



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

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## Epidemiology

Oropharyngeal and esophageal candidiasis are common in HIV-infected patients.<sup>1,2</sup> Most such infections are caused by *Candida albicans*. The occurrence of oropharyngeal or esophageal candidiasis is recognized as an indicator of immune suppression and is most often observed in patients with CD4 T lymphocyte (CD4) cell counts <200 cells/mm<sup>3</sup>, with esophageal disease typically occurring at lower CD4 counts than oropharyngeal disease.<sup>1,2</sup> In contrast, vulvovaginal candidiasis—whether a single episode or recurrent—is common in healthy, adult women and does not suggest HIV infection. The advent of antiretroviral therapy (ART) has led to a dramatic decline in the prevalence of oropharyngeal and esophageal candidiasis and a marked diminution in cases of refractory disease.

Fluconazole (or azole) resistance is predominantly the consequence of previous exposure to fluconazole (or other azoles), particularly repeated and long-term exposure.<sup>3-5</sup> In this setting, *C. albicans* resistance has been associated with a gradual emergence of non-*albicans* *Candida* species, particularly *Candida glabrata*, as a cause of refractory mucosal candidiasis in patients with advanced immunosuppression and low CD4 counts.<sup>3,6</sup>

## Clinical Manifestations

Oropharyngeal candidiasis is characterized by painless, creamy white, plaque-like lesions that can occur on the buccal surface, hard or soft palate, oropharyngeal mucosa, or tongue surface. Lesions can be easily scraped off with a tongue depressor or other instrument. Less commonly, erythematous patches without white plaques can be seen on the anterior or posterior upper palate or diffusely on the tongue. Angular cheilosis also can be caused by *Candida*. Because a proportion of HIV-infected patients with oropharyngeal candidiasis also manifest esophageal involvement, clinicians should ascertain whether there are symptoms suggestive of esophageal disease in patients with oropharyngeal candidiasis. Esophageal candidiasis generally presents with retrosternal burning pain or discomfort along with odynophagia; occasionally esophageal candidiasis can be asymptomatic. Endoscopic examination reveals whitish plaques similar to those observed with oropharyngeal disease. On occasion, the plaques may progress to superficial ulcerations of the esophageal mucosa with central or peripheral whitish exudates.

In HIV-infected women, *Candida* vulvovaginitis usually presents with white adherent vaginal discharge associated with mucosal burning and itching of mild-to-moderate severity and sporadic recurrences. In women with advanced immunosuppression, episodes may be more severe and recur more frequently. In contrast to oropharyngeal candidiasis, vulvovaginal candidiasis is less common and rarely refractory to azole therapy.

## Diagnosis

Oropharyngeal candidiasis is usually diagnosed clinically based on the characteristic appearance of lesions. In contrast to oral hairy leukoplakia, the white plaques of oropharyngeal candidiasis can be scraped off the mucosa. If laboratory confirmation is required, scrapings can be examined microscopically for characteristic yeast or hyphal forms, using a potassium hydroxide preparation. Cultures of clinical exudative material yield the species of *Candida* present.

The diagnosis of esophageal candidiasis is often made empirically based on symptoms plus response to therapy, or visualization of lesions plus fungal smear or brushings without histopathologic examination. The definitive diagnosis of esophageal candidiasis requires direct endoscopic visualization of lesions with histopathologic demonstration of characteristic *Candida* yeast forms in tissue and confirmation by fungal culture and speciation.

Vulvovaginal candidiasis usually is diagnosed based on the clinical presentation coupled with the

demonstration of characteristic blastosphere and hyphal yeast forms in vaginal secretions when examined microscopically after potassium hydroxide preparation. Culture confirmation is rarely required but may provide supportive information. Self-diagnosis of vulvovaginitis is unreliable; microscopic and culture confirmation is required to avoid unnecessary exposure to treatment.

## Preventing Exposure

*Candida* organisms are common commensals on mucosal surfaces in healthy individuals. No measures are available to reduce exposure to these fungi.

