



## **Guidelines for the Prevention and Treatment of Opportunistic Infections Among HIV-Exposed and HIV-Infected Children**

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## Histoplasmosis (Last updated November 6, 2013; last reviewed November 6, 2013)

### Panel's Recommendations

- Routine use of antifungal medications for primary prophylaxis of histoplasmosis in children is not recommended (**BIII**).
- Amphotericin B is preferred for initial treatment of moderately severe to severe infections (**AI\***).
- Itraconazole is the azole preferred for treatment of histoplasmosis (**AIII**).
- In manifestations of histoplasmosis in which antigenuria is demonstrated, antigen levels should be monitored during therapy and for 1 year thereafter to identify relapse (**AIII**).
- For severe or moderately severe acute primary pulmonary histoplasmosis, amphotericin B should be administered for at least 1 to 2 weeks (and clinical improvement) (**AIII**). After treatment with amphotericin, patients with intact immunity should receive itraconazole for at least 12 weeks (**AIII**). Adults with CD4 T lymphocyte (CD4) cell counts  $<150$  cells/mm<sup>3</sup> and HIV-infected children with severe immunosuppression should receive itraconazole consolidation therapy for at least 12 months (**AIII**).
- The preferred treatment for severe or moderately severe progressive disseminated histoplasmosis is initial (induction) therapy with amphotericin B for  $\geq 2$  weeks (and favorable clinical response), followed by consolidation therapy with itraconazole for at least 12 months (**AI\***).
- Itraconazole monotherapy for 12 months is recommended for HIV-infected children with mild to moderate progressive disseminated histoplasmosis (**AII\***).
- Liposomal amphotericin B for 4 to 6 weeks is the preferred initial treatment in the presence of focal brain lesions (**BIII\***). Thereafter, children should receive itraconazole consolidation therapy for at least 12 months and until cerebrospinal fluid abnormalities, including histoplasma antigen, have resolved (**AII\***).
- In the event of immune reconstitution inflammatory syndrome, antiretroviral therapy should be continued along with antifungal therapy (**AIII**).
- Longer-term suppressive therapy (secondary prophylaxis) with itraconazole may be required in HIV-infected children who are severely immunosuppressed (meaning CD4 percentage  $<15\%$  at any age or CD4 count  $<150$  cells/mm<sup>3</sup> in children aged  $\geq 6$  years) and patients who experience relapse despite receipt of appropriate therapy (**AIII**).

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials *in children*<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials *in adults* with clinical outcomes and/or validated laboratory endpoints with accompanying data *in children*<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies *in children*<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies *in adults* with long-term clinical outcomes with accompanying data *in children*<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## Epidemiology

Histoplasmosis is caused by inhalation of microconidia produced by the mycelial form of *Histoplasma capsulatum*, an endemic dimorphic fungus, and cases have been reported from all continents except Antarctica. In the United States, it is most highly endemic in the Ohio and Mississippi river valleys. Infections in regions in which histoplasmosis is not endemic often result from travel to endemic regions within and outside the United States (e.g., Mexico, Central and South America). Risk factors predisposing to infection are exposure to activities that disturb contaminated sites and are accompanied by aerosolization of spores and (in HIV-infected adults) a CD4 T lymphocyte (CD4) cell count  $<150$  cells/mm<sup>3</sup>. Because yeast forms of the fungus may remain viable within granulomas formed after successful treatment or spontaneous resolution of infection, late relapse can occur if cellular immune function wanes, although the magnitude of this risk appears very low.<sup>1</sup> Infection can occur during pregnancy, and transplacental infection has rarely been reported.<sup>2</sup>

During the era before combination antiretroviral therapy (cART), histoplasmosis was reported in 2% to 5% of HIV-infected adults living in regions with endemic disease; rates of 25% have been reported in some cities.<sup>3</sup> In a highly endemic region, histoplasmosis was the AIDS-defining illness in 25% of adults and 8% of children.<sup>4</sup> Progressive disseminated histoplasmosis (PDH) occurred in 5% of HIV-infected children in another highly endemic region (M. Kleiman, unpublished data). The overall incidence of histoplasmosis in children has not been examined systematically but appeared to be low, even during the pre-cART era.<sup>5</sup> An HIV-positive infant with probable congenital histoplasmosis has been reported in a non-endemic area.<sup>6</sup>

