Opportunistic Infections: Prevention

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Section 1: Co-Occurring Conditions
Topic 2: Opportunistic Infections: Prevention

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Background and Overview

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Despite the widespread availability and use of potent antiretroviral therapy, individuals living with HIV 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 decrease in the rate of AIDS-defining opportunistic infections in the United States. Data from the Centers for Disease Control and Prevention (CDC)-sponsored HIV Outpatient Study (HOPS) showed this decline was dramatic in the mid-1990s, continued through 2007 (Figure 1), and included major deceases in the rates of all major AIDS-defining opportunistic infections (Figure 2).[1,2] Subsequent data from 16 cohorts in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) study during 2000 through 2010 (in the United States and Canada) showed relatively low rates of AIDS-defining opportunistic infections and a continued overall decline during the study period (Figure 3).[3] Nonetheless, AIDS-defining opportunistic infections still occur in individuals living with HIV, 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 prevention, diagnosis, and treatment of common AIDS-defining 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 Adult and Adolescent Opportunistic Infection 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. 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 fewer than 1 case per 100 person-years and now occurs mostly among persons who are unaware of their HIV infection, those not on stable antiretroviral therapy, or in those not engaged in care.[2,3,5] *Pneumocystis jirovecii* 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* pneumonia increases markedly with advanced immunosuppression and approximately 90% of individuals 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 Adult and Adolescent Opportunistic Infection 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 if antiretroviral therapy must be delayed and CD4 monitoring (e.g. every 3 months) is not possible (**BII**)

Note: Individuals receiving treatment for toxoplasmosis with pyrimethamine and sulfadiazine do not require *Pneumocystis* pneumonia prophylaxis (**AII**).[8,9]

Recommended Regimens for Primary Prophylaxis

The Adult and Adolescent Opportunistic Infection Guidelines provide 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.[10,11,12]
- **Alternative Therapy**: If a patient cannot tolerate daily dosing of trimethoprim-sulfamethoxazole, alternative regimens include trimethoprim-sulfamethoxazole (as a double-strength tablet three times per week),[13] dapsone once daily, atovaquone once daily, or inhaled pentamidine once monthly.[11,13] 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 there are limited data to support this regimen for *Pneumocystis* pneumonia prophylaxis.[14] 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.[11]
- **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.[15] 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 studies where one double-strength tablet taken twice daily two or three times per week provided adequate protection against *Toxoplasma* encephalitis.[14,16] Dapsone 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 Adult and Adolescent Opportunistic Infection 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 to 200 cells/mm^3 and HIV RNA levels remain below the limit of detection for at least 3 to 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.[17,18,19] . 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 to 200 cells/mm^3 who stopped or never took *Pneumocystis* pneumonia prophylaxis if they had suppressed HIV RNA levels.[20,21,22]

Restarting Primary Prophylaxis

Primary prophylaxis for *Pneumocystis* pneumonia should be restarted if (1) the CD4 count declines to less than 100 cells/mm^3 regardless of HIV RNA level or (2) if the CD4 count is 100 to 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.[23] 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;[23] 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).[24]
- **Inhaled Pentamidine**: Inhaled pentamidine can induce cough and bronchospasm though generally is well tolerated.[25,26]
- **Atovaquone**: Atovaquone causes few serious adverse effects but the liquid formulation can be difficult for patients due to the bad taste.[27,28]

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 4).[15] Most cases of toxoplasmosis in persons with HIV infection result from reactivation of latent *T. gondii* cysts as immunity wanes. In the United States, prior to the availability of effective antiretroviral therapy, the incidence of *Toxoplasma* encephalitis among patients with AIDS with a CD4 count less than 100 cells/mm^3 was 40 per 1,000 person-years;[29] 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.[15] 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 Adult and Adolescent Opportunistic Infection Guidelines recommend the following as an indication for initiating primary prophylaxis for *Toxoplasma* encephalitis.[15]

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

Recommended Regimens for Primary Prophylaxis

The following summarizes the Adult and Adolescent Opportunistic Infection Guidelines recommendations for *Toxoplasma* encephalitis prophylaxis (Table 2).[15] 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.[14,30]
- **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.[14,16,31,32] 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.[33,34] 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 Adult and Adolescent Opportunistic Infection Guidelines list the following indications for discontinuation of primary *Toxoplasma* encephalitis prophylaxis.[15]

- 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 to 200 cells/mm^3 and HIV RNA levels remain below the limit of detection for at least 3 to 6 months (**BII**)

Numerous studies have consistently shown that *Toxoplasma* encephalitis prophylaxis can be safely discontined 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).[35,36,37,38,39] In these studies, most patients had suppressed HIV RNA levels at the time prophylaxis was discontinued. Stopping primary prophylaxis does not require brain imaging.

Restarting Primary Prophylaxis

Primary prophylaxis should be restarted if the CD4 count decreases to less than 100 to 200 cells/mm^3.[15]

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.[40] *Mycobacterium avium* complex represents a group of nontuberculous mycobacteria that are ubiquitous in the environment.[41] 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.[42] 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.[43,44,45] In the era prior to use of effective antiretroviral therapy, the incidence of MAC disease in patients with advanced immunosuppresion was common, but rates declined dramatically after the broad use of effective antiretroviral therapy (Figure 5).[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.[41] 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 through 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 6).[46] 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 Adult and Adolescent Opportunistic Infection Guidelines recommend the following regarding primary prophylaxis against disseminated MAC:[42]

- Primary prophylaxis for MAC is not recommended in persons with HIV if antiretroviral therapy is immediately started, regardless of the individual's CD4 cell count (**AIII**). This recommendation is based on data from several observational cohort studies that found no benefit in starting MAC prophylaxis in persons with a CD4 count less than 50 cells/mm^3 who started on antiretroviral therapy and achieved virologic suppression.[46,47,48]
- Persons with HIV who have a CD4 count less than 50 cells/mm^3 should receive MAC prophylaxis if they are not on fully suppressive antiretroviral therapy (**AI**). In this situation, MAC prophylaxis should start after ruling out disseminated MAC disease based on clinical assessment, which may include mycobacterial blood cultures (**AI**). The clinical assessment for disseminated MAC should include evaluation of characteristic signs and symptoms of disseminated MAC—fever, weight loss, night sweats, fatigue, diarrhea, and anemia. With disseminated MAC, 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 can be 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 Adult and Adolescent Opportunistic Infection Guidelines provide recommendations for preferred and alternative agents for primary prophylaxis for disseminated MAC (Table 3).[42]

- **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.[49] 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.[50] 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.[51]
- **Alternative Therapy**: Rifabutin is moderately effective in reducing the risk of disseminated MAC.[52] 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.[40] 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.[51,53]

Discontinuing Primary Prophylaxis

Primary MAC prophylaxis may be discontinued if the following criterion is met:[42]

- Effective antiretroviral therapy has been started, regardless of the CD4 cell count (**AI**).

