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

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Coccidioidomycosis (Last updated November 10, 2016; last reviewed November 10, 2016)

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 and other arid regions in southern California; much of Arizona; the southern regions of Utah, Nevada, and New Mexico; and western Texas.[2] Recently, cases of coccidioidomycosis that appeared to be acquired in eastern Washington state have been reported.[3] Whether this is anomalous or is a manifestation of an expanding area of endemicity is not clear at this time. In some instances, coccidioidomycosis has been diagnosed in patients with HIV infection well outside the known endemic regions. These have presumably been the result of reactivation of a previously acquired infection.

The risk of developing symptomatic coccidioidomycosis after infection is increased in HIV-infected patients who have CD4 T lymphocyte (CD4) counts <250 cells/mm^3 or who have been diagnosed with AIDS.[4] The incidence and severity of HIV-associated coccidioidomycosis have declined since the introduction of effective antiretroviral therapy (ART).[5,6]

Clinical Manifestations

Lack of suppression of HIV replication and lower CD4 cell counts are associated with the severity of the presentation of coccidioidomycosis.[6] Four common syndromes of coccidioidomycosis have been described in HIV-infected patients: focal pneumonia, diffuse pneumonia, extrathoracic involvement including meningitis, and positive coccidioidal serology tests without evidence of localized infection.[7] In addition, patients with HIV infection may develop dissemination to other extrathoracic sites, including the bones and joints.

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.[8,9] However, coccidioidomycosis may present with hilar or mediastinal adenopathy, upper lobe infiltrates, night sweats, and peripheral blood eosinophilia, all of which are uncommon in bacterial pneumonia. The syndromes other than focal pneumonia usually occur in more immunosuppressed patients. Diffuse pulmonary disease presents with fever and dyspnea and can be difficult to clinically distinguish from *Pneumocystis* pneumonia.[10] Hypoxemia may be severe and serological tests are frequently negative at the time of presentation. Routine bacterial cultures from pulmonary secretions frequently reveal *Coccidioides* after an incubation time of less than one week. Meningitis presents with a persistent headache and progressive lethargy. The cerebrospinal fluid (CSF) profile demonstrates low glucose levels with elevated protein and a lymphocytic pleocytosis. In addition, immunosuppressed patients with HIV infection may present with elevated coccidioidal serological titers without evidence of disease. A study in the era prior to potent ART described 13 patients, all with CD4 counts <350 cells/mm^3 and positive coccidioidal serologic tests. Five patients subsequently developed clinical illness at a median CD4 count of 10 cells/mm^3.[11]

Diagnosis

The diagnosis of coccidioidomycosis is confirmed by culture of the organism from clinical specimens or by demonstration of spherules on histopathological examination of infected tissue. Blood cultures are positive in a minority of patients, usually those with diffuse pulmonary disease. Cultures of the CSF are positive in fewer than one-third of patients with coccidioidal meningitis. Unlike other endemic mycoses, *Coccidioides* grows relatively rapidly at 37°C on routine bacterial media, especially blood agar. Growth of a non-pigmented mould may be observed in as few as 3 days and can be confirmed as *Coccidioides* by gene probe. *Coccidioides* growing on an agar plate is a significant laboratory hazard because of the risk of inhalation of dislodged arthroconidia. Laboratory personnel should be alerted to the possibility of *Coccidioides* at the time the

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specimen is sent to the laboratory, and the plate lid securely taped.[12] Identification of the fungus should be performed in biosafety level 3 (BSL 3) containment laboratory.

Most commonly, the diagnosis of coccidioidomycosis is based on a positive coccidioidal serological test associated with a compatable clinical syndrome. Patients with past coccidioidal infection without disease activity usually have negative serological tests. The nomenclature and variety of coccidioidal serological tests can be confusing.[13] The original assays examined two reactions. The first was the development of a precipitate in a tube when incubated with a heat-stable coccidioidal antigen preparation. This has been termed "tube precipitin" or TP response. It is due to an IgM antibody reaction, is not titratable, not useful in the diagnosis of meningitis, and is positive early in disease. If performed by immunodiffusion, it is termed IDTP. The second reaction originally detected the loss of serum complement activity in the presence of a heat-labile coccidioidal antigen preparation. This is called "complement-fixing" or CF, is due to an IgG response, is titratable, and its detection in the CSF is indicative of meningitis. CF antibody responses can also be measured by immunodiffusion (IDCF). In general, elevated CF titers suggest clinically active disease. Several companies offer enzyme immunoassays (EIAs). They appear to be similar to IDTP and IDCF with the following caveats. The IgM EIA has been associated with false positive results and the IgG EIA is not titratable. Both CF and EIA tests appear to be more sensitive than immunodiffusion assays. All coccidioidal serologic tests are positive less frequently in HIV infected patients with low CD4 cell counts than in those who are immunocompetent.[14] It is strongly recommended that clinical samples for serological testing be sent to laboratories with expertise in performing these assays.