Few epidemiologic data have been reported on disseminated histoplasmosis in HIV-infected children and adolescents treated with cART. In several combined Pediatric AIDS Clinical Trial Group cohorts, the incidence rate of all non-*Candida* invasive fungal infection was 0.10 infections per 100 child-years (95% CI 0.05–0.20) during the pre-cART era, and 0.08 infections per 100 child-years (95% CI 0.03–0.17) since the advent of cART.<sup>5,7</sup> These data were contributed from centers that underrepresented the geographic regions of maximal histoplasmosis prevalence, so the statistical power to detect decreases in incidence rates associated with cART may have been limited. However, none of the rates of domestic endemic fungal infections (e.g., histoplasmosis, coccidioidomycosis, and blastomycosis) are likely to exceed these estimates in HIV-infected children and adolescents.

## Clinical Manifestations

In HIV-uninfected children, acute pulmonary manifestations are common; chronic pulmonary infection has not been described. Because of greater airway pliability in children, airway obstruction from mediastinal lymphadenopathy is more common in children.<sup>8</sup> Meningitis often accompanies progressive disseminated infection in infancy; subacute meningitis and parenchymal lesions characteristic of central nervous system (CNS) disease in adults are unusual in children.<sup>9</sup> Isolated pulmonary granulomas resulting from past infections are common incidental findings in chest radiographs of asymptomatic persons who have resided in histoplasmosis-endemic regions.

The most frequent clinical manifestation of histoplasmosis in HIV-infected children with AIDS is PDH, which is fatal if untreated. Prolonged fever and failure to thrive are uniform presenting complaints. Few reports have been published of presenting signs and symptoms in children with PDH complicating AIDS.<sup>4,10-12</sup> However, most are similar to those seen in PDH in otherwise normal infants and in infections in patients with other primary or acquired cellular immunodeficiencies. These include splenomegaly, cough, respiratory distress, hepatomegaly, septic appearance, generalized lymphadenopathy, interstitial pneumonitis, cytopenia(s), coagulopathy, oropharyngeal/gastrointestinal (GI) ulcerations, and erythematous nodular/ulcerative cutaneous lesions.<sup>13-15</sup>

## Diagnosis

Culture and histopathologic, serologic, antigen-detection, and molecular diagnostic techniques have been developed to aid in diagnosing histoplasmosis.<sup>16,17</sup> Understanding their uses and limitations is essential to interpreting results.

Histoplasmin skin tests are no longer available and were not useful in diagnosing disseminated disease.<sup>14,15</sup> Although isolation of the fungus using culture is diagnostic, it often requires invasive procedures, is insensitive, and may take 10 to 30 days for growth to occur. Lysis-centrifugation methodology facilitates growth of *H. capsulatum*, and a DNA probe permits prompt identification of isolates.<sup>18</sup> Histopathologic demonstration of typical yeast forms in tissue specimens, bone marrow, or peripheral blood can be performed rapidly and, when positive, is highly suggestive of active infection. However, results are positive in only 12% to 43% of adults with PDH.<sup>16</sup> Polymerase chain reaction and DNA probes have been developed to detect *H. capsulatum* DNA in tissues<sup>19</sup> and body fluids<sup>20</sup> but neither is sufficiently sensitive and DNA probes may lack adequate specificity.<sup>16,17</sup>

Interpretation of serologic testing using complement fixation (CF) and immunodiffusion methods is problematic in immunocompromised hosts with PDH. CF titers of  $\geq 1:32$  to the yeast and/or mycelial antigens or detection of H and/or M bands with the immunodiffusion test are considered strongly suggestive of active or recent infection. However, only 41% to 69% of HIV-infected adults are seropositive, compared with 82% of adults with PDH and no underlying immunodeficiency.<sup>21,22</sup> Thus, seronegativity cannot be used to exclude active infection, especially PDH. Although a fourfold increase in CF antibody is diagnostic of active infection, 2 to 4 weeks is needed to determine this. CF antibody titers of cerebrospinal fluid (CSF) may be useful for diagnosing meningitis. In these instances, the assay should begin with undiluted specimens. Concurrent serum titers should be evaluated to exclude false positivity caused by blood contamination of the CSF.<sup>9</sup>

