Opportunistic Infections: Prevention

Background and Overview

Background and Overview

Despite the widespread availability and use of potent antiretroviral therapy, individuals with HIV infection continue to suffer significant morbidity and mortality from opportunistic infections, defined as infections that are more frequent or severe due to immunosuppression. The introduction of effective antiretroviral therapy in the mid-1990s led to a dramatic decline in opportunistic infections (Figure 1).[1,2,3] Including substantial decrease in all of the major opportunistic infections (Figure 2).[2] Nonetheless, opportunistic infections still occur in individuals with HIV infection, particularly in the setting of undiagnosed HIV, late diagnosis of HIV, or known HIV infection with poor retention in care. Clinicians who provide care to persons with HIV infection should have basic competency in the diagnosis, prevention, and treatment of common opportunistic infections. This Topic Review outlines the standard of care for the prophylaxis of the most common and important opportunistic infections that occur in persons with HIV infection. The content is based on recommendations in the Health and Human Services (HHS) Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (referred to hereafter as the Opportunistic Infections Guidelines).[4]
**Pneumocystis Pneumonia**

**Background**

*Pneumocystis* pneumonia (PCP) is an important cause of morbidity and mortality in persons with HIV infection. *Pneumocystis* pneumonia is caused by *Pneumocystis jirovecii*, a ubiquitous organism that has been classified as a fungus, and PCP. The previously used name *Pneumocystis carinii* is no longer used after a taxonomy reclassification when it became clear that *P. jirovecii* infects humans and *P. carinii* infects rats. Before the use of effective antiretroviral therapy and *Pneumocystis* pneumonia prophylaxis, PCP occurred in up to 80% of patients with AIDS; the incidence among patients with AIDS in the United States and Western Europe has dropped substantially to less than 1 case per 100 person-years and now occurs mostly among patients who are unaware of their HIV infection or in those not engaged in care.[2,3,5] *Pneumocystis* is most likely transmitted via the airborne route and disease occurs by acquisition of new infection or by reactivation of latent infection. The risk of developing *Pneumocystis* increases markedly with advanced immunosuppression and approximately 90% of patients with PCP have a CD4 count less than 200 cells/mm$^3$.[6,7]

**Indications for Initiating Primary Prophylaxis**

Prophylaxis is considered primary (preventing the first episode of *Pneumocystis* pneumonia) or secondary (preventing recurrence of *Pneumocystis* pneumonia). The Opportunistic Infections Guidelines recommend the following as indications for initiating primary PCP prophylaxis:[8]

- CD4 count less than 200 cells/mm$^3$ (AI) or
- CD4 percentage less than 14% cells/mm$^3$ (BII) or
- CD4 count greater than 200 cells/mm$^3$ but less than 250 cells/mm$^3$ and CD4 monitoring (e.g., every 3 months) is not possible (BII)

**Recommended Regimens for Primary Prophylaxis**

The Opportunistic Infections Guidelines provides recommendations for preferred and alternative agents for *Pneumocystis* pneumonia primary prophylaxis (Table 1).[8]

