



Florida/Caribbean AIDS Education and Training Center

HIV CareLink

A Newsletter for HIV/AIDS Primary Care Providers

ABOUT US

The Florida/Caribbean AIDS Education and Training Center provides state-of-the-art HIV education, consultation, and resource materials to health care providers in Florida, Puerto Rico and the US Virgin Islands.

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Prevention and Treatment of Opportunistic Infections (OIs) in HIV-Infected Adults and Adolescents Guidelines Summary

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This CareLink summarizes selected sections of the 2009 [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#) as recommended by an expert panel from Centers for Disease Control and Prevention (CDC), the National Institutes of Health and the HIV Medicine Association of the Infectious Diseases Society of America (IDSA). A summary of the [Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the IDSA](#) with an emphasis on HIV-infected individuals is also provided.

The major changes in the 2009 CDC OI guidelines from the 2004 version include: 1) emphasis on importance of antiretroviral therapy (ART) for preventions of OIs, especially those lacking specific prophylaxis or treatment; 2) updated discussion on immune reconstitution inflammatory syndromes (IRIS); 3) use of interferon-gamma release assays (IGRAs) for diagnosis of latent *Mycobacterium tuberculosis* (TB) infection; 4) updates on drug interactions among ART and rifamycins; 5) an additional section on hepatitis B infection; and, 6) the malaria section added to the list of OIs. In this summary, we will address the importance of antiretroviral therapy and disease-specific treatments and preventions for selected OIs.

INITIATING ART IN TREATMENT-NAÏVE PATIENTS WITH AN ACUTE OI

- Starting ART while acutely ill may pose several problems (e.g., malabsorption, drug interactions, adverse reaction and IRIS).
- There is no consensus regarding the optimal time to start ART in acute OIs, but a randomized controlled trial showed clinical and survival benefits with ART initiation within the first 2 weeks of starting OI treatment, excluding TB.
 - Please refer to the [January 2011 HIV CareLink on the Updated Adult/Adolescent Department of Health and Human Services Antiretroviral](#) guidelines which includes detailed recommendations on the timing of ART initiation in HIV/TB co-infected patients.
- Potential benefits of starting ART early include faster resolution of OIs and prevention of a second concomitant OI due to improved immune function.
- OIs can occur when a patient recently starts ART (e.g., within 12 weeks) and is not necessarily a sign of treatment failure.
- The term IRIS refers to a group of clinical syndromes that can be seen due to immune reconstitution following ART initiation. The manifestations can vary but usually include fever and worsening of symptoms of the OI or unmasking a previously undiagnosed OI. IRIS is most commonly seen with TB and disseminated *Mycobacterium avium* complex disease but can be seen with other OIs.

DISEASE SPECIFIC RECOMMENDATIONS

Cryptococcus

Cryptococcus is an encapsulated fungus that is a common worldwide opportunistic pathogen in a variety of hosts from immunocompromised transplant recipients and HIV-infected individuals to the apparently immunocompetent host. It is found in soil worldwide, usually in association with bird droppings. Susceptible hosts are thought to inhale the fungus from the environment causing symptoms that range from asymptomatic colonization to pneumonia and acute respiratory distress syndrome, which can then spread to any organ in the human body resulting in a variety of clinical manifestations, but most commonly the central nervous system (CNS) is involved. The majority of cases have been in patients with CD4+ counts < 50 cells/mm³.

Clinical Manifestations and Diagnosis

- CNS. Acute, subacute or chronic meningitis is common. Less commonly seen as single or multiple space occupying lesions (cryptococcoma). Most common manifestation in HIV-infected patients disseminated disease is common and can involve any organ.
- Lung. Typical lower respiratory tract infection symptoms with any pattern of infiltrate to asymptomatic. Coinfection with other opportunists is common.

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- Skin. Almost any type of skin lesion can occur. Can be mistaken for molluscum contagiosum, acne vulgaris, squamous cell carcinoma or basal cell carcinoma.
- Genitourinary Tract. Most commonly seen as silent prostate infection.
- Eye. Most common findings are ocular palsies and papilledema. Can lead to blindness from optic neuritis or cerebral edema from unrelieved high intracranial pressures.
- Cerebrospinal fluid is India ink positive in >80% of patients with AIDS. It is not useful on other body fluids. Narrow-based budding yeast can be seen with Geimsa stain.