Discontinuing MAC prophylaxis decreases pill burden and reduces the overall likelihood of developing medication-related interactions and side effects.

Restarting MAC Prophylaxis

Primary prophylaxis should be restarted if the CD4 count again drops below 50 cells/mm^3 (only if the person is not receiving fully suppressive antiretroviral therapy).[42]

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.[54,55] 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.[56] 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 limited access to health care.[57] In either situation, patients with cryptococcal meningitis usually have a CD4 count less than 100 cells/mm^3.

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/mm^3 who were enrolled in the Multicenter AIDS Cohort Study or the Women's Interagency HIV Study, 2.9% (55 of 1,872) samples tested positive for cryptococcal antigen.[58,59] Further analysis showed the rate was 4.3% among those with a CD4 count less than or equal to 50 cells/mm^3 compared with 1.7% in those with a CD4 count of 51 to 100 cells/mm^3.[60] Based on these data, the Adult and Adolescent Opportunistic Infection Guidelines state that some experts recommend routine serum cryptococcal antigen (CrAg) testing on all patients with a CD4 count less than 100 cells/mm^3 (particularly those with a CD4 count less than or equal to 50 cells/mm^3); if the CrAg is positive, the patient should undergo lumbar puncture with cerebrospinal fluid evaluation for meningitis.[61]

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/mm^3.[62,63,64] Nevertheless, the Adult and Adolescent Opportunistic Infection Guidelines do not recommend prophylaxis against cryptococcal meningitis for individuals without a positive serum cryptococcal meningitis, due to the low risk of disease, lack of survival benefit with prophylaxis, possible drug interactions, and potential development of antifungal drug resistance (**BIII**).[61] 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.

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.[65,66,67,68] 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/mm^3.[69,70] In persons with HIV infection, retinitis is the most common manifestation of CMV-related end-organ disease.[68,69] 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.[70] 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.[3,71,72,73]

Primary Prophylaxis and Preemptive Therapy Not Recommended

The most important way to prevent CMV end-organ disease in persons with HIV is to use antiretroviral therapy to restore and optimize immune system function in those with severe immunosuppression.[70] 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,[74] 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/mm^3 (on stable antiretroviral therapy) and CMV viremia, but this strategy of preemptive therapy was not protective.[73] Thus, in the modern antiretroviral therapy era, the Adult and Adolescent Opportunistic Infection Guidelines do not recommend prophylactic or preemptive therapy as a strategy to prevent CMV disease.[70]

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, since some individuals may be asymptomatic early on in CMV retinitis, most experts recommend a formal ophthalmologic examination for any person with HIV with a CD4 count less than 50 cells/mm^3 (and a positive CMV antibody or presumptive positive CMV antibody) to rule out evidence of retinitis. The screening ophthalmologic examination is particularly important for patients anticipating starting antiretroviral therapy, since patients with untreated or unrecognized CMV retinitis are at significant risk of developing CMV immune reconstitution inflammatory syndrome following initiation of antiretroviral therapy.[70]

Histoplasmosis

Background

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum*, which is the most common endemic mycosis in the United States.[75] The central and south-central regions of the United States, especially along the Ohio and Mississippi River valleys, are considered hyperendemic, as are many regions in Mexico and South America (Figure 7).[75,76] Histoplasmosis is considered the most common endemic mycosis that causes hospitalization in the United States.[75,77] The organism *H. capsulatum* grows in soil enriched with nitrogen, as occurs with soil that has abundant bird or 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 8). 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.[78] 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.[79] Routine screening of asymptomatic patients using the urinary *Histoplasma* antigen is not recommended.

Preventing Exposure

The Adult and Adolescent 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 (**BIII**).[80]

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 among individuals with advanced HIV infection; use of itraconazole was associated with a significant delayed time to onset of histoplasmosis, but no demonstrable survival benefit.[62] The Adult and Adolescent Opportunistic Infection Guidelines recommend the following as an indication for histoplasmosis primary prophylaxis:[80]

- 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 (greater 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.[81] 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 9). 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, which then undergo morphologic changes inside the human host to endospores that can disseminate and cause disease in almost any organ (Figure 10). Only a low inoculum of arthroconidia are needed to establish infection.[82] 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, typically less than 250 cells/mm^3, predict more severe coccidioidomycosis infections.[83]

Preventing Exposure

Persons with HIV infection should be aware of the geographic regions that are endemic for coccidioidomycosis. They should receive counseling regarding avoiding exposure to *C. immitis*, including avoiding significant contact with dust, dust storms, or any area with recently disturbed soil, such as an excavation site (**BIII**).[81]

Primary Prophylaxis Not Indicated

The Adult and Adolescent Opportunistic Infection Guidelines recommend against the routine use of primary antifungal prophylaxis for coccidioidomycosis, even in endemic regions.[81] Instead, the guidelines suggest obtaining annual (or biannual) serologic testing for coccidioidomycosis in persons with HIV who are living in or have previously lived (or extensively traveled) in endemic areas. Individuals with a newly positive coccidioidal serologic test (either IgM or IgG) should undergo further clinical evaluation and therapy as needed. If no clinical or laboratory evidence of active coccidioidomycosis is found and the individual has a CD4 count less than 250 cells/mm^3, treatment with fluconazole 400 mg once daily should be started (**AIII**); the fluconazole should be continued until the CD4 count is 250 cells/mm^3 or higher and they have consistently suppressed HIV RNA levels (**BIII**). The Adult and Adolescent Opportunistic Infection 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).[81]

Discontinuing Prophylaxis

The Adult and Adolescent Opportunistic Infection 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.[81]

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 and *Toxoplasma* encephalitis.
- Prophylaxis for disseminated *Mycobacterium avium* complex is not necessary in persons initiating suppressive antiretroviral therapy, regardless of CD4 cell count.