A coccidioidomycosis-specific antigen assay is commercially available. It has been shown to detect antigen in urine,[15] serum[16] and other body fluids in samples from individuals with active coccidioidomycosis. It is most useful in diagnosing extrathoracic disseminated coccidioidomycosis. A recent study suggests that detection of coccidioidal antigen in the cerebrospinal fluid has a very high sensitivity and specificity for diagnosing coccidioidal meningitis.[17]

Preventing Exposure

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

Preventing Disease

Primary antifungal prophylaxis (i.e. prophylaxis for individuals with negative serologic tests for *Coccidioides*) is of little benefit to patients with low CD4 cell counts who live in regions where *Coccidioides* is endemic[5] and it **is not recommended (AIII)**. Yearly or twice-yearly serological testing for coccidioidomycosis is reasonable for serologically negative HIV-infected individuals who live in regions endemic for coccidioidomycosis. Testing is also advised for individuals who have traveled to or lived in endemic areas in the past. Both IgM and IgG antibody testing using either an EIA or immunodiffusion technique are recommended. A new positive test suggests possible active disease in patients with low CD4 cell counts[11] and further clinical evaluation should be undertaken. If no signs, symptoms or laboratory abnormalities compatible with active coccidioidomycosis are identified, antifungal therapy with fluconazole 400 mg daily is recommended for those with CD4 counts <250 cells/mm^3 **(AIII)**. This should be continued until the CD4 count is ≥250 cells/mm^3 and ART has fully suppressed HIV replication **(BIII)**. Outside endemic regions, routine testing does not appear to be useful and **should not be performed (CIII)**.

Treating Disease

Initial therapy with a triazole antifungal agent given orally is appropriate for patients who have clinically mild infection, such as focal pneumonia **(AII)**. When prescribing triazoles, it should be noted that all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with drugs that are principally based on CYP 3A4 enzyme for metabolism. Therapeutic drug monitoring and dosage

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adjustments, may be necessary. Clinicians should refer to Table 5 for dosage guidance when triazoles are used with other drugs for treatment of OI, and to the antiretroviral treatment guidelines for interaction recommendations with ARV, especially when used with ritonavir- or cobicistat-containing regimens.

Without concomitant interacting drugs, fluconazole should be given as 400 mg daily **(AII)**, while itraconazole should be given in divided doses of 200 mg two to three times daily **(BII)**.[18,19] Itraconazole is preferred for those who have bone or joint disease **(AI)**.[20] Serum itraconazole levels should be measured after reaching steady state at 2 weeks to ensure adequate absorption. Data are limited for treatment with posaconazole[21,22] and voriconazole, but these agents are useful for patients who fail to respond to fluconazole or itraconazole **(BII)**. The dose of voriconazole is 200 mg twice daily after a loading dose of 400 mg twice daily for the first day **(AIII)**. Trough serum levels should be measured to ensure efficacy and avoid toxicity; a level of 1-5 mg/L is desired. Several dosage formulations of posaconazole have been studied for coccidioidomycosis. A dose of 400 mg twice daily of the older liquid formulation of posaconazole has been used **(BII)**,[22] but the current extended-release tablet formulation is better tolerated by patients and provides more reliable absorption and serum levels. There is no established dosage with the tablet formulation for coccidioidomycosis but 300 mg daily is reasonable **(BIII)**. There are no published data on the use of the newly approved triazole antifungal isavuconazole for coccidioidomycosis in patients with HIV infection. Among nine patients with pulmonary disease without HIV infection, initial therapy with isavuconazole resulted in complete or partial success in 5 (56%).[23]

Patients with HIV infection and positive coccidioidal serologies but without clinical illness should be treated with antifungal therapy as previously described in the same manner as patients with focal pneumonia **(AII)**. For patients with CD4 cell counts <250/mm^3 who are not receiving suppressive antiretroviral therapy, fluconazole 400 mg daily should be given and continued until the CD4 cell count is ≥250/mm^3 and HIV RNA suppression has been achieved **(AIII)**. For those with CD4 cell counts already ≥250/mm^3 and on suppressive antiretroviral therapy, close clinical follow-up is recommended **(BIII)**.