Treatment Cryptococcal Meningitis

Induction Therapy

- Amphoterecin B deoxycholate (AmB) 0.7-1 mg/kg IV once daily + flucytosine 25 mg/kg/dose po 4x/day for ≥ 2 weeks (AI)
 - For patients who develop renal dysfunction or have increased risk for renal toxicity, [liposomal AmB (AmBisome[®]) 3-4 mg/kg IV once daily or AmB lipid complex (ABLC, Abelcet[®]) 5 mg/kg IV once daily] + flucytosine as above (dose reduce flucytosine when CrCL < 40 mL/min)
- Liposomal AmB or ABLC (dosed as above) alone for ≥ 4 to 6 weeks for flucytosine intolerant patients (AI).
- **Consolidation Therapy:** fluconazole 400 mg po once daily for ≥ 8 weeks.
- **Maintenance Therapy:** fluconazole 200 mg po once daily. Consider stopping after ≥ 1 year of antifungal therapy in patients virologically controlled on ART with CD4 ≥ 100 cells/mm³ for ≥ 3 months. Restart if CD4 falls to < 100 cells/mm³.
- Initiate ART 2-10 weeks after antifungal therapy begun.
- See the [Cryptococcal 2010 Guidelines](#) for nonmeningeal cryptococcus, cerebral cryptococcoma, or alternative treatment and maintenance regimens for cryptococcal meningitis.
- IRIS occurs in as many as 30% of HIV patients with cryptococcal meningitis (more likely if ART naïve and high viral load). If mild-moderate IRIS, continue ART and antifungal therapy. If severe IRIS with increased ICP, consider corticosteroids for 2-6 weeks.

Prevention

- Impossible to avoid exposure. Patients should not be restricted from birds or caving.
- Primary prophylaxis not recommended.

Pneumocystis Pneumonia (PCP)

PCP is caused by a ubiquitous organism, *Peumocystis jirovecii*, which is classified as a fungus, but also has biologic characteristics of a protozoa. PCP is thought to occur as a new infection or reactivation of a latent infection (66% of healthy children are

P. jirovecii antibody (+) by age 2-4 years). With the use of ART and PCP prophylaxis, the incidence of PCP in the U.S. has greatly decreased with the majority of cases occurring in patients unaware of their HIV diagnosis, in HIV patients out of care, and in patients who are severely immunosuppressed (CD4<100).

Clinical Manifestations

- Progressive dyspnea, fever, nonproductive cough and chest discomfort are common. These symptoms usually worsen within days or weeks. Upon exertion, tachycardia, tachypnea and diffuse dry rales may be observed. Oral candidiasis is commonly seen as a coinfection.
- Hypoxemia is the most characteristic lab abnormality.
- Radiographic findings show diffuse, bilateral, symmetrical interstitial infiltrations and/or patchy ground-glass attenuation on chest computerized tomography (CT) scan.
- In moderate or severe cases, confirmation of diagnosis is highly recommended. Bronchoscopy will help to confirm diagnosis, even after empiric treatment for PCP.

PCP Treatment and Prophylaxis

- As the guidelines for treatment and prevention of PCP have not changed significantly over recent years, the clinician is encouraged to refer to the full [OI prevention and treatment guidelines](#) as well as the [Opportunistic Infections \(OIs\) in HIV/AIDS pocket card from the Florida/Caribbean AETC](#) for recommendations.

Toxoplasma gondii Encephalitis (TE)

TE is frequently due to reactivation of latent infection in protozoan *Toxoplasma gondii* IgG (+) patients. It rarely occurs in patients with CD4 > 200 cells/mm³. TE in Toxoplasma-IgG (-) persons is rare but can occur as primary infection or reactivation in patients who have negative insensitive assays or in those unable to produce detectable antibody.

Toxoplasmosis can be contracted by touching the hands to the mouth after gardening, cleaning a cat's litter box, or anything that came into contact with cat feces. It can also be contracted by eating raw or partly cooked meat, especially pork or lamb, or eating fruits and vegetables that are not washed, cooked or peeled.