- 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.

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Figures

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

Source: Brooks JT, Kaplan JE, Holmes KK, Benson C, Pau A, Masur H. HIV-associated opportunistic infections--going, going, but not gone: the continued need for prevention and treatment guidelines. Clin Infect Dis. 2009;48:609-11.

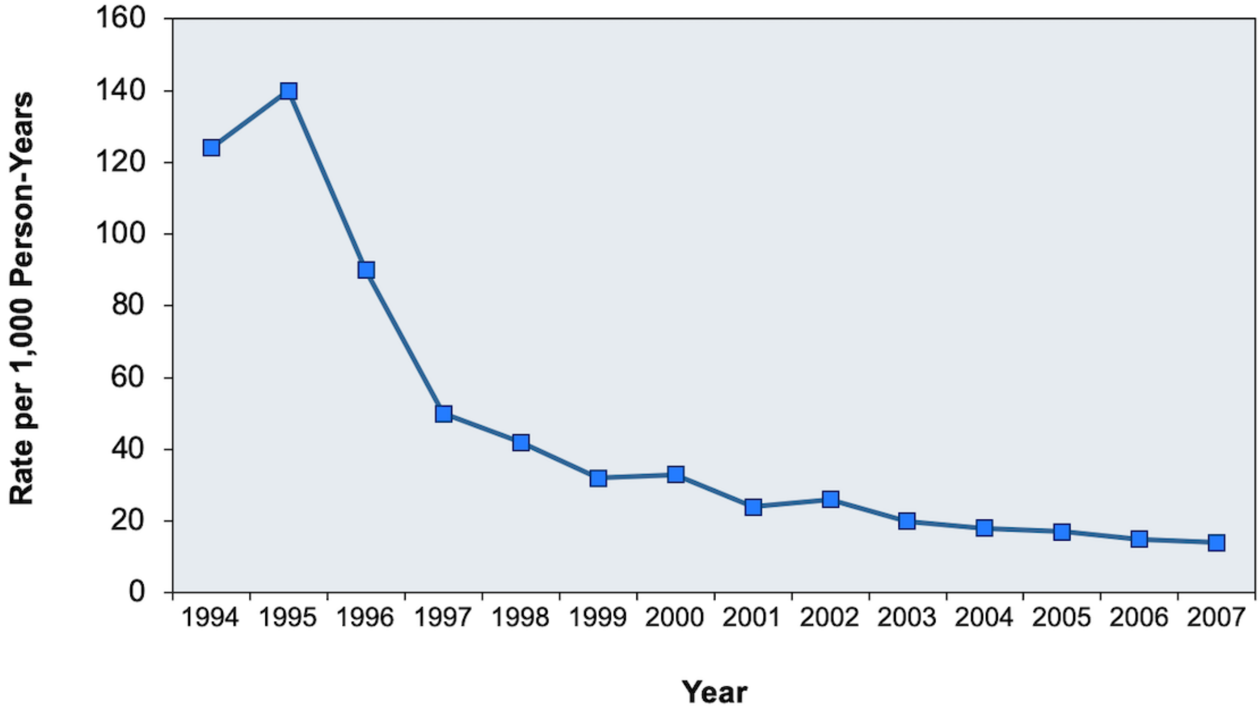

Figure 2 AIDS-Defining Opportunistic Illnesses in United States, HIV Outpatient Cohort Study, 1994–2007

Source: Buchacz K, Baker RK, Palella FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. AIDS. 2010;24:1549-59.

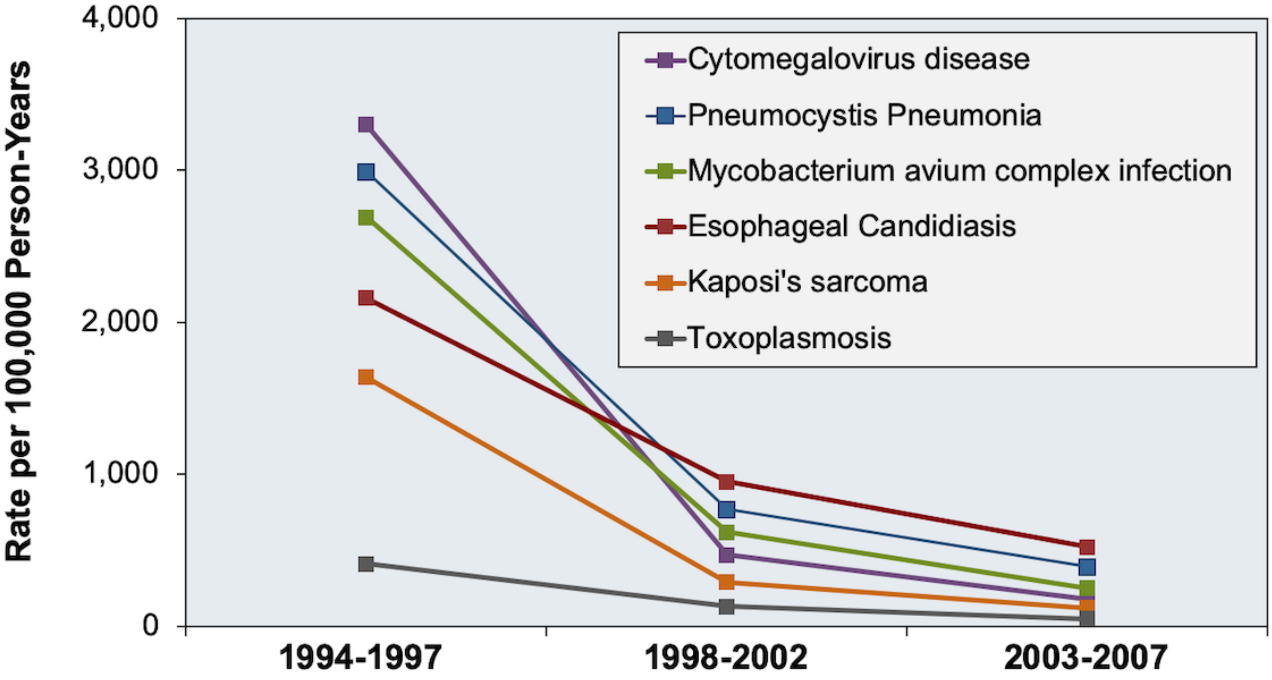

Figure 3 AIDS-Defining Opportunistic Illnesses in United States and Canada, NA-ACCORD, 2000–2010

