptoms consisting of fever and headache, and approximately 65 to 75% do not have classic signs of meningeal irritation early in their course of meningitis.\[81\] As the disease progresses, more neurologic-specific manifestations typically develop, including altered mental status, neck stiffness, or cranial nerve abnormalities (Figure 12).\[82\] Approximately 10% of individuals with disseminated cryptococcal disease have cutaneous manifestations that may resemble molluscum contagiosum.\[83\] Individuals with HIV can develop pulmonary cryptococcal disease, with or without central nervous system involvement.

Diagnosis

The diagnosis of cryptococcal meningitis is usually made by obtaining a positive cryptococcal antigen test on a cerebrospinal fluid sample. Among persons with HIV who have cryptococcal meningitis, the cerebrospinal fluid and serum cryptococcal antigen test are positive in more than 95%, with titers often greater than 1:2048.\[84, 85, 86\] A positive serum cryptococcal antigen, however, is not sufficient to diagnose central nervous system disease and all persons with suspected cryptococcal meningitis should undergo lumbar puncture, both to perform diagnostic tests for C. neoformans and to evaluate for other causes of altered mental status. Most experts would recommend performing a brain CT prior to lumbar puncture to evaluate for a brain mass lesion that could result in brain herniation during the procedure. Tests done on cerebrospinal fluid should include cryptococcal antigen, fungal culture, glucose, protein, cell count with differential, Gram's stain, and bacterial culture. More than 50% of individuals with cryptococcal meningitis have fewer than 20 leukocytes/mm$^3$ on the CSF cell count. Opening pressure should be measured at the time of lumbar puncture in all persons with suspected cryptococcal meningitis since a significant proportion will have an elevated CSF pressure (Figure 13).\[87\]

Treatment of Cryptococcal Meningitis

The\[81\] recommended treatment of cryptococcal meningitis involves three phases: induction therapy, consolidation therapy, and chronic maintenance therapy (Table 7).\[81, 88\] Serial monitoring of cryptococcal antigen to determine response to therapy has shown minimal benefit and is not recommended.\[89\]

Induction Therapy for Cryptococcal Meningitis

- **Preferred Regimens:** The recommended initial induction therapy for cryptococcal meningitis consists of either intravenous liposomal amphotericin B plus oral flucytosine or intravenous amphotericin B deoxycholate plus oral flucytosine.\[81\] Liposomal amphotericin B has similar efficacy as amphotericin B deoxycholate, but is associated with a lower risk of renal...
toxicity. Flucytosine, when added to either liposomal amphotericin B or amphotericin B deoxycholate, results in more rapid CSF sterilization.

- **Alternative Regimens:** Alternative regimens consist of amphotericin B lipid complex plus flucytosine, liposomal amphotericin B plus fluconazole, amphotericin B deoxycholate plus fluconazole, liposomal amphotericin B alone, amphotericin B deoxycholate alone, and high-dose fluconazole alone.

- **Evaluation After Course of Induction Therapy:** If there is substantial clinical improvement after completing the 2-week induction course, lumbar puncture should be performed to obtain cerebrospinal fluid fungal cultures. If the patient does not improve clinically, then induction therapy should be continued until the cerebrospinal fluid cultures are negative.

- **Monitoring Flucytosine Levels:** If this testing is available, a flucytosine level can be checked after administering 3 to 5 doses of flucytosine, approximately 2 hours after taking the dose. The target serum flucytosine level is 25 to 100 mg/L. The flucytosine dose must be adjusted in persons with renal impairment.

### Consolidation Therapy for Cryptococcal Meningitis

After at least 2 weeks of successful initial induction therapy, with success measured by significant clinical improvement and a negative cerebrospinal fluid culture, consolidation therapy with oral fluconazole can be started and continued for at least 8 weeks. The preferred consolidation dosing of fluconazole is 800 mg once daily (AI), but if a clinically stable person has evidence of negative cerebrospinal fluid culture and has been initiated on antiretroviral therapy, the dose of fluconazole can be decreased to 400 mg once daily (AII). If the patient improves clinically but the cerebrospinal fluid cultures are positive after 2 weeks of induction therapy, then use a higher dose of fluconazole (1,200 mg once daily), repeat lumbar puncture 2 weeks later; the testing will need to be performed. The duration of consolidation therapy is 8 weeks from the time of negative CSF culture.

### Management of Increased Intracranial Pressure

Cryptococcal meningitis is often associated with increased intracranial pressure (opening pressure greater than 20 cm H$_2$O) and appropriate management of increased intracranial pressure can improve survival and neurologic outcomes. In a retrospective study performed in the United States, investigators showed that patient outcomes strongly correlated with the use of serial lumbar punctures to manage increased intracranial pressure during the first 2 weeks of therapy for cryptococcal meningitis (Figure 14). A more recent study of patients with acute cryptococcal meningitis in Africa showed a marked survival benefit if therapeutic lumbar punctures were performed. The following summarizes recommendations from the Adult and Adolescent OI Guidelines for managing elevation in intracranial pressure in persons with cryptococcal meningitis.

- **Lowering Opening Pressure at Initial Lumbar Puncture:** If the opening pressure is elevated, the recommended approach is to remove ample cerebrospinal fluid (20 to 30 mL) to reduce the opening pressure to a normal pressure (less than 20 cm H$_2$O), or at least by 50% if not able to achieve a normal pressure with removal of 20 to 30 mL.

- **Serial Lumbar Punctures:** For persons with ongoing symptoms, such as headache or confusion, serial lumbar punctures with cerebrospinal fluid drainage may be required on a daily basis to maintain opening pressure less than 20 cm H$_2$O; daily lumbar punctures should be continued until the opening pressure normalizes and symptoms resolve.

- **Use of Lumbar Drains or Ventriculostomy:** If the person initially has focal neurologic deficits, or serial lumbar puncture with removal of cerebrospinal fluid fails to control increased intracranial pressures, a lumbar drain or ventriculostomy may be required.

- **Medical Therapy for Reducing Intracranial Pressure:** For persons with acute cryptococcal meningitis, attempts to treat increased intracranial pressure with medical therapy, such as mannitol, acetazolamide, or corticosteroids, is not effective and is not recommended.
Cryptococcal Meningitis and IRIS

A paradoxical worsening of cryptococcal meningitis occurs in up to 30% of persons with HIV who start antiretroviral therapy at the same time (or soon after) they start treatment for cryptococcal meningitis.[95] If cryptococcal meningitis-associated IRIS develops, it is often life-threatening. Baseline factors associated with an increased risk of developing cryptococcal meningitis-associated IRIS include lack of prior antiretroviral therapy, high baseline HIV RNA, low white blood cell count in cerebrospinal fluid, and a high cerebrospinal fluid fungal burden.[7] The challenge of such cases is differentiating between cryptococcal meningitis treatment failure, a new central nervous system disorder, or IRIS. Persons with IRIS typically have negative cerebrospinal fluid fungal cultures, whereas those with treatment failure will have positive cultures. If a new central nervous system problem and treatment failure are ruled out and IRIS is the most likely diagnosis, antiretroviral therapy and antifungal therapy should be continued in conjunction with careful lowering of intracranial pressure, if indicated. Mild cases can be managed with nonsteroidal antiinflammatory medications and most experts would use oral corticosteroids in severe cases.

Timing of Initiating Antiretroviral Therapy

To reduce the risk of IRIS in patients with cryptococcal meningitis, the Adult and Adolescent OI Guidelines recommend delaying initiation of antiretroviral therapy for 4 to 6 weeks after starting treatment for cryptococcal meningitis and ideally after negative CSF cryptococcal cultures have been obtained.[81] A 2014 study from Uganda and South Africa demonstrated that deferral of antiretroviral therapy for 5 weeks was associated with a significant improvement in survival, as compared with initiating antiretroviral therapy at 1 to 2 weeks, especially among patients with a low white blood cell count in cerebrospinal fluid.[96] Several additional studies support the approach of deferring antiretroviral therapy for at least several weeks.[97,98]

Maintenance Therapy (Preventing Recurrence)

Maintenance Therapy for Cryptococcal Meningitis

Maintenance therapy with fluconazole 200 mg once daily is required for at least 1 year after successful induction and consolidation treatment of cryptococcal meningitis.[81] Separate studies have shown that fluconazole is superior to intravenous amphotericin B and to oral itraconazole for chronic maintenance therapy, so the latter two are not recommended.[99,100]

Discontinuing Maintenance Therapy

Maintenance therapy for cryptococcal meningitis can be discontinued when a patient has met all the following criteria:[81]

- At least 1 year from initiation of antifungal therapy for cryptococcal meningitis, and
- Has no signs or symptoms of cryptococcal infection, and
- The CD4 count is greater than or equal to 100 cells/mm³ and the HIV RNA is suppressed in response to antiretroviral therapy

Restarting Chronic Maintenance Therapy

Maintenance therapy for cryptococcal meningitis should be restarted if the CD4 count again declines to 100 cells/mm³ or less.[81]

Additional Treatment Considerations

The following summarizes the recommended treatment approach for: (1) cryptococcal infection that does not involve the lungs or central nervous system (CNS), diffuse cryptococcal pulmonary disease, and asymptomatic persons with Isolated cryptococcal antigenemia.[81] All asymptomatic persons with HIV
who have isolated cryptococcal antigenemia must have their CSF evaluated for occult cryptococcal meningitis.[81]

- **Treating Non-CNS Extrapulmonary, Diffuse Pulmonary Disease, or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA titer greater than or equal to 1:640), without evidence of CNS Disease**: The recommendation is to use the same treatment as recommended for cryptococcal meningitis, but without the need for follow-up lumbar puncture and CSF analysis.[81]

- **Treating Non-CNS Focal Pulmonary Disease or Asymptomatic Patients with Isolated Cryptococcal Antigenemia (Serum LFA titer less than or equal to 1:320), without evidence of CNS Disease**: The recommended treatment is fluconazole 400 to 800 mg PO daily for 10 weeks, followed by fluconazole 200 mg daily, with a total duration of therapy of 6 months.[81]
Cytomegalovirus Disease

Background

Cytomegalovirus (CMV) is a double-stranded DNA virus in the herpes family that can cause invasive disease, including retinitis, colitis, and central nervous system disease, in persons with advanced immunosuppression (CD4 count less than 50 cells/mm$^3$).[101,102] Among people with HIV, retinitis is the most common form of CMV end-organ disease. Typically, CMV disease in people with HIV and advanced immunosuppression occurs due to reactivation of latent CMV infection. Among men with HIV who have sex with men, CMV-positive antibody rates are greater than 90%. Additional risk factors for the development of clinical CMV disease include previous opportunistic infections, a high HIV RNA level (greater than 100,000 copies/mL), and a high level of CMV viremia.[103] Following the widespread availability and use of effective antiretroviral therapy, the incidence of CMV retinitis has declined by more than 90%.[103,104,105,106,107]

Clinical Manifestations

Retinitis

Individuals with CMV retinitis most often develop on or more of the manifestations commonly referred to as the four “F’s”: floaters, flashes, field deficits, or failing vision.[108] These manifestations can represent loss of peripheral and central vision. Individuals with CMV retinitis do not have pain related to the lesions, nor do they present with redness of the eye. Although only one eye is usually involved at the initial presentation, CMV disease can progress to affect the contralateral eye, particularly in individuals who are not on antiretroviral therapy.[104] On dilated funduscopic examination, the CMV-associated retinal lesions typically appear as yellow or white patches caused by retinal necrosis, with or without hemorrhage, usually following a vascular distribution (Figure 15).[102] The findings of CMV retinitis should not be confused with findings caused by HIV retinopathy (Figure 16).