- **Preferred Therapy**: Trimethoprim-sulfamethoxazole is the preferred agent for *Pneumocystis* pneumonia prophylaxis in individuals with HIV infection and studies have shown that either a double-strength tablet or a single-strength tablet taken daily is effective in preventing *Pneumocystis* pneumonia.[9,10,11]
- **Alternative Therapy**: If a patient cannot tolerate daily dosing of trimethoprim-sulfamethoxazole, alternative regimens include trimethoprim-sulfamethoxazole three times per week,[12] dapsone once daily, atovaquone once daily, or inhaled pentamidine once monthly.[10,12] In addition, prior to starting dapsone, it is necessary to check a glucose-6-phosphate dehydrogenase (G6PD) level since dapsone may trigger hemolytic anemia in patients who have G6PD deficiency. Three times weekly trimethoprim-sulfamethoxazole may provide adequate prophylaxis for *Toxoplasma* encephalitis, but this has not been adequately studied. Although atovaquone has efficacy similar to dapsone for *Pneumocystis* pneumonia prophylaxis, it is considerably more expensive and available only as a liquid formulation. Aerosolized inhaled pentamidine is conveniently dosed once monthly, but has multiple disadvantages including a contraindication for use in patients with underlying reactive airways or pulmonary disease, poor penetration to the peripheral regions of the lung, and lack of systemic protection against *P. jirovecii*. Although aerosolized pentamidine performed better than placebo, it is less effective than trimethoprim-sulfamethoxazole, especially at CD4 count less than 100 cells/mm$^3$ and also must be administered in a clinic or hospital setting using a special Respirgard II nebulizer.[10]
• **Cross Protection Against Toxoplasma Encephalitis:** Use of daily double strength trimethoprim-sulfamethoxazole provides effective primary prophylaxis for Toxoplasma encephalitis and is the preferred dose to use if Toxoplasma encephalitis prophylaxis is needed.[13] Use of lower doses of trimethoprim-sulfamethoxazole (single strength taken once daily or double strength taken three times per week) are considered acceptable alternative Toxoplasma encephalitis primary prophylaxis regimens. The cross protection with lower dose trimethoprim-sulfamethoxazole was suggested in a study where one double strength tablet taken twice daily two times per week provided adequate protection against Toxoplasma encephalitis.[14] Dapsone, when given alone, does not provide sufficient protection against Toxoplasma encephalitis and must be combined with pyrimethamine and leucovorin. The medication leucovorin must be used with pyrimethamine to prevent pyrimethamine-related bone marrow toxicity. Atovaquone is an alternative for Toxoplasma encephalitis primary prophylaxis, but some experts recommend adding pyrimethamine and leucovorin.

**Discontinuing Primary Prophylaxis**

Primary prophylaxis against Pneumocystis pneumonia should be discontinued when possible to reduce pill burden, minimize risk of toxicity and drug interactions, and prevent the selection of drug-resistant pathogens. The Opportunistic Infections Guidelines list the following indications for discontinuation of primary Pneumocystis pneumonia prophylaxis.[8]

- CD4 count increase from less than 200 cells/mm$^3$ to 200 cells/mm$^3$ or greater for at least 3 months in response to antiretroviral therapy (AI)
- Can consider if CD4 count 100-200 cells/mm$^3$ and HIV RNA levels remain below the limit of detection for at least 3-6 months (BII)

The first recommendation is based on multiple studies that have shown very low risk of developing Pneumocystis pneumonia if primary prophylaxis is discontinued after responding to antiretroviral therapy with a CD4 cell count increase to above 200 cells/mm$^3$.[15,16,17] The second recommendation is based on primary data from several studies that reported a very low incidence of Pneumocystis pneumonia among individuals with a CD4 count between 100 and 200 cells/mm$^3$ who stopped or never took Pneumocystis pneumonia prophylaxis if they had suppressed HIV RNA levels.[18,19,20] Primary prophylaxis for Pneumocystis pneumonia should be restarted if (1) the CD4 count declines to less than 100 cells/mm$^3$ regardless or HIV RNA level or (2) if the CD4 count is 100-200 cells/mm$^3$ and the HIV RNA is detectable.[8]

**Adverse Effects of Pneumocystis Pneumonia Prophylaxis**

- **Trimethoprim-sulfamethoxazole:** Adverse reactions to trimethoprim-sulfamethoxazole occur in 10 to 64% of patients who take it, and these reactions are most often rash, fever, nausea and a transient increase in aminotransferase levels.[21] The mean onset of symptoms is 10 to 14 days after starting the medication. Gradual introduction of trimethoprim-sulfamethoxazole (using a suspension to titrate up on the dose) reduces the incidence and severity of treatment-limiting reactions compared to routine initiation of a double-strength tablet daily;[21] this strategy allows successful reintroduction of the drug in up to 70% of patients. Therapy should be discontinued permanently, with no rechallenge, in patients whose previous reactions included hepatitis, aseptic meningitis, or hypersensitivity reaction suggestive of Stevens-Johnson syndrome or toxic epidermal necrolysis.
- **Dapsone:** Patients who are intolerant to trimethoprim-sulfamethoxazole are also at risk of developing rash when taking dapsone. In addition, dapsone can cause hemolytic anemia secondary to G6PD deficiency, methemoglobinemia, peripheral neuropathy, and sulfone syndrome (fever, lymphadenopathy, rash, hepatitis and lymphocytosis).
- **Inhaled Pentamidine:** Inhaled pentamidine can induce cough and bronchospasm though generally is well tolerated.
• **Atovaquone**: Atovaquone causes few serious adverse effects but the liquid formulation can be difficult for patients due to the bad taste.
Toxoplasma Encephalitis