This graph shows AIDS-Defining Opportunistic Illnesses 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. These data show opportunistic infections occurred at a relatively low rate and declined during the study time period.

Source: Buchacz K, Lau B, Jing Y, et al. Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000-2010. J Infect Dis. 2016;214:862-72.

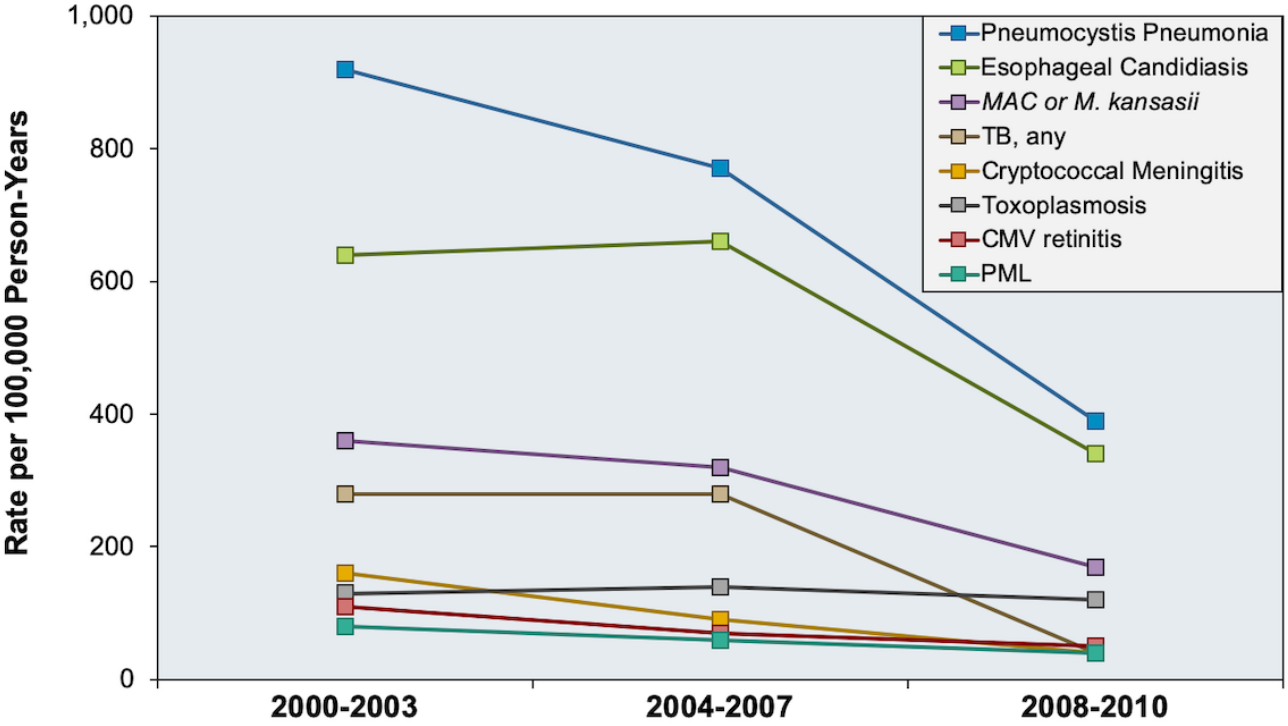

Figure 4 *Toxoplasma gondii* Life Cycle and Human Infection

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.