## Preventing Disease

Data from prospective controlled trials indicate that fluconazole can reduce the risk of mucosal disease (i.e., oropharyngeal, esophageal, and vulvovaginal) in patients with advanced HIV.<sup>7-10</sup> However, routine primary prophylaxis is not recommended because mucosal disease is associated with very low attributable morbidity and mortality and, moreover, acute therapy is highly effective. Primary antifungal prophylaxis can lead to infections caused by drug-resistant *Candida* species and introduce significant drug-drug interactions. In addition long-term oral prophylaxis is expensive. Therefore, routine primary prophylaxis **is not recommended (AIII)**.

## Treating Disease

### *Oropharyngeal Candidiasis*

Oral fluconazole is as effective or superior to topical therapy for oropharyngeal candidiasis. In addition, oral therapy is more convenient than topical therapy and usually better tolerated. Moreover, oral therapy has the additional benefit over topical regimens in being efficacious in treating esophageal candidiasis. Oral fluconazole at 100 mg once a day is considered the drug of choice to treat oropharyngeal candidiasis except during pregnancy (**AI**). One to two weeks of therapy is recommended for oropharyngeal candidiasis; two to three weeks of therapy is recommended for esophageal disease.<sup>11</sup>

Using topical agents to treat oropharyngeal candidiasis reduces systemic drug exposure, diminishes risk of drug-drug interactions and systemic adverse events, and may reduce the likelihood that antifungal resistance develops. Unfavorable taste and multiple daily dosing such as in the cases of clotrimazole and nystatin may lead to decreased tolerability of topical therapy. As an alternative to oral fluconazole, once-daily miconazole in 50-mg mucoadhesive buccal tablets (**BI**) or five-times-per-day clotrimazole troches can be used to treat oropharyngeal candidiasis (**BI**); these regimens were equivalent as shown in a multicenter, randomized study.<sup>12</sup> Nystatin suspension or pastilles four times daily remains an additional alternative (**BII**).<sup>13</sup>

Itraconazole oral solution for 7 to 14 days is as effective as oral fluconazole for oropharyngeal candidiasis but less well tolerated (**BI**).<sup>13</sup> Posaconazole oral suspension<sup>14</sup> is also as effective as fluconazole and generally better tolerated than itraconazole solution (**BI**). Both antifungals are alternatives to oral fluconazole, although few situations require that these drugs be used in preference to fluconazole solely to treat mucosal candidiasis. In a multicenter, randomized study, posaconazole was found to be more effective than fluconazole in sustaining clinical success after antifungal therapy was discontinued.<sup>14</sup> A new solid oral delayed-release tablet formulation of posaconazole is now available.<sup>15</sup> Whether it offers any advantage for the treatment of oropharyngeal candidiasis is unknown and it currently is indicated only for prophylaxis of invasive *Aspergillus* and *Candida* infection.<sup>16</sup> Itraconazole capsules are less effective than fluconazole because of their more variable absorption and they are associated with more drug-drug interactions than fluconazole.

### *Esophageal Candidiasis*

Systemic antifungals are required for effective treatment of esophageal candidiasis (**AI**). A 14- to 21-day course of either fluconazole (oral or intravenous [IV]) or oral itraconazole solution is highly effective (**AI**). However, patients with severe symptoms initially may have difficulty swallowing oral drugs. As with

oropharyngeal candidiasis, itraconazole capsules for esophageal candidiasis are less effective than fluconazole because of variable absorption (**CII**). Voriconazole, amphotericin B (either deoxycholate or lipid formulations) and the echinocandins caspofungin, micafungin, and anidulafungin all are effective in treating esophageal candidiasis (**BI**). However, esophageal candidiasis appears to have a higher relapse rate after treatment with the echinocandins.<sup>17,18</sup> Therefore, oral or IV fluconazole remains the preferred therapy for esophageal candidiasis (**AI**). Although other pathogens (e.g., cytomegalovirus, herpes simplex virus esophagitis) can mimic the symptoms of esophageal candidiasis, a diagnostic and therapeutic trial of antifungal therapy is usually warranted before endoscopy. In those who do not respond to antifungal therapy, endoscopy is recommended to identify different causes of esophagitis or drug-resistant *Candida* (**AII**).