Gastrointestinal

Odynophagia is usually the most prominent symptom with CMV esophagitis.[109] Persons with HIV and CMV colitis typically have weight loss, malaise, anorexia, abdominal pain, debilitating diarrhea (sometimes bloody), with the potential to develop gastrointestinal perforation as a life-threatening complication.[110,111]

Neurologic

Less frequently, individuals with HIV and CMV infection can have neurologic manifestations, including myelitis, polyradiculomyelopathy, encephalitis, and ventriculitis.[112] In the absence of antiretroviral therapy or anti-CMV treatment, CMV end-organ disease will inevitably progress over a matter of days to weeks.

Diagnosis

Most individuals with HIV and CMV retinitis, colitis, or other end-organ disease have CMV viremia that can be detected by PCR, antigen assays, or culture, but testing for CMV viremia is not recommended for the diagnosis of CMV-related end-organ disease.[102,103]

Retinitis

The diagnosis of CMV retinitis is a clinical diagnosis based on characteristic findings observed during a dilated funduscopic examination by an ophthalmologist.[102,103] With a handheld monocular direct ophthalmoscope, a clinician can visualize all of zone 1 (including the optic nerve head and the macula), less than half of zone 2, and none of zone 3 (Figure 17). Thus, all patients suspected of having CMV retinitis should see an ophthalmologist for a full retinal examination. Obtaining PCR of aqueous or vitreous specimens can be...
helpful, but is not practical in most situations.

Gastrointestinal

The diagnosis of CMV esophagitis or colitis is suggested by observing mucosal ulcerations on endoscopy, but a definitive diagnosis requires characteristic biopsy findings showing intranuclear and intracytoplasmic inclusions.\[111\] Abdominal computed tomographic scans may show colonic thickening, but this finding is nonspecific.

Neurologic

The diagnosis of CMV central nervous system disease is usually made based on compatible clinical findings in conjunction with a positive cerebrospinal fluid PCR test for CMV.\[113\]

Treatment of CMV Disease

The Adult and Adolescent OI Guidelines recommendations for the treatment of CMV disease vary based on the organ system affected.\[103\]

Initial Treatment of CMV Retinitis

The treatment of CMV retinitis depends on whether the individual has sight-threatening retinitis or peripheral lesions; lesions are considered sight-threatening if they are within 1,500 microns of the fovea (Table 8).\[103\]

- **Initial Therapy for Sight-Threatening Lesions (within 1,500 microns of the fovea)**

  - **Preferred Therapy:** The preferred initial treatment for immediate sight-threatening retinitis consists of 14 to 21 days of induction therapy with intravenous ganciclovir 5mg/kg every 12 hours (AI) or valganciclovir 900 mg orally every 12 hours (AI). Most experts prefer intravenous therapy with sight-threatening lesions, but it can be switched at any time if the retinitis is clinically improving and there are no concerns regarding gastrointestinal absorption of oral medications.\[114\] Clinicians may supplement the systemic treatment of immediate sight-threatening CMV retinitis with repeated intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection), given every 7 days until lesion inactivity is achieved (AIII).\[115,116,117\] The intravitreal injections are given initially to provide immediate high intraocular drug levels until steady state levels of intraocular ganciclovir can be achieved with systemic therapy, but the clinical benefit of these intravitreal injections have not been verified in clinical trials, and the procedure has risks, such as retinal detachment, hemorrhage, and iatrogenic bacterial or fungal infections.

  - **Alternative Therapy:** Some individuals may not tolerate the preferred induction treatment regimen of ganciclovir or valganciclovir, typically due to toxicities such as severe cytopenias. In addition, some may require alternative therapy due to ganciclovir-resistant CMV. When alternative therapy is needed, the recommended options for initial therapy are to give weekly intravitreal injections (with ganciclovir or foscarnet) in combination with 14 to 21 days of systemic intravenous therapy with foscarnet (BI) or cidofovir (CI).\[118,119,120\] Although intravenous foscarnet and cidofovir are effective therapy for CMV retinitis, both of these medications are associated with significant toxicity, particularly nephrotoxicity. In addition, cidofovir requires the concomitant use of probenecid and this should not be used in persons with a sulfa allergy due to cross-hypersensitivity with probenecid and sulfa medications.

- **Initial Therapy for Peripheral Lesions:** For small peripheral lesions that are not vision-threatening, treating with oral valganciclovir 900 mg orally every 12 hours is usually sufficient. If infection is unilateral, systemic therapy helps to prevent disease in the contralateral eye. Overall, early anti-CMV therapy and initiation of antiretroviral therapy significantly decreases the incidence of vision loss from CMV retinitis.\[121\]
Maintenance Therapy for CMV Retinitis

After completion of 14 to 21 days of induction therapy for CMV retinitis, persons should transition to chronic maintenance therapy.

- **Preferred Therapy**: The initial intravenous ganciclovir induction therapy should be followed by maintenance therapy with either oral valganciclovir 900 mg once daily or intravenous ganciclovir 5mg/kg once daily. If oral therapy was used for the initial therapy, it should be followed by maintenance therapy with oral valganciclovir 900 mg once daily.

- **Alternative Therapy**: If foscarnet or cidofovir was required for initial therapy, they can be continued for maintenance therapy, but expert consultation is advised since these agents are very likely to cause significant toxicity if continued for prolonged periods of time.

Discontinuing Maintenance Therapy for CMV Retinitis

Chronic maintenance therapy for CMV retinitis can be discontinued when the following criteria are met:

- At least 3 to 6 months of CMV treatment has been completed, and
- No retinal lesions are active, and
- The CD4 count is above 100 cells/mm³ for 3 to 6 months in response to antiretroviral therapy, and
- An ophthalmologist has been consulted.

Note: After stopping maintenance therapy ophthalmologic monitoring for early detection of CMV relapse should be ideally be performed every 3 months to evaluate for early relapse of retinitis and to detect immune reconstitution uveitis. After sustained immune reconstitution has occurred, periodic ophthalmologic examinations should be performed as indicated and feasible.

Restarting Chronic Maintenance Therapy

Chronic maintenance therapy should be restarted if the CD4 count decreases to less than 100 cells/mm³.

Treatment of CMV Esophagitis or Colitis

The following summarizes the Adult and Adolescent OI Guidelines recommendations for the treatment of CMV esophagitis or colitis. ([Table 9](#table9)).

- **Preferred Therapy**: For persons with CMV esophagitis or colitis, the preferred therapy is intravenous ganciclovir. ([103],[122],[123]) Often persons with gastrointestinal CMV infection cannot take oral medications or may not adequately absorb oral medications. Once initial improvement occurs and the person can take and absorb oral medications, treatment can be switched to oral valganciclovir.

- **Alternative Therapies**: The recommended alternative therapy for CMV esophagitis or colitis is intravenous foscarnet, but this should only be used in persons who have treatment-limiting toxicities with the preferred agent or who have ganciclovir-resistant CMV. In persons with mild disease that does not significantly interfere with oral absorption, oral valganciclovir can be used.

- **Duration of Therapy**: The duration of therapy is 21 to 42 days or until clinical symptoms resolve. Most individuals can successfully be treated with 21 to 42 days of therapy and maintenance therapy is usually not required.

Treatment of CMV Pneumonia and CMV Encephalitis

There are limited, mostly anecdotal, data for the treatment of CMV pneumonia and CMV neurological disease. The recommended treatment for CMV pneumonia consist of either intravenous ganciclovir or intravenous foscarnet. ([103]) For neurological disease, many clinical experts would initiate a combined antiviral intravenous regimen of ganciclovir and foscarnet, despite the toxicities associated with using these drugs.
simultaneously.[103]

**Adverse Effects Associated with CMV Therapy**

Cytopenias (anemia, thrombocytopenia, neutropenia) are the most important toxicity associated with ganciclovir and valganciclovir use. The neutropenia can be mitigated by using granulocyte colony-stimulating factor (G-CSF).[103,124] During induction with ganciclovir or valganciclovir, a complete blood count and serum creatinine should be monitored at least twice weekly and then once weekly during maintenance. Foscarnet use can be associated with nephrotoxicity and electrolyte derangements. Toxicity monitoring during foscarnet therapy should include serum electrolytes and serum creatinine at least twice weekly during induction and once weekly while on maintenance treatment. Intravenous cidofovir use can lead to nephrotoxicity, ocular hypotony, and neutropenia. Aggressive intravenous fluid hydration and oral probenecid administration immediately prior to cidofovir dosing can help to attenuate the renal issues.[103]

**Cytomegalovirus and IRIS**

The ocular form of CMV-associated IRIS, typically referred to as immune reconstitution uveitis, is characterized by inflammation in the anterior chamber or vitreous; vision loss from macular edema, cataracts, or epiretinal membranes can occur.[105,125,126,127] Immune reconstitution uveitis tends to occur in the first 3 months after starting antiretroviral therapy but can occur even years after treatment of acute CMV retinitis.[103] The risk of developing CMV-associated IRIS is highest when the CMV disease involves more than 30% of the retina.[128] The treatment of immune reconstitution uveitis typically consists of continued CMV treatment with the addition of corticosteroids (intravitreal or oral).[103,129]

**Timing of Initiating Antiretroviral Therapy**

Among persons with HIV who develop CMV retinitis, the risk of developing CMV-associated IRIS is greater when antiretroviral therapy is started immediately when compared with deferring antiretroviral therapy until the CMV retinitis is initially controlled.[130] Individuals with newly diagnosed CMV who are not on antiretroviral therapy should promptly start treatment for CMV retinitis or CMV end-organ disease and then start antiretroviral therapy no more than 2 weeks later.[103] There is also a significant concern for development of CMV-related IRIS in persons who have CMV neurologic disease.
Progressive Multifocal Leukoencephalopathy

Background

Progressive multifocal leukoencephalopathy (PML) is a focal demyelinating disease of the central nervous system caused by reactivation of the John Cunningham (JC) virus in persons who have impaired immunity, most often in the setting of HIV-associated immunosuppression.[131] Infection with JC virus is common, and antibodies to JC virus are detected in more than 80% of humans worldwide.[132] Although the incidence of PML has decreased with the widespread use of effective antiretroviral therapy, mortality remains high for those persons with HIV who develop PML.[133,134]

Clinical Manifestations

Persons with HIV who develop PML typically present with subacute, progressive focal neuropsychiatric signs and symptoms, including cognitive disturbances, visual changes, limb paresis, hemisensory deficits, dysmetria, and ataxia.[132,135,136] The clinical presentation with PML may be difficult to distinguish from severe HIV-associated dementia or a slowly evolving stroke.[131,137] Approximately 15 to 20% of persons with PML will have at least one seizure.[138,139] Headache, fever, acute encephalopathy, and spinal cord manifestations are rare. In persons with AIDS, if immunosuppression is not reversed with antiretroviral therapy, PML will have a relentless progression and will lead to death within 6 months.[131]

Diagnosis

Brain biopsy is the gold standard for diagnosis, but it is not usually performed since a presumptive diagnosis can be made based on brain magnetic resonance imaging (MRI) findings. Brain MRI usually shows focal white matter lesions that correlate anatomically to the patient’s neurological deficits; these multiple high-signal intensity lesions are best seen on T2-weighted and FLAIR sequences (Figure 18).[131] In addition, 70 to 90% of persons with PML who are not taking antiretroviral therapy have a positive JC virus DNA PCR in the cerebrospinal fluid (this number drops to about 60% among persons who are taking antiretroviral therapy).[140] Detection of JC virus in the cerebrospinal fluid is not necessary to confirm the diagnosis of PML if the clinical picture and brain MRI findings are consistent with the diagnosis, but may support the diagnosis of PML in atypical cases. Plasma PCR detection of JC virus DNA can be a useful adjunct test, especially when CSF is not readily available, with the test having high specificity but relatively low sensitivity.[140]

Treatment

There is no specific antiviral therapy for JC virus.[131] The cornerstone of treatment of PML in persons with HIV is antiretroviral therapy, with resultant immune restoration.[140] Antiretroviral therapy should promptly be initiated or optimized in all persons with HIV who are diagnosed with PML. Among those with HIV and PML who receive effective antiretroviral therapy, the 1-year survival rate is only 55 to 60% and survivors often have some permanent neurologic deficits.[131,141] Multiple therapies have been attempted for treatment of PML in persons with HIV, but none (except for antiretroviral therapy-related immune reconstitution) has been shown to be effective. The Adult and Adolescent OI Guidelines specifically recommend against the use of the following therapies for PML in persons with HIV: intravenous cytarabine, intrathecal cytarabine, cidofovir, mefloquine, mirtazapine, olanzapine, ziprasidone, cyproheptadine, risperidone, and interferon-alfa, and check-point inhibitors such as pembrolizuma.[140]

Timing of Initiating Antiretroviral Therapy

Individuals with HIV newly diagnosed with PML who are not on HIV antiretroviral therapy should immediately start on a fully suppressive antiretroviral therapy.[140] There is no rationale to delay therapy since there is no known effective antiviral therapy specific for PML that could be used to reduce the JC virus load prior to starting HIV antiretroviral therapy. Individuals diagnosed with PML who are taking antiretroviral therapy but
do not have optimal suppression of HIV should receive a fully suppressive antiretroviral regimen.