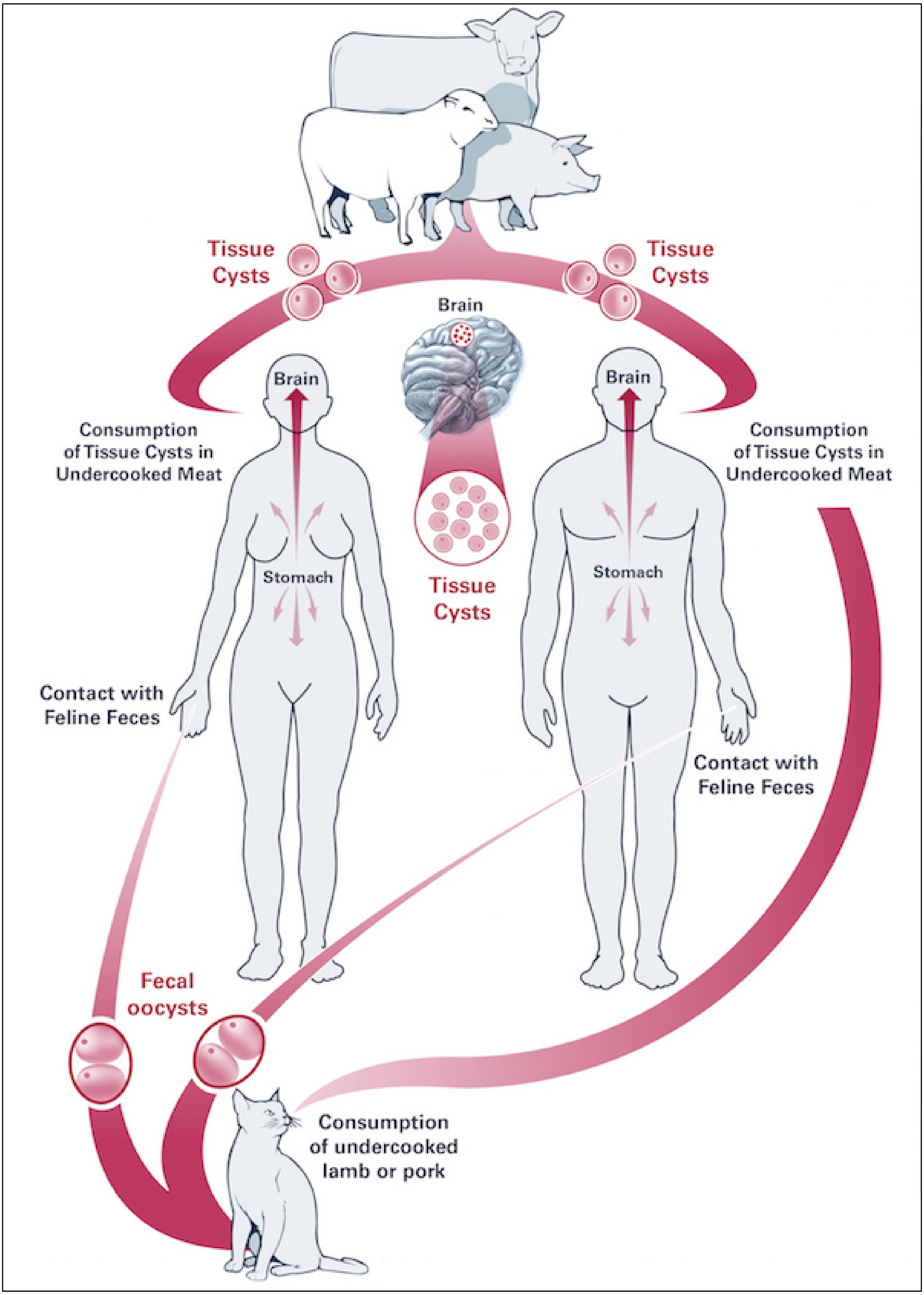
Tissue Cysts
Tissue Cysts
Brain
Brain
Brain
Consumption of Tissue Cysts in Undercooked Meat
Consumption of Tissue Cysts in Undercooked Meat
Stomach
Stomach
Tissue Cysts
Contact with Feline Feces
Contact with Feline Feces
Fecal oocysts
Consumption of undercooked lamb or pork

Figure 5 Incidence of Disseminated *Mycobacterium avium* Complex Infection, 1994-2007

Source: Buchacz K, Baker RK, Palella FJ Jr, et al. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study. AIDS. 2010;24:1549-59.

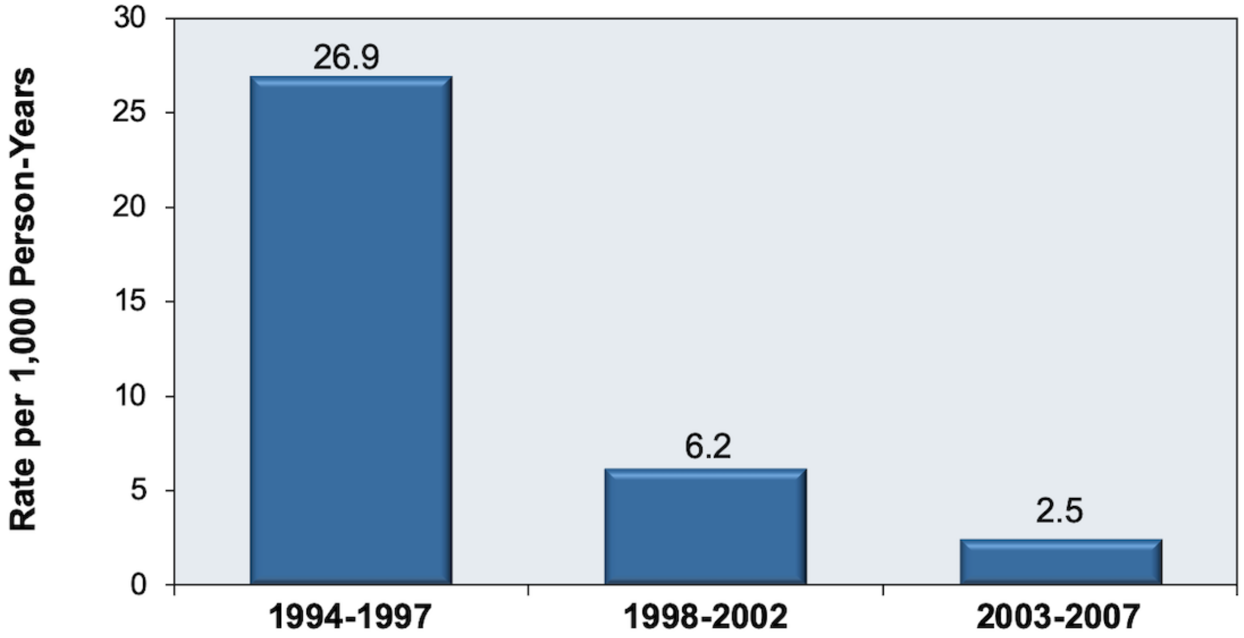

Figure 6 *Mycobacterium avium* Complex Infection Rate in the HIV Outpatient Study, 1996-2007

In the 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

Source: Yangco BG, Buchacz K, Baker R, Palella FJ, Armon C, Brooks JT. Is primary *Mycobacterium avium* complex prophylaxis necessary in patients with CD4