Amphotericin B is the preferred initial therapy for patients who have diffuse pulmonary involvement or are severely ill with extrathoracic disseminated disease **(AII)**.[19] Most experience has been with the deoxycholate formulation, using an initial dose of 0.7 to 1.0 mg/kg intravenously (IV) daily. There are no reported studies that have used lipid formulations of amphotericin B for the treatment of coccidioidomycosis, but these are likely to be as effective as the deoxycholate formulation and should be considered as an equivalent initial therapy, particularly if there is underlying renal dysfunction **(AIII)**. An initial daily dose of 3 to 5 mg/kg is appropriate.

Therapy with amphotericin B should continue until clinical improvement is observed and then changed to an oral triazole antifungal **(BIII)**. Some specialists recommend combining amphotericin B with a triazole antifungal (fluconazole or itraconazole) 400 mg daily at initiation of therapy, and then continuing the triazole once amphotericin B is stopped **(CIII)**.[19]

Treatment of patients with coccidioidal meningitis requires consultation with a specialist **(AIII)**. Therapy should begin with a triazole antifungal. IV or oral fluconazole at a dose of 400 to 800 mg daily is preferred **(AII)**,[24] but itraconazole also has been successfully used (BII).[25] Therapy with posaconazole **(CIII)**[22,26] or voriconazole **(BIII)**[27-29] has been described in individual cases. Despite appropriate 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)**. If intrathecal therapy is required, it should be administered by someone very experienced in this technique.

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

Monitoring the CF antibody titer 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 previously, 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 therapeutic drug monitoring and dosage adjustments, where feasible.

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The immune reconstitution inflammatory syndrome (IRIS) has been infrequently reported in HIV-infected persons with concomitant coccidioidomycosis.[30-32] Because of this, delaying initiation of potent antiretroviral therapy while treating coccidioidomycosis is not recommended **(AIII)**.

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 a lipid formulation **(AIII)**. For patients who are not severely ill, posaconazole **(BII)** and voriconazole **(BIII)** are appropriate alternatives. Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir or cobicistat-boosted regimens (see Table 5). Posaconazole has fewer known drug interactions with ARV medications than does voriconazole.

Therapy after Immune Reconstitution

Patients with peripheral blood CD4 lymphocyte counts ≥250/mm^3 appear capable of maintaining their coccidioidal-specific cellular immune response.[33] Moreover, a prospective study has demonstrated that the severity of coccidioidomycosis is less in those with lower HIV RNA and higher CD4 cell counts.[6] Given these facts, in HIV-infected patients with undetectable HIV RNA on potent ARV therapy who have a CD4 ≥250/mm^3, coccidioidomycosis should be managed no differently than it is in the general population **(AII)**.

For patients who meet the above criteria with focal pulmonary disease, treatment with triazole antifungal should continue for a minimum of 6 months **(AII)**. For patients with diffuse pulmonary disease and those with extrathoracic dissemination, antifungal therapy should continue for at least 12 months and usually much longer. Discontinuation of therapy should be based on clinical and immunological response in consultation with an expert. For patients with detectable HIV viremia or CD4 <250/mm^3, antifungal therapy at full dose should continue **(BIII)**.

Prevention of Relapse

Relapse occurs in 25% to 33% of HIV-uninfected patients who have diffuse pulmonary disease or nonmeningeal disseminated coccidioidomycosis[34,35] and may occur in HIV-infected patients with CD4 counts ≥250 cells/mm^3 on potent ART.[36] Continued monitoring during coccidiomycosis therapy and after such therapy has been discontinued with clinical follow-up, serial chest radiographs and coccidioidal serology every 3 to 6 months should be performed. Because relapses have been reported in 80% of patients with meningitis in whom triazoles have been discontinued,[37] therapy for coccidioidal meningitis should be continued for life **(AII)**.