Management of Immune Reconstitution Syndrome

Persons with HIV may develop PML immune reconstitution syndrome in the first weeks to months after starting antiretroviral therapy. The increased inflammation in the central nervous system may potentially cause mass effect and herniation. For individuals with a contrast-enhanced imaging that shows significant inflammation, use of corticosteroids can be considered.[140] There is no consensus on the dosage or duration of corticosteroids for PML IRIS; the Adult and Adolescent OI Guidelines suggest one approach modeled on treating flares of multiple sclerosis, which is to start with a 3- to 5-day course of intravenous methylprednisolone (1 gram per day) and then transition to oral prednisone 60 mg once daily and taper over 1 to 6 weeks.[140] Some experts recommend obtaining a brain MRI at 2 to 6 weeks after starting corticosteroid therapy to reevaluate edema and inflammation, which can inform the taper dose and duration, and establish a new baseline.
Esophageal Candidiasis

Background

Esophageal candidiasis remains a significant cause of morbidity in persons with HIV, but the incidence has declined markedly since the widespread use of highly effective antiretroviral therapy [107]. When esophageal candidiasis occurs, it usually involves individuals with a CD4 cell count less than 100 cells/mm³ [142]. *Candida albicans* is the most common species involved, but non-*albicans* species (*C. dubliniensis*, *C. glabrata*, *C. tropicalis*) can also cause disease. [143] In addition, *Candida glabrata* is associated with azole resistance among patients with advanced immunosuppression, particularly those who have received repeated or prolonged courses of oral fluconazole. [144, 145, 146]

Clinical Manifestations

Esophageal candidiasis usually causes retrosternal burning pain and odynophagia. [147, 148] Persons with HIV and esophageal candidiasis often also have oropharyngeal candidiasis, which typically presents with painless, creamy white plaques or patches on the tongue, buccal mucosa, or pharynx that can be easily scraped off with a tongue blade.

Diagnosis

A presumptive diagnosis of esophageal candidiasis is based on typical clinical symptoms and response to empiric antifungal treatment; a definitive diagnosis can be made with endoscopic evaluation with visualization and obtaining fungal culture (with speciation), but this approach is generally reserved for patients who do not respond within 7 days after starting antifungal therapy. [147, 149] If endoscopy is performed, it also is important to evaluate for other potential causes of esophagitis.

Treatment

The Adult and Adolescent OI Guidelines recommend an initial course of treatment for esophageal candidiasis that is 14 to 21 days in duration (Table 10). [147]

Initial Therapy

- **Preferred Therapy:** For initial treatment of esophageal candidiasis, the preferred therapy should be oral fluconazole, intravenous fluconazole, or oral itraconazole solution. [147, 150, 151]
- **Alternative Therapy:** Alternative therapies include voriconazole, posaconazole, isavuconazole, caspofungin, micafungin, anidulafungin, amphotericin B, or lipid formulations of amphotericin B. [152, 153, 154, 155, 156] Available data suggest that persons with esophageal candidiasis have higher relapse rates when treated with an echinocandin than with fluconazole. [147, 157]
- **Therapy During Pregnancy:** During the first trimester of pregnancy, amphotericin B is recommended for treatment of esophageal candidiasis. Data derived from women with vulvovaginal candidiasis suggest that fluconazole should not be used in the first trimester due to the risk of spontaneous abortion. [158, 159, 160, 161] Isavuconazole is not recommended in pregnancy, especially in first trimester, due to animal data indicating higher perinatal mortality and skeletal defects. [161] Itraconazole at high doses has been shown to be teratogenic in animals and human pregnancy data is extremely limited. [147] Similarly, human pregnancy data is not available for voriconazole or the echinocandins, so their use in pregnancy is not recommended. [147]

Timing of Starting Antiretroviral Therapy

Antiretroviral therapy should be initiated without delay in patients with *Candida* esophagitis. [147]
Chronic Suppressive Therapy

Chronic suppressive therapy for *Candida* is not recommended for persons with isolated episodes of esophageal candidiasis because therapy for acute episodes of disease is effective, mortality from candidiasis is low, drug interactions can occur, and suppressive therapy may increase drug-resistant species.[147] The use of chronic suppressive therapy for persons with esophageal candidiasis is usually limited to situations when individuals with a CD4 count less than 200 cells/mm$^3$ who have severe bouts of esophageal candidiasis or frequent recurrences. If the decision is made to administer chronic suppressive therapy for patients with esophageal candidiasis, the recommended options are either oral fluconazole 100 to 200 mg daily or posaconazole oral solution 400 mg twice daily.[147] Chronic suppressive therapy is not recommended in pregnancy.[147]
Histoplasmosis

Background

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*, which is endemic to the central and south-central United States (especially the Mississippi and Ohio River Valley areas), as well as to many regions of Latin America.[162,163] *Histoplasma* infections are acquired through inhalation and asymptomatic extrapulmonary infection is common. Individuals with HIV who have a CD4 count below 150 cells/mm³ have an increased risk of developing symptomatic illness following acute infection, and most cases in nonendemic areas are attributed to reactivation of latent infection.[164,165] The incidence of symptomatic histoplasmosis declined after the introduction of potent antiretroviral therapy.[1]

Clinical Manifestations

*Histoplasma* infection can be asymptomatic or symptomatic, acute or chronic, and focal or disseminated. Disseminated disease often develops in persons with HIV, particularly in those who have a CD4 count less than 150 cells/mm³.[163,164] Symptoms of disseminated histoplasmosis may include fever, fatigue, weight loss, hepatosplenomegaly, cough, chest pain, and dyspnea.[166] Approximately 50% of cases include respiratory complaints, and chest radiography often shows diffuse or patchy opacities that can mimic *Pneumocystis* pneumonia (Figure 19). Less often, the chest radiograph shows focal infiltrates, nodules, or cavities. Persons with HIV and histoplasmosis may also have hepatosplenomegaly (25%), lymphadenopathy (25%), sepsis (10 to 20%), central nervous system involvement (10 to 20%), or gastrointestinal involvement (10 to 20%).[163] Some with disseminated disease may have oral lesions.[167] In rare situations, individuals with disseminated histoplasmosis may develop hemophagocytic syndrome, also known as hemophagocytic lymphohistiocytosis (HLH), which is a dysregulated immune response to infection that causes a multisystem illness characterized by fever, hepatosplenomegaly, and cytopenias.[168,169]

Diagnosis

**Disseminated Disease:** Disseminated histoplasmosis in persons with HIV is usually diagnosed by detecting *Histoplasma* antigen in blood or urine (Figure 20).[163,170,171] Serological testing for antibodies to *H. capsulatum* is not very useful for diagnosis of disseminated histoplasmosis in persons with AIDS.[170,171,172] In some cases, peripheral blood smears and biopsy samples of involved tissues may show budding yeasts (Figure 21).[173] Although more than 85% of adults with AIDS and disseminated histoplasmosis will have a positive culture for *H. capsulatum* from a body source (blood, bone marrow, respiratory secretion, or skin lesions), obtaining culture has limited clinical diagnostic utility since the organism usually takes several weeks to grow.[171] In contrast, results with the *Histoplasma* antigen assay (on urine or serum samples) are typically available in 1 to 2 days. Evaluation of tests for the diagnosis of disseminated histoplasmosis in adults with AIDS have shown that sensitivity was 100% with urinary antigen and 92% with serum antigen.[174]

**Pulmonary Disease:** The detection of *Histoplasma* antigen in bronchoalveolar lavage fluid may be helpful for the diagnosis of acute pulmonary histoplasmosis infections.[170,175]

**Meningitis:** Typical cerebrospinal fluid findings among individuals with *Histoplasma* meningitis include lymphocytic pleocytosis, elevated protein, and low glucose. Confirming a diagnosis of *Histoplasma* meningitis can be challenging due to poor sensitivity of most diagnostic tests—fungal stains are usually negative and cerebrospinal fungal cultures are positive in less than 40% of individuals. Cerebrospinal fluid testing for *Histoplasma* antibodies and antigen can aid with diagnosing *Histoplasma* meningitis, as detection of either *Histoplasma* antibodies or antigen in the cerebrospinal fluid confirms active central nervous system *Histoplasma* infection.[170,176] Often, a presumptive diagnosis of *Histoplasma* meningitis is made when an individual with CNS infection has evidence of disseminated histoplasmosis at another site and no other obvious etiology for their neurological symptoms.[170]
Treatment

The Adult and Adolescent OI Guidelines for the treatment of disseminated histoplasmosis in persons with HIV are based on the severity of the disease (Table 11).[170] Treatment consists of induction therapy and maintenance therapy. Note that with itraconazole, the oral solution provides improved absorption and higher serum levels when compared with the capsule. Unless the patient is on a medication that would significantly boost itraconazole levels, the oral solution is recommended, but it is less well tolerated. Serum itraconazole levels should be checked after 2 weeks of therapy, due to potential drug interactions with several HIV antiretroviral medications, with dosage adjustment made based on the drug levels. The target itraconazole serum level is between 1.0 and 10.0 µg/mL. Of note, a new formulation of itraconazole (SUBA-itraconazole) is now available, and it is absorbed well; it is not currently indicated for the treatment of Histoplasma meningitis due to inadequate data. Similarly, isavuconazole, a new azole drug with broad spectrum antifungal activity, is not approved for the treatment of histoplasmosis. The following summarizes the Adult and Adolescent OI Guidelines recommendations for the treatment of histoplasmosis.[170]

Treating Moderately Severe to Severe Disseminated Disease

- **Induction Therapy:** The preferred treatment for moderately severe to severe disseminated histoplasmosis is intravenous liposomal amphotericin B.[177] The alternative therapies for moderately severe to severe disseminated histoplasmosis are amphotericin B lipid complex. The induction therapy should be given for at least 2 weeks or until clinical improvement.
- **Maintenance Therapy:** Following the intravenous induction therapy, patients should receive maintenance therapy. The preferred maintenance therapy is oral itraconazole 200 mg three times daily for 3 days, then twice daily for at least 12 months.[178] The systemic absorption of itraconazole can be erratic and potentially affected by drug interactions with many medications, including commonly used antiretroviral agents. Consequently, a random serum level of itraconazole should be measured approximately 2 weeks after treatment initiation with itraconazole. A therapeutic level of itraconazole is 1 to 2 µg/mL is recommended. The risk of side effects and toxicities with itraconazole increase with serum levels greater than or equal to 4 µg/mL.[170,179]

Treating Less Severe Disseminated Disease

- **Induction and Maintenance Therapy:** For persons with less severe disseminated disease, the preferred induction and maintenance therapy consists of oral itraconazole 200 mg three times daily for 3 days, then twice daily for at least 12 months.[180] This regimen is considered as both induction and maintenance therapy. The liquid formulation of itraconazole is preferred over the capsule as it is better absorbed and does not require gastric acid for absorption (the capsule requires gastric acid for adequate absorption). Thus, itraconazole capsules should not be prescribed to individuals who are also taking gastric acid suppressive medications.[170]
- **Alternative Therapy:** For persons intolerant of itraconazole, alternative agents include posaconazole, voriconazole, or fluconazole.[181] If voriconazole is used, serum trough levels should be measured 5 days after treatment initiation. The therapeutic level is between 2 and 5 ug/mL; levels higher than 5 ug/mL can lead to drug toxicities, including neurotoxicity and hepatotoxicity. Posaconazole serum levels should be measured 5 days after treatment initiation; the therapeutic level is greater than 1 ug/mL. Fluconazole, although less effective than itraconazole for the treatment for disseminated histoplasmosis, can be moderately effective at a dose of 800 mg daily.

