Histoplasmosis

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Epidemiology

Histoplasmosis is a fungal infection caused by the dimorphic fungus *Histoplasma capsulatum (H. capsulatum)*. The fungal infection is endemic to the central and south-central United States, where it is especially common in the Ohio and Mississippi River valleys. Microfoci of infection exist elsewhere in the eastern United States. Histoplasmosis is also found in Latin America and the Caribbean, Asia, and Africa. In some Latin American countries, histoplasmosis is one of the most common opportunistic infections in people with HIV, even during the era of highly active antiretroviral therapy (ART).[1-3] A CD4 T lymphocyte (CD4) cell count <150 cells/mm^3 is associated with an increased risk of symptomatic illness in people with HIV.[4,5] The risk for and incidence of symptomatic disease is generally higher at lower CD4 counts in people with HIV, but disease can present with counts as high as 350 cells/mm^3.

Histoplasmosis is acquired by the inhalation of microconidia that form in the mycelial phase of the fungus in the environment. Asymptomatic dissemination of infection beyond the lungs is common, and cellular immunity is critical in controlling infection. Diminished cellular immunity can lead to a reactivation of a quiescent focal infection acquired years earlier; this is the presumed mechanism for disease occurrence in nonendemic areas.

Clinical Manifestations

There is a spectrum of disease from asymptomatic and self-limited pulmonary disease to disseminated disease in those with low CD4 counts (≤200 cells/mm^3). In people with advanced HIV, common clinical manifestations of progressive disseminated histoplasmosis include fever, fatigue, weight loss, and hepatosplenomegaly. Cough and dyspnea occur in approximately 50% of patients.[4,6] Gastrointestinal (GI) disease usually manifests as fever, nausea and vomiting, diarrhea, abdominal pain, and weight loss.[7] In a case series of people with HIV in Panama, diarrhea with or without fever was seen in 50% of the patients with histoplasmosis,[8] and in another series from French Guiana, GI symptoms occurred in 70% of patients with histoplasmosis.[3] Central nervous system (CNS) and cutaneous manifestations occur in no more than 20% of patients. People with CNS histoplasmosis typically experience fever and headache; if brain involvement is present, they may also experience seizures, focal neurological deficits, septic meningitis, or changes in mental status.[4] Approximately 10% of patients with low CD4 counts experience septic shock, multiorgan failure, and/or pericardial effusion and pericarditis requiring rapid therapy.[4] In such cases, blood cultures and *Histoplasma* antigen tests of serum and urine are helpful diagnostically.[4,9] In patients with CD4 counts >200 cells/mm^3, histoplasmosis is often limited to the respiratory tract, and they may present with cough, pleuritic chest pain, and/or fever.[9]

Diagnosis

The detection of *Histoplasma* antigen in blood or urine (the detection method preferred by the World Health Organization) is a sensitive method for the rapid diagnosis of disseminated histoplasmosis in people with HIV.[10] This test should be obtained for any person with HIV and low CD4 counts who

has the above-mentioned symptoms and who lives, or has previously lived, in an area in which *H. capsulatum* is commonly found.

In a study using a certain quantitative enzyme immunoassay (EIA), *Histoplasma* antigen was detected in 100% of urine samples and 92% of serum samples from people with AIDS and disseminated histoplasmosis.[11] Another EIA employs a monoclonal antibody to detect *Histoplasma* galactomannan and has been reported to have a sensitivity of 91% and a specificity of 91%.[12] A lateral flow assay for the detection of *Histoplasma* antigen in urine was reported to have a sensitivity of 96% and specificity of 96%.[13] Antigen detection in bronchoalveolar lavage fluid may also be a useful method for the diagnosis of pulmonary histoplasmosis.[14]

In people with severe disseminated histoplasmosis, peripheral blood smears might occasionally show the organisms engulfed by white blood cells if observed with careful attention. Histopathological examination of biopsy material from involved tissues often demonstrates small yeast cells 2 to 4 μm in diameter, which are characteristic of histoplasmosis.