Clinical Manifestations

- TE commonly presents with headache, confusion, fever or motor weakness which can progress to seizures, changes in mental status and coma.
- CT or MRI shows multiple contrast-enhancing lesions with surrounding edema. It also can present as a single brain lesion.
- Differential diagnosis includes CNS lymphoma, tuberculoma, cryptococcoma, bacterial brain abscess, Chagas disease and

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rarely, progressive multifocal leukoencephalopathy (PML). Most clinicians initially place the patients on empiric therapy; brain biopsy is reserved for patients who fail to respond to treatment.

TE Treatment and Prophylaxis

- As the guidelines for treatment and prevention of TE have not changed significantly over recent years, the clinician is encouraged to refer to the full [OI prevention and treatment guidelines](#) as well as the [Opportunistic Infections \(OIs\) in HIV/AIDS pocket card from the Florida/Caribbean AETC](#) for recommendations.

Tuberculosis (TB)

TB is the cause of death for 13% of HIV-infected patients, according to the World Health Organization (WHO). The estimated annual risk of reactivation of latent TB infection (LTBI) to active TB in the general population is about 12.9 per 1,000 persons-years. In contrast, the risk is increased and ranges from 35-162 per 1,000 person-years in HIV-infected individuals.

Clinical Manifestations and Diagnosis

- Patients with LTBI are asymptomatic.
- Patients with $CD4 > 350$ cells/mm³ usually have similar TB manifestations to non-HIV infected population. Although the majority of those patients have pulmonary TB, extrapulmonary diseases should be considered in all HIV-infected patients regardless of the CD4 count.
- In patients with advanced AIDS, chest radiographic findings differ from the classic pulmonary TB findings. They have less cavitory lesions and have more lower lobe, middle lobe, interstitial and miliary infiltrates. Mediastinal lymphadenopathy is also more common.
- Diagnosis of LTBI can be done by using the tuberculin skin test (TST) or using interferon gamma release assays (IGRA). IGRAs have more consistent and higher specificity (92%-97% vs. 56%-95% by TST). IGRAs also has less cross-reactivity with previous Bacillus Calmette-Guérin (BCG) vaccination. However, as with TST, severe immunosuppression can lead to false-negative results.
- Diagnosis of active TB is discussed in [Treatment of Tuberculosis American Thoracic Society, CDC, and Infectious Diseases Society of America, MMWR June 20, 2003 / 52\(RR11\);1-77](#) and the [CDC's OI guidelines](#).

Treatment of Drug susceptible TB

- Initial phase-2 months
 - Isoniazid (INH) + [rifampin (RIF) or rifabutin (RBT)] + ethambutol (EMB) + pyrazinamide (PZA) (AI).
- Continuation phase

- INH + (RIF or RBT) daily or three times a week (AIII), or twice weekly, but only if $CD4 > 100$ cells/mm³ (CIII).
- Duration of therapy: pulmonary TB-6 months; Pulmonary TB with cavitory lesion and positive culture after 2 months of TB therapy-9 months; extrapulmonary TB w/CNS, bone, joints infection-9 to 12 months; extrapulmonary TB in other sites- 6 to 9 months.
- IRIS (when it occurs) usually occurs in the first 3 months after ART is started while on TB therapy. The risk is increased in the first 2 months with $CD4 < 100$ cells/mm³. IRIS in these patients can present with high fever, increased respiratory symptoms, increased serositis and increased size and inflammation of the lymph nodes. Mild or moderate cases of IRIS can be treated with NSAIDs without changing anti-tuberculous treatment. In severe cases prednisone or methyl prednisolone at a dose of 1mg/kg gradually tapered after 1-2 weeks can be used.
- See [Table 2](#), [Table 6](#), and [Table 3](#), in the [OI guidelines](#) for detailed information regarding TB treatment dosing, drug-drug interactions among rifamycins and ART, and drug resistant TB.

Prevention

- Chronic suppression to prevent recurrent disease is not recommended.
- Preventing active TB is to treat LTBI either by INH daily or twice weekly for 9 months.

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