Treating Histoplasma Meningitis

- **Induction Therapy:** The preferred induction treatment for Histoplasma meningitis is intravenous liposomal amphotericin B, given for 4 to 6 weeks.[177]
- **Maintenance Therapy:** Individuals with Histoplasma meningitis should receive maintenance therapy following the intravenous induction therapy with liposomal amphotericin B. The preferred maintenance therapy is oral itraconazole 200 mg taken two or three times daily for at least 12 months.
and the dose should not be changed to suppressive once-daily dosing until resolution of abnormal cerebrospinal fluid findings.[178]

- **Alternative Maintenance Therapy**: Posaconazole, voriconazole, or fluconazole can be used as alternative agents for individuals who are intolerant of itraconazole.

### Long-Term Suppressive Therapy

For individuals with severe disseminated disease or central nervous system infection, after at least 12 months of maintenance itraconazole therapy, the oral itraconazole dose should be reduced from 200 mg twice daily to 200 mg once daily for long-term suppressive therapy. The alternative for long-term suppressive therapy is oral posaconazole 300 mg daily, oral voriconazole 200 mg twice daily, or oral fluconazole 400 mg daily.

### Discontinuing Long-Term Suppressive Therapy

Secondary prophylaxis can be discontinued when the patient meets the following criteria:[170]

- Received azole therapy for longer than 1 year, and
- Has negative fungal blood cultures, and
- Serum or urine *Histoplasma* antigen is below the level of quantitation, and
- Plasma HIV RNA levels are undetectable, and
- The CD4 count increases to 150 cells/mm³ or greater for at least 6 months in response to antiretroviral therapy

### Restarting Long-Term Suppressive Therapy

Long-term suppressive therapy should be restarted if the CD4 count decreases to less than 150 cells/mm³.[170]

### Timing of Initiating Antiretroviral Therapy

Individuals diagnosed with histoplasmosis should be started on antiretroviral therapy as soon as possible after starting antifungal treatment for histoplasmosis. Available data suggest that IRIS infrequently occurs in persons with HIV who have disseminated histoplasmosis.[170,182]
Bartonella

Background

*Bartonella* species cause a wide range of clinical infections, including cat scratch disease, trench fever, retinitis, relapsing bacteremia, endocarditis, bacillary angiomatosis, and bacillary peliosis hepatitis.[183,184,185] There are more than twenty *Bartonella* species, but *B. henselae* and *B. quintana* are the two species that can cause disease among persons with HIV.[186] Transmission of *B. henselae* occurs via cat scratches and fleas (cats are the zoonotic reservoir) whereas *B. quintana* is transmitted primarily by lice and is epidemiologically linked with homelessness (humans are the presumed reservoir).

Clinical Manifestations

Among persons with HIV, *Bartonella* infections show a predilection for the skin, liver, and spleen.[185,186] In persons with a CD4 count below 100 cells/mm³, bacillary angiomatosis typically manifests as nodular, vascular skin lesions, that can be confused with Kaposi’s sarcoma lesions. *Bartonella* infection can also cause fever, culture-negative endocarditis, osteomyelitis, peliosis hepatitis, and other invasive manifestations.[187] Less commonly, persons with HIV and *Bartonella* infection develop disseminated disease and present with systemic symptoms, such as fever, weight loss, and night sweats.

Diagnosis

The diagnosis of bacillary angiomatosis is usually made based on clinical manifestations combined with a variety of testing modalities, including histologic findings on a skin biopsy sample, a positive *Bartonella* serologic test, or a positive molecular polymerase chain reaction (PCR) test on a tissue sample obtained from a biopsy or resection.[184,188,189,190] *Bartonella* skin lesions can mimic many other conditions, including Kaposi’s sarcoma, pyogenic granuloma, fibrosarcoma, and epithelioid sarcoma.[183,188] If a skin biopsy is performed to evaluate skin lesions of unknown cause, the diagnosis of Bartonella can be made by Warthin-Starry silver staining that shows characteristic bacilli or direct detection of *Bartonella* organisms using polymerase chain reaction (PCR) techniques. Isolating *Bartonella* species in culture is very difficult.

Treatment

The approach to treating *Bartonella* infection depends on the organ involved (Table 12).[184] In general, doxycycline is a preferred agent, often in combination with other agents, for treatment of *Bartonella* infection.

- **Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis**: The treatment of choice for bacillary angiomatosis, peliosis hepatitis, bacteremia (without endocarditis), and osteomyelitis is doxycycline or erythromycin.[183,184]
- **Central Nervous System**: For infections of the central nervous system, the recommended treatment is doxycycline, with or without rifampin.[183,184]
- **Endocarditis**: If endocarditis is confirmed, the preferred treatment is intravenous doxycycline plus rifampin for 6 weeks, followed by doxycycline alone for at least 3 months.[183,184]

Treatment Duration

The treatment duration for all *Bartonella* infections in persons with HIV is at least 3 months. Alternative therapies for *Bartonella* infections (other than for endocarditis) include azithromycin or clarithromycin.

Timing for Initiating Antiretroviral Therapy

For most persons with HIV and *Bartonella* infection, antiretroviral therapy does not need to be delayed. If, however, the individual is diagnosed with ophthalmic *Bartonella* infection, then antiretroviral therapy should
be delayed until they have completed a 2 to 4 week treatment course with doxycycline plus rifampin. [184]
Coccidiomycosis

Background

Coccidioidomycosis is caused by a soil-dwelling fungus, *Coccidioides immitis*, and may cause a wide spectrum of clinical diseases among individuals with HIV. The risk of developing symptomatic coccidioidomycosis in persons with HIV is significantly increased in persons with a CD4 count less than 250 cells/mm$^3$ who live (or previously lived) in a region endemic for coccidioidomycosis. In persons with HIV, rates of coccidioidomycosis have been higher in Black individuals than in Whites.\[191\] The incidence of coccidioidomycosis has decreased in the era of potent antiretroviral therapy.\[192\]

Clinical Manifestations

In adults with CD4 cell count greater than 250 cells/mm$^3$, coccidioidomycosis typically presents as an acute or subacute localized pulmonary infection that mimics community-acquired pneumonia. Persons with lower CD4 counts may develop diffuse pneumonia with reticulonodular infiltrates (that may resemble *Pneumocystis* pneumonia), or disseminated extrapulmonary infection that may cause skin lesions, meningitis, or involvement of lymph nodes or liver.\[193,194,195\] Cutaneous findings in acute coccidioidomycosis infection may include erythema multiforme or erythema nodosum, whereas cutaneous findings in disseminated disease may include papules, pustules, nodules, and ulcerated lesions.

Diagnosis

The initial evaluation of a person with suspected coccidioidomycosis should be guided by the clinical manifestations. The diagnosis is made based on the clinical presentation combined with laboratory testing that may include serologic tests, antigen testing, histologic staining, and fungal cultures.\[194,196,197\] A definitive diagnosis can be established with a positive culture of the organism from a clinical sample or by detecting spherules on histopathological examination of tissue.\[194\]

- **Serologic Testing**: For person with HIV who have symptoms consistent with coccidioidomycosis, serologic testing is the most frequently used test to make a presumptive diagnosis. A negative serologic test, however, does not exclude the diagnosis, since formation of antibodies takes several weeks after initial infection.\[194\] As such, repeat serological testing should be performed every 1 to 2 weeks in individuals without a diagnosis who exhibit a clinical syndrome compatible with coccidioides disease.\[194\] For persons with HIV who have suspected coccidioidomycosis, the EIA (for IgG and IgM) is the recommended initial diagnostic test, but the sensitivity of this test is significantly reduced in those with a low CD4 count.\[194,198\] Accordingly, serologic testing should not be considered reliable for ruling out coccidioidomycosis in persons with HIV who have advanced immunosuppression.\[193,199\] In addition, problems have been reported with false-positive IgM EIA *Coccidioides* serologic tests.\[200\] If the EIA test is positive (for either IgG or IgM), the result should be confirmed using immunodiffusion or complement fixation tests.\[194\]

- **Antigen Testing**: A coccidioides antigen test is commercially available and can be performed on urine, serum or other body fluids of individuals with active disease. This antigen test is most useful for the diagnosis of extra-thoracic disseminated coccidioidomycosis, especially coccidioidal meningitis.\[194,199,201,202\]

- **Real-Time Polymerase Chain Reaction**: To help establish a diagnosis of coccidioides, real time PCR (RT-PCR) can be performed on formalin-fixed tissue or unfixed clinical specimens. While there is a commercially available Coccidioides RT-PCR assay, it has not been approved by the FDA for use in people with HIV due to lack of data in this population.\[194,203\]

- **Fungal Culture**: The diagnosis of coccidioidomycosis can be confirmed by isolating *C. immitis* from a clinical specimen (bronchoalveolar lavage fluid, cerebrospinal fluid, or tissue sample).\[194\] When performing fungal cultures with an attempt to isolate *C. immitis*, the microbiology laboratory must have established biocontainment procedures to prevent infection in laboratory staff.
- **Staining**: The diagnosis of coccidioidomycosis can be made by identifying characteristic *Coccidioides* spherules (8 to 10 microns in diameter) that contain multiple endospores (2 to 5 microns in diameter); depending on the clinical sample, the staining may be performed on a wet mount (using saline or potassium hydroxide) of a sample or on a histopathology specimen (usually with hematoxylin and eosin staining).

**Initial Treatment of Coccidioidomycosis**

The initial treatment of coccidioidomycosis is based on whether the disease is considered mild (e.g. focal pneumonia) or severe (e.g. disseminated or diffuse pulmonary disease) (Table 13).[194] The recommended treatment for persons with mild disease is fluconazole (400 mg once daily) or itraconazole (200 mg three times daily for 3 days, then 200 mg twice daily once daily); if bone or joint disease is present, itraconazole is preferred. For disseminated disease or diffuse pulmonary disease, which carry high mortality rates, recommended therapy is amphotericin B (or lipid formulation of amphotericin B).[193,194] In persons with severe non-meningeal disease, initial therapy with amphotericin B should be continued until clinical improvement has occurred, and then treatment can be switched to oral fluconazole or oral itraconazole. To treat coccidioidal meningitis, the Adult and Adolescent OI Guidelines recommend using high-dose fluconazole (400 to 800 mg intravenously or orally), in consultation with an expert.