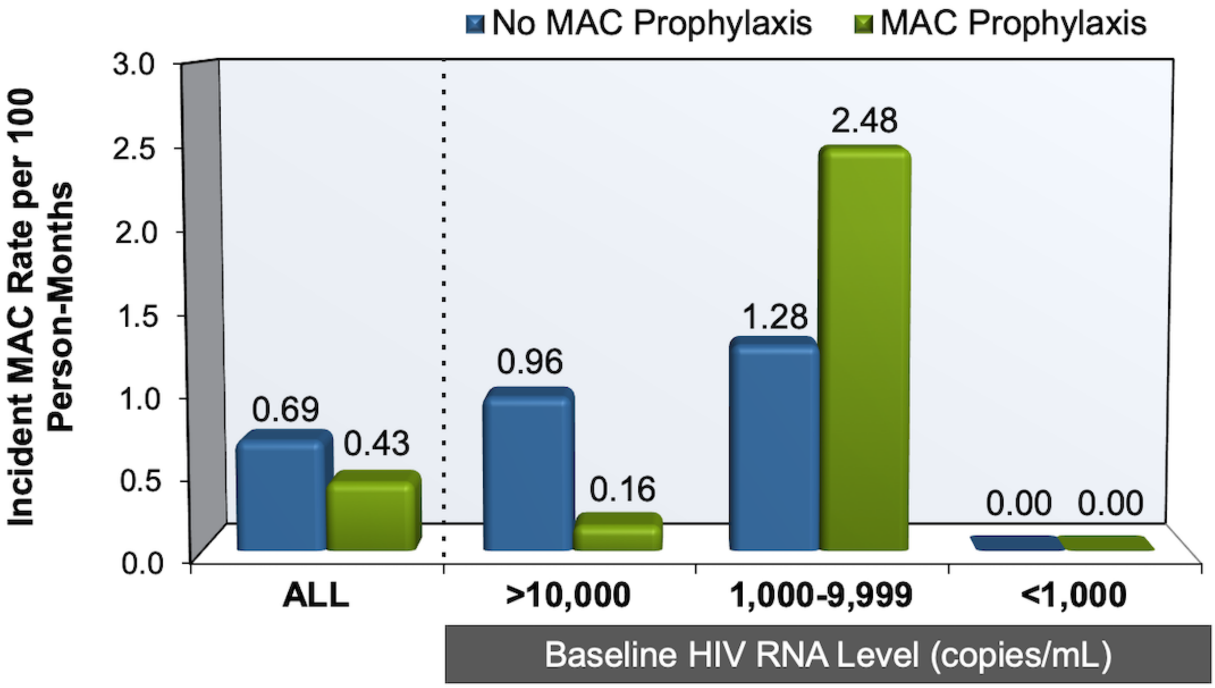

Figure 7 Endemic Regions for Histoplasmosis in United States

Source: Centers for Disease Control and Prevention (CDC)

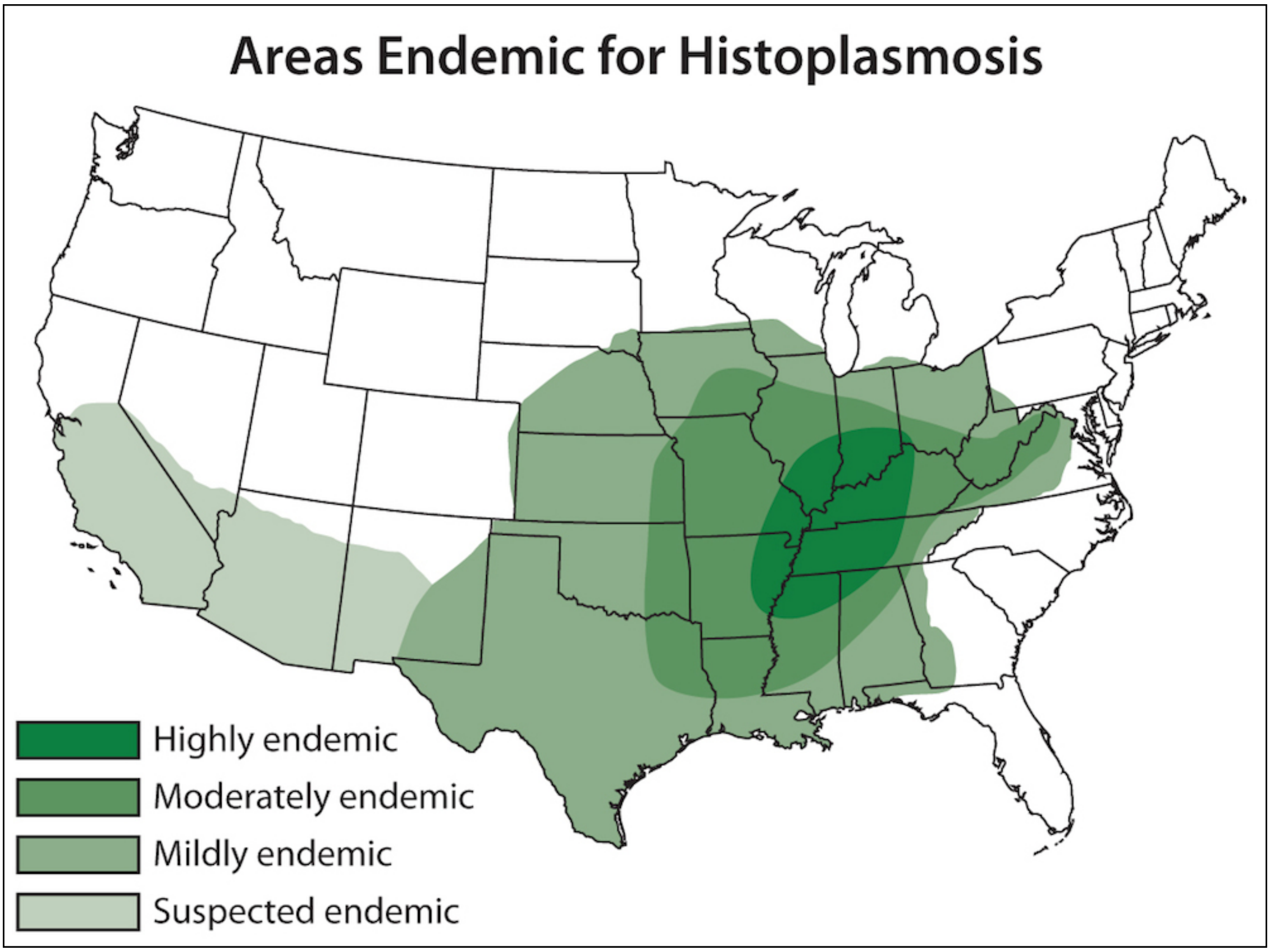

Figure 8 Histoplasmosis: Life Cycle

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)