An enzyme-linked immunoassay (EIA) that rapidly identifies and quantifies histoplasma antigen in body fluids fills most of the gaps left by other diagnostic methods.<sup>22</sup> EIA is especially suited for evaluating patients with large fungal burdens, a feature of infection in immunocompromised hosts. EIA can detect antigen in serum, bronchoalveolar lavage, and CSF specimens. The reported sensitivity of antigen detection is 91% to 92% in adults with PDH, and 95% in adults with AIDS;<sup>16,17</sup> sensitivity in children with underlying cellular immunodeficiency, including those who are HIV-infected, and in otherwise normal infants approaches 100%.<sup>14,23</sup>

The third-generation EIA is standardized by extrapolating antigen concentrations from a calibration curve that is linear to a value of 39 ng/mL. However, urine antigen concentrations in serious infections frequently exceed this value. In these instances, serum specimens should be followed because maximum serum concentrations are lower than those in urine and thus more likely to be in a range in which differences can be accurately measured. After resolution of the antigenemia, urine concentrations can be followed to monitor the effectiveness of treatment and, thereafter, to identify relapse. Antigenuria is identified in 90% of patients whose histoplasmosis relapses.<sup>8</sup> Interpretation is complicated by cross-reactions with blastomycosis, paracoccidioidomycosis, and *Penicillium marneffei* infections.<sup>16,17</sup> Distinctive clinical and geographic features of these endemic fungal infections permit accurate differentiation. Urine antigen is detectable in 75% to 81% of immunocompetent hosts with acute, primary pulmonary infection. This occurs early in infection, reflecting the primary fungemia that is aborted by an effective cellular immune response. Thus, antigenuria in a patient with HIV who retains normal cellular immunity may not necessarily presage development of disseminated infection. Based on adult data, testing both serum and urine following high inoculum exposure may improve sensitivity of detecting antigen in acute primary pulmonary infection, especially in patients with less severe CD4 depletion and milder illness, in whom sensitivity in urine may be lower.<sup>24</sup>

Diagnosis of CNS infection is difficult, particularly in patients who have isolated meningitis without disseminated disease.<sup>9</sup> Highest sensitivity is achieved by testing CSF for histoplasma antigen, antibody, and large-volume culture. In adults, CSF culture is positive in 20% to 60% of patients, CSF antigen is positive in 40% to 70%, and CSF antibody is positive in 70% to 90%.<sup>16,17</sup> Meningitis frequently accompanies PDH of infancy,<sup>13</sup> an entity that has not been associated with a recognized immunodeficiency disorder.

## Prevention Recommendations

### *Preventing Exposure*

Most infections occur without a recognized history of exposure to a high-risk site or activity. Therefore, complete avoidance of exposure in histoplasmosis-endemic regions is not possible. Sites and conditions sometimes implicated in high-risk exposure and point-source outbreaks include disturbances of contaminated areas resulting in aerosolization of spores. These include soil contaminated with bird or bat droppings, older urban and rural structures, decaying vegetation or trees, and caves. Dry and windy conditions, excavation, demolition, renovation, gardening, and agricultural activities often predispose to aerosolization of spores. Education should be directed toward avoidance of these activities. If not feasible, reducing the release of spores by wetting soil, renovation sites, and other potentially contaminated areas, and use of protective respiratory devices,<sup>25</sup> should be recommended.

## ***Preventing First Episode of Disease***

Prophylaxis with itraconazole is recommended for HIV-infected adults with CD4 counts <150 cells/mm<sup>3</sup> and who reside in areas where histoplasmosis is highly endemic (that is, incidence >10 cases per 100 patient-years) and in instances in which risk of occupational exposure is high. Prophylaxis has no effect on survival.<sup>8</sup> Given the low incidence of histoplasmosis in HIV-infected children, possibility for drug interaction, development of antifungal drug resistance, and cost, routine use of antifungal medications for primary prophylaxis of histoplasma infections in children is not recommended (**BIII**).