**Discontinuation of Therapy**

Discontinuation of therapy for coccidioidomycosis depends on the type and severity of the coccidioidomycosis infection, the CD4 cell count, whether virologic suppression on antiretroviral therapy has been achieved, and if continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology (Table 14).[194]
Cryptosporidiosis

Background

Cryptosporidiosis is an intestinal infection caused by the protozoan parasite Cryptosporidium (Figure 22).[204,205] The life cycle of this organism in humans is complex and all stages of development can take place within a single host (Figure 23).[204] Cryptosporidiosis can be transmitted through contaminated water sources (including swimming pools, lakes, and public water supplies), can persist despite chlorination, and can also be transmitted from person-to-person, especially among men who have sex with men.[206] In the current HIV era, the incidence of cryptosporidiosis in persons with HIV is very low (less than 1 case per 1,000 person-years).[1,206]

Clinical Manifestations

The incubation period for cryptosporidiosis is typically 7 to 10 days.[204] Infection of the gastrointestinal tract by Cryptosporidium impairs absorption and enhances secretion, typically manifesting as watery diarrhea and often accompanied by nausea, vomiting, and intestinal cramping. The severity and duration of disease depend on the host immune response, ranging from an asymptomatic or mild self-limited illness, to chronic low-level diarrhea, to a profuse cholera-like illness. For persons with HIV, the CD4 cell count is a strong predictor of severity of illness (Figure 24).[207] In a retrospective analysis, adults with HIV and self-limited cryptosporidiosis had a mean CD4 count of 312 cells/mm$^3$ versus a mean CD4 count of 57 cells/mm$^3$ in those with persistent infection. In some cases, biliary complications (primarily cholangiopathy) can develop from Cryptosporidium infection.[208]

Diagnosis

Diagnostic testing for Cryptosporidium should be performed in persons with HIV and acute diarrhea, chronic diarrhea, or biliary tract disease, especially if their CD4 count is less than 200 cells/mm$^3$. The diagnosis can be made by identifying oocysts in stool or tissue; the recommended test to identify Cryptosporidium depends on the available tests at the laboratory used by the clinician.[209]

- **Ova and Parasite Examination of Stool**: Routine ova and parasite testing does not detect Cryptosporidium and thus should not be relied on to diagnose Cryptosporidium.
- **Modified-Acid Fast Stain**: The modified acid-fast stain, which stains the organism red, is the most common method used to detect Cryptosporidium on microscopic examination of a stool sample (Figure 25).
- **Immunofluorescence Antigen Testing**: Many centers now offer detection of Cryptosporidium using direct immunofluorescence antigen testing, most often with an enzyme-linked immunoassay (ELISA) (Figure 26).
- **Enteric Pathogen PCR Panel**: In recent years, some laboratories offer a multiplex enteric pathogen panel for evaluation of patients with diarrhea.[210] This test is a molecular assay that utilizes polymerase chain reaction (PCR) technology. Most of these panels will detect common bacterial, viral, and parasitic pathogens. Many, but not all, include detection of Cryptosporidium. These multiplex molecular tests are often better at identifying cases of cryptosporidium infection than direct microscopy.[211,212,213]

Treatment

- **Antiretroviral Therapy and Immune Reconstitution**: The most important aspect of treatment for cryptosporidiosis is immune restoration with antiretroviral therapy (Table 15).[206,214,215]
- **Supportive Therapy**: Since immune reconstitution may take months, supportive care plays a vital role in managing the symptoms, and may include oral rehydration, intravenous rehydration, replacement of electrolytes, and symptomatic treatment of diarrhea.
• **Antimicrobial Therapy**: Antimicrobial treatments have been studied, including nitazoxanide, paromomycin, or azithromycin, but none of these options has been consistently effective in the absence of antiretroviral therapy.[216,217,218,219,220] For severe disease, some experts recommend giving a trial of nitazoxanide in addition to antiretroviral therapy, a recommendation based on a few studies that demonstrated improvement in diarrhea symptoms and reduced parasite burden in individuals with CD4 counts greater than 50 cells/mm$^3$.[206,219,220,221]

**Timing of Antiretroviral Therapy**

Since antiretroviral therapy is the mainstay of cryptosporidiosis treatment for patients with HIV, antiretroviral therapy should be started as soon as possible after the diagnosis of cryptosporidiosis.[206]
Microsporidiosis

Background

Microsporidiosis is a ubiquitous group of protists (single-celled organisms that do not fit into any other category) that are related to fungi. Infection with microsporidia is usually acquired by drinking untreated water or ingesting water from lakes, pools, or hot tubs.[222,223]

Clinical Manifestations

The clinical syndromes usually correlate with the infecting Microsporidia species (Figure 27).[224] Most often persons with microsporidiosis present with nonbloody diarrhea, although certain Microsporidia species can cause encephalitis, ocular disease, sinusitis, myositis, or disseminated disease. The incidence of microsporidiosis has declined with the widespread use of antiretroviral therapy.

Diagnosis

The diagnosis of microsporidiosis is usually made by directly detecting Microsporidia in a clinical sample with a stain. Microscopic diagnosis typically involves examination under high magnification (1000x) and use of a special selective stain, depending on whether the specimen is tissue, stool, or fluids. Stains utilized include modified trichrome stains (Figure 28) or fluorochromes (Chromotrope 2R, Calcofluor White, or Uvitex 2B).

Treatment

Effective treatment of microsporidiosis usually requires immune restoration with antiretroviral therapy; antiretroviral therapy should be started or optimized as quickly as possible after the diagnosis of microsporidiosis.[224] Available data suggest that most individuals experience resolution of symptoms caused by enteric microsporidiosis once the CD4 count increases to greater than 100 cells/mm$^3$.[215,224,225] Initial treatment often includes supportive care (rehydration and nutritional supplementation). Depending on the organ system involved and the species of microsporidia identified, additional therapeutic measures are recommended (Table 16).[224,226,227]

Gastrointestinal Infections Caused by Enterocytozoon bieneusi

Individuals with gastrointestinal Enterocytozoon bieneusi infection should receive antiretroviral therapy; if they have diarrhea and dehydration they should receive fluid support and antimotility agents. The medication fumagillin and TNP-470 (a synthetic analog of fumagillin) have shown activity against E. bieneusi, but these agents are not routinely available in oral formulations in the United States.[226,227] It may be possible to get fumagillin, in severe cases, as a compassionate use medication from Sanofi in France (Sanofil Compassionate Use/Managed Access Program).[224] One study suggested clinical improvement with nitazoxanide to treat diarrhea caused by E. bieneusi, but the benefit was minimal in persons with low CD4 cell counts.[228] If fumagillin is not available, nitazoxanide is recommended as the best option to treat E. bieneusi-induced diarrhea.[224] Albendazole may have benefit in treating diarrhea or systemic disease caused by Microsporidia other than E. bieneusi or Vittaforma corneae.[229,230,231]

Intestinal and Disseminated Infection (not E. bieneusi and Vittaforma corneae)

For intestinal and disseminated microsporidiosis (non-ocular) that is caused by a Microsporidia species other than E. bieneusi and Vittaforma corneae, the recommended treatment is antiretroviral therapy plus albendazole 400 mg twice daily; this therapy should be continued until the individual’s CD4 cell count is greater than 200 cells/mm$^3$ for more than 6 months while receiving antiretroviral therapy.[224]

Disseminated Infection Caused by Trachipleistophora or Ann caliia
For persons with HIV who have disseminated disease caused by *Trachipleistophora* or *Anncaliia*, the recommended treatment is antiretroviral therapy, supportive therapy, and combination oral antimicrobial therapy with itraconazole 400 mg daily and albendazole 400 mg twice daily.

**Microsporidiosis Ocular Infection**

For ocular infection caused by a *Microsporidia* species, the recommended therapy is topical fumagillin eye drops combined with oral albendazole (to treat systemic infection that is often present); treatment should be continued until the infection is resolved and the CD4 count is greater than 200 cells/mm$^3$.[224] Topical fumagillin needs to be made by a specialty compounding pharmacy.

**Timing of Antiretroviral Therapy**

Antiretroviral therapy is the mainstay of treatment for persons with HIV and microsporidiosis and should be initiated immediately.[224]
Cystoisosporiasis (formerly Isosporiasis)

Background

*Cystoispora belli* (formerly *Isospora belli*) is a parasite that primarily affects immunocompromised persons in tropical and subtropical areas of the world.\[232,233\] Infection is acquired via the ingestion of food or water that is contaminated with human feces that contain *C. belli* oocysts.\[233,234\] Most persons with HIV who develop *Isospora* disease have a CD4 count less than 250 cells/mm\(^3\) and have current or past residence in a high-risk geographic region; in the United States most cases of cystoisosporiasis occur in persons who have recently immigrated from (or traveled to) Haiti or Latin America.\[235,236,237\]

Clinical Manifestations

Individuals with HIV and cystoisosporiasis typically develop watery diarrhea, nausea, vomiting, intestinal cramping, anorexia, and low-grade fever.\[236\] These symptoms often resemble those seen with other gastrointestinal opportunistic infections in persons with HIV. Several reports have documented cases of extraintestinal disease, including involvement of gallbladder, lymph nodes, and spleen, but such cases are rare.

Diagnosis

The diagnosis of cystoisosporiasis is made by performing a modified acid-fast stain on a stool sample and identifying oocysts that are relatively large (15 to 20 microns in diameter).\[238\] The unsporulated *Cystoispora* oocysts appear elliptical, with one or both ends slightly tapered.\[233\] Modified acid-fast staining of a stool sample can identify *C. belli* oocysts—in the early phase, oocysts have an internal granular mass (Figure 29) and as they mature, one or two internal sporoblasts may be seen (Figure 30). The *C. belli* oocysts are approximately 30 by 15 microns in size and are distinctly larger and more oval than the *C. parvum* oocysts (4 to 6 microns in diameter) and *Cyclospora* spp. oocysts (6 to 10 microns in diameter).\[233\] Several techniques other than modified acid-fast staining have been used on wet mounts to identify *C. belli*, including bright-field microscopy, differential interference contrast, and ultraviolet fluorescence microscopy (Figure 31). More recently, molecular diagnostic methods using PCR (Enteric Multiplex PCR) have increasingly been used as a diagnostic tool for gastrointestinal pathogens, but many of the commercially available tests do not include *C. belli* in the testing panel.

Treatment for Acute Infection

Treatment of acute cystoisosporiasis includes supportive care (rehydration and nutritional supplementation) and antimicrobial therapy targeted against *C. belli* (Table 17).\[239\]

- **Preferred Therapy:** Several treatment studies in persons with HIV showed good responses to trimethoprim-sulfamethoxazole.\[235,236,240\] Based on available data, the preferred acute therapy consists of trimethoprim-sulfamethoxazole (160/800 mg) 4 times daily for 10 days, with twice-daily dosing considered an acceptable option.\[239\] Some experts prefer to initiate treatment with trimethoprim-sulfamethoxazole (160/800 mg) twice daily and increase the dose to four times daily, if symptoms worsen or persist, and possibly extend the duration of acute therapy up to 4 weeks.
- **Alternative Therapy:** Alternatives include pyrimethamine or ciprofloxacin.\[241\] Note that pyrimethamine may not be easily available due to the extremely high cost of this medication.

