Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

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Coccidioidomycosis (Last updated May 7, 2013; last reviewed May 7, 2013)

Epidemiology

Coccidioidomycosis is caused by a soil-dwelling fungus that consists of two species, *Coccidioides immitis* and *Coccidioides posadasii*. Most cases of coccidioidomycosis in HIV-infected individuals have been reported in the areas in which the disease is highly endemic.[1] In the United States, these areas include the lower San Joaquin Valley in California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas.[2] Cases have been diagnosed outside those areas, presumably as a result of reactivation of an infection previously acquired in an endemic region.

Risk of developing symptomatic disease is increased in HIV-infected patients living in an endemic area who have CD4 T lymphocyte (CD4) cell counts <250 cells/mm^3 or who have been diagnosed with AIDS.[3] Incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[4,5]

Clinical Manifestations

Lack of suppression of HIV replication and lower CD4 cell counts are significantly associated with the severity of the presentation of coccidioidomycosis.[5] Six common syndromes of coccidioidomycosis have been described in HIV-infected patients: focal pneumonia, diffuse pneumonia, cutaneous disease, meningitis, liver or lymph node involvement, and positive coccidioidal serology tests without evidence of localized infection.[6]

Focal pneumonia is most common in patients with CD4 counts ≥250 cells/mm^3. This diagnosis can be difficult to distinguish from a bacterial community-acquired pneumonia; patients present with symptoms that include cough, fever, and pleuritic chest pain.[7,8] The other syndromes usually occur in more immunosuppressed patients. Diffuse pulmonary disease presents with fever and dyspnea and can be difficult to clinically distinguish from *Pneumocystis* pneumonia.[9] Meningitis presents with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile demonstrates a low glucose level with elevated protein and a lymphocytic pleocytosis.

Diagnosis

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of the typical spherule on histopathological examination of involved tissue. Blood cultures are positive in a minority of patients, usually those with diffuse pulmonary disease. Coccidioidal immunoglobulin M (IgM) and immunoglobulin G (IgG) serology, performed by enzyme immunoassay, immunodiffusion, or classical tube precipitin or complement fixation methodology, is useful in diagnosis but may be positive less often in patients with low CD4 cell counts than in those who are immunocompetent.[10] Complement fixation IgG antibody often is detected in the CSF in coccidioidal meningitis and is useful in establishing this diagnosis. Culture of the CSF is positive in less than one-third of patients with meningitis. A coccidioidomycosis-specific antigen assay recently has become commercially available. It has been shown to detect antigen in urine[11] and serum[12] samples from HIV-infected individuals with active coccidioidomycosis and appears to be useful in diagnosing coccidioidomycosis in such patients.

Preventing Exposure

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

Preventing Disease

Primary antifungal prophylaxis is of little benefit to patients with low CD4 cell counts who live in regions where *Coccidioides* spp. are endemic[4] and it **is not recommended (AIII)**.

Yearly serologic testing for coccidioidomycosis is reasonable for HIV-infected individuals who live in regions endemic for coccidioidomycosis. In such settings, a new positive test suggests imminent active disease in patients with low CD4 cell counts[13] and pre-emptive antifungal therapy with fluconazole 400 mg daily is recommended for those with CD4 counts <250/mm^3 **(BIII)**. Outside endemic regions, routine testing does not appear to be useful and should not be performed.

Treating Disease

Initial therapy with a triazole antifungal is appropriate for patients who have clinically mild infection, such as focal pneumonia **(BII)**. Fluconazole or itraconazole at doses of 400 mg daily is recommended.[14,15] Data are limited on the newer triazoles (posaconazole[16,17] and voriconazole), but these agents may be useful for patients who fail to respond to fluconazole or itraconazole.

Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or are severely ill with extrathoracic disseminated disease **(AII)**.[15] Most experience has been with the deoxycholate formulation, using an initial dose of 0.7 to 1.0 mg/kg intravenously (IV) daily. No data exist about use of lipid formulations of amphotericin B, but they are likely to be as effective as the deoxycholate formulation and may be considered as an alternative initial therapy **(AIII)**.

Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists recommend combining amphotericin B with a triazole (either fluconazole or itraconazole, with itraconazole preferred for bone disease) at 400 mg daily at initiation of therapy, and then continue the triazole once amphotericin B is stopped **(BIII)**.[15]

Treatment of patients with coccidioidal meningitis requires consultation with a specialist. Therapy should begin with a triazole antifungal. IV or oral fluconazole at a dose of 400 to 800 mg daily is preferred **(AII)**,[18] but itraconazole also has been used successfully **(BII)**.[19] Successful therapy with posaconazole **(CIII)**[17,20] and voriconazole **(BIII)**[21-23] has been described in individual cases. Despite successful antifungal therapy, some patients may develop hydrocephalus and require CSF shunting. In some instances, triazole antifungals are ineffective and intrathecal amphotericin B is recommended **(AIII)**. Intrathecal amphotericin B should be administered by someone with experience in this technique.

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with coccidioidomycosis should be started on ART as soon as possible after initiating antifungal therapy **(AIII)**. Immune reconstitution inflammatory syndrome (IRIS) has been reported once[24] but concern for the syndrome should not delay initiation of ART **(AIII)**.

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

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

Managing Treatment Failure

Patients with severe coccidioidomycosis who fail treatment with fluconazole or itraconazole should have their treatment changed to IV amphotericin B, either deoxycholate or lipid formulation **(AIII)**. For patients who are not severely ill, posaconazole **(BII)** and voriconazole **(BIII)**—both given in doses of 200 mg orally twice

daily—can be considered, although data are limited regarding their efficacy. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir (see Table 5). Posaconazole has fewer known drug interactions with ARV medications than does voriconazole.

