



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

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## Histoplasmosis (Last updated May 7, 2013; last reviewed May 7, 2013)

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### Epidemiology

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. Infection is endemic to the central and south-central United States and is especially common in the Ohio and Mississippi River Valleys. It is also endemic in Latin America, including Puerto Rico. In endemic areas, annual incidence approaches 5% in HIV-infected individuals. A CD4 T lymphocyte (CD4) count <150 cells/mm<sup>3</sup> is associated with an increased risk of symptomatic illness.<sup>1,2</sup>

Virtually all cases of primary histoplasmosis are acquired by inhalation of microconidia that form in the mycelial phase. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. When cellular immunity wanes, reactivation of a silent focus of infection that was acquired years earlier can occur, and it is the presumed mechanism for disease occurrence in nonendemic areas. Incidence of symptomatic histoplasmosis in HIV-infected patients appears to have declined with the advent of effective antiretroviral therapy (ART). When histoplasmosis does occur, however, it is reported as the AIDS-defining illness in 25% to 61% of patients.<sup>3,4</sup>

### Clinical Manifestations

In HIV-infected patients, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough, chest pain, and dyspnea occur in approximately 50% of patients.<sup>1,4</sup> Central nervous system (CNS), gastrointestinal, and cutaneous manifestations occur in a smaller percentage, although in a series from Panama, diarrhea occurred in 50% of patients.<sup>5</sup> Approximately 10% of patients experience shock and multi-organ failure. Patients with CNS histoplasmosis typically experience fever and headache, and also (if brain involvement is present) seizures, focal neurological deficits, and changes in mental status.<sup>6</sup> Gastrointestinal disease usually manifests as diarrhea, fever, abdominal pain, and weight loss.<sup>7</sup> For patients whose CD4 counts are >300 cells/mm<sup>3</sup>, histoplasmosis is often limited to the respiratory tract and usually presents with cough, pleuritic chest pain, and fever.

### Diagnosis

Detection of *Histoplasma* antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis and acute pulmonary histoplasmosis<sup>8</sup> but is insensitive for chronic forms of pulmonary infection. Using a newer quantitative assay, antigen was detected in the urine of 100% and in the serum of 92% of AIDS patients with disseminated histoplasmosis.<sup>9</sup> Antigen detection in bronchoalveolar lavage fluid appears to be a useful method for diagnosis of pulmonary histoplasmosis.<sup>10</sup> In patients with severe disseminated histoplasmosis, peripheral blood smears can show the organisms engulfed by white blood cells. Histopathological examination of biopsy material from involved tissues demonstrates the characteristic 2 to 4 µm budding yeast and can provide a rapid diagnosis.

*H. capsulatum* can be cultured from blood, bone marrow, respiratory secretions, or other involved sites in >85% of patients with AIDS and disseminated histoplasmosis, but the organism requires several weeks to grow.<sup>11</sup> Serologic tests are less useful than antigen assays in AIDS patients with disseminated histoplasmosis but may be helpful in patients who have reasonably intact immune responses with pulmonary disease.<sup>11,12</sup>

The diagnosis of meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are a lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.<sup>6</sup> However, *Histoplasma* antigen or antibodies against *H. capsulatum* can be detected in CSF in up to 70% of cases, and a positive result for either test is diagnostic. For some patients, none of these specific tests is positive, and a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not explained by another cause.

## Preventing Exposure

HIV-infected individuals who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to it, but those with CD4 counts  $<150$  cells/mm<sup>3</sup> should avoid activities known to be associated with increased risk (**BIII**). These include creating dust when working with surface soil; cleaning chicken coops that are contaminated with droppings; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing old buildings; and exploring caves.

## Preventing Disease

### *When to Start Primary Prophylaxis*

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the frequency of histoplasmosis, although not mortality, in patients who have advanced HIV infection and who live in areas where histoplasmosis is highly endemic.<sup>13</sup> Prophylaxis with itraconazole at a dose of 200 mg daily can be considered for patients with CD4 counts  $<150$  cells/mm<sup>3</sup> who are at high risk because of occupational exposure or who live in a community with a hyperendemic rate of histoplasmosis ( $>10$  cases/100 patient-years) (**BI**).

### *When to Stop Primary Prophylaxis*

If used, primary prophylaxis can be discontinued in patients on potent ART once CD4 counts are  $\geq 150$  cells/mm<sup>3</sup> for 6 months (**BIII**). Prophylaxis should be restarted if the CD4 count falls to  $<150$  cells/mm<sup>3</sup> (**BIII**).