### ***Vulvovaginal Candidiasis***

In most HIV-infected women, vulvovaginal candidiasis is uncomplicated and responds readily to short-course oral or topical treatment with any of several therapies, including:

- Oral fluconazole (**AII**)
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) (**AII**)
- Itraconazole oral solution (**BII**)

Severe or recurrent episodes of vaginitis should be treated with oral fluconazole or topical antifungal therapy for  $\geq 7$  days (**AII**).

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

There are no special considerations regarding initiation of ART in patients with mucocutaneous candidiasis. Specifically, there is as yet no evidence that treatment with ART needs to be delayed until treatment for candidiasis has been completed.

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

For most patients with mucocutaneous candidiasis, response to antifungal therapy is rapid; signs and symptoms improve within 48 to 72 hours. Short courses of topical therapy rarely result in adverse effects, although patients may experience cutaneous hypersensitivity reactions characterized by rash and pruritus. Oral azole therapy can be associated with nausea, vomiting, diarrhea, abdominal pain, or transaminase elevations. Periodic monitoring of liver function studies should be considered if azole therapy is anticipated for  $>21$  days, especially in patients with other hepatic comorbidities (**AII**). The echinocandins appear to be associated with very few adverse reactions: histamine-related infusion toxicity, transaminase elevations, and rash have been attributed to these drugs. No dose adjustments are required in renal failure.

Immune reconstitution inflammatory syndrome with ART has not yet been reported for mucocutaneous candidiasis in HIV-infected patients. Indeed, ART is associated with a markedly reduced incidence of candidiasis.

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

Antifungal treatment failure is typically defined as the persistence of signs or symptoms of oropharyngeal or esophageal candidiasis after 7 to 14 days of appropriate antifungal therapy. Refractory disease occurs in approximately 4% to 5% of HIV-infected patients with oral or esophageal candidiasis, typically those with CD4 cell counts  $<50$  cells/mm<sup>3</sup> and who have received multiple courses of azole antifungals.<sup>4</sup> Confirmatory culture and, in the case of esophageal candidiasis, endoscopy are necessary to confirm treatment failure due to azole resistance or other causes of esophagitis, especially if these procedures were not initially performed.

Posaconazole immediate-release oral suspension (400 mg twice daily for 28 days) is effective in 75% of patients with azole-refractory oropharyngeal or esophageal candidiasis (**AI**).<sup>19</sup> Again, although the new solid delayed-release tablet formulation has been recently made available, it is not known if it offers an advantage over the suspension for treating this particular disease. Alternatively, oral itraconazole solution is effective, at least transiently, in approximately two-thirds of patients with fluconazole-refractory mucosal candidiasis

**(BII)**.<sup>13</sup> If necessary, azole-refractory esophageal candidiasis also can be treated with anidulafungin **(BII)**, caspofungin **(BII)**, micafungin **(BII)**, or voriconazole **(BII)**.

IV amphotericin B is usually effective for treating refractory disease **(BII)**. Both amphotericin B deoxycholate and the lipid preparations of amphotericin B have been used successfully **(BII)**. Amphotericin B oral suspension (1 mL of the 100-mg/mL suspension 4 times daily) is sometimes effective in patients whose oropharyngeal candidiasis does not respond to itraconazole **(BII)**, but this product is not commercially available in the United States.

## Preventing Recurrence

### *When to Start Secondary Prophylaxis*

A randomized clinical trial<sup>10</sup> in HIV-infected patients with CD4 counts <150 cells/mm<sup>3</sup> documented a significantly lower number of episodes of oropharyngeal candidiasis and other invasive fungal infections with continuous fluconazole therapy (3 times a week) compared with episodic fluconazole treatment for recurrences. This clinical trial also demonstrated no difference in the risk of developing clinically significant fluconazole resistance between the two groups among those receiving ART.

