



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

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## Penicilliosis marneffeii (Last updated May 7, 2013; last reviewed September 13, 2017)

**NOTE: Update in Progress**

### Epidemiology

Penicilliosis is caused by the dimorphic fungus *Penicillium marneffeii*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.<sup>1-3</sup> More recently, indigenous cases of penicilliosis have been seen in several states of India, particularly Manipur, which is a new endemic area for this fungus.<sup>4-6</sup>

Before the era of antiretroviral therapy (ART), penicilliosis was the presenting AIDS-defining illness in 6.8% of HIV-infected patients from the northern provinces of Thailand and less common elsewhere.<sup>7</sup> Most cases of penicilliosis are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/mm<sup>3</sup>.<sup>8</sup> The infection is associated with a high mortality rate if timely treatment with appropriate antifungal drugs is not administered.<sup>9</sup>

No data are available on acquisition and transmission of penicilliosis. However, like histoplasmosis, it is believed to be acquired by inhalation of microconidia from the mycelial phase of the organism. Reactivation of a silent focus of infection that was acquired years earlier can occur when cellular immunity wanes and it is the presumed mechanism for disease occurrence in nonendemic areas. Evidence exists for seasonality in penicilliosis infections; increased cases have been noted during the rainy months.<sup>10,11</sup>

### Clinical Manifestations

The common clinical manifestations include fever, anemia, weight loss, and generalized skin papules with central umbilication resembling molluscum contagiosum.<sup>1,5</sup> Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia. Involvement of other organs, such as the central nervous system, bone marrow, lymph node, lung, liver, and intestine, has been reported. Patients with hepatic penicilliosis have fever, abdominal pain, hepatomegaly, and a marked increase in serum alkaline phosphatase levels.<sup>3</sup>

### Diagnosis

The definitive diagnosis of penicilliosis is based on isolation of organisms from cultures of blood or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. *P. marneffeii* exhibits dimorphic growth in culture. At 25°C, the fungus grows as a mold, demonstrating characteristic colonies that include a flat green surface and underlying deep red coloring. At 37°C the fungus grows as white colonies of yeast.<sup>12</sup>

An early presumptive diagnosis can be made several days before the results of fungal cultures are available by microscopic examination of Wright-stained samples of skin scrapings, bone marrow aspirate, or lymph node biopsy specimens. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast-like organisms can be seen, some with clear central septation, which is a characteristic feature of *P. marneffeii*.<sup>1,5</sup> In some patients, the fungus can be identified by microscopic examination of a Wright's-stained peripheral blood smear.<sup>13</sup>

### Preventing Exposure

Available information does not support specific recommendations regarding exposure avoidance. However, patients with advanced HIV disease should avoid visiting endemic areas, and particularly rural areas in those regions (**BIII**).

### Preventing Disease

A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole, 200 mg daily for primary prophylaxis, significantly reduced occurrence of systemic fungal infections

(cryptococcosis and penicilliosis) in HIV-infected patients with CD4 counts  $<200$  cells/mm<sup>3</sup>.<sup>8</sup> Fluconazole may also be effective prophylaxis.<sup>14</sup> For most patients from the United States, such primary prophylaxis would only be indicated in unusual situations in which those who are highly immunosuppressed have to travel to high-risk areas.

### ***Indication for Primary Prophylaxis***

All HIV-infected patients with CD4 counts  $<100$  cells/mm<sup>3</sup> who reside or stay for a long period in northern Thailand, Vietnam, and southern China, and particularly in rural areas, should be administered primary prophylaxis (**BI**). The preferred drug for prophylaxis is oral itraconazole, 200 mg/day (**BI**). An alternative drug is oral fluconazole 400 mg once weekly (**BII**). Primary prophylaxis is not indicated in other geographic areas.<sup>15</sup>

### ***Discontinuation of Primary Prophylaxis***

No randomized, controlled study has demonstrated the safety of discontinuation of primary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse in penicilliosis and invasive fungal infections after discontinuation of itraconazole in patients receiving ART who had CD4 counts  $>100$  cells/mm<sup>3</sup>.<sup>16</sup> Therefore, primary prophylaxis for penicilliosis can logically be discontinued in AIDS patients who receive combination ART and have CD4 counts  $>100$  cells/mm<sup>3</sup> for  $\geq 6$  months but there are no convincing data addressing this issue (**CII**). Primary prophylaxis should be reintroduced if the CD4 count decreases to  $<100$  cells/mm<sup>3</sup> (**BIII**).

## **Treating Disease**

The recommended treatment is liposomal amphotericin B, 3 to 5 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks (**AII**), followed by secondary prophylaxis.<sup>17</sup> Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for 8 weeks (**BII**),<sup>18</sup> followed by 200 mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when taken with or immediately after a meal. Itraconazole oral solution can be taken on an empty stomach.

The alternative drug for primary treatment in the hospital is IV voriconazole, 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day 1, and then 200 mg twice daily for 12 weeks (**BII**).<sup>19</sup> The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.

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

No studies exist regarding the optimal time to start ART in HIV-infected patients with acute penicilliosis, but anecdotal experience and information from clinical trials on other HIV associated opportunistic infections suggests that in those with active penicilliosis who have CD4 counts  $\leq 50$  cells/mm<sup>3</sup>, ART should be started as soon as possible after the initiation of antifungal therapy (**BIII**). In patients with CD4 counts  $>50$  cells/mm<sup>3</sup>, it may be prudent to delay initiation of ART until after completion of the first 2 weeks of induction therapy for penicilliosis (**CIII**).

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

Patients treated with amphotericin B should be monitored for dose-dependent nephrotoxicity and electrolyte disturbances. Pre-infusion administration of 500 to 1000 mL of normal saline reduces the risk of nephrotoxicity during treatment (**BII**). Infusion-related adverse reactions can be ameliorated by pretreatment with acetaminophen and diphenhydramine.

Because absorption of itraconazole can be erratic and because itraconazole can interact with some antiretroviral drugs, serum itraconazole levels should be obtained in all patients to ensure adequate drug exposure (**AIII**). The serum concentration should be  $>1$   $\mu\text{g/mL}$ . Itraconazole solution is recommended over the capsule formulation because of better bioavailability, but this has not been studied specifically in AIDS patients.

Azoles and antiretroviral drugs such as protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) do interact (see [Table 5](#)). Through the CYP3A4 mechanism, itraconazole and voriconazole can increase blood levels and effects of PIs and NNRTIs. On the other hand, NNRTIs can slightly decrease blood levels of itraconazole and voriconazole. Close monitoring should be done when using these drugs together.

The unmasking type of immune reconstitution inflammatory syndrome (IRIS) has been reported in several patients with penicilliosis.<sup>20,21</sup> No paradoxical IRIS responses have been reported when ART is initiated in patients with established penicilliosis. ART should not be withheld because of concern for possible development of IRIS (**AIII**).

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

Voriconazole has been reported to have good outcomes and can be used in patients whose infections fail to respond to initial therapy with amphotericin B followed by itraconazole (**BII**).<sup>19</sup>

## **Preventing Recurrence**

### ***When To Start Secondary Prophylaxis***

A study showed that more than 50% of patients not treated with ART had relapse of *P. marneffei* within 6 months after discontinuation of antifungal therapy.<sup>18,22</sup> A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients, reduced the relapse rate for *P. marneffei* from 57% to 0% ( $P < 0.001$ ).<sup>22</sup> All patients who successfully complete treatment for penicilliosis should receive secondary prophylaxis (chronic maintenance therapy) with oral itraconazole 200 mg/day (**AI**) and should be started on ART if that was not done during acute disease (**AIII**).

### ***When To Stop Secondary Prophylaxis***

No randomized, controlled study has demonstrated the safety of discontinuation of secondary prophylaxis for penicilliosis. However, a retrospective cohort study reported no relapse of penicilliosis after discontinuation of itraconazole in patients receiving ART whose CD4 cell counts were  $>100$  cells/mm<sup>3</sup>.<sup>16</sup> Therefore, secondary prophylaxis for penicilliosis can be discontinued in AIDS patients who receive combination ART and have CD4 cell counts  $>100$  cells/mm<sup>3</sup> for at least 6 months (**BII**). Secondary prophylaxis should be reintroduced if the CD4 cell count decreases to  $<100$  cells/mm<sup>3</sup> (**AIII**).

## **Special Considerations During Pregnancy**

Diagnosis and treatment of penicilliosis during pregnancy are similar to those in non-pregnant adults, with the following considerations regarding antifungal use in pregnancy. Amphotericin B has not been shown to be teratogenic in animals, and no increase in anomalies has been seen with its use in humans. Neonates born to women on 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 the data are not applicable. Case series in humans do not suggest an increased risk of birth defects with itraconazole, but experience is very limited. Voriconazole is Food and Drug Administration category D because of cleft palate and renal defects seen in rats and embryotoxicity in rabbits. No human data on use of voriconazole are available, so use in the first trimester is not recommended. No evidence of birth defects has been seen after episodic exposure to single, 150-mg doses of fluconazole. With chronic use of doses  $\geq 400$  mg in pregnancy, however, 5 cases of a syndrome of craniosynostosis, characteristic facies, digital synostosis, and limb contractures have been reported (fluconazole embryopathy).<sup>23</sup>

Substitution of amphotericin B for high-dose azoles in the first trimester is recommended (**BIII**). Women on secondary prophylaxis with itraconazole or other azoles should postpone pregnancy until their CD4 cell counts have been restored with ART, such that prophylaxis can be discontinued (**BIII**).

## Recommendations for Preventing and Treating *Penicillium marneffe* Infection

### Preventing 1st Episode of Penicilliosis (Primary Prophylaxis)

#### Indication for Primary Prophylaxis:

- Patients with CD4 count  $<100$  cells/mm<sup>3</sup> who reside or stay for a long period in northern Thailand, Vietnam, and Southern China, in particular in rural areas **(BI)**

#### Preferred Therapy:

- Itraconazole<sup>a</sup> 200 mg PO once daily **(BI)**

#### Alternative Therapy:

- Fluconazole 400 mg PO once weekly **(BII)**

#### Indication for Discontinuing Primary Prophylaxis:

- CD4 count  $>100$  cells/mm<sup>3</sup> for  $\geq 6$  months in response to ART **(CII)**

#### Indication for Restarting Primary Prophylaxis:

- CD4 count decreases to  $<100$  cells/mm<sup>3</sup> **(BIII)**g/mL.

### Treating Acute Infection in Severely Ill Patients

#### Preferred Therapy:

- Liposomal amphotericin B, 3 to 5 mg/kg/day IV for 2 weeks; followed by itraconazole<sup>a</sup> 200 mg PO BID for 10 weeks **(AII)**, followed by chronic maintenance therapy **(AII)**

#### Alternative Therapy:

- Voriconazole<sup>a</sup> 6 mg/kg IV q12h for 1 day, then 4 mg/kg q12h for at least 3 days, followed by voriconazole<sup>a</sup> 200 mg PO BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy **(BII)**

### Treating Mild Disease

#### Preferred Therapy:

- Itraconazole<sup>a</sup> 200 mg PO BID for 8 weeks **(BII)**, followed by chronic maintenance therapy. **(BII)**

#### Alternative Therapy:

- Voriconazole<sup>a</sup> 400 mg PO BID for 1 day, then 200 mg BID for a maximum of 12 weeks **(BII)**, followed by chronic maintenance therapy. **(BII)**

### Chronic Maintenance Therapy (Secondary Prophylaxis)

- Itraconazole<sup>a</sup> 200 mg PO daily **(AI)**

#### Criteria for Discontinuing Chronic Maintenance Therapy:

- CD4 count  $>100$  cells/mm<sup>3</sup> for  $\geq 6$  months in response to ART **(BII)**

#### Criteria for Restarting Chronic Maintenance Therapy:

- CD4 count  $<100$  cells/mm<sup>3</sup> **(AIII)**, *or*
- If penicilliosis recurs at CD4 count  $>100$  cells/mm<sup>3</sup> **(CIII)**

### Other Considerations:

- ART should be administered simultaneously with treatment for penicilliosis to improve outcome. **(CIII)**
- Because of the erratic absorption and potential for drug interactions with ARV therapy, itraconazole concentration should be monitored, and serum concentration should be  $> 1$  mc

<sup>a</sup> Both itraconazole and voriconazole can have significant drug-drug interactions with various ARV drugs, dosage adjustment may be necessary, consider therapeutic drug monitoring to guide therapy. See [Table 5](#) for drug interaction information

**Key to Acronyms:** CD4 = CD4 T lymphocyte; PO = orally; IV = intravenous; q(n)h = every “n” hours; BID = twice daily; ART = antiretroviral therapy, ARV = antiretroviral

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