In >85% of people with HIV and disseminated histoplasmosis, *H. capsulatum* can be cultured from blood (using the lysis-centrifugation technique), bone marrow, respiratory secretions, or samples from other involved sites; however, the organism requires several weeks to grow before final results can be interpreted.[15] Serologic tests for antibodies are less useful than antigen assays for people with HIV and disseminated histoplasmosis but may be helpful for those with pulmonary disease and reasonably intact immune responses.[15,16]

The diagnosis of *Histoplasma* meningitis is often difficult. The usual cerebrospinal fluid (CSF) findings are lymphocytic pleocytosis, elevated protein, and low glucose. Fungal stains are usually negative, and CSF cultures are positive in a minority of cases.[17] In a review of CNS histoplasmosis that included people with HIV, cultures were positive in 38% of study participants.[18] *Histoplasma* antigen can be detected in CSF in a far greater number of cases, and antibodies against *H. capsulatum* are seen in at least one-half of cases.[18] A positive antigen or antibody test result from CSF is diagnostic for histoplasmosis. In cases in which none of these specific tests are positive, a presumptive diagnosis of *Histoplasma* meningitis is appropriate if the patient has disseminated histoplasmosis and findings of CNS infection not attributable to another cause.

Preventing Exposure

People with HIV who live in or visit areas in which histoplasmosis is endemic cannot completely avoid exposure to *H. capsulatum*, but those with CD4 counts <200 cells/mm^3 should be counseled to minimize exposure to activities associated with an increased risk for histoplasmosis **(BIII).** These activities include creating dust when working with surface soil; cleaning chicken coops; disturbing areas contaminated with bird or bat droppings; cleaning, remodeling, or demolishing buildings; and exploring caves.[19]

Preventing Disease

Preventing the First Episode of *Histoplasma capsulatum* Infection (Primary Prophylaxis)
Indications for Initiating Primary Prophylaxis (BI)
• People with CD4 count <150 cells/mm^3 and who are at high risk because of occupational histoplasmosis exposure *or* who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 person-years)
Preferred Therapy
• Itraconazole 200 mg PO once daily (BI)
Criteria for Discontinuing Primary Prophylaxis (BIII)
• Stable ART, *and*
• CD4 count ≥150 cells/mm^3 for 6 months, *and*
• Undetectable HIV-1 viral load
Indication for Restarting Primary Prophylaxis
• CD4 count <150 cells/mm^3 (BIII)

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; PO = orally

Data from a prospective, randomized, controlled trial indicate that itraconazole can reduce the incidence of histoplasmosis, although not mortality, in people who have advanced HIV (CD4 counts <150 cells/mm^3) and live in areas where histoplasmosis is highly endemic.[20] Based on these data, the Panel on Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV (the Panel) continues to recommend itraconazole at a dose of 200 mg daily as primary prophylaxis **(BI)** to people with CD4 counts <150 cells/mm^3 who are at high risk because of occupational histoplasmosis exposure or who live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 person-years) **(BI).** However, as with other opportunistic infections in the current era of more effective ART, it may be reasonable to consider withholding primary prophylaxis if ART can be immediately initiated and there is an accompanying rise in CD4 cell count above the threshold of risk **(CIII).** Fluconazole has yet to show activity in a prophylaxis setting for histoplasmosis. The role of screening for *Histoplasma* antigen to define people at risk for developing infection has not been studied.

If used, primary prophylaxis should be discontinued in people on ART once CD4 counts are ≥150 cells/mm^3 for 6 months and HIV-1 viral loads are undetectable **(BIII).** Prophylaxis should be restarted if the CD4 count falls to <150 cells/mm^3 **(BIII).**

Treating Disease

Treating *Histoplasma capsulatum* Infections
Treating Severe Disseminated Disease
Induction Therapy (≥2 Weeks or Until Clinically Improved)
Preferred Therapy
• Liposomal amphotericin B 3 mg/kg IV daily (AI)

Alternative Therapy

- Amphotericin B lipid complex 5 mg/kg IV daily (AIII)

Maintenance Therapy (**≥12** Months)

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day (AII)

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole and only moderately ill.