## ***Discontinuing Primary Prophylaxis***

Not applicable.

## **Treatment Recommendations**

### ***Treating Disease***

PDH is fatal without treatment. The clinical response to amphotericin B is faster than that of itraconazole and it is preferred for initial treatment of severe infections (**AI\***). Following amphotericin B induction, itraconazole, the azole preferred for treatment of histoplasmosis (**AI\***),<sup>8</sup> is used to complete the course of therapy. A trial in adults<sup>26</sup> demonstrated that induction with liposomal amphotericin B was associated with less toxicity and improved survival, compared with induction using amphotericin B deoxycholate. Recommendations for HIV-infected children are derived from trials in adults and from anecdotal experience in children.<sup>8</sup> Because of important differences in managing PDH in children, consultation with experts should be considered.

Itraconazole is usually well tolerated in children. Itraconazole has a long half-life and reaches steady-state levels at 2 weeks. The interval needed to achieve desired serum concentrations can be shortened if the recommended dose is administered 3 times daily for the first 3 days of therapy (i.e., loading dose); the recommended dose, administered twice daily, should be started thereafter. **Itraconazole solution is preferred to the capsule formulation because it is better absorbed and serum concentrations are 30% higher than those achieved with the capsules.** The solution should be taken on an empty stomach or with a carbonated beverage. If capsules are used, they should be taken with meals. Because absorption of itraconazole varies considerably from patient to patient, serum concentrations should be measured to ensure effective levels of drug, monitor changes in dosage, and assess compliance (**BIII**). The minimal inhibitory concentration of *H. capsulatum* is 0.01 µg/mL, and although minimally effective serum concentrations have not been determined, a serum concentration of 1.0 µg/mL is recommended; dosage should be reduced if concentrations exceed 10 µg/mL.<sup>8</sup>

Fluconazole is an alternative for patients with mild histoplasmosis and who are intolerant of itraconazole or in whom desired serum levels of itraconazole cannot be attained. Fluconazole is less effective than itraconazole and has been associated with development of drug resistance.<sup>27</sup>

### **Acute Primary Pulmonary Histoplasmosis**

Patients with acute primary pulmonary histoplasmosis can present with a wide spectrum of symptoms, ranging from dyspnea with high fever to only mild respiratory symptoms, and variable fever. Chest radiographs may show mediastinal adenopathy with or without focal pulmonary infiltrate and/or a diffuse miliary-like pattern in high-inoculum exposure; radiographic findings may mimic those of tuberculosis. For severe or moderately severe symptoms, liposomal amphotericin B should be administered for 1 to 2 weeks (**AI\***).<sup>8</sup> After clinical improvement, adults with CD4 counts >300 cells/mm<sup>3</sup> and, by extrapolation, HIV-infected children with CD4 percentage >20% or, if ≥ 6 years, CD4 count >300 cells/mm<sup>3</sup>, should receive itraconazole, beginning with a loading dose (see above) for the first 3 days, followed by the recommended doses administered twice daily for at least 12 weeks (**AIII**). All other HIV-infected children should receive itraconazole for 12 months (**AIII**). Urine antigen usually is elevated in these situations and should be monitored to gauge clinical response and, after treatment, identify relapse (**AIII**).

HIV-infected children, particularly those with CD4 percentage >20% (or, if  $\geq 6$  years, CD4 counts >300 cells/mm<sup>3</sup>) compatible with functional cellular immunity, occasionally present with fever, mild primary pulmonary infection, and histoplasma antigenuria. Although an effective cellular immune response may limit such illnesses, it may be prudent to treat with itraconazole for 12 weeks and monitor histoplasma urine antigen concentrations to ensure that concentrations decrease (**BIII**).