However, secondary prophylaxis (chronic suppressive therapy) is not recommended by most HIV specialists for recurrent oropharyngeal or vulvovaginal candidiasis unless patients have frequent or severe recurrences **(BIII)** because therapy for acute disease is effective, mortality associated with mucocutaneous disease is low, potential exists for drug interactions and for the development of antifungal-resistant *Candida*, and prophylaxis is costly.

If recurrences are frequent or severe, oral fluconazole can be used as suppressive therapy for either oropharyngeal **(BI)**, esophageal **(BI)**, or vulvovaginal **(BII)** candidiasis.<sup>7-9</sup> Oral posaconazole twice daily is also effective for esophageal candidiasis **(BII)**.<sup>20</sup> The potential for development of secondary azole resistance should be considered when contemplating chronic maintenance therapy using azoles in HIV-infected patients who are severely immunocompromised. Several important factors should be taken into account when making the decision to use secondary prophylaxis. These include the effect of recurrences on the patient's well-being and quality of life, the need for prophylaxis against other fungal infections, cost, adverse events and, most importantly, drug-drug interactions.<sup>21</sup>

Rates of relapse are high in patients with azole-refractory oropharyngeal or esophageal candidiasis who have initially responded to echinocandins, voriconazole, or posaconazole therapy. In such patients, secondary prophylaxis should be instituted until ART produces immune reconstitution **(AIII)**.

### *When to Stop Secondary Prophylaxis*

In situations where secondary prophylaxis has been instituted, no data exist to guide recommendations regarding its discontinuation. On the basis of experience with other opportunistic infections, it would be reasonable to discontinue secondary prophylaxis when the CD4 count has risen to >200 cells/mm<sup>3</sup> following initiation of ART **(AIII)**.

## Special Considerations During Pregnancy

Pregnancy increases the risk of vaginal colonization with *Candida* species. Diagnosis of oropharyngeal, esophageal, and vulvovaginal candidiasis is the same in pregnant women as in those who are not pregnant.

Topical therapy is preferable for treatment of oral or vaginal candidiasis in pregnancy, when possible **(AIII)**. Although single-dose, episodic treatment with oral fluconazole has not been associated with birth defects in humans,<sup>22</sup> its use has not been widely endorsed.<sup>23</sup> Five cases of a syndrome consisting of craniosynostosis, characteristic facies, digital synostosis, and limb contractures (fluconazole embryopathy) have been reported in women chronically prescribed fluconazole at doses of 400 mg daily or higher in pregnancy.<sup>24</sup> On the basis of these data, substitution of amphotericin B for high-dose fluconazole in the first trimester is recommended

for invasive or refractory esophageal candidal infections (**AIII**). Neonates born to women receiving chronic amphotericin B at delivery should be evaluated for renal dysfunction and hypokalemia. Itraconazole has been shown to be teratogenic in animals at high doses, but the metabolic mechanism accounting for these defects is not present in humans, so these data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole,<sup>25</sup> but experience is limited. Human data are not available for posaconazole; however, the drug was associated with skeletal abnormalities in rats and was embryotoxic in rabbits when given at doses that produced plasma levels equivalent to those seen in humans. Voriconazole is considered a Food and Drug Administration Category D drug because of its association with cleft palate and renal defects seen in rats, as well as embryotoxicity seen in rabbits. However, human data on the use of voriconazole are not available, so use in the first trimester is not recommended. Multiple anomalies have been seen in animals exposed to micafungin, and ossification defects have been seen with use of anidulafungin and caspofungin.<sup>26</sup> Human data are not available for these drugs, thus their use in human pregnancy is not recommended (**AIII**).