- Posaconazole 300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily (BIII), *or*
- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII), *or*
- Fluconazole 800 mg PO once daily (CII)

Treating Mild-to-Moderate Disseminated Disease or Acute Pulmonary Histoplasmosis in People With CD4 <300 cells/mm^3

Induction and Maintenance Therapy (≥12 Months)

Preferred Therapy

- Itraconazole 200 mg PO three times a day for 3 days, then 200 mg PO two times a day (AII)

Alternative Therapy

- Posaconazole 300 mg extended-release tablet PO twice daily for 1 day, then 300 mg PO once daily (BIII), *or*
- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII), *or*
- Fluconazole 800 mg PO once daily (CII)

Treating Histoplasma Meningitis

Induction Therapy (4–6 Weeks Depending on Symptom Resolution and Improvement of CSF Findings)

Preferred Therapy

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

Alternative Therapy

- Amphotericin B deoxycholate 0.7–1.0 mg/kg IV daily (BIII)

Maintenance Therapy **(≥12** Months and Until Resolution of Abnormal CSF Findings)

Preferred Therapy

- Itraconazole 200 mg PO two or three times a day (AIII)

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole and only moderately ill.

- Voriconazole 400 mg PO twice daily for 1 day, then 200 mg PO twice daily (BIII), *or*
- Fluconazole 800 mg PO once daily (CII)—for people who cannot tolerate both itraconazole and voriconazole

Long-Term Suppressive Therapy

Indications

- Severe disseminated or CNS infection after completing maintenance therapy for ≥12 months of treatment (AIII), *or*
- Relapse despite appropriate initial therapy (after reinduction therapy) (BIII)

Preferred Therapy

- Itraconazole 200 mg PO once daily (AIII)

Alternative Therapy

Note: These recommendations are based on limited clinical data for people who are intolerant to itraconazole.

- Fluconazole 400 mg PO once daily (CII), *or*
- Voriconazole 200 mg PO twice daily (BIII), *or*
- Posaconazole 300 mg PO daily (BIII)

Criteria for Discontinuing Long-Term Suppressive Therapy (AII)

- Receipt of azole treatment for >1 year, *and*
- Negative fungal blood cultures, *and*
- Serum or urine *Histoplasma* antigen below the level of quantification, *and*
- Undetectable HIV viral load on stable ART, *and*
- CD4 count ≥150 cells/mm^3 and on ART for ≥6 months

Indication for Restarting Long-Term Suppressive Therapy

- CD4 count <150 cells/mm^3 (BIII)

Other Considerations

- Random itraconazole serum concentrations should be measured in all patients after 2 weeks of therapy (the time it usually takes to reach a steady state) to ensure adequate absorption and to assess changes in hepatic metabolism due to drug interactions (AIII).
- Random serum concentrations (itraconazole plus hydroxyitraconazole) should be between 1 and 2 μg/mL. Concentrations ≥5 μg/mL are associated with an increased frequency and severity of adverse effects.
- Oral itraconazole liquid solution is preferred over the capsule formulation because of improved absorption but is less well tolerated. However, it is not necessary to use the liquid solution if random serum itraconazole concentration is ≥1.0 μg/mL with the capsule formulation (AIII).
- Trough voriconazole serum concentrations should be measured after 5 days of therapy (the time it usually takes to reach a steady state) with the goal of achieving a concentration of 1 to 5 μg/mL. Concentrations are highly variable among patients, and for individual patients, concentrations can vary because of drug–drug interactions. Neurotoxicity and hepatotoxicity are associated with serum concentrations >5 μg/mL, but some patients can experience adverse effects with lower serum concentrations (AIII).
- Trough posaconazole serum concentrations should be measured after 5 days of therapy (the time it usually takes to reach a steady state) to ensure adequate absorption, with a goal of achieving a concentration >1 μg/mL (AIII).
- Acute pulmonary histoplasmosis in patients with HIV and CD4 count ≥300 cells/mm^3 should be managed the same as in immunocompetent patients (AIII).