### **Moderately Severe to Severe PDH**

Data derived from experience in HIV-infected adults suggest that HIV-infected children with moderately severe to severe disseminated histoplasmosis should be treated with an IV amphotericin B formulation for  $\geq 2$  weeks (and until they clinically improve), followed by itraconazole for 12 months (**AI\***). HIV-infected adults with moderately severe to severe PDH have a higher response rate to treatment with liposomal amphotericin B than with the deoxycholate formulation (88% vs. 64%) and a lower death rate (2% vs. 13%); therefore liposomal preparations are preferred in adults and, by extrapolation, in children (**AI\***).<sup>8</sup> A loading dose (see above) of itraconazole should be used for the initial 3 days. If itraconazole is not well tolerated, a 4- to 6-week course of amphotericin B can be used (**AIII**). Progressive decline in histoplasma urine and serum antigen levels is expected with effective treatment, and monitoring levels for lack of such decline can detect relapse.

Although therapeutic trials of amphotericin B deoxycholate used to treat PDH in HIV-infected children have not been performed, this formulation is effective for treating severe PDH in infants,<sup>13,28</sup> including those with CNS infection,<sup>13</sup> and in children with other primary or acquired immunodeficiency states. Amphotericin B deoxycholate is better tolerated by children than by adults, and it is less costly than other formulations. It can be used if cost or availability of lipid formulations precludes their use (**AIII**).

### **Mild to Moderate PDH**

In 80% to 100% of patients without signs of CNS infection, mild to moderate PDH responds favorably to itraconazole monotherapy for 12 months (**AII\***).<sup>8,29</sup> This regimen also is recommended for HIV-infected children with mild to moderate PDH (**AII\***). A loading dose of itraconazole (see above) should be administered at the onset of treatment and serum concentrations monitored. Urine antigen concentrations should also be monitored.

### **CNS Infection**

CNS infection that accompanies PDH is expected to respond to the regimen recommended for moderately severe to severe PDH. Isolated CNS infection is unusual in children. In adults, frequent failure and relapse are common, and aggressive therapy is recommended. Penetration into the CSF is poor with all amphotericin B formulations. Liposomal amphotericin B is preferred for CNS disease in children and adults because it achieves higher concentrations in the brain (**AII\***); the deoxycholate formulation is an alternative. Another lipid formulation can be used at the same dosage if cost is a concern or in patients who cannot tolerate liposomal amphotericin B (**AIII**). Amphotericin should be administered for 4 to 6 weeks. Thereafter, a child should receive a loading dose of itraconazole and continuation of itraconazole for 12 months and until CSF abnormalities, including histoplasma antigen, have resolved (**AII\***).

Itraconazole levels should be followed and the dose adjusted to ensure optimal serum concentrations (**AIII**).

### **Asymptomatic Histoplasma Granuloma**

In asymptomatic HIV-infected children who have intact cellular immunity (meaning CD4 >15% for all ages and CD4 cell count >150 cells/mm<sup>3</sup> for ages  $\geq 6$  years) and have resided in an area with endemic histoplasmosis, the presence of a typical granuloma in a chest radiograph should prompt evaluation of histoplasma urine antigen and both CF and immunodiffusion antibody. If any of these tests are positive, treatment with itraconazole for 12 weeks is prudent (**BIII**). If these tests are negative, therapy need not be used, and close clinical follow-up is recommended. In either instance, histoplasma urine antigen testing should be considered if unexplained fever, weight loss, or other systemic symptoms occur.

## ***Monitoring and Adverse Events (Including IRIS)***

In manifestations of histoplasmosis in which antigenuria is demonstrated, antigen levels should be monitored during therapy and for a year thereafter to identify relapse (AIII).<sup>8</sup> After a recommended course of therapy and in the absence of symptoms, low-level, stable antigenuria may not constitute a basis for prolonging the recommended course of therapy. Serum levels of itraconazole should be monitored in patients receiving treatment (AIII).

Adverse effects of amphotericin B are primarily nephrotoxicity; permanent nephrotoxicity is related to cumulative dose. Infusion-related fevers, chills, nausea, and vomiting can occur, especially early in treatment, although they are less frequent in children than in adults. Renal dysfunction and electrolyte imbalances are the primary toxicities; these parameters should be monitored during therapy.

Itraconazole, like other azoles, has relatively low rates of toxicity. GI upset is seen occasionally and its principal toxicity is hepatic. Because the azole drugs inhibit CYP450-dependent hepatic enzymes, drug interactions—particularly with antiretroviral drugs—should be carefully evaluated before initiation of therapy.