Timing of Initiating Antiretroviral Therapy

Limited data exist regarding the timing of initiating antiretroviral therapy in patients with acute cystoisosporiasis. Nevertheless, the Adult and Adolescent OI Guidelines recommend starting antiretroviral therapy at the time treatment for cystoisosporiasis is started, unless there is concern that the antiretroviral
therapy medications will not be absorbed well.[239]

**Chronic Maintenance Therapy**

Individuals with HIV and a CD4 count less than 200 cells/mm$^3$ have a high rate of relapse with cystoisosporiasis and thus should receive chronic maintenance therapy with trimethoprim-sulfamethoxazole (160/800 mg) 3 times weekly (Table 18).[239] Pyrimethamine or ciprofloxacin may be options for those unable to take trimethoprim-sulfamethoxazole.[239]

**Discontinuing Chronic Maintenance Therapy**

Chronic maintenance therapy for cystoisosporiasis in persons with HIV can be discontinued if the following criteria are met:

- The person has experienced a sustained increase in CD4 count to above 200 cells/mm$^3$ for more than 6 months in response to antiretroviral therapy, and
- There is no evidence of active *C. belli* infection
Summary Points

- In people with HIV, major opportunistic infections primarily affect those with a CD4 count of less than 200 cells/m$^3$.
- In some people with HIV, major opportunistic infections are unrecognized prior to the initiation of antiretroviral therapy and can paradoxically worsen in the setting of immune recovery (immune reconstitution inflammatory syndrome [IRIS]).
- Adults with HIV who have a CD4 count below 200 cells/mm$^3$ are at significant risk of developing *Pneumocystis* pneumonia; the recommended therapy is trimethoprim-sulfamethoxazole and the use of adjunctive corticosteroids improves survival for individuals with moderate-to-severe disease.
- *Toxoplasma* encephalitis is typically caused by reactivation of latent organisms in persons with a CD4 count below 100 cells/mm$^3$; *Toxoplasma* encephalitis is usually a presumptive diagnosis based on characteristic clinical and neuroradiographic findings combined with a positive serum anti-*Toxoplasma* antibody.
- *Mycobacterium avium* complex is a non-tuberculous mycobacterial infection that can cause multiorgan disease in persons with a CD4 count of less than 50 cells/mm$^3$; therapy requires a prolonged course with at least two active drugs.
- Patients with cryptococcal meningitis typically have a CD4 count of less than 100 cells/mm$^3$. Initial antifungal therapy with liposomal amphotericin B and flucytosine is recommended for the induction phase. All persons with elevated intracranial pressure should have this managed through serial therapeutic lumbar punctures with CSF removal. Initiation of antiretroviral therapy should be delayed until completion of 2 to 10 weeks of antifungal therapy.
- Cytomegalovirus (CMV) has the potential to cause retinitis in persons with HIV who have a CD4 count below 50 cells/mm$^3$. Therapy usually consists of ocular injections of antiviral medications combined with systemic CMV therapy. Persons with HIV can also develop gastrointestinal and neurologic CMV infections.
- Progressive multifocal leukoencephalopathy (PML) is a focal demyelinating disease caused by the JC virus; immune restoration with antiretroviral therapy is the mainstay of therapy.
- *Candida* esophagitis typically occurs only in patients who have a CD4 count below 100 cells/mm$^3$. Treatment requires 2 to 3 weeks of antifungal therapy, preferably with fluconazole.
- *Histoplasma* and *Coccidioides* can cause a wide spectrum of clinical diseases in persons with HIV in the setting of immunosuppression; severe infection may require treatment with intravenous amphotericin B. The liposomal formulation of amphotericin B causes less renal toxicity than standard amphotericin.
- Multiple intestinal parasites (e.g., *Cryptosporidium, Microsporidium, Cystoisospora*) can cause intestinal disease in persons with HIV; treatment generally includes supportive care and antiretroviral therapy to restore immune function.
Citations


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Figures

Figure 1 Incidence of *Pneumocystis* Pneumonia in United States and Canada: NA-ACCORD, 2000-2010

This graph shows the incidence of *Pneumocystis* Pneumonia among participants in 16 cohorts in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) during 2000-2010 in the United States and Canada.

Figure 2 Pneumocystis Pneumonia: Chest Radiograph

This chest radiograph scan shows extensive bilateral infiltrates in an adult with HIV and *Pneumocystis* pneumonia.

Source: Brian R. Wood, MD
**Figure 3 Pneumocystis Pneumonia: Chest Computed Tomographic (CT) Scan**

This chest CT scan shows extensive bilateral infiltrates in an adult with HIV and *Pneumocystis* pneumonia.

Source: Brian R. Wood, MD
Figure 4 *Pneumocystis* Pneumonia: Pneumothorax

This chest radiograph scan shows a right lung pneumothorax (white arrows) in an adult with HIV and *Pneumocystis* pneumonia.

Source: Brian R. Wood, MD
**Figure 5 Symptoms of Patients with Acute *Toxoplasma* Encephalitis**

This graphic shows the frequency of symptoms present in 115 persons with HIV and *Toxoplasma* encephalitis seen at San Francisco General Hospital during the years 1981-1990.

**Figure 6 Clinical Signs in Patients with Acute *Toxoplasma* Encephalitis**

Frequency of signs present in 115 persons with HIV and *Toxoplasma* encephalitis seen at San Francisco General Hospital during the years 1981-1990; focal signs consisted of hemiparesis (39%), ataxia (30%), cranial-nerve palsies (28%), sensory deficits (12%), aphasia (8%), and hemianopia (7%).

Figure 7 Contrast Brain Computed Tomographic (CT) Scan in Person with HIV and *Toxoplasma* Encephalitis

This contrast CT scan shows multiple ring-enhancing lesions with surrounding vasogenic edema.

Source: David H. Spach, MD
**Figure 8 Brain Magnetic Resonance Imaging (MRI) Scan in Person with HIV and Toxoplasma Encephalitis**

The MRI scan shows multiple lesions.

Source: David H. Spach, MD
Figure 9 Timing of Neurologic Response in Patients with *Toxoplasma* Encephalitis

The timing of neurologic response in 35 adults with HIV and *Toxoplasma* encephalitis who improved with treatment is shown. A neurologic response was defined as improvement in at least half of the baseline neurologic abnormalities. Individuals who did not have a neurologic response are not included in this graphic.

Figure 10 Risk of Developing MAC Bacteremia Related to Baseline CD4 Cell Count

Figure 11 Common Clinical Manifestations of Persons with HIV and MAC Bacteremia

Figure 12 Clinical Manifestations of Persons with HIV and Cryptococcal Meningitis at the Time of Diagnosis

The graph represents the clinical manifestations of 65 adults with HIV from France at the time of diagnosis of cryptococcal meningitis. The mean CD4 count at the time of diagnosis was 46 cells/mm³.

**Figure 13 Cerebrospinal Fluid Opening Pressure in Persons with HIV and Cryptococcal Meningitis at the Time of Diagnosis**

This graph represents data from 221 individuals with HIV and cryptococcal meningitis who had CSF opening pressure measured prior to receiving therapy. The investigators defined a normal CSF opening pressure as less than 190 cm H₂O.

Figure 14 Patient Outcomes Related to Change in Cerebrospinal Fluid (CSF) Opening Pressure in Persons with HIV and Cryptococcal Meningitis

The graph represents outcomes of 161 individuals with AIDS and cryptococcal meningitis who had lumbar puncture with opening pressure measured prior to therapy and 2 weeks after treatment. The investigators defined clinical failure as persistent or worsening signs and symptoms of cryptococcal meningitis after 2 weeks of therapy; mycologic failure was defined as positive CSF culture after 2 weeks of therapy.

Figure 15 (Image Series) - Retinitis Findings on Fundoscopic Examination (Image Series) - Figure 15 (Image Series) - Retinitis Findings on Fundoscopic Examination
Image 15A: Normal Retina

This image of a normal retina identifies important landmarks visible with a hand-held ophthalmoscope. The macula is in the center of the retina; it contains densely packed cones that specialize in visual acuity and color vision. The fovea is the central depression within the macula. The optic nerve functions to transmit impulses from the retina to the brain and the visible portion of the optic nerve is known as the optic nerve head or optic disc. Retinal veins and arteries are prominently seen extending from the optic nerve.
Figure 15 (Image Series) - Retinitis Findings on Fundoscopic Examination
Image 15B: Cytomegalovirus Retinitis, Central Portion of Retina

This retinal photograph taken from a person with AIDS and cytomegalovirus retinitis shows an opacified, edematous retina (yellow) and hemorrhage (red); the retinitis involves the optic nerve head and extends adjacent to the macula along the retinal blood vessels. This lesion is considered an immediate sight-threatening lesion.
Figure 15 (Image Series) - Retinitis Findings on Fundoscopic Examination
Image 15C: Cytomegalovirus Retinitis, Brushfire Pattern

This retinal photograph taken from a person with AIDS and cytomegalovirus retinitis shows extensive retinitis in a brushfire pattern in the upper and right region of the image. In the area farthest to the upper right, retinal necrosis and atrophy have led to retinal pigment epithelial change, as evident by the darkly pigmented appearance.
**Figure 15 (Image Series) - Retinitis Findings on Fundoscopic Examination**  
**Image 15D: Cytomegalovirus Retinitis, Smoldering Lesion**

This retinal photograph is taken from a person with AIDS in whom cytomegalovirus retinitis (arrow) developed in a slower fashion ("smoldering CMV retinitis"). This "smoldering" type of lesion often does not cause noticeable symptoms, and may escape detection until it extends closer to the site-threatening region (zone 1).
**Figure 16 HIV Retinopathy**

This retinal photograph taken from a person with HIV retinopathy shows multiple "cotton wool spots". These "cotton wool spots" represent nerve fiber layer infarcts, identical to those often seen in persons with hypertension or diabetes mellitus. These lesions do not cause symptoms and resolve spontaneously.
Figure 17 Retinal Anatomic Zones

This illustration shows a schematic representation of an entire retina with superimposed anatomic zones (as defined by the UCLA CMV Retinopathy Study Group). Using a standard direct ophthalmologic examination, only a small portion of the retina is visualized (all of zone 1 and some of zone 2). Zone 1 comprises less than 10% of the entire retina. The retina lines most of the inner wall of the back of the eyeball and it is comprised of thin, multi-layered neural tissue; the retina receives and transmits images. The medial region is also known as the nasal region and the lateral region is also referred to as the temporal region.

Illustration credit: David Ehlert, Cognition Studio.
Figure 18 Magnetic Resonance Imaging (MRI) in Person with HIV and Progressive Multifocal Leukoencephalopathy

This T2-weighted MRI scan shows diffuse confluent lesions most prominent in the occipital lobes.

Source: David H. Spach, MD
Figure 19 Chest Radiograph of a Person with AIDS and Disseminated Histoplasmosis

This chest radiograph in a person with AIDS and disseminated histoplasmosis shows subtle diffuse ground-glass pulmonary infiltrates.

Source: David H. Spach, MD
**Figure 20 Estimated Sensitivity of Diagnostic Tests for Disseminated Histoplasmosis in Persons with AIDS**

These data reflect the sensitivity of four different tests used to diagnose histoplasmosis in persons with AIDS who have disseminated histoplasmosis. These data include samples from blood, bone marrow, respiratory secretions, or localized skin lesions.

**Figure 21 Disseminated Histoplasmosis and Peripheral Blood Smear**

This peripheral blood smear from a person with AIDS shows a cluster of intracellular *Histoplasma capsulatum* organisms (white arrow). Blood cultures subsequently grew *Histoplasma capsulatum*.
**Figure 22 Cryptosporidium**

This illustration is showing *Cryptosporidium* oocysts with sporozoites.

Source: Centers for Disease Control and Prevention
Figure 23 Life Cycle of Cryptosporidium

Source: from Chen XM, Keithly JS, Paya CV, LaRusso NF. Cryptosporidiosis. N Engl J Med. 2002; 346:1723-31. Reproduced with permission from the Massachusetts Medical Society. Copyright © 2002 Massachusetts Medical Society. All rights reserved.
Figure 24 Relationship of CD4 Cell Count and Cryptosporidiosis Disease in Persons with HIV

Figure 25 Modified Acid-fast Staining of Stool Samples Showing *Cryptosporidium* Oocysts

The black arrows point to multiple *Cryptosporidium* oocysts.

Image courtesy of Carolyn Wallis, Harborview Medical Center Microbiology Laboratory.
Figure 26 Immunofluorescence Microscopy for Detection of Oocysts

Oocysts of Cryptosporidium parvum (smaller ovals on left and top) and Giardia intestinalis (larger ovals and lower right) stained with immunofluorescent antibodies.

Source: Centers for Disease Control and Prevention
Figure 27 Correlation of Clinical Manifestations with Different *Microsporidia* species
Figure 28 Microsporidiosis Identified on Modified Trichrome Stain

Image courtesy of Carolyn Wallis, Harborview Medical Center Microbiology Laboratory.
Figure 29 *Cystoisospora belli* Oocyst with Granular Mass

Modified acid-fast smear of stool sample showing *Cystoisospora belli* oocyst with internal granular mass (zygote).