• All triazole antifungals have the potential to interact with certain ART agents and other anti-infective agents. These interactions are complex and can be bidirectional. The Drug–Drug Interactions section in the Adult and Adolescent Antiretroviral Guidelines lists these interactions and recommends dose adjustments where feasible. The University of Liverpool HIV Drug Interactions Database provides more detailed information on interactions.
Pregnancy Considerations
• Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis during pregnancy, especially during the first trimester (AIII). • In the second and third trimester of pregnancy, itraconazole can be considered if the benefit outweighs the potential risk (CIII). • Azole antifungals **should be avoided** during the first trimester of pregnancy (BIII). • Use of fluconazole, voriconazole, and posaconazole **should be avoided** in pregnancy, especially in the first trimester (AIII).

Key: ART = antiretroviral therapy; CD4 = CD4 T lymphocyte; CNS = central nervous system, CSF = cerebrospinal fluid; IV = intravenous; PO = orally

In a randomized clinical trial, intravenous (IV) liposomal amphotericin B (3 mg/kg daily) induced a more rapid and complete response, lowered mortality rates, and reduced toxicity more efficaciously than standard IV amphotericin B deoxycholate (0.7 mg/kg daily) for the treatment of histoplasmosis associated with AIDS.[21] Based on these findings, patients with symptomatic severe disseminated histoplasmosis should be treated with IV liposomal amphotericin B (3 mg/kg daily) for ≥2 weeks or until they clinically improve **(AI).** IV amphotericin B lipid complex (5 mg/kg daily) can be used if cost is a concern, or if the patient cannot tolerate liposomal amphotericin B **(AIII).**

Step-down therapy to oral itraconazole, 200 mg three times a day for 3 days followed by 200 mg two times a day, should be given for ≥12 months **(AII).**[22] Because absorption of itraconazole can be erratic and because of potential drug interactions between itraconazole and protease inhibitors, efavirenz, rilpivirine, etravirine, and many other drugs that are cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, random serum concentration of itraconazole should be measured 2 weeks after the start of therapy (see The University of Liverpool HIV Drug Interactions Database) **(AIII).** Combined serum itraconazole and hydroxyitraconazole concentrations should be 1 to 2 μg/mL. Adverse events become more frequent and severe as concentrations increase, with a 26% increase observed when concentrations exceed 5 μg/mL.[23] Itraconazole is a moderately strong CPY3A4 inhibitor, so ART effectiveness also must be considered.

In patients with mild-to-moderate disseminated histoplasmosis, oral itraconazole, 200 mg three times daily for 3 days followed by 200 mg twice daily for ≥12 months, is an appropriate initial therapy **(AII).**[22,24] 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 **(AIII).** However, the capsule formulation of itraconazole is better tolerated than the liquid formulation. If a serum random itraconazole concentration of 1.0 to 2.0 μg/mL has been achieved with the capsule formulation, it is not necessary to use the liquid solution. The capsule formulation should be given with food and cannot be used when the patient requires gastric acid–inhibiting drugs. A formulation of itraconazole, SUBA-itraconazole, has improved absorption and is most likely of all formulations to achieve random itraconazole level (≥1.0 μg/mL).[25] Although this agent likely will prove useful in treating histoplasmosis, SUBA-itraconazole cannot be routinely recommended due to cost and the need for further clinical data on its use for this purpose .