Background

*Toxoplasma gondii* is a protozoan parasite that can infect humans and cause encephalitis and more rarely, retinitis, pneumonitis, and disseminated disease. Risk factors for acquiring *T. gondii* include exposure to cat feces and eating undercooked red meat or raw shellfish (Figure 3).[13] Most cases of toxoplasmosis in persons with HIV infection result from reactivation of latent *T. gondii* cysts as immunity wanes. Prior to the availability of effective antiretroviral therapy, the incidence of *Toxoplasma* encephalitis among AIDS patients with CD4 less than 100 cells/mm$^3$ in the United States was 40 per 1,000 person-years;[22] this rate has decreased significantly with widespread use of antiretroviral therapy and trimethoprim-sulfamethoxazole for *Pneumocystis* pneumonia prophylaxis. All persons with HIV infection should having testing for IgG antibody to *T. gondii* performed as soon as possible after the initial diagnosis of HIV.[13] Patients who test negative should receive counseling on how to avoid becoming infected with *T. gondii* (e.g., avoid exposure to cat feces and do not eat undercooked red meat or raw shellfish). Individuals who previously had a negative IgG antibody to *Toxoplasma* and experience a CD4 count decline to less than 100 cells/mm$^3$ should undergo repeat *Toxoplasma* IgG antibody testing if they are not already taking a medication that provides effective prophylaxis for *Toxoplasma* encephalitis.

Indications for Initiating Primary Prophylaxis

Prophylaxis for *Toxoplasma* encephalitis is classified as either primary prophylaxis (preventing the first episode of *Toxoplasma* encephalitis) or maintenance therapy (secondary prophylaxis) for preventing the recurrence of *Toxoplasma* encephalitis. The Opportunistic Infections Guidelines recommend the following as an indication for initiating primary prophylaxis for *Toxoplasma* encephalitis.[13]

- All persons with HIV infection and a CD4 count less than 100 cells/mm$^3$ who are also seropositive (IgG) for *Toxoplasma*.

Recommended Regimens for Primary Prophylaxis

The Opportunistic Infections Guidelines recommends preferred and alternative regimens for *Toxoplasma* encephalitis prophylaxis (Table 2).[13] Note that all recommended regimens for *Toxoplasma* encephalitis prophylaxis are also effective for *Pneumocystis* pneumonia prophylaxis.

- **Preferred Therapy**: Trimethoprim-sulfamethoxazole is the preferred agent for *Toxoplasma* encephalitis prophylaxis in individuals with HIV infection.[23,24]
- **Alternative Therapy**: The alternative regimens include lower dose trimethoprim-sulfamethoxazole (one double-strength tablet three times a week or one single strength tablet daily), dapsone plus pyrimethamine plus leucovorin, or atovaquone with or without pyrimethamine and leucovorin.[14,24,25,26] The medication leucovorin does not directly protect against *Toxoplasma* encephalitis, but is added to prevent pyrimethamine-related bone marrow toxicity. The use of atovaquone is considered the least preferable of the recommended options. The recommendation for atovaquone is primarily based on data from two maintenance therapy (secondary prophylaxis) studies; in these studies, the use of atovaquone alone or with pyrimethamine was well tolerated and effective in preventing relapse of *Toxoplasma* encephalitis.[27,28] Individuals with G6PD deficiency should not be prescribed dapsone due to the risk of hemolytic anemia, and a desensitization protocol may be helpful for patients who develop mild adverse reactions to first-line prophylaxis with trimethoprim-sulfamethoxazole.

Discontinuing Primary Prophylaxis
The Opportunistic Infections Guidelines list the following indications for discontinuation of primary *Toxoplasma* encephalitis prophylaxis.

- CD4 count greater than 200 cells/mm$^3$ for more than 3 months in response to antiretroviral therapy (AI)
- Can consider if CD4 count 100-200 cells/mm$^3$ and HIV RNA levels remain below the limit of detection for at least 3-6 months (BII)

Numerous studies have consistently shown that *Toxoplasma* encephalitis prophylaxis can safely be discontinued when patients respond to antiretroviral therapy and have immune reconstitution (most studies evaluated for CD4 counts that increased above 200 cells/mm$^3$ for more than 3 months). [29, 30, 31, 32, 33] In these studies, most patients had suppressed HIV RNA levels at the time prophylaxis was discontinued. Stopping primary prophylaxis does not require brain imaging. Primary prophylaxis should be restarted if the CD4 count decreases to less than 100 to 200 cells/mm$^3$. 