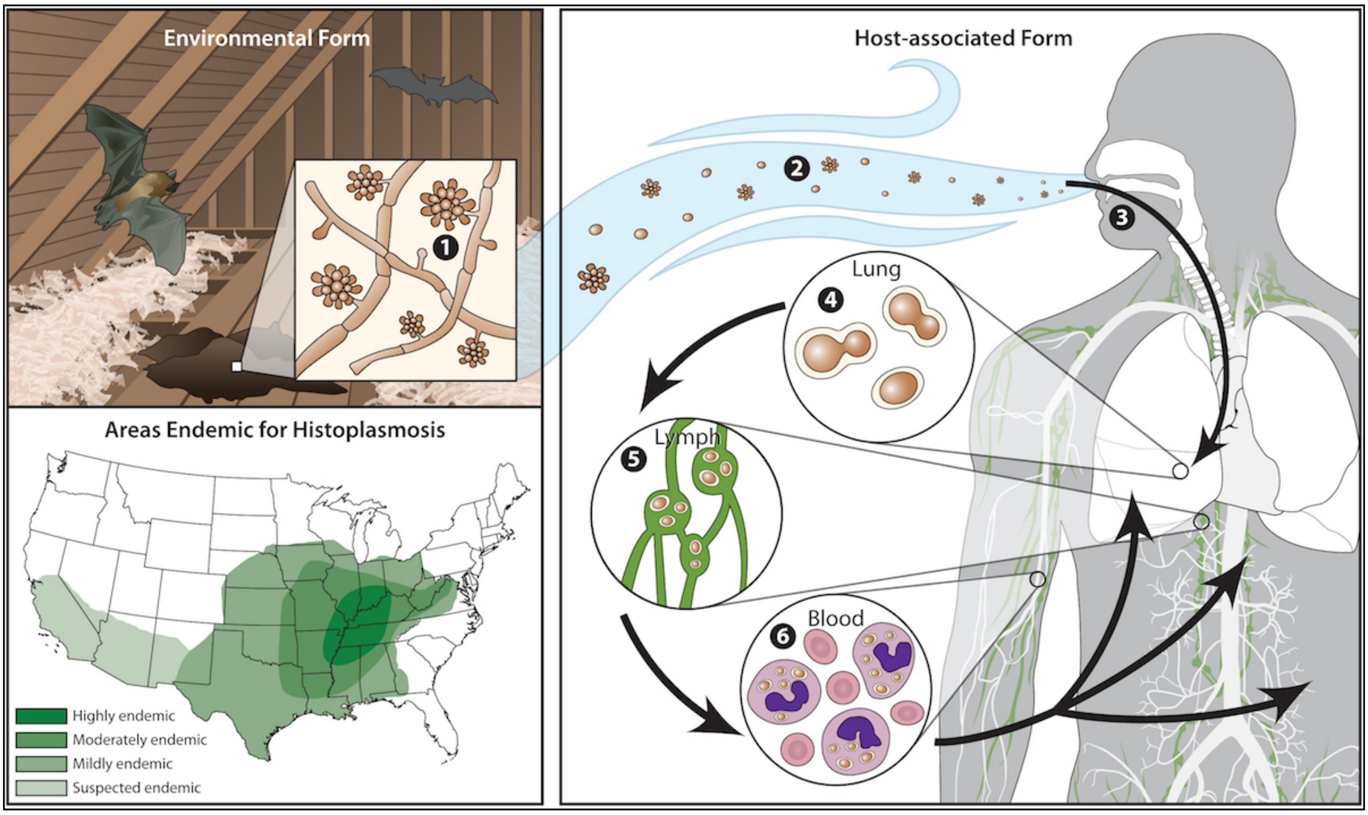

Figure 9 Endemic Regions for Coccidioidomycosis in United States

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)