Acute pulmonary histoplasmosis in a person with HIV who has a CD4 count ≥300 cells/mm^3 should be managed the same way as acute pulmonary histoplasmosis in an immunocompetent person **(AIII).**[22] For acute pulmonary histoplasmosis in a person with HIV who has a CD4 count <300 cells/mm^3, the patient should receive therapy similar to that of mild-to-moderate disseminated disease **(AIII).**

In patients with confirmed meningitis, liposomal amphotericin B should be administered as initial therapy at a dose of 5 mg/kg IV daily for 4 to 6 weeks depending on the resolution of symptoms and improvement of abnormal CSF findings **(AIII).** Amphotericin B deoxycholate 0.7 to 1.0 mg/kg IV daily can be used as an alternative if liposomal amphotericin B is not available **(BIII).** A reduction in *Histoplasma* antigen is encouraging. This initial IV therapy with amphotericin B should be followed by maintenance therapy with oral itraconazole at a dose of 200 mg two or three times daily for ≥12 months with dose adjustment based on interactions with ART and itraconazole serum concentration until abnormal CSF findings are resolved **(AIII).**[22] Voriconazole is an alternative to itraconazole for *Histoplasma* meningitis **(BIII).** The Panel recommends fluconazole 800 mg daily as an alternative maintenance therapy for those who are intolerant of itraconazole and voriconazole **(CII).**[26]

Oral posaconazole and voriconazole have been reported to be effective in treating histoplasmosis in a small number of people with HIV or other immunosuppressive conditions[27-30] and are therefore recommended as alternatives for those who are only moderately ill and intolerant of itraconazole **(BIII).** Oral voriconazole should be administered at a dose of 400 mg two times a day for 1 day, then 200 mg two times a day **(BIII).** If voriconazole is used, trough serum concentrations should be measured after 5 days of therapy, with a goal of achieving a serum concentration of l to 5 μg/mL **(AIII).** Concentrations are highly variable among different people and over time within a given person and may vary because of absorption issues and drug–drug interactions (see The University of Liverpool HIV Drug Interactions Database). Neurotoxicity and hepatotoxicity are associated with serum concentrations >5 μg/mL, but individual patients can experience adverse effects, such as hepatitis and neurotoxicity, even with lower serum concentrations. Oral posaconazole should be administered at a dose of 300 mg of extended-release tablets twice daily for 1 day, then 300 mg once daily **(BIII).** Posaconazole serum concentrations should be measured after 5 days of therapy to ensure adequate absorption, with a goal of achieving a concentration of >1 μg/mL **(AIII).**

Fluconazole is less effective than itraconazole for the treatment of histoplasmosis but has been shown to be moderately effective at a dose of 800 mg daily **(CII).**[26] Isavuconazole has been used in too few patients with histoplasmosis to be routinely recommended at this time but might be considered when other triazoles such as itraconazole, voriconazole, and posaconazole cannot be used. The echinocandins do not have activity against *H. capsulatum* and **should not be used** to treat patients with histoplasmosis **(AIII).**

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

Serial monitoring of serum or urine for *Histoplasma* antigen is useful for determining a response to therapy. Antigen titers should be checked monthly for the first 3 months and then every 3–4 months, until negative. Blood titers will drop faster than urine titers, and titers will drop faster with polyene treatment compared to azole treatment.[31] A significant rise in antigen level suggests relapse and consideration for treatment changes.

People with HIV diagnosed with histoplasmosis should start ART as soon as possible after initiating antifungal therapy **(AIII).** Life-threatening immune reconstitution inflammatory syndrome (IRIS) has been uncommonly reported in people with HIV who have histoplasmosis.[32,33] Therefore, ART should not be withheld because of concern for the possible development of IRIS **(AIII).**[34]

All triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. Refer to Table 4. Significant Pharmacokinetic Interactions Between Drugs Used to Treat or Prevent Opportunistic Infections and the Drug–Drug Interactions section of the Adult and Adolescent Antiretroviral Guidelines for a list of interactions and recommendations for dose adjustments, where feasible. Itraconazole has caused worsening heart failure, adrenal insufficiency, and transaminitis. Table 5. Serious and/or Common Adverse Reactions Associated With Systemically Administered Drugs Used to Treat or Prevent Opportunistic Infections provides a list of antifungal adverse reactions.