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Disseminated *Mycobacterium avium* Complex

Background

*Mycobacterium avium* complex (MAC) infection is a common complication of advanced HIV disease and is an independent predictor of mortality and shortened survival.[34] *Mycobacterium avium* complex represents a group of non-tuberculous mycobacteria that are ubiquitous in the environment.[35] Disease rates vary by geographic regions though there does not seem to be any way to prevent or reduce environmental exposure. Among individuals with HIV infection who develop disseminated MAC, more than 95% have *Mycobacterium avium* as the etiologic agent.[36] The mode of transmission is thought to occur via inhalation, ingestion, or inoculation via the respiratory or gastrointestinal tract. Most persons with HIV infection who are diagnosed with disseminated MAC have a CD4 count less than 50 cells/mm$^3$.[37, 38, 39] In the era prior to use of effective antiretroviral therapy, the incidence of MAC disease in patients with advanced immunosuppression was common, but rates have declined dramatically since the broad use of effective antiretroviral therapy (Figure 4).[2, 3] Other factors that increase susceptibility to disseminated MAC infection include high HIV RNA levels (greater than 100,000 copies/mL), previous opportunistic infections, and previous colonization of the respiratory or gastrointestinal tract with MAC.[35] A retrospective analysis of patients with a CD4 count less than 50 cells/mm$^3$ who were enrolled in the HIV Outpatient Study from 1996-2007 reported a very low overall incidence of MAC infection and no cases of disseminated MAC infection occurred in patients with an HIV RNA less than 1,000 copies/mL (Figure 5).[40] In the modern HIV era, disseminated MAC infection most often affects individuals who are unaware of their HIV diagnosis or those not taking antiretroviral therapy.

Indications for Initiating Primary Prophylaxis

The Opportunistic Infections Guidelines recommend the following as an indication for primary prophylaxis against disseminated MAC:[36]

- CD4 count less than 50 cells/mm$^3$ after ruling out disseminated MAC disease based on clinical assessment (which may include mycobacterial blood culture for some patients) (AI)

Prophylaxis for disseminated MAC is especially important for individuals who do not have suppressed HIV RNA levels. Prior to initiating prophylaxis for MAC, active disseminated infection should be evaluated by performing a clinical assessment and, if indicated, obtaining a mycobacterial blood culture; signs and symptoms of disseminated MAC include fever, weight loss, night sweats, fatigue, diarrhea, and anemia. In a patient with MAC bacteremia, growth of MAC is slow and it often takes several weeks before a positive culture is identified. If MAC blood cultures are obtained, it is prudent to defer MAC prophylaxis until the return of blood culture results so that active disease has been ruled out, thereby avoiding inadvertent use of MAC monotherapy in a patient with active MAC. In addition, it is important to avoid use of rifabutin MAC prophylaxis in any patient with possible active tuberculosis, since monotherapy with rifabutin could result in rapid emergence of rifabutin and rifampin resistant *M. tuberculosis*.

Recommended Regimens for Primary Prophylaxis

The Opportunistic Infections Guidelines provides recommendations for preferred and alternative agents for primary prophylaxis for disseminated MAC (Table 3).[36]

- **Preferred Therapy:** The preferred MAC prophylaxis regimens are azithromycin and clarithromycin. In a randomized placebo-controlled trial of patients, azithromycin was safe and effective in preventing disseminated MAC.[41] In a similar placebo-controlled trial clarithromycin was also shown to be safe and effective in preventing disseminated MAC, but clarithromycin-resistant MAC was detected in 58% of the prophylaxis failures.[42] Most
Clinicians prefer use of azithromycin over clarithromycin due to better tolerance, fewer drug interactions, and the more convenient dosing. The California Collaborative Treatment group compared weekly azithromycin, daily rifabutin, or the combination of both in preventing disseminated MAC and found that azithromycin was more effective than rifabutin; in addition they found that azithromycin plus rifabutin was the most effective regimen but was poorly tolerated.[43] 