Immune reconstitution inflammatory syndrome (IRIS) caused by an inflammatory response to histoplasmosis unmasked by cART-induced improvement in cellular immunity is unusual, and symptoms are often mild.<sup>30</sup> In the event of IRIS, cART should be continued along with antifungal therapy (AIII). IRIS related to histoplasmosis has not been reported in children.

## ***Managing Treatment Failure***

Both voriconazole and posaconazole have been used successfully in a small number of refractory cases in adults.<sup>8</sup> Because little experience has been reported using the newer azoles and data are limited on use of these agents in children, expert consultation is recommended for cases refractory to first-line agents.

## ***Preventing Recurrence***

Following initial amphotericin B treatment (induction) and subsequent oral itraconazole consolidation therapy for at least 1 year, longer-term suppressive therapy with itraconazole may be required in HIV-infected children who remain immunosuppressed (i.e., CD4 percentage <15% at any age or <150 cells/mm<sup>3</sup> in children aged ≥6 years) and in those who experience relapse despite receipt of appropriate therapy (AII\*).<sup>8,31</sup> Fluconazole is less effective than itraconazole (CII\*), and experience with voriconazole is limited in children. Adherence to both antifungal treatment and cART should be monitored carefully, as non-adherence can increase the risk of relapse.

## ***Discontinuing Secondary Prophylaxis***

Discontinuation of secondary prophylaxis (suppressive therapy) has not been examined in children. Based on data from a clinical trial, adults with immune restoration on cART can discontinue itraconazole if itraconazole has been received for ≥1 year, blood cultures are negative, histoplasma serum antigen is <2 ng/mL, CD4 counts are >150 cells/mm<sup>3</sup>, and there is good adherence to cART.<sup>31</sup> Extrapolating these recommendations to HIV-infected children on cART with immune restoration (meaning CD4 percentage ≥15% at any age; CD4 count >150 cells/mm<sup>3</sup> in children aged ≥6 years) seems reasonable (CIII). Secondary prophylaxis should resume if these parameters are not met. Chronic suppressive therapy is recommended for relapse that occurs despite appropriate treatment (BIII).

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## Dosing Recommendations for Preventing and Treating Histoplasmosis (page 1 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
<b>Primary Prophylaxis</b>	N/A	N/A	<p>Primary Prophylaxis indicated for selected HIV-infected adults but not children.</p> <p><u>Criteria for Discontinuing Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> <li>• N/A</li> </ul> <p><u>Criteria for Restarting Primary Prophylaxis:</u></p> <ul style="list-style-type: none"> <li>• N/A</li> </ul>
<b>Secondary Prophylaxis (Suppressive Therapy)</b>	Itraconazole oral solution 5–10 mg/kg body weight (maximum 200 mg) per dose by mouth daily	Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily	<p><u>Secondary Prophylaxis Indicated:</u></p> <ul style="list-style-type: none"> <li>• Documented histoplasmosis in a patient with impaired immune function</li> </ul> <p><u>Criteria For Discontinuing Secondary Prophylaxis</u></p> <p><i>If All of the Following Criteria Are Fulfilled:</i></p> <ul style="list-style-type: none"> <li>• CD4 percentage &gt;15% at any age; or CD4 cell count &gt;150 cells/mm<sup>3</sup> aged ≥6 years.</li> <li>• Received ≥1 year itraconazole maintenance therapy</li> <li>• Established (e.g., ≥6 months) adherence to effective cART</li> <li>• Negative <i>Histoplasma</i> blood cultures</li> <li>• Serum Histoplasma antigen &lt;2 ng/mL</li> </ul> <p>Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules.</p>
<b>Treatment</b>	<p><u>Acute Primary Pulmonary Histoplasmosis:</u></p> <ul style="list-style-type: none"> <li>• Itraconazole oral solution loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth twice daily for 12 months. Duration of 12 weeks is sufficient for HIV-infected children, with functional cellular immunity (CD4 percentage &gt;20% or if aged ≥6, CD4 cell count &gt;300 cells/mm<sup>3</sup>), provided monitoring confirms clinical improvement and decreased urine antigen concentrations.</li> </ul> <p><u>Mild Disseminated Disease:</u></p> <ul style="list-style-type: none"> <li>• Itraconazole oral solution loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for</li> </ul>	<p><u>Acute Primary Pulmonary Histoplasmosis:</u></p> <ul style="list-style-type: none"> <li>• Fluconazole 3–6 mg/kg body weight (maximum 200 mg) by mouth once daily</li> </ul> <p><u>Mild Disseminated Disease:</u></p> <ul style="list-style-type: none"> <li>• Fluconazole 5–6 mg/kg body weight IV or by mouth (maximum 300</li> </ul>	<p>Use same initial itraconazole dosing for capsules as for solution. Itraconazole solution is preferred to the capsule formulation because it is better absorbed; solution can achieve serum concentrations 30% higher than those achieved with the capsules.</p> <p>Urine antigen concentration should be assessed at diagnosis. If &gt;39 ng/mL, serum concentrations should be followed. When serum levels become undetectable, urine concentrations should be monitored monthly during treatment and followed thereafter to identify relapse.</p> <p>Serum concentrations of itraconazole should be monitored and achieve a level of 1 µg/mL at steady-state. Levels</p>