Preventing Recurrence

When To Start Secondary Prophylaxis

Patients who complete initial therapy for coccidioidomycosis should be considered for lifelong suppressive therapy using either fluconazole 400 mg daily or itraconazole 200 mg twice daily if their CD4 counts remain <250 cells/mm^3 **(AII)**. Posaconazole 200 mg twice daily **(BII)** or voriconazole 200 mg twice daily **(BIII)** are alternatives if the patient did not initially respond to either fluconazole or itraconazole.

When To Stop Secondary Prophylaxis

Patients with focal coccidioidal pneumonia who have clinically responded to antifungal therapy appear to be at low risk of recurrence of coccidioidomycosis if their CD4 cell counts are ≥250 cells/mm^3 and they are receiving effective ART. A reasonable plan for treating these individuals is to discontinue secondary prophylaxis after 12 months of therapy **(AII)** and continue monitoring for recurrence with serial chest radiographs and coccidioidal serology.

Relapse occurs in 25% to 33% of HIV-uninfected patients who have diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis[25,26] and can occur in HIV-infected patients with CD4 counts ≥250 cells/mm^3 on potent ART;[27] therefore, some clinicians would continue antifungal therapy indefinitely **(BIII)**, although this decision should be made in conjunction with expert consultation. Because relapses have been reported in 80% of patients with meningitis in whom triazoles have been discontinued,[28] therapy for coccidioidal meningitis should be lifelong **(AII)**.

Special Considerations During Pregnancy

Coccidioidomycosis is more likely to disseminate if acquired during the second or third trimester of pregnancy.[29] Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of coccidioidomycosis in pregnant patients. Extensive clinical use of amphotericin has not been associated with teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia.

Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy.[30] Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure to fluconazole, most of these involved low doses and short term exposure.[31,32] Based on the reported birth defects, the Food and Drug Administration has changed the pregnancy category from C to D for fluconazole for any use other than a single, 150 mg dose to treat vaginal candidiasis (http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm). Although there are case reports of birth defects in infants exposed to itraconazole, prospective cohort studies of over 300 women with first trimester exposure did not show an increased risk of malformation.[33,34] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII)**. One problematic area is coccidioidal meningitis, in which the only alternative treatment to triazole antifungals is intrathecal amphotericin B. For such situations, the decision regarding choice of treatment should be based on considerations of benefit versus potential risk and made in consultation with the mother, the infectious diseases consultant, and the obstetrician.[35] Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; there are no adequate controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Recommendations for Preventing and Treating Coccidiodomycosis (page 1 of 2)

Primary Prophylaxis

Indication:

- A new positive IgM or IgG serologic test in patients who live in a disease-endemic area and with CD4 counts <250 cells/μL **(BIII)**

Regimen:

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

Treating Mild Infections (Such As Focal Pneumonia)

Preferred Therapy:

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

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

- Posaconazole 200–400 mg PO twice daily **(BII)**; *or*
- Voriconazole 200 mg PO twice daily **(BIII)**

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

Preferred Therapy:

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily **(AII)**, *or*
- Lipid formulation amphotericin B 4–6 mg/kg IV daily **(AIII)**

Duration:

- Until clinical improvement, then switch to triazole **(BIII)**

Alternative Therapy:

- Some specialists add a triazole (either fluconazole or itraconazole, with itraconazole preferred for bone disease) at 400 mg daily to amphotericin B therapy and continue triazole once amphotericin B is stopped **(BIII)**

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

Preferred Therapy:

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

Alternative Therapy:

- Itraconazole 200 mg PO twice daily **(BII)**, *or*
- Posaconazole 200–400 mg PO twice daily **(CIII)**, *or*
- Voriconazole 200–400 mg PO twice daily **(BIII)**, *or*
- Intrathecal amphotericin B **(AIII)** when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by someone with experience in this technique.

Chronic Suppressive Therapy

Preferred Therapy:

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

Alternative Therapy (If Patients Did Not Initially Respond to Fluconazole or Itraconazole):

- Posaconazole 200 mg PO twice daily **(BII)**, *or*
- Voriconazole 200 mg PO twice daily **(BIII)**

Discontinuing Chronic Suppressive Therapy

*Focal Coccidioidal Pneumonia, Suppressive Therapy Can Be Stopped If **(AII)**:*

- Clinically responded to >12 months of antifungal therapy, *and*
- CD4 count ≥250 cells/mm^3, *and*
- Receiving effective ART, *and*
- Continued monitoring for recurrence using serial chest radiograph and coccidioidal serology.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

- Relapse can occur in 25% to 33% of HIV-negative patients, and can occur in HIV patients with CD4 count >250 cells/mm^3
- Some clinicians would continue therapy indefinitely; this decision should be made in consultation with experts **(BIII)**.

Coccidioidal Meningitis:

- Relapse has been reported in 80% of patients after stopping triazoles, therefore, suppressive therapy should be lifelong **(AII)**

Other Considerations:

- Certain patients with meningitis may develop hydrocephalus and require CSF shunting in addition to antifungal therapy.
- All the triazole antifungals have the potential to interact with certain antiretroviral agents and other anti-infective agents. These interactions are complex and can be bidirectional. Table 5 lists these interactions and recommends dosage adjustments where feasible.

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

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