- **Alternative Therapy:** Rifabutin is moderately effective in reducing the risk of disseminated MAC.[44] Although rifabutin is considered an acceptable alternative for patients intolerant to azithromycin and clarithromycin, a systematic review has found significantly higher rates of disseminated MAC in patients treated with rifabutin alone compared to those treated with either azithromycin or clarithromycin.[34] The combination of rifabutin with either azithromycin or clarithromycin provides better protection against MAC infection, but is not recommended due to increased risk of adverse reactions and lack of survival benefit when compared with azithromycin or clarithromycin.[43,45] 

### Discontinuing Primary Prophylaxis

Primary MAC prophylaxis may be discontinued if the following criteria is met:

- The CD4 count has increased to greater than 100 cells/mm$^3$ for at least 3 months in response to antiretroviral therapy (AI)

This recommendation is based on the results of two randomized, placebo-controlled trials, one cohort study, and one retrospective review.[46,47,48] Discontinuing MAC prophylaxis decreases pill burden and reduces the overall likelihood of developing medication-related interactions and side effects. Primary prophylaxis should be restarted if the CD4 count again drops below 50 cells/mm$^3$. 
Cryptococcal Meningitis

Background

Cryptococcal disease is an opportunistic fungal infection that causes significant morbidity and mortality in persons with HIV infection who have severe immunosuppression. The global disease burden is high, with an estimated 223,100 cases of cryptococcal meningitis occurring in 2014, mostly in sub-Saharan Africa; this estimated number of cases is significantly lower than the 957,900 cases per year estimated in 2008.[49,50] Most cryptococcal infections in persons with HIV infection are caused by Cryptococcus neoformans, though Cryptococcus gattii has increasingly been recognized as a causative agent of cryptococcal meningitis in certain geographic areas, particularly in the Pacific Northwest.[51] As with other opportunistic infections, the widespread use of highly active antiretroviral therapy has led to a decrease in the incidence of cryptococcal meningitis in the United States, and most cases are identified in persons with recently diagnosed HIV infection who have advanced immunosuppression or those with a known diagnosis of HIV but have limited access to health care.[52] In either situation, patients with cryptococcal meningitis usually have a CD4 count less than 100 cells/mm³.

Primary Prophylaxis Not recommended

Studies have shown that prophylactic use of fluconazole or itraconazole reduces the frequency of primary cryptococcal disease in persons with HIV infection who have a CD4 count below 100 cells/mm³.[53,54,55] Nevertheless, the Opportunistic Infections Guidelines do not recommend prophylaxis against cryptococcal meningitis in the United States due to the low risk of disease in the United States, lack of survival benefit with prophylaxis, possible drug interactions, and potential development of antifungal drug resistance.[56] It is not feasible to avoid exposure to C. neoformans, which is found in soil throughout the United States, so the chief means of prevention is the use of antiretroviral therapy to optimize immune function.

Routine Cryptococcal Antigen Screening

In retrospective analysis of 1,872 serum samples collected during 1986-2012 from patients with a CD4 count less than or equal to 100 cells/mm³ who were enrolled in the Multicenter AIDS Cohort Study or the Women's Interagency HIV Study, 55 (2.9%) of 1,872 samples tested positive for cryptococcal antigen.[57,58] Further analysis showed the rate was 4.3% among those with a CD4 count less than or equal to 50 compared with 1.7% in those with a CD4 count of 51-100 cells/mm³.[57,58] Based on these data, the Opportunistic Infections Guidelines state that some experts recommend routine serum cryptococcal antigen (CrAg) testing on all patients with a CD4 count less than 100 cells/mm³ (particularly those with a CD4 count less than or equal to 50 cells/mm³); if the CrAg is positive, the patient should undergo lumbar puncture with cerebrospinal fluid evaluation for meningitis.[56]
Cytomegalovirus

Background

Cytomegalovirus (CMV) is a double-stranded DNA herpes virus that can cause invasive disease in persons with HIV infection, including CMV retinitis, colitis, esophagitis, and neurologic disease. [59, 60, 61, 62] Most cases of CMV end-organ disease in persons with HIV infection result from reactivation disease in CMV-seropositive patients who have a CD4 count less than 50 cells/mm³. [63, 64] In persons with HIV infection, retinitis is the most common manifestation of CMV-related end-organ disease. [59, 63] Among men with HIV infection who have sex with men, CMV antibody positivity 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. [64] The incidence of CMV end-organ disease, such as CMV retinitis, is now low and it has declined by more than 95% following the widespread availability of effective antiretroviral therapy. [3, 65, 66, 67]