Chemoprophylaxis, either chronic maintenance therapy or secondary prophylaxis, against oropharyngeal, esophageal, or vaginal candidiasis using systemically absorbed azoles **should not be initiated** during pregnancy (**AIII**). Furthermore, prophylaxis with systemic azoles **should be discontinued** in HIV-infected women who become pregnant (**AIII**).

## Recommendations for Treating Mucosal Candidiasis (page 1 of 2)

### Treating Mucosal Candidiasis

#### **Oropharyngeal Candidiasis: Initial Episodes (Duration of Therapy: 7–14 days)**

##### *Preferred Oral Therapy:*

- Fluconazole 100 mg PO once daily (**AI**), *or*

##### *Alternative Therapy:*

- Clotrimazole troches 10 mg PO 5 times daily (**BI**), *or*
- Miconazole mucoadhesive buccal tablet 50 mg: Apply to mucosal surface over the canine fossa once daily (do not swallow, chew, or crush tablet). Refer to product label for more detailed application instructions, (**BI**) *or*
- Itraconazole oral solution 200 mg PO daily (**BI**), *or*
- Posaconazole oral suspension 400 mg PO BID for one day, then 400 mg daily (**BI**), *or*
- Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily (**BII**)

#### **Esophageal candidiasis (Duration of Therapy: 14–21 days)**

**Note:** Systemic antifungals are required for effective treatment of esophageal candidiasis (**AI**)

##### *Preferred Therapy:*

- Fluconazole 100 mg (up to 400 mg) PO or IV daily (**AI**), *or*
- Itraconazole oral solution 200 mg PO daily (**AI**)

##### *Alternative Therapy:*

- Voriconazole 200 mg PO or IV BID (**BI**), *or*
- Caspofungin 50 mg IV daily (**BI**), *or*
- Micafungin 150 mg IV daily (**BI**), *or*
- Anidulafungin 100 mg IV for one dose, then 50 mg IV daily (**BI**), *or*
- Amphotericin B deoxycholate 0.6 mg/kg IV daily (**BI**), *or*
- Lipid formulation of amphotericin B 3–4 mg/kg IV daily (**BIII**)

**Note:** A higher rate of esophageal candidiasis relapse has been reported with echinocandins than with fluconazole.

#### **Uncomplicated Vulvovaginal Candidiasis**

##### *Preferred Therapy:*

- Oral fluconazole 150 mg for 1 dose (**AII**); *or*
- Topical azoles (i.e., clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (**AII**)

##### *Alternative Therapy:*

- Itraconazole oral solution 200 mg PO daily for 3–7 days (**BII**)

**Note:** Severe or recurrent vaginitis should be treated with oral fluconazole (100–200 mg) or topical antifungals for  $\geq 7$  days (**AII**)

## Recommendations for Treating Mucosal Candidiasis (page 2 of 2)

### Chronic Suppressive Therapy

- Chronic suppressive therapy is usually not recommended unless patients have frequent or severe recurrences (**BIII**).
- If used, it is reasonable to discontinue therapy if CD4 count >200 cells/mm<sup>3</sup> (**AIII**).

### If Decision Is To Use Suppressive Therapy

#### Oropharyngeal Candidiasis:

- Fluconazole 100 mg PO once daily or 3 times weekly (**BI**)

#### Esophageal Candidiasis:

- Fluconazole 100–200 mg PO daily (**BI**)
- Posaconazole oral suspension 400 mg PO BID (**BII**)

#### Vulvovaginal Candidiasis:

- Fluconazole 150 mg PO once weekly (**BII**)

### Other Considerations

- Chronic or prolonged use of azoles might promote development of resistance.
- Systemic azoles may have significant drug-drug interactions with ARV drugs and other drugs for treatment of OI; refer to [Table 5](#) for dosing recommendations. Consider therapeutic drug monitoring if prolonged use is indicated.

**Key to Acronyms:** ARV = antiretroviral; BID = twice daily; CD4 = CD4 T lymphocyte; IV = intravenous; OI = opportunistic infection; PO = orally; QID = four times daily

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