## Treating Disease

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) was more effective than standard IV amphotericin B deoxycholate (0.7 mg/kg daily), induced a more rapid and complete response, lowered mortality, and reduced toxicity.<sup>14</sup> Based on these findings, patients with moderately severe to severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for at least 2 weeks or until they clinically improve (**AI**). Another lipid formulation of amphotericin B can be used at the same dosage if cost is a concern or in patients who cannot tolerate liposomal amphotericin B (**AIII**). Step-down therapy to oral itraconazole, 200 mg 3 times daily for 3 days, and then 200 mg twice daily, should be given for a total of at least 12 months (**AII**).<sup>15</sup> Because of potential drug interactions between itraconazole and both protease inhibitors and efavirenz, it is advisable to obtain serum levels of itraconazole after 2 weeks of therapy. A randomly obtained serum level of at least 1.0  $\mu\text{g/mL}$  is recommended and levels  $>10$   $\mu\text{g/mL}$  are unnecessary.

In patients with less severe disseminated histoplasmosis, oral itraconazole, 200 mg 3 times daily for 3 days followed by 200 mg twice daily, is appropriate initial therapy (**AII**).<sup>15,16</sup> The liquid formulation of itraconazole, which should be given on an empty stomach, is preferable because it is better absorbed and does not require gastric acid for absorption, but it is less well tolerated than the capsule formulation, which should be given with food.

Acute pulmonary histoplasmosis in an HIV-infected patient with intact immunity, as indicated by a CD4 count  $>300$  cells/mm<sup>3</sup>, should be managed in a manner similar to that used for a nonimmunocompromised host (**AIII**).<sup>15</sup>

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dosage of 5 mg/kg daily for 4 to 6 weeks (**AIII**). This should be followed by maintenance therapy with itraconazole at a dose of 200 mg 2 or 3 times daily for at least 1 year and until resolution of abnormal CSF findings (**AIII**).<sup>15</sup>

Oral posaconazole and voriconazole have been reported to be effective for histoplasmosis in a small number of patients who had AIDS or other immunosuppressive conditions<sup>17-20</sup> and may be reasonable alternatives for patients intolerant of itraconazole who are only moderately ill (**BIII**). Fluconazole is less effective than

itraconazole for histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily and may also be a reasonable alternative at this dose for those intolerant of itraconazole (**CII**).<sup>21</sup> The echinocandins are not active against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis (**AIII**).

### ***Special Considerations with Regard to Starting ART***

HIV-infected individuals diagnosed with histoplasmosis should be started on ART as soon as possible after initiating antifungal therapy (**AIII**). Immune reconstitution inflammatory syndrome (IRIS) is reportedly uncommon in HIV-infected patients with histoplasmosis.<sup>22,23</sup> ART should, therefore, **not** be withheld because of concern for the possible development of IRIS (**AIII**).

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 these interactions and recommendations for dosage adjustments, where feasible.

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

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining response to therapy. A rise in antigen level suggests relapse. Because absorption of itraconazole can be erratic, a random serum itraconazole level should be obtained after 2 weeks of therapy if there is concern about adherence or if medications with potentially adverse interactions are added to the drug regimen. The serum concentration should be >1 µg/mL.

As previously indicated, IRIS is uncommon in HIV-infected individuals with histoplasmosis.<sup>22,23</sup>

### ***Managing Treatment Failure***

Mortality rates remain high for patients with AIDS who develop disseminated histoplasmosis, many of whom had never received ART before diagnosis with histoplasmosis.<sup>3-5,12</sup> Liposomal amphotericin B should be used in patients who are severely ill or who have failed to respond to initial azole antifungal therapy (**AIII**). Oral posaconazole and voriconazole are reasonable alternatives for patients intolerant of itraconazole who are only moderately ill (**BIII**);<sup>17-20</sup> fluconazole also can be used at a dose of 800 mg daily (**CII**).<sup>21</sup> Drug interactions may limit the use of voriconazole in patients who are taking non-nucleoside reverse transcriptase inhibitors or ritonavir ([Table 5](#)). Posaconazole has fewer known drug interactions with ARV medications than voriconazole.

## **Preventing Recurrence**

### ***When to Start Secondary Prophylaxis***

Long-term suppressive therapy with itraconazole (200 mg daily) should be administered to patients with severe disseminated or CNS infection (**AIII**) and after re-induction therapy in those whose disease relapses despite initial receipt of appropriate therapy (**BIII**). Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily.<sup>21,24</sup> The role of voriconazole or posaconazole has not been evaluated.

### ***When to Stop Secondary Prophylaxis***

An AIDS Clinical Treatment Group (ACTG)-sponsored study reported that discontinuing itraconazole was safe for patients treated for histoplasmosis who have a good immunologic response to ART.<sup>25</sup> Subjects in that trial had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum antigen <2 units, and CD4 counts ≥150 cells/mm<sup>3</sup>; and had been on effective ART for 6 months. No relapses were evident in 32 subjects who were followed for a median of 24 months.<sup>25</sup> Thus, discontinuing suppressive azole antifungal therapy appears to be safe for patients who meet the previously described criteria, noting that the detectable antigen level is now designated as 2 ng/mL (**AI**). Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm<sup>3</sup> (**BIII**).

## Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia. 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.<sup>26,27</sup> However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy (**BIII**). Congenital malformations similar to those observed in animals, including craniofacial and limb abnormalities, have been reported in infants born to mothers who received fluconazole at doses of 400 mg/day or more through or beyond the first trimester of pregnancy.<sup>28</sup> Although several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, most of these studies involved low doses and short term exposure to fluconazole.<sup>29,30</sup> 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, low dose for treatment of vaginal candidiasis (<http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm>). 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 *Histoplasma capsulatum* Infections (page 1 of 2)

### Preventing 1st Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)

#### Indications for Initiating Primary Prophylaxis:

- CD4 count <150 cells/mm<sup>3</sup> and at high risk because of occupational exposure or living in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-years) (**BI**)

#### Preferred Therapy:

- Itraconazole 200 mg PO once daily (**BI**)

#### Discontinue Primary Prophylaxis:

- If used, may discontinue if CD4 count ≥150 cells/mm<sup>3</sup> for 6 months on ART (**BIII**)

#### Indication for Restarting Primary Prophylaxis:

- CD4 count <150 cells/mm<sup>3</sup> (**BIII**)

### Treating Moderately Severe to Severe Disseminated Disease

#### Induction Therapy

##### Preferred Therapy:

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

##### Alternative Therapy:

- Amphotericin B lipid complex or amphotericin B cholesteryl sulfate complex 3 mg/kg IV daily (**AIII**)

##### Duration:

- For at least 2 weeks or until clinically improved

#### Maintenance Therapy

##### Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then BID for at least 12 months (**AII**), with dosage adjustment based on interactions with ARV (see [Table 5](#)) and itraconazole serum concentration

### Treating Less Severe Disseminated Disease

#### Induction and Maintenance Therapy

##### Preferred Therapy:

- Itraconazole 200 mg PO TID for 3 days, then 200 mg PO BID for ≥12 months (**AII**), with dosage adjustment based on interactions with ARV and itraconazole serum concentration

## Recommendations for Preventing and Treating *Histoplasma capsulatum* Infections (page 2 of 2)

### Alternative Therapy:

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

- Posaconazole 400 mg PO BID (**BIII**)
- Voriconazole 400 mg PO BID for 1 day, then 200 mg PO BID (**BIII**)
- Fluconazole 800 mg PO daily (**CII**)

### Treating *Histoplasma* Meningitis

#### Induction Therapy (4–6 Weeks):

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

#### Maintenance Therapy

- Itraconazole 200 mg PO BID (TID for at least 12 months and until resolution of abnormal CSF findings) with dosage adjustment based on interactions with ARV and itraconazole serum concentration (**AIII**)

### Long-Term Suppressive Therapy (Secondary Prophylaxis)

#### Indications:

- For patients with severe disseminated or CNS infection after completion of at least 12 months of treatment (**AIII**), and
- In patients who relapsed despite appropriate initial therapy (**BIII**)

#### Preferred Therapy:

- Itraconazole 200 mg PO daily (**AIII**)

#### Alternative Therapy:

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

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

- Received azole treatment for >1 year, and
- Negative fungal blood cultures, and
- Serum *Histoplasma* antigen <2 ng/mL, and
- CD4 count >150 cells/mm<sup>3</sup> for ≥6 months in response to ART

#### Indication for Restarting Secondary Prophylaxis:

- CD4 count <150 cells/mm<sup>3</sup> (**BIII**)

### Other Considerations:

- Itraconazole serum concentrations should be performed in all patients to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions (**AIII**). Random serum concentrations (itraconazole + hydroxyitraconazole) should be >1 µg/mL.
- Itraconazole oral solution is preferred over capsule because of improved absorption, but is less well tolerated. However, this formulation may not be necessary if itraconazole concentration is increased by concomitant use of a CYP3A4 inhibitor such as ritonavir-boosted PIs.
- Acute pulmonary histoplasmosis in HIV-infected patients with CD4 count >300 cells/mm<sup>3</sup> should be managed the same as for non-immunocompromised patients (**AIII**)
- All the triazole antifungals have the potential to interact with certain ARV agents and other anti-infective agents. These interactions are complex and can be bidirectional. [Table 5](#) lists these interactions and recommends dosage adjustments where feasible.

**Key to Acronyms:** ART = antiretroviral therapy; ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte cell; CNS = central nervous system, CSF = cerebrospinal fluid; CYP3A4 = Cytochrome P450 3A4; IV = intravenous; PI = protease inhibitor; PO = orally; TID = three times daily

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