Primary Prophylaxis and Preemptive Therapy Not Recommended

The most important way to prevent CMV end-organ disease in persons with HIV infection is to use antiretroviral therapy to restore and optimize immune system function in those with advanced severe immunosuppression. [64] In the pre-antiretroviral era, one study that evaluated oral ganciclovir (no longer marketed in the United States) for primary prophylaxis showed a reduction in CMV disease, [68] but use of ganciclovir for prophylaxis was not recommended due to toxicity and cost. Another more recent trial (ACTG protocol A5030) evaluated preemptive valganciclovir therapy for patients with a CD4 count less than 100 cell/mm³ (on stable antiretroviral therapy) and CMV viremia, but this strategy of preemptive therapy showed no protective effect. [67] Thus, in the modern antiretroviral therapy era, prophylactic or preemptive therapy is not recommended as a strategy to prevent CMV disease. [64]

Patient Education and Screening Examinations

Recognizing early signs of CMV-related disease and implementing appropriate therapy will diminish the severity of disease. Individuals with HIV infection and advanced immunosuppression should be educated about the warning signs of active CMV retinitis, including floaters, flashing lights, or any decrease in vision. In addition, most experts recommend a formal ophthalmologic examination in any patient with HIV infection who has a CD4 count less than 50 cells/mm³ (and a positive CMV antibody or presumptive positive CMV antibody) to rule out evidence of active CMV disease. The screening ophthalmologic examination is particularly important for patients anticipating starting antiretroviral therapy, since patients with untreated CMV retinitis have a significant risk of developing CMV immune reconstitution inflammatory syndrome after starting antiretroviral therapy.
Histoplasmosis

Background

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*, which is endemic to the central and south-central United States as well as to Latin America (Figure 6). The regions along the Ohio and Mississippi River valleys are considered hyperendemic, as are many regions in Mexico and South America. The organism *H. capsulatum* grows in soil enriched with nitrogen, as occurs with soil that has abundant bird bat guano. *Histoplasma* infections are acquired through inhalation of microconidia in the mycelial phase; the microconidia convert to the yeast forms once in the lungs (Figure 7). Most cases of histoplasmosis in persons with HIV infection result from reactivation of latent infection only after the CD4 count has declined to less than 150 cells/mm$^3$. The incidence of histoplasmosis declined markedly after the widespread use of effective antiretroviral therapy. In some instances, however, immune reconstitution in response to antiretroviral therapy may unmask latent, undiagnosed *Histoplasma* infection. Routine screening of asymptomatic patients using the urinary *Histoplasma* antigen is not recommended.

Preventing Exposure

The Opportunistic Infection guidelines recommend that persons with HIV infection who have a CD4 counts less than 150 cells/mm$^3$ and who live in or visit a histoplasmosis endemic area should avoid the following activities known to increase the risk of exposure to *H. capsulatum*: working with surface soil, cleaning chicken coops that are contaminated with droppings, disturbing areas that are contaminated with bird or bat droppings, cleaning or remodeling old buildings, or exploring caves.

Indications for Initiating Primary Prophylaxis

In a National Institute of Allergy and Infectious Diseases Mycoses Study Group, placebo-controlled, double-blind study, itraconazole 200 mg daily was evaluated as prophylaxis for fungal infections in patients with advanced HIV infection; use of itraconazole was associated with a significant delayed time to onset of histoplasmosis, but there was no demonstrable survival benefit. The Opportunistic Infections guidelines recommend the following as an indication for histoplasmosis primary prophylaxis:

- CD4 count less than 150 cells/mm$^3$ and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (grater than 10 cases/100 patient-years) (BI)

Recommended Regimens for Primary Prophylaxis

- **Preferred Therapy**: If prophylaxis for histoplasmosis is used, the recommended therapy is itraconazole 200 mg once daily (BI)
- **Alternative Therapy**: There are no alternative therapies recommended for prophylaxis of histoplasmosis.