Special Considerations During Pregnancy

Women are generally at less risk than men for severe coccidioidomycosis and disease does not appear to worsen in women with prior coccidioidomycosis during pregnancy. However, coccidioidomycosis is likely to be severe and disseminated if infection is acquired during the second or third trimester of pregnancy.[38]

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.[39] A recent systematic review and meta-analysis of cohort or case–control studies reporting fetal outcomes after exposure to any dose of fluconazole used in the first trimester of pregnancy found an increased risk of heart defects[40] but did not find an increase in the rate of overall malformations or in craniofacial defects. One registry-based cohort study (included in the systematic review)[41] and a more recent large population-based case-control study[42] specifically noted an increase in conotruncal heart defects. The latter study also suggested an increase in cleft lip with cleft palate.

In addition in a nation-wide cohort study from Denmark oral fluconazole in pregnancy was associated with an increase risk of spontaneous abortion compared to unexposed women or those with topical azole exposure only.[42] Most of the studies regarding effects of fluconazole in pregnancy have involved low doses and short

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term exposure. 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.[43,44] However, in general, all 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 IV or 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.[45] Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies; for voriconazole, these occurred at doses lower than recommended for humans. There are no adequately controlled studies in humans. These drugs **should be avoided** in pregnancy, especially in the first trimester **(AIII)**.

Intravenous amphotericin B, formulated with deoxycholate or as a lipid preparation, is the preferred treatment for non-meningeal coccidioidomycosis during the first trimester of pregnancy **(AIII)**. Extensive clinical use of amphotericin B has not been associated with teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia.

Recommendations for Treating Coccidioidomycosis (page 1 of 2)

Treating Mild Infections (Such As Focal Pneumonia or asymptomatic patients with positive serology and CD4 count <250 cells/mm^3)

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):

- Voriconazole 200 mg PO twice daily after a loading dose of 400 mg twice on first day **(BIII)***; *or*
- Posaconazole (delayed release tablet) 300 mg PO daily after a loading dose of 300 mg twice daily for one day, then 300 mg once daily* **(BIII)*** *or*
- Posaconazole (oral suspension) 400 mg PO twice daily **(BII)***

Treating Bone or Joint Infections

Preferred Therapy:

- Itraconazole 200 mg PO twice daily **(AI)***

Alternative Therapy:

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

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

Preferred Therapy:

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

Alternative Therapy:

- Some specialists add a triazole (either fluconazole 400 mg daily or itraconazole 200 mg twice daily, with itraconazole preferred for bone or joint disease) to amphotericin B therapy and continue the triazole once amphotericin B is stopped **(BIII)**

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

Preferred Therapy:

- Fluconazole 400–800 mg PO daily **(AII)**; IV if patient unable to take orally.

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Alternative Therapy:

- Itraconazole 200 mg PO twice to three-times daily* **(BII)**, *or*
- Voriconazole 200–400 mg PO twice daily after loading dose* **(BIII)**, *or*
- Posaconazole (delayed release tablet) loading dose of 300 mg twice daily on first day, then 300 mg once daily* **(CIII)**, *or*
- Posaconazole (oral suspension) 400 mg PO twice daily* **(CIII)**, *or*
- Intrathecal amphotericin B **(AIII)** when triazole antifungals are not effective. Use in consultation with a specialist and should be administered by a clinician experienced in this technique.

Duration of Therapy

*Focal Coccidioidal Pneumonia, or Asymptomatic Patients with Positive Serology and CD4 Count <250 cells/mm^3, Therapy Can Be Stopped If **(AII)**:*

- Clinically responded to ≥6 months of antifungal therapy (for patients with focal pneumonia), *and*
- CD4 count ≥250 cells/mm^3, *and*
- Receiving effective ART with virologic suppression, *and*
- Continued monitoring for recurrence should be performed using serial chest radiograph and coccidioidal serology every six to twelve months.

Diffuse Pulmonary Disease or Non-Meningeal Disseminated Coccidioidomycosis:

- Relapse can occur in 25% to 33% of HIV-seronegative patients, and can occur in HIV patients with CD4 count >250 cells/mm^3
- Therapy is at least 12 months and usually much longer; discontinuation is dependent on clinical and serological response and should be made in consultation with experts **(BIII)**.

Coccidioidal Meningitis:

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

Other Considerations:

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

* It should be noted that all of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with drugs that are principally based on CYP 3A4 enzyme for metabolism. Therapeutic drug monitoring and dosage adjustments, may be necessary. Clinicians should refer to Table 5 for dosage guidance when triazoles are used with other drugs for treatment of OI, and to the antiretroviral treatment guidelines for interaction recommendations with ARV, especially when used with efavirenz, ritonavir- or cobicistat-containing regimens.

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

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