Image courtesy of Carolyn Wallis, Harborview Medical Center Microbiology Laboratory.
Figure 30 *Cytoisospora belli* Oocyst with Internal Sporoblast

Image courtesy of Carolyn Wallis, Harborview Medical Center Microbiology Laboratory.
Figure 31 Wet Mount Staining Techniques for *Cystoisospora belli*

These stool sample wet mount tests show three wet mount techniques for diagnosing *Cystoisospora belli*: bright-field microscopy (A and D); differential interference contrast (DIC) (B and E); and blue UV fluorescence microscopy (C and F). The images on the top row (A, B, and C) show *C. belli* with a single internal sporoblast and the images on the bottom row (C, D, and E) show two internal sporoblasts.

Source: Centers for Disease Control and Prevention.
Table 1. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

**Treating Mild-Moderate PCP—Total Duration = 21 Days (AII)**

Note—Patients who develop PCP despite trimethoprim-sulfamethoxazole prophylaxis usually can be treated effectively with standard doses of trimethoprim-sulfamethoxazole (BIII)

**Preferred Therapy:**

- Trimethoprim-sulfamethoxazole: (trimethoprim 15–20 mg and sulfamethoxazole 75–100 mg)/kg/day, given PO in 3 divided doses (AI), or
- Trimethoprim-sulfamethoxazole DS: 2 tablets PO three times daily (AI)

**Alternative Therapy:**

- Dapsone* 100 mg PO daily + Trimethoprim 15 mg/kg/day PO (3 divided doses) (BI) or
- Primaquine* 30 mg (base) PO daily + Clindamycin PO (450 mg q6h or 600 mg q8h) (BI)
- Atovaquone 750 mg PO BID with food (BI)

*Whenever possible, patients should be tested for G6PD deficiency before administration of dapsone or primaquine. Alternative agent should be used if the patient is found to have G6PD deficiency.

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

Table 2. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

**Treating Moderate-Severe PCP—Total Duration = 21 days (AI)**

Note—Patients who develop PCP despite trimethoprim-sulfamethoxazole prophylaxis usually can be treated effectively with standard doses of trimethoprim-sulfamethoxazole (BIII)

**Preferred Therapy:**

- Trimethoprim-sulfamethoxazole: (trimethoprim 15–20 mg and sulfamethoxazole 75–100 mg)/kg/day IV given q6h or q8h (AI), may switch to PO formulations after clinical improvement (AI)

**Alternative Therapy:**

- Pentamidine 4 mg/kg IV once daily infused over at least 60 minutes (AI); may reduce the dose to 3 mg/kg IV once daily in the event of toxicities (BI) or
- Primaquine* 30 mg (base) PO once daily + (Clindamycin [IV 600 q6h or 900 mg q8h] or [PO 450 mg q6h or 600 mg q8h]) (AI)

**Adjunctive Corticosteroids: for Moderate to Severe PCP Based on Following Criteria: (AI):**

- PaO₂ <70 mm Hg at room air or
- Alveolar-arterial O₂ gradient ≥35 mm Hg

Dosing Schedule: Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) (AI):

- Days 1–5: 40 mg PO BID
- Days 6–10: 40 mg PO daily
- Days 11–21: 20 mg PO daily

IV methylprednisolone can be given as 75% of prednisone dose

*Whenever possible, patients should be tested for G6PD deficiency before administration of primaquine. Alternative agent should be used if the patient is found to have G6PD deficiency.

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Pneumocystis Pneumonia.* Updated: March 28, 2019. [HIV.gov]
Table 3. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Preventing Subsequent Episodes of *Pneumocystis* Pneumonia (Secondary Prophylaxis)

**Indications for Initiating Secondary Prophylaxis:**

- Prior *Pneumocystis* Pneumonia

**Preferred Therapy:**

- Trimethoprim-sulfamethoxazole: 1 DS PO daily (AI), or
- Trimethoprim-sulfamethoxazole: 1 SS PO daily (AI)

**Alternative Therapy:**

- TMP-SMX 1 DS PO three times weekly (BI) or
- Dapsone[b,c] 100 mg PO daily or 50 mg PO BID (BI) or
- Dapsone[b] 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly (BI) or
- (Dapsone[b] 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly (BI) or
- Aerosolized pentamidine[c] 300 mg via Respirgard II™ nebulizer every month (BI) or
- Atovaquone 1500 mg PO daily with food (BI) or
- (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily with food (CIII)

**Indications for Discontinuing Secondary Prophylaxis:**

- CD4 count increased from <200 cells/mm³ to >200 cells/mm³ for >3 months as a result of antiretroviral therapy (BII) or
- Can consider if CD4 count 100-200 cells/mm³ and HIV RNA remain below limits of detection for ≥3 months to 6 months (BII)
- For patients in whom PCP occurs at a CD4 count >200 cells/mm³ while not on antiretroviral therapy, 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).

Note: If an episode of PCP occurs at a CD4 count >200 cells/mm³ while a patient is on antiretroviral therapy, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of antiretroviral therapy (BIII).

**Indications for Restarting Secondary Prophylaxis:**

- CD4 count <100 cells/mm³ regardless of HIV RNA (AIII)
- CD4 count 100-200 cells/mm³ and HIV RNA above detection limit of the assay used (AIII)

Whenever possible, patients should be tested for G6PD deficiency before administration of dapsone or primaquine. Alternative agent should be used if the patient is found to have G6PD deficiency. Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for *Pneumocystis* pneumonia prophylaxis in patients who are seropositive for *Toxoplasma gondii*.

**Rating System for Prevention and Treatment Recommendations**

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from
the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Pneumocystis* Pneumonia. Updated: March 28, 2019. [HIV.gov]
Table 4. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Initial Therapy for *Toxoplasma gondii* Encephalitis

Note—if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine (BI). For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies (BI). Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved (CIII).

**Preferred Regimen (AI):**

- Pyrimethamine 200 mg PO once, followed by dose based on body weight:
  - **Body weight ≤60 kg:** pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)
  - **Body weight >60 kg:** pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)

**Alternative Therapy:**

- (Pyrimethamine + leucovorin)\(^c\) + clindamycin 600 mg IV or PO q6h (AI); preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine; must add additional agent for PCP prophylaxis, or
- TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID (BI), or
- Atovaquone\(^b\) 1500 mg PO BID + (pyrimethamine + leucovorin)\(^c\) (BII), or
- Atovaquone\(^b\) 1500 mg PO BID + sulfadiazine\(^d\) (BII), or
- Atovaquone\(^b\) 1500 mg PO BID (BII)

**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

\(^b\) Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

\(^c\) Pyrimethamine and leucovorin doses: Same as doses listed in Preferred Regimen for Acute Infection

\(^d\) Sulfadiazine dose: Same as weight-based dose listed in Preferred Regimen for Acute Infection

Rating System for Prevention and Treatment Recommendations

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Toxoplasma gondii* encephalitis. Updated: July 25, 2017. [HIV.gov]
Table 5. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

**Chronic Maintenance Therapy for Toxoplasma gondii Encephalitis**

**Preferred Regimen:**
- Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily (AI)

**Alternative Regimen:**
- Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily (BI); must add additional agent to prevent PCP (AII), or
- TMP-SMX DS 1 tablet BID (BII), or
- TMP-SMX DS 1 tablet daily (BII), or
- Atovaquone\(^b\) 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, or
- Atovaquone\(^b\) 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) (BII), or
- Atovaquone\(^b\) 750–1500 mg PO BID (BII)

**Discontinuing Chronic Maintenance Therapy:**
- Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and CD4 count >200 cells/mm\(^3\) for >6 months in response to ART (BI)

**Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance Therapy:**
- CD4 count <200 cells/mm\(^3\) (AIII)

\(^b\) Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption.

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**
- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *Toxoplasma gondii* encephalitis. Updated: July 25, 2017. [HIV.gov]
Table 6. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Treating Disseminated MAC Disease

Preferred Therapy:

At least 2 drugs as initial therapy to prevent or delay emergence of resistance (AI)

- Clarithromycin 500 mg PO twice daily (AI) + ethambutol 15 mg/kg PO daily (AI), or
- Azithromycin 500–600 mg (AII) + ethambutol 15 mg/kg PO daily (AI) when drug interactions or intolerance precludes the use of clarithromycin

Note: Testing of susceptibility to clarithromycin or azithromycin is recommended.

Alternative Therapy:

Addition of a third or fourth drug should be considered for patients with advanced immunosuppression (CD4 count <50 cells/mm³), high mycobacterial loads (>2 log CFU/mL of blood), or in the absence of effective antiretroviral therapy (CIII).

The 3rd or 4th drug options may include:

- Rifabutin 300 mg PO daily (CI) (dosage adjusted may be necessary based on drug-drug interactions), or
- An aminoglycoside (CIII) such as amikacin 10-15 mg/kg IV daily or streptomycin 1 gm IV or IM daily, or
- A fluoroquinolone (CIII) such as levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily

Rating System for Prevention and Treatment Recommendations

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Mycobacterium avium complex disease. Updated: February 15, 2019. [HIV.gov]
Table 7. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

**Treating Cryptococcal Meningitis: Induction and Consolidation Therapy**

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

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

*Preferred Regimens*

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

*Note:* Flucytosine dose should be adjusted in renal impairment

*Alternative Regimens*

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

*Note:* If the person treated does not improve clinically or remains clinically unstable, continue induction therapy until the CSF culture is confirmed to be negative (BIII).

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

*Preferred Regimen*

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

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention
and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Cryptococcosis. Updated: July 1, 2021. [HIV.gov]
Recommendations for the Treatment of CMV Retinitis

Managing CMV Retinitis

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

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

**Preferred Therapy**

- Ganciclovir 5 mg/kg IV every 12 hours for 14–21 days, then 5 mg/kg IV daily (AI), or
- Ganciclovir 5 mg/kg IV every 12 hours for 14–21 days, then valganciclovir 900 mg PO daily (AI), or
- Valganciclovir 900 mg PO every 12 hours for 14–21 days, then 900 mg daily (AI);

  with or without

- Intravitreal injections of ganciclovir (2 mg/injection) or foscarnet (2.4 mg/injection) repeat weekly until lesion inactivity is achieved. This is to provide higher intraocular levels of drug and faster control of the infection until steady state intraocular ganciclovir concentrations are achieved (AIII);
  - **Note**: IV ganciclovir can be switched to oral valganciclovir if the patient is clinically improving and there are no concerns about gastrointestinal absorption.

**Alternative Therapy**

- Intravitreal injections as listed above (AIII); plus one of the following systemic therapies:
  - Foscarnet 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours for 14–21 days, then 90–120 mg/kg IV every 24 hours (BI), or
  - Cidofovir 5 mg/kg/week IV for 2 weeks, then 5 mg/kg every other week; each dose should include saline hydration before and after therapy and probenecid 2 g PO 3 hours before the dose followed by 1 g PO 2 hours after the dose, and 1 g PO 8 hours after the dose (total of 4 g) (CI). Cidofovir is contraindicated in patients with a serum creatinine >1.5 mg/kL, a calculated creatinine clearance ≤5 mL/min or a urine protein ≥100 mg/kL (equivalent to ≥2+ proteinuria). Given the nephrotoxic potential of cidofovir, cautious use of cidofovir with tenofovir is advised.
    - **Note**: This regimen should be avoided in patients with sulfa allergy because of cross hypersensitivity with probenecid.

For Peripheral Lesions

- Valganciclovir 900 mg PO every 12 hours for 14–21 days, then 900 mg once daily (AII) for the first 3–6 months until antiretroviral therapy-induced immune recovery.

**Immune Reconstitution Uveitis**

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

**Treatment of Immune Reconstitution Uveitis**
• Periocular or intravitreal corticosteroid or a short course of systemic steroid (BIII).

Rating System for Prevention and Treatment Recommendations

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

Source:

• Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Cytomegalovirus disease. Updated: July 1, 2021. [HIV.gov]
Table 9. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Treatment of CMV Esophagitis or Colitis

Preferred Therapy:

- Ganciclovir 5 mg/kg IV every 12 hours; may switch to valganciclovir 900 mg PO every 12 hours once the patient can absorb and tolerate PO therapy (BII).

Alternative Therapy:

- Foscarnet 60 mg/kg IV every 8 hours or 90 mg/kg IV every 12 hours (BIII)—for patients with treatment-limiting toxicities to ganciclovir or with ganciclovir resistance; or
- Oral valganciclovir (900 mg PO every 12 hours) may be used if symptoms are not severe enough to interfere with oral absorption (BIII)

Duration of Anti-CMV Therapy:

- 21–42 days or until signs and symptoms have resolved (CII).

Note: Maintenance therapy is usually not necessary, but should be considered after relapses (BII).

Rating System for Prevention and Treatment Recommendations

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Cytomegalovirus disease. Updated: July 1, 2021. [HIV.gov]
Table 10. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

**Treating Esophageal Candidiasis (Duration of Therapy 14 to 21 Days)**

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

**Preferred Therapy:**

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

**Alternative Therapy:**

- Voriconazole 200 mg PO or IV BID (BI), *or*
- Isavuconazole 200 mg PO as a loading dose, followed by 50 mg PO daily (BI), *or*
- Isavuconazole 400 mg PO as a loading dose, followed by 100 mg PO daily (BI), *or*
- Isavuconazole 400 mg PO once-weekly (BI), *or*
- Caspofungin 50 mg IV daily (BI), *or*
- Micafungin 150 mg IV daily (BI), *or*
- Anidulafungin 100 mg IV for one dose, then 50 mg IV daily (BI), *or*
- Amphotericin B deoxycholate 0.6 mg/kg IV daily (BI), *or*
- Lipid formulation of amphotericin B 3-4 mg/kg IV daily (BIII)

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

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

Table 11. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

**Treatment of Disseminated Histoplasmosis**

*Treating Moderately Severe to Severe Disseminated Disease*

*Induction Therapy*

**Preferred Therapy:**

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

**Alternative Therapy:**

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

**Duration:**

- For at least 2 weeks or until clinically improved

*Maintenance Therapy*

**Preferred Therapy:**

- Itraconazole 200 mg PO three times daily for 3 days, then twice daily for at least 12 months (AII), with dosage adjustment based on interactions with antiretroviral medications and results from itraconazole serum concentration

*Treating Less Severe Disseminated Disease*

*Induction and Maintenance Therapy*

**Preferred Therapy:**

- Itraconazole 200 mg PO three times daily for 3 days, then 200 mg PO twice daily for ≥12 months (AII), with dosage adjustment based on interactions with antiretroviral medications and results from itraconazole serum concentration

**Alternative Therapy:**

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

  - Posaconazole, extended release tablet, 300 mg PO twice daily for 1 day, then 300 mg PO once daily (BIII)
  - Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII)
  - Fluconazole 800 mg PO once daily (CII)

*Treating Histoplasma Meningitis*

*Induction Therapy (4-6 weeks)*

**Preferred Therapy:**

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

**Maintenance Therapy**

- Itraconazole 200 mg PO twice or three times daily for at least 12 months and until resolution of abnormal cerebrospinal findings with dosage adjustment based on interactions with antiretroviral medications and results from itraconazole serum concentration (AIII)

**Alternative Maintenance Therapy**
Note: These recommendations are based on limited clinical data for patients intolerant to itraconazole.

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII)
- Posaconazole, extended release tablet, 300 mg PO twice daily for 1 day, then 300 mg PO once daily (BIII)
- Fluconazole 800 mg PO once daily (CII)

**Long Term Suppressive Therapy**

**Indications**

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

**Preferred Therapy**

- Itraconazole 200 mg PO once daily (AII)

**Alternative Therapy**

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

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

- Received azole treatment for >1 year, and
- Negative fungal blood cultures, and
- Serum or urine Histoplasma antigen below the level of quantification, and
- Have an undetectable HIV viral load, and
- CD4 count >150 cells/mm$^3$ for ≥6 months in response to antiretroviral therapy

**Indication for Restarting Secondary Prophylaxis**

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

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Histoplasmosis. Last updated: September 13, 2019. [HIV.gov]
Table 12. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

**Treating Bartonella Infections**

**Preferred Therapy**

*For Cat Scratch Disease, Bacillary Angiomatosis, Peliosis Hepatis, Bacteremia, and Osteomyelitis:*

- Doxycycline 100 mg PO or IV every 12 hours (AII), or
- Erythromycin 500 mg PO or IV every 6 hours (AII)

*For Infections Involving the Central Nervous System (CNS):*

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

*For Confirmed Bartonella Endocarditis:*

- (Doxycycline 100 mg IV every 12 hours + rifampin 300 mg IV or PO every 12 hours) for 6 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months (BII), or
- (Doxycycline 100 mg IV every 12 hours + gentamicin 1 mg/kg IV every 8 hours) for 2 weeks, then continue with doxycycline 100 mg IV or PO every 12 hours for ≥3 months (BII) (second line due to potential gentamicin nephrotoxicity as glomerulonephritis frequently complicates Bartonella endocarditis)

*For Other Severe Bartonella Infections (Multifocal Disease with Clinical Decompensation):*

- Doxycycline 100 mg PO or IV every 12 hours + rifampin 300 mg PO or IV every 12 hours (BIII), or
- Erythromycin 500 mg PO or IV every 6 hours + rifampin 300 mg PO or IV every 12 hours (BIII)

**Note:** IV therapy may be needed initially (AIII)

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

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

**Duration of Therapy:**

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

**Indication for Long-Term Suppressive Therapy**

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

- A macrolide or doxycycline as long as the CD4 count remains <200 cells/mm³ (AIII)

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

- Received at least 3 to 4 months of treatment; and
- CD4 count >200 cells/mm³ for at least 6 months
- Some specialists would only discontinue therapy if Bartonella titers have also decreased by four-fold

**Other Considerations**

- Rifamycin class antibiotics are potent hepatic enzyme inducers and may lead to significant interaction with many drugs, including antiretroviral agents.
- In pregnancy, erythromycin or an alternative macrolide should be used as first-line therapy (AIII) rather than doxycycline due to toxicity profile; third-generation cephalosporins may have efficacy but are second line.
Rating System for Prevention and Treatment Recommendations

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Bartonellosis. Updated: June 11, 2021. [HIV.gov]
Table 13. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

### Initial Treatment of Coccidioidomycosis

**Treating Mild-to-Moderate Pulmonary Infections**

**Indications for Treatment:**

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

**Preferred Therapy:**

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

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

- Voriconazole loading dose of 400 mg twice daily for the first day followed by 200 mg PO twice daily (BIII), or
- Posaconazole (extended-release tablet) 300 mg PO twice daily for the first day and then 300 mg daily (BIII)

**Treating Severe Pulmonary or Extrapulmonary Infection (except meningitis):**

**Preferred Therapy:**

- Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII), or
- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AII)
- Use until clinical improvement, then switch to triazole (BIII)

**Alternative Therapy:**

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

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

**Preferred Therapy:**

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

**Alternative Therapy:**

- Itraconazole 200 mg PO two to three-times daily (BII), or
- Voriconazole 200–400 mg PO twice daily (BIII), or
- Posaconazole (delayed release tablet) 300 mg twice on first day, then 300 mg once daily (CIII), or
- Isavuconazole 372 mg every 8 hours for 6 doses, then 372 mg daily (CIII)

**Intrathecal amphotericin B (AIII) when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by a clinician experienced in this drug delivery technique.**

Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.

### Treatment in Pregnancy

Azole antifungal agents are contraindicated and should be avoided in the first trimester of pregnancy because of potential teratogenic effect and risk of spontaneous abortion (AIII).
• Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (AIII), or
• Lipid formulation amphotericin B 3–5 mg/kg IV daily (AIII)

All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Adult and Adolescent ARV Guidelines DDI tables list these interactions and recommend dosage adjustments where feasible.

Rating System for Prevention and Treatment Recommendations

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

Source:

• Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Coccidioidomycosis. Updated: February 17, 2021. [HIV.gov]
Table 14. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

Discontinuing Therapy for Coccidioidomycosis

Focal Coccidioidal Pneumonia
Therapy can be stopped if (All):

- Clinically responded to 3 to 6 months of antifungal therapy, and
- CD4 count \(\geq 250\) cells/mm\(^3\), and
- Virologic suppression on antiretroviral therapy, and
- Continued monitoring for recurrence can be performed using serial chest radiograph and coccidioidal serology

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis
- Relapse can occur in 25% to 33% of patients without HIV and can occur in patients with HIV who have a CD4 count >250 cells/mm\(^3\)
- Therapy duration is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts (BIII).

Coccidioidal Meningitis
- Relapse has been reported in 80% of patients after stopping triazoles; therefore, suppressive therapy should be lifelong (All)

Other Considerations
- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Adult and Adolescent ARV Guidelines DDI tables list these interactions and recommend dosage adjustments where feasible.

Rating System for Prevention and Treatment Recommendations

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Coccidioidomycosis. Updated: February 17, 2021. [HIV.gov]
Table 15. **Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV**

**Managing Cryptosporidiosis**

**Preferred Management Therapy:**

- Initiate or optimize ART for immune restoration to CD4 count >100 cells/mm$^3$ (AII).
- Aggressive oral and/or IV rehydration and replacement of electrolyte loss (AIII), and symptomatic treatment of diarrhea with anti-motility agent (AIII).
- Tincture of opium may be more effective than loperamide (CIII).

**Alternative Management Strategies:**

No therapy has been shown to be effective without ART. Trial of these agents may be used in conjunction with, but not instead of, ART:

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

**Other Considerations:**

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

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Cryptosporidiosis. Last updated: July 16, 2019. [HIV.gov]
Managing Microsporidiosis

General Recommendations:

- Initiate or optimize antiretroviral therapy with immune restoration to CD4 count >100 cells/mm$^3$ (AII).
- Severe dehydration, malnutrition, and wasting should be managed by fluid support (AII) and nutritional supplements (AIII).
- Anti-motility agents can be used for diarrhea control, if required (BIII).

For Gastrointestinal Infections Caused by \textit{Enterocytozoon bieneusi}

- The best treatment option is antiretroviral therapy and fluid support (AII).
- No specific therapeutic agent is available for this infection.
- Fumagillin 60 mg PO daily (BII) and TNP-470 (BIII) are two agents that have some effectiveness, but neither agent is available in the United States.
- Nitazoxanide may have some effect, but the efficacy is minimal in patients with low CD4 cell counts (CIII).

For Intestinal and Disseminated (Not Ocular) Infection Caused by Microsporidia Other Than \textit{E. bieneusi} and \textit{Vittaforma corneae}

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

For Disseminated Disease Caused by \textit{Trachipleistophora} or \textit{Annclalia}

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

For Ocular Infection

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

Rating System for Prevention and Treatment Recommendations

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

Source:

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Microsporidiosis. Last updated: June 14, 2019. [HIV.gov]
Table 17. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

**Initial Treatment of Cystoisospora belli Infection**

**General Management Considerations:**

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

**Preferred Therapy for Acute Infection:**

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

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

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

Abbreviations: TMP-SMX = trimethoprim-sulfamethoxazole

**Rating System for Prevention and Treatment Recommendations**

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

**Source:**

- Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. Cystoisosporiasis (formerly Isosporiasis). Last updated: September 10, 2015. [HIV.gov]
Table 18. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV

**Cystoisospora belli Infection: Chronic Maintenance Therapy (Secondary Prophylaxis) in Patients with CD4 count < 200 cells/mm³**

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

**Alternative Therapy:**
- TMP-SMX (160 mg/800 mg) PO daily (BIII), or
- TMP-SMX (320 mg/1600 mg) PO 3 times weekly (BIII), or
- Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily (BIII)
- Ciprofloxacin 500 mg PO 3 times weekly (CI) as a second line alternative

**Criteria for Discontinuation of Chronic Maintenance Therapy**
- Sustained increase in CD4 count >200 cells/mm³ for >6 months in response to ART and without evidence of active *C. belli* infection (BIII)

Abbreviations: TMP-SMX = trimethoprim-sulfamethoxazole

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