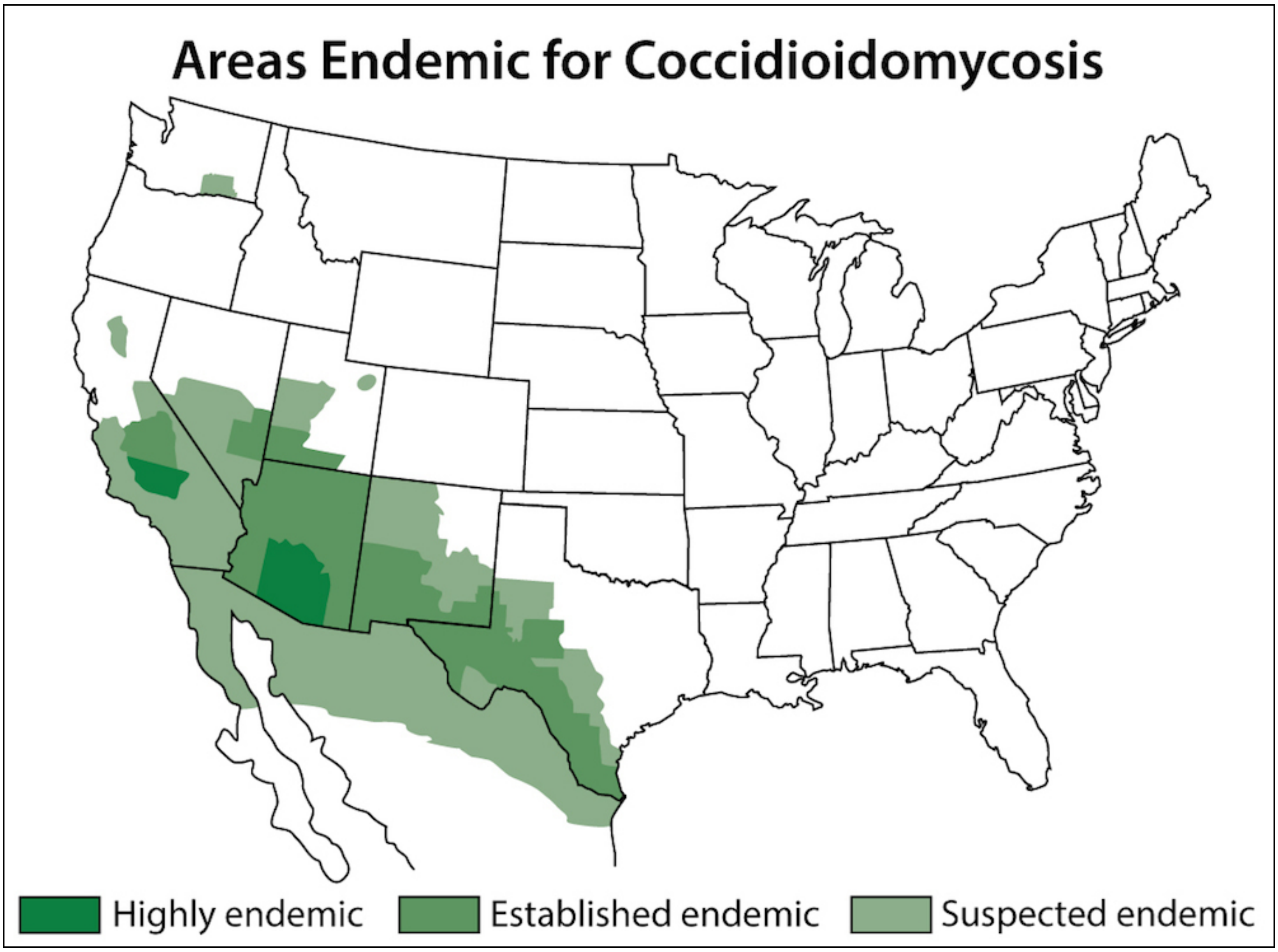

Figure 10 Coccidioidomycosis: Life Cycle

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)

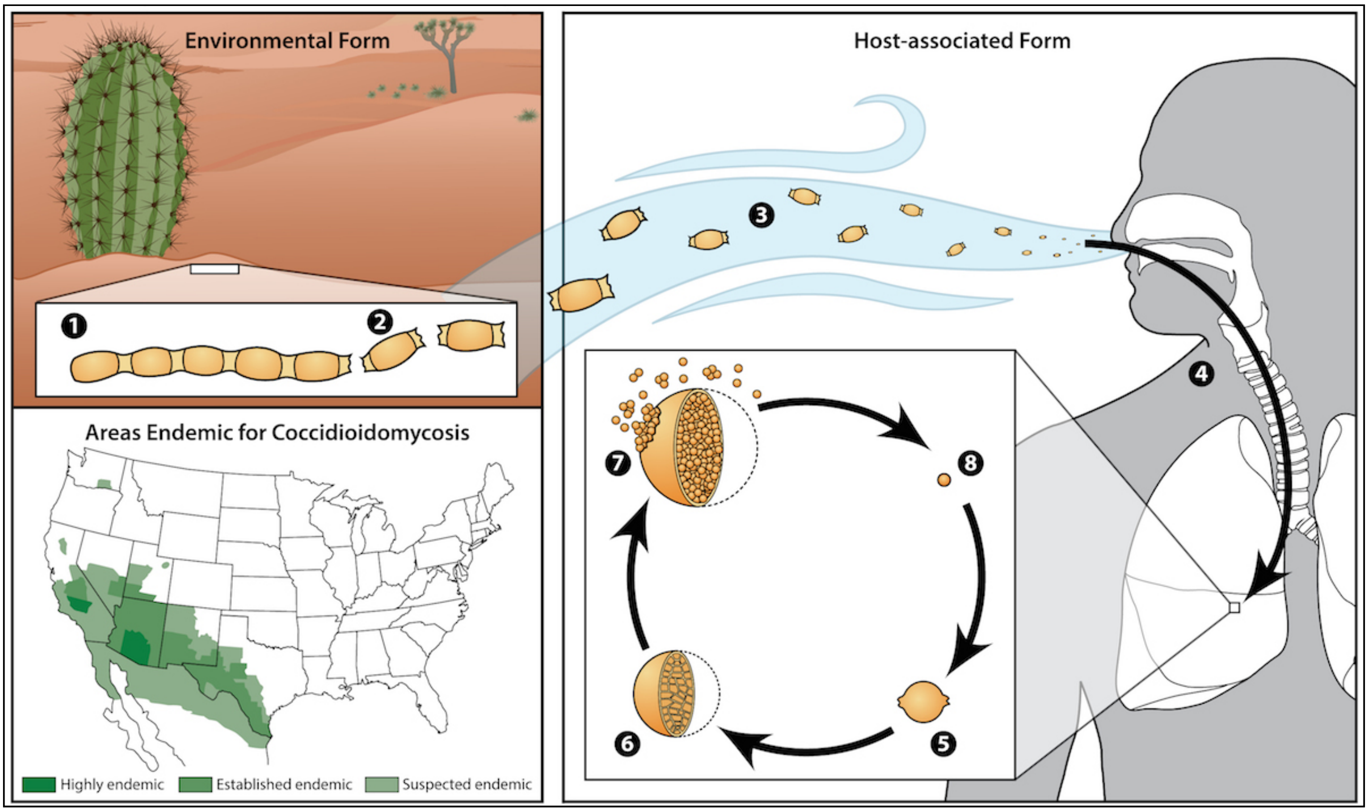

Table 1. **Guidelines for the Prevention and Treatment of Opportunistic Infections** **Regimens for *Pneumocystis* Pneumonia Primary Prophylaxis**
Preferred Therapy: • Trimethoprim-sulfamethoxazole, 1 DS PO daily[a] (AI) *or* • Trimethoprim-sulfamethoxazole, 1 SS PO daily[a] (AI).
Alternative Therapy: • 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:

- 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. Last updated: March 28, 2019. [AIDSinfo]

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 administrating dapsone. Alternative agent should be used if the patient is found to have G6PD deficiency. [b]Atovaquone should be taken with meals or nutritional supplement to ensure adequate oral absorption. Key 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:

- 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. Last updated: July 25, 2017. [AIDSinfo]

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:

- 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. Disseminated *Mycobacterium avium* Complex Disease. Last updated: February 15, 2019. [AIDSinfo]