Discontinuing Primary Prophylaxis

Primary prophylaxis for *Histoplasma* can be stopped in patients on effective antiretroviral therapy once the CD4 count is 150 cells/mm$^3$ or greater for at least 6 months (BIII). Primary prophylaxis should be restarted if the CD4 count drops below 150 cells/mm$^3$ (BIII).
Coccidioidomycosis

Background

Coccidioidomycosis is caused by a soil-dwelling fungus, *Coccidioides immitis*, and encompasses a wide spectrum of clinical disease among individuals with HIV infection. In the setting of HIV infection, the risk of developing symptomatic coccidioidomycosis is significantly increased in those who have a CD4 count less than 250 cells/mm$^3$ and live (or have lived) in a region endemic for coccidioidomycosis.[73] The endemic areas for coccidioidomycosis include the Southwest desert region of the United States, as well as parts of Central and South America. The regions in the United States identified as highly endemic are the lower San Joaquin Valley in California, most of Arizona, the southern regions of Utah, Nevada, and New Mexico, and western Texas (Figure 8). In addition, the risk of developing disseminated coccidioidomycosis is enhanced in black and Filipino men, as well as in pregnant women in their second or third trimester. Infection results from inhalation of the *C. immitis* arthroconidia (Figure 9). Patients who live in an endemic area should receive counseling regarding exposure to *C. immitis*, such as attempting to avoid dust storms or significant contact with dust, particularly with construction or excavation sites. The incidence of coccidioidomycosis has decreased in the era of potent antiretroviral therapy, and lower CD4 counts predict more severe coccidioidomycosis infections.[74]

Preventing Exposure

Persons with HIV infection should be aware of the geographic regions that are endemic for coccidioidomycosis so that they can avoid extensive exposure to locations that have disturbed soil, such as an excavation site.[73]

Primary Prophylaxis Not Indicated

The Opportunistic Infections Guidelines recommend against the routine use of primary antifungal prophylaxis for coccidioidomycosis, even in endemic regions.[73] Instead, the guidelines state it is reasonable to obtain yearly serologic testing for coccidioidomycosis in patients with HIV infection who live in endemic areas. For those patients with HIV infection and a CD4 count less than 250 cells/mm$^3$, a newly positive coccidioidal serologic test (either IgM or IgG) warrants presumptive therapy with fluconazole 400 mg once daily. The Opportunistic Infections Guidelines do not clarify the approach for a patient who tests positive for coccidioidomycosis but has not had previous serologic testing (making it unclear whether the results truly represent a new positive test).

Discontinuing Prophylaxis

The Opportunistic Infections Guidelines do not specify whether primary prophylaxis with fluconazole should be discontinued if it was started in a patient with a new positive serologic test for coccidioidomycosis.
Summary Points

- The overall incidence of opportunistic infections has markedly decreased with the widespread use of highly active antiretroviral therapy and the routine use of chemoprophylaxis against common infections.
- Primary prophylaxis (to prevent the first episode of an infection) based on established CD4 count thresholds is indicated for *Pneumocystis* pneumonia, *Toxoplasma* encephalitis, and disseminated *Mycobacterium avium* complex.
- Primary prophylaxis is not indicated for cryptococcal meningitis, cytomegalovirus infection, or coccidioidomycosis, and it is only recommended for histoplasmosis in endemic regions.
- Primary prophylaxis should be discontinued after immune restoration has occurred with antiretroviral therapy in order to reduce pill burden, cost, the risk of drug interactions and toxicity, and the possibility of engendering drug resistance.
Citations


4. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: 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. [AIDSinfo]


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References


Figures

Figure 1 Incidence of First AIDS-Defining Opportunistic Infection, HIV Out-Patient Study, 1994-2007

Figure 2 AIDS-Defining Opportunistic Illnesses in US, HIV Outpatient Cohort Study, 1994–2007

Figure 3 *Toxoplasma gondii* Life Cycle and Human Infection

Humans predominantly acquire *T. gondii* infection by either having contact with infected cat feces contaminated with *T. gondii* oocysts or by ingestion of *T. gondii* tissue cysts in undercooked red meat or shellfish. Cats can also become infected by consuming tissue cysts in undercooked or raw red meat. After humans ingest *T. gondii*, the infection can spread throughout the body. Among persons with HIV infection, latent *T. gondii* infection in the brain can reactivate with severe immunosuppression and cause Toxoplasma encephalitis.