Managing Treatment Failure

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 oral voriconazole are recommended as reasonable alternatives for patients intolerant of itraconazole who are only moderately ill **(BIII);**[27-30] fluconazole at a dose of 800 mg daily also can be used **(CII).**[26] Drug interactions may limit the use of voriconazole in patients who are taking certain non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, etravirine) or protease inhibitors. Posaconazole has fewer known drug interactions with ART medications than voriconazole.

Prevention of Relapse

Long-term suppressive therapy with oral itraconazole (200 mg daily) should be administered to people with severe disseminated infection or CNS infection for ≥12 months after completing induction therapy **(AIII)** or after reinduction therapy to those whose disease relapsed despite initial receipt of an appropriate therapy **(BIII).**[35,36] Fluconazole is less effective than itraconazole for this purpose but has some efficacy at 400 mg daily **(CII).**[26,37] Although the role of voriconazole or posaconazole has not been evaluated in sufficiently powered studies, they may be reasonable options for patients who received these drugs as maintenance therapy **(BIII).** Long-term therapy is started after symptoms have abated and antigen titer is decreasing.

A study sponsored by the AIDS Clinical Trials Group (ACTG) reported that it was safe to discontinue itraconazole treatment for histoplasmosis in people who had received >1 year of itraconazole therapy; had negative fungal blood cultures, a *Histoplasma* serum or urine antigen <4.1 units, and a CD4 count >150 cells/mm^3; and had been on ART for 6 months.[35] No relapses were evident among 32 study participants who were followed for a median of 24 months. Thus, it appears safe to discontinue suppressive azole antifungal therapy in patients who have a serum or urine antigen below the limit of quantification in ng/mL, with CD4 count ≥150 cells/mm^3, on ART for 6 months, and who have an undetectable HIV viral load **(AII).** Suppressive therapy should be resumed if the CD4 count decreases to <150 cells/mm^3 **(BIII).**[35]

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of histoplasmosis during pregnancy, especially during the first trimester **(AIII).** Extensive clinical

experience with amphotericin B has not documented teratogenicity. Because amphotericin B crosses the placenta, infants born to those treated with amphotericin B should be evaluated for adverse effects, including renal dysfunction and hypokalemia.[38]

Although the safety of amphotericin B in pregnancy is well established, less is known about itraconazole. The drug is known to be embryotoxic and teratogenic in rodents. Teratogenic effects included major skeletal defects, encephaloceles, and macroglossia. Because of this, the manufacturer recommends that people of childbearing potential use contraceptives during and for 2 months after treatment.[39] Interestingly, prospective cohort studies of more than 200 women with first trimester itraconazole exposure did not show an increased risk of congenital malformation, but these studies reported uncontrolled doses and durations and have low power to detect differences.[40,41] In the second and third trimester of pregnancy, itraconazole can be considered if the benefit outweighs the potential risk **(CIII).**[40,41] However, in general, azole antifungals **should be avoided** during the first trimester of pregnancy **(BIII).**[42] Although several cohort studies and a systematic review 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.[43-45] Reports of increased birth defects associated with fluconazole use include data from the Quebec Pregnancy Cohort, a population-based cohort with a prospective data collection on all pregnancies covered by Quebec Prescription Drug Insurance from 1998 to 2015, which demonstrated an association between higher fluconazole exposures (>150 mg dosing) during the first trimester and cardiac septal closure defects.[46] In addition, five cases of fluconazole embryopathy—a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures—have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.[47-50] Additionally, fluconazole use in the first trimester has been associated with an increased risk of spontaneous abortion and stillbirth.[51] Data derived from the Quebec Pregnancy Cohort supported an increased risk of spontaneous loss with fluconazole use at low doses but found no association with risk of stillbirth.[46] A recent analysis of registry data from Sweden and Norway did not find an increase in stillbirth or neonatal death associated with exposure to fluconazole at any dose during pregnancy.[52]

In animals, voriconazole (at doses lower than recommended human doses) and posaconazole are teratogenic and embryotoxic. No adequately controlled studies have been conducted of these drugs in humans. Use of fluconazole, voriconazole, and posaconazole **should be avoided** in pregnancy, especially in the first trimester **(AIII).**

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