## Dosing Recommendations for Preventing and Treating Histoplasmosis (page 2 of 2)

Indication	First Choice	Alternative	Comments/Special Issues
<b>Treatment, continued</b>	<p>first 3 days of therapy, followed by 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth twice daily for 12 months</p> <p><u>Moderately Severe to Severe Disseminated Disease</u></p> <p><i>Acute Therapy (Minimum 2-Week Induction, Longer if Clinical Improvement is Delayed, Followed by Consolidation Therapy):</i></p> <ul style="list-style-type: none"> <li>• Liposomal amphotericin B 3–5 mg/kg body weight, IV once daily (preferred)</li> <li>• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative)</li> </ul> <p><i>Consolidation Therapy (Followed by Chronic Suppressive Therapy):</i></p> <ul style="list-style-type: none"> <li>• Itraconazole oral solution initial loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth given twice daily for 12 months</li> </ul> <p><u>Central Nervous System Infection</u></p> <p><i>Acute Therapy (4–6 Weeks, Followed by Consolidation Therapy):</i></p> <ul style="list-style-type: none"> <li>• Liposomal amphotericin B, 5 mg/kg body weight IV once daily <b>(All)</b></li> </ul> <p><i>Consolidation Therapy (Followed by Chronic Suppressive Therapy):</i></p> <ul style="list-style-type: none"> <li>• Itraconazole oral solution initial loading dose of 2–5 mg/kg body weight (maximum 200 mg) per dose by mouth 3 times daily for first 3 days of therapy, followed by 2–5 mg/kg body weight (max 200 mg) per dose by mouth given twice daily for ≥12 months and until histoplasma antigen is no longer detected in cerebrospinal fluid</li> </ul>	<p>mg) per dose, twice daily (maximum 600 mg/day) for 12 months</p> <p><u>Moderately Severe to Severe Disseminated Disease:</u></p> <ul style="list-style-type: none"> <li>• If itraconazole not tolerated, amphotericin alone for 4–6 weeks can be used with monitoring that confirms decline in histoplasma urine and serum antigen levels.</li> <li>• Liposomal amphotericin B 3–5 mg/kg body weight IV once daily (preferred) for 4–6 weeks</li> <li>• Amphotericin B deoxycholate 0.7–1 mg/kg body weight IV once daily (alternative) for 4–6 weeks</li> </ul>	<p>exceeding 10 µg/mL should be followed by dose reduction.</p> <p>High relapse rate with CNS infection occurs in adults and longer therapy may be required; treatment in children is anecdotal and expert consultation should be considered.</p> <p>Chronic suppressive therapy (secondary prophylaxis) with itraconazole is recommended in adults and children following initial therapy.</p> <p>Amphotericin B deoxycholate is better tolerated in children than in adults. Liposomal amphotericin B is preferred for treatment of parenchymal cerebral lesions.</p>

**Key to Acronyms:** cART = combination antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system; IV = intravenous