Illustration by David Ehlert, Cognition Studio, Inc.
Figure 4 Incidence of Disseminated *Mycobacterium avium* Complex Infection, 1994-2007

Figure 5 *Mycobacterium avium* Complex Infection Rate in the HIV Outpatient Study, 1996-2007

In this study, HIV Outpatient Study (HOPS) investigators performed a retrospective analysis to determine the MAC incidence rate in 369 individuals with HIV infection, a CD4 count less than 50 cells/mm$^3$, and no prior history of MAC infection.
Figure 6 Endemic Regions for Histoplasmosis in United States

Source: Centers for Disease Control and Prevention (CDC)
**Figure 7 Histoplasmosis: Life Cycle**

In the environment, *Histoplasma capsulatum* exists as a mold (1) with aerial hyphae. The hyphae produce macroconidia and microconidia (2) spores that are aerosolized and dispersed. Microconidia are inhaled into the lungs by a susceptible host (3). The warmer temperature inside the host signals a transformation to an oval, budding yeast (4). The yeast are phagocytized by immune cells and transported to regional lymph nodes (5). From there they travel in the blood to other parts of the body (6).

Source: Centers for Disease Control and Prevention (CDC)
Figure 8 Endemic Regions for Coccidioidomycosis in United States

This map is based on studies performed in the late 1940s and 1950s and also on locations of more recent outbreaks and cases. Coccidioides might also live in similar areas with hot, dry climates that are not shaded on the map.

Source: Centers for Disease Control and Prevention (CDC)
In the environment, *Coccidioides* spp. exists as a mold (1) with septate hyphae. The hyphae fragment into arthroconidia (2), which measure only 2-4 μm in diameter and are easily aerosolized when disturbed (3). Arthroconidia are inhaled by a susceptible host (4) and settle into the lungs. The new environment signals a morphologic change, and the arthroconidia become spherules (5). Spherules divide internally until they are filled with endospores (6). When a spherule ruptures (7) the endospores are released and disseminate within surrounding tissue. Endospores are then able to develop into new spherules (6) and repeat the cycle.

Source: Centers for Disease Control and Prevention (CDC)
### Table 1. Guidelines for the Prevention and Treatment of Opportunistic Infections

#### Regimens for Pneumocystis Pneumonia Primary Prophylaxis

**Preferred Therapy:**
- Trimethoprim-sulfamethoxazole, 1 DS PO daily\(^a\) (AI) or
- Trimethoprim-sulfamethoxazole, 1 SS PO daily\(^a\) (AI).

**Alternative Therapy:**
- Trimethoprim-sulfamethoxazole 1 DS PO three times weekly (BI) or
- Dapsone\(^b,c\) 100 mg PO daily or 50 mg PO twice daily (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 Respigard 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)

\(^a\) Trimethoprim-sulfamethoxazole DS once daily also confers protection against toxoplasmosis and many respiratory bacterial infections; lower dose also likely confers protection.

\(^b\) 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.

\(^c\) Aerosolized pentamidine or dapsone (without pyrimethamine) should not be used for PCP prophylaxis in patients who are seropositive for *Toxoplasma gondii*.

**Key to Acronyms:** DS = double strength; PO = orally; SS = single strength.

**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

#### Regimens for Toxoplasma Encephalitis Primary Prophylaxis

**Preferred Regimen:**

- Trimethoprim-sulfamethoxazole, 1 DS PO daily (AII)

**Alternative Regimens:**

- Trimethoprim-sulfamethoxazole 1 DS tablet PO three times weekly (BIII), or
- Trimethoprim-sulfamethoxazole SS tablet PO daily (BIII), or
- Dapsone\(^a\) 50 mg PO daily plus (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly (BI), or
  - (Dapsone\(^a\) 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly (BI), or
  - Atovaquone\(^b\) 1500 mg PO daily (CIII), or
  - (Atovaquone\(^b\) 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily (CIII)

\(^a\)Whenever possible, patients should be tested for G6PD deficiency before administering dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency.

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

Key to Acronyms: DS = double strength; PO = orally; SS = single strength.

#### 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 3. **Guidelines for the Prevention and Treatment of Opportunistic Infections**

**Regimens for Disseminated MAC Primary Prophylaxis**

**Preferred Therapy:**
- Azithromycin 1200 mg PO once weekly (AI), or
- Clarithromycin 500 mg PO twice daily (AI), or
- Azithromycin 600 mg PO twice weekly (BIII)

**Alternative Therapy:**
- Rifabutin 300 mg PO daily (BI) (dosage adjusted may be necessary based on drug-drug interactions)

**Note:** Active TB should be ruled out before starting rifabutin

Key to Acronyms: MAC = *Mycobacterium avium* complex; PO = orally.

**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: