



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

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 12/22/2015

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

Epidemiology

Invasive aspergillosis is rare in HIV-infected individuals but often overlooked antemortem. In a recent autopsy series of HIV-infected patients from Italy, invasive aspergillosis was the second most frequently identified invasive mycosis in fatal cases, 88% of which were diagnosed only postmortem.¹ Illness most often is caused by *Aspergillus fumigatus*, but *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus* have been noted to cause disease. Invasive aspergillosis occurs in patients with advanced HIV infection and was more common before the advent of effective antiretroviral therapy (ART).¹⁻³ Specific risk factors include neutropenia, use of corticosteroids, exposure to broad-spectrum antibacterial therapy, and underlying lung disease. Patients who have had HIV-associated aspergillosis typically have CD4 T lymphocyte (CD4) cell counts <100 cells/mm³, a history of other AIDS-defining opportunistic infections, and are not receiving potent ART.⁴

Clinical Manifestations

In HIV-infected patients, invasive aspergillosis most commonly presents as a respiratory illness that can be a necrotizing pneumonia or a tracheobronchitis.⁵ Symptoms of pneumonia include fever, cough, dyspnea, chest pain, hemoptysis, and hypoxemia; chest radiograph may demonstrate a diffuse, focal, or cavitary infiltrate. A halo of low attenuation surrounding a pulmonary nodule or a cavity on a computed tomography (CT) scan of the lung is suggestive of pulmonary aspergillosis. Tracheobronchitis is associated with fever, cough, dyspnea, stridor, and wheezing. Bronchoscopic examination demonstrates ulcerative or plaque-like lesions adherent to the tracheal wall.⁶ Extrapulmonary forms of invasive aspergillosis include sinusitis, cutaneous disease, osteomyelitis, and brain abscess.⁷

Diagnosis

The diagnosis of probable invasive pulmonary aspergillosis is based on isolation of *Aspergillus* spp. from respiratory secretions or the finding of septate hyphae consistent with *Aspergillus* spp. in respiratory samples in association with typical CT findings. Histological evidence of tissue invasion by septate hyphae with a positive culture for *Aspergillus* spp. establishes a definitive diagnosis.⁸

Detection of *Aspergillus* cell wall galactomannan by enzyme-linked immunosorbent assay (ELISA) performed on serum or bronchoalveolar lavage fluid has not been formally evaluated in HIV-infected patients. It has proven useful, however, in other immunosuppressed patients, especially recipients of stem cell transplants,⁹ and is listed by the European Organisation for Research and Treatment of Cancer/U.S. Mycosis Study Group Consensus Group as one of the criteria for establishing a diagnosis of probable invasive aspergillosis.⁸ Bronchoalveolar lavage galactomannan is probably more sensitive than serum galactomannan for diagnosis. The test is highly specific.

Preventing Exposure

Aspergillus spp. are ubiquitous in the environment, and exposure is unavoidable. Avoiding particularly dusty environments, especially areas of construction, is prudent because spore counts likely are higher in such settings.

Preventing Disease

No data exist about the prevention of primary aspergillosis in HIV-infected patients, although posaconazole has been reported to be effective in patients with certain hematological malignancies and neutropenia.¹⁰ At this time, antifungal therapy **is not recommended** for prevention of aspergillosis in HIV-infected individuals (AIII).

Treating Disease

Treatment of aspergillosis in HIV-infected patients has not been systematically examined. Voriconazole is the

recommended treatment for invasive aspergillosis in HIV-uninfected patients (**AI**).¹¹ Because of drug-drug interactions, however, voriconazole should be used cautiously with protease inhibitors (PIs) and efavirenz (see [Table 5](#)). Alternatively, lipid-formulation amphotericin B or amphotericin B deoxycholate can be used (**AII**). Second-line agents include echinocandins (such as caspofungin, anidulafungin, or micafungin) or posaconazole (**BIII**). The role of combination antifungal therapy for primary treatment of invasive aspergillosis is being evaluated in a large, randomized trial comparing voriconazole alone with voriconazole plus anidulafungin in recipients of stem cell transplants. The length of therapy has not been established, but treatment should continue at least until the peripheral blood CD4 count is >200 cells/mm³ and the infection appears to be resolved (**BIII**).

Special Considerations with Regard to Starting ART

HIV-infected individuals diagnosed with aspergillosis should be started on ART as soon as possible after initiating antifungal therapy (**AIII**). Immune reconstitution inflammatory syndrome (IRIS) has rarely been reported in HIV-infected patients with invasive aspergillosis¹² and concern for the syndrome should not delay initiation of ART (**AIII**).

All of the triazole antifungals have the potential for complex, and possibly bidirectional, interactions with certain antiretroviral agents and other anti-infective agents. [Table 5](#) lists such interactions and recommendations for dosage adjustments, where feasible.

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

Data are limited with regard to monitoring of *Aspergillus* galactomannan levels in response to therapy. As previously stated, IRIS rarely has been reported in HIV-infected patients with invasive aspergillosis¹² and new or recurrent signs and symptoms should prompt evaluation for relapse or recurrence of aspergillosis.

Managing Treatment Failure

The overall prognosis for invasive aspergillosis is poor in patients with advanced immunosuppression and in the absence of effective ART. No data are available to guide recommendations for management of treatment failure. If voriconazole was used initially, substitution can be considered with an amphotericin B formulation or with echinocandins in combination with voriconazole or amphotericin B (**BIII**).

Preventing Recurrence

No data are available on which to base a recommendation for or against chronic maintenance or suppressive therapy in patients who have successfully completed an initial course of treatment.

Special Considerations During Pregnancy

Amphotericin B or its lipid formulations are the preferred initial regimen for the treatment of aspergillosis in pregnant patients. Extensive clinical experience with amphotericin has not documented teratogenicity. At delivery, infants born to women treated with amphotericin B should be evaluated for renal dysfunction and hypokalemia.

Voriconazole and posaconazole are teratogenic and embryotoxic in animal studies, voriconazole at doses lower than recommended human doses; here are no adequate controlled studies in humans. These drugs **should generally be avoided** in pregnancy, especially in the first trimester (**AIII**). The echinocandins are associated with bony and visceral abnormalities in animal studies, but no human experience is documented. These agents should be avoided in the first trimester of pregnancy; use in later pregnancy should be based on consideration of benefit versus potential risk.

Recommendations for Treating Invasive Aspergillosis

Treating Invasive Aspergillosis

Preferred Therapy:

- Voriconazole^a 6 mg/kg IV q12h for 1 day, then 4 mg/kg IV q12h, followed by voriconazole PO 200 mg q12h after clinical improvement (**AI**)

Alternative Therapy:

- Lipid formulation amphotericin B 5 mg/kg/day IV (**AII**), or
- Amphotericin B deoxycholate 1 mg/kg/day IV (**AII**), or
- Caspofungin 70 mg IV once, then 50 mg IV daily (**BIII**), or
- Micafungin 100–150 mg IV daily (**BIII**), or
- Anidulafungin 200 mg IV once, then 100 mg IV daily (**BIII**), or
- Posaconazole 200 mg QID PO, then 400 mg BID PO after condition improved (**BIII**)

Duration (**BIII**):

- Until CD4 count >200 cells/mm³ and infection appears to be resolved.

^a Potential for significant pharmacokinetic interactions between protease inhibitors or non-nucleoside reverse transcriptase inhibitors with voriconazole (see [Table 5](#)); this agent should be used cautiously in these situations. Therapeutic drug monitoring and dosage adjustment, if necessary, should be performed when using voriconazole.

Key to Acronyms: BID = twice daily; IV = intravenous; PO = orally; Q(n)h = every “n” hours; QID = four times a day

References

1. Antinori S, Nebuloni M, Magni C, et al. Trends in the postmortem diagnosis of opportunistic invasive fungal infections in patients with AIDS: a retrospective study of 1,630 autopsies performed between 1984 and 2002. *Am J Clin Pathol*. Aug 2009;132(2):221-227. Available at <http://www.ncbi.nlm.nih.gov/pubmed/19605816>.
2. Mylonakis E, Barlam TF, Flanigan T, Rich JD. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest*. Jul 1998;114(1):251-262. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9674477>.
3. Holding KJ, Dworkin MS, Wan PC, et al. Aspergillosis among people infected with human immunodeficiency virus: incidence and survival. Adult and Adolescent Spectrum of HIV Disease Project. *Clin Infect Dis*. Nov 2000;31(5):1253-1257. Available at <http://www.ncbi.nlm.nih.gov/pubmed/11073760>.
4. Wallace JM, Lim R, Browdy BL, et al. Risk factors and outcomes associated with identification of *Aspergillus* in respiratory specimens from persons with HIV disease. Pulmonary Complications of HIV Infection Study Group. *Chest*. Jul 1998;114(1):131-137. Available at <http://www.ncbi.nlm.nih.gov/pubmed/9674459>.
5. Lortholary O, Meyohas MC, Dupont B, et al. Invasive aspergillosis in patients with acquired immunodeficiency syndrome: report of 33 cases. French Cooperative Study Group on Aspergillosis in AIDS. *Am J Med*. Aug 1993;95(2):177-187. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8395142>.
6. Kemper CA, Hostetler JS, Follansbee SE, et al. Ulcerative and plaque-like tracheobronchitis due to infection with *Aspergillus* in patients with AIDS. *Clin Infect Dis*. Sep 1993;17(3):344-352. Available at <http://www.ncbi.nlm.nih.gov/pubmed/8218674>.
7. Mylonakis E, Paliou M, Sax PE, Skolnik PR, Baron MJ, Rich JD. Central nervous system aspergillosis in patients with human immunodeficiency virus infection. Report of 6 cases and review. *Medicine (Baltimore)*. Jul 2000;79(4):269-280. Available at <http://www.ncbi.nlm.nih.gov/pubmed/10941356>.
8. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. Jun 15 2008;46(12):1813-1821. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18462102>.
9. Maertens JA, Klont R, Masson C, et al. Optimization of the cutoff value for the *Aspergillus* double-sandwich enzyme immunoassay. *Clin Infect Dis*. May 15 2007;44(10):1329-1336. Available at

<http://www.ncbi.nlm.nih.gov/pubmed/17443470>.

10. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. Jan 25 2007;356(4):348-359. Available at <http://www.ncbi.nlm.nih.gov/pubmed/17251531>.
11. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. Feb 1 2008;46(3):327-360. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18177225>.
12. Sambatakou H, Denning DW. Invasive pulmonary aspergillosis transformed into fatal mucous impaction by immune reconstitution in an AIDS patient. *Eur J Clin Microbiol Infect Dis*. Sep 2005;24(9):628-633. Available at <http://www.ncbi.nlm.nih.gov/pubmed/16177885>.