



Florida/Caribbean AIDS Education and Training Center

HIV CareLink

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EDITORS

Jeffrey Beal, MD, AAHIVS
(239) 839-4645
aetcbear@embarqmail.com

Joanne Orrick, PharmD, BCPS
(352) 273-7845
orricj@ufl.edu

MANAGING EDITOR

Kimberly Alfonso, MAcc
(813) 974-4430
alfonso@fmhi.usf.edu

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

Swati Modi, MD

Assistant Professor
University of Florida, Jacksonville
UF Center for HIV/AIDS Research, Education and Service (UF CARES)

The following is a summary of the new Guidelines published June 18th, 2008 which provide an update to previous guidelines and now combines Guidelines for Prevention and Tx of OIs into one document. The clinician is encouraged to download the complete document available online at http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf

Optimal Time to Start ART if OI Recently Diagnosed:

- Early initiation of ART near time of OI tx (within 1st 2 wks) should be considered for most pts with an acute OI, excluding TB
- For TB disease, awaiting a response to OI tx may be warranted before initiation of ART

Management of Acute OIs in Pts Receiving ART:

- **OI within 12 wks after starting ART:** Start tx of OI and continue ART
- **OI 12 wks after starting ART (despite complete virologic suppression):** Initiate tx for OI and continue ART. If CD4 ↑ suboptimal, consider ART modification.
- **OI among pts experiencing virologic and immunologic failure while on potent ART:** Start OI tx, modify ART using resistance testing.

Immune Reconstitution Inflammatory Syndromes (IRIS)

Symptoms:

- Usually fever and worsening of clinical manifestations of underlying OI
- Manifestations may be at site of previously recognized opportunistic

disease or may "unmask" disease at new sites; may also represent a response to a new pathogen.

- Usually develops within 4 to 8 wks after ART start and in pts with high VL and very ↓ CD4. However, IRIS has occurred many wks after ART and in sequestered sites such as bone.

Diagnosis of IRIS:

- Involves differentiation from progression of initial OI due to antimicrobial resistance and tx failure, vs. new OI, unrelated organ dysfunction, or drug toxicity

Therapy:

- Empiric. No well-controlled trials to guide use of nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids or when ART should be stopped. Inflammation may take wks or mos to subside.
- Moderate to severe symptoms should receive initial NSAID tx.
- If IRIS symptoms fail to improve, short-term corticosteroid successful in ↓ symptoms and morbidity
- IRIS does not appear to have implications toward pt survival, with the possible exception of cryptococcal meningitis IRIS

Save the Date

May 1-2, 2009

Rosen Centre Hotel
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18th Annual
HIV CONFERENCE



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IRIS with Cryptococcosis:

- As many as 30% of HIV pts with cryptococcal meningitis develop IRIS after ART
- Pt more likely to be ART naïve and have higher VL
- Mild-moderate IRIS: Continue ART and antifungal tx
- Severe IRIS: May be beneficial to delay ART until completion of induction tx (the 1st 2 wks) for severe cryptococcosis, especially if ↑ intracranial pressure (ICP). Some recommend short-course glucocorticosteroids.

Interferon-gamma release assays (IGRAs) for the detection of latent *Mycobacterium tuberculosis* infection:

- QuantiFERON-TB Gold and QuantiFERON-TB Gold In-Tube (Cellestis Limited) are FDA approved and available in the US. The T-SPOT.TB assay (Oxford Immunotec) is pending FDA approval.
- IGRAs have more consistent and higher specificity (92%–97%) compared to tuberculin skin test (TST) (56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*, and ↓ cross reactivity due to Bacillus Calmette-Guérin (BCG) vaccination or other nontuberculous mycobacteria exposure than the TST
- Estimated sensitivity is also ↑ with IGRAs: QFT-Gold (76–80%), T-SPOT.TB (87–88%), TST (~70%)
- For both the TST and IGRAs, advanced immunosuppression due to HIV may give false (-) results
- No. of pt visits to complete testing protocol can be ↓ to one with IGRAs
- TST remains useful for diagnosing LTBI, particularly in non-BCG-vaccinated pts and in cost-constrained settings
- More HIV studies needed to define IGRA role

ART in Management of TB Disease:

- Both rifampin (RIF) and rifabutin (RBT) induce CYP3A enzymes; RBT is not as potent as RIF but it is a substrate, leading to drug interactions with PIs and NNRTIs
- Concomitant use of RIF with ritonavir-boosted PIs results in subtherapeutic levels of PI and ↑ risk of hepatotoxicity
- For pts undergoing tx for active TB, starting ART with an efavirenz (EFV) or nevirapine (NVP)-based regimen is preferred - fewer interactions with RIF and evidence supporting use with RIF in the tx of active TB.
- Underdosing of ARVs or RBT can → HIV drug-resistant mutants or acquired rifamycin resistance. Overdosing RBT may → neutropenia and uveitis. Therapeutic drug monitoring for RBT and/or PIs or NNRTIs may be needed.
- Refer to guidelines for dose adjustments of Rifamycins with ARV therapy or consult an expert

Optimal Time to Start ART in ART-Naïve Pts with Active TB: Pending Results of Ongoing Studies, Experts Recommend Making the Decision Based Upon the Immunological Status of the Pt:

- Anti-TB tx must be started immediately
- **CD4 count <100 cells/μL:** start ART after ≥2 wks of TB tx to ↓ confusion about overlapping toxicities, drug interactions, and paradoxical reactions or IRIS
- **CD4 count of 100–200 cells/μL:** Some experts delay ART initiation until the end of the 2-mo intensive phase of anti-TB tx
- **CD4 count >200 cells/μL:** start ART during the anti-TB maintenance phase
- **CD4 count >350 cells/μL:** start ART after finishing anti-TB tx

TB Tx in Pts Already on ART:

- Anti-TB tx must be started immediately
- Modify ART to ↓ drug interactions and maintain virological suppression
- If TB occurs in the setting of virologic failure, perform resistance testing and construct new ART minimizing drug interactions with anti-TB agents. Consider expert consultation.

Paradoxical TB-associated IRIS:

- Exaggerated inflammatory response to TB tx
- Usually occurs 1–3 mos after starting ART
- Risk is > when ART is started within the first 2 mos of TB tx and when CD4 count is <100 cells/μL
- Tx symptomatically with NSAIDs without a change in anti-TB tx or ART if not severe
- Improvement has been observed with prednisone or methylprednisolone (approximately 1 mg/kg body weight; taper after 1–2 wks)

Hepatitis B Virus (HBV) Infection and HIV:

Prevention of the Disease:

- Majority of HIV-infected pts with isolated anti-HBc are not immune and should be vaccinated with a primary series of HBV vaccine (consider HBV DNA to r/o chronic HBV)
- CD4 <200 cells/μL: Vaccinate and test for anti-HBs 1 month after series complete. If no response, revaccination should be considered or delay until sustained ↑ CD4 count achieved on ART.
- Optimizing ART to attain good immunological response is associated with better HBV vaccine response
- If anti-HBs (1 mo after series) is < 10 IU/mL, a 2nd series is recommended



- Some experts suggest once yearly evaluations for pts who have an ongoing risk of HBV acquisition, as in dialysis pts (loss of antibody among dialysis pts has translated into loss of protection against HBV infection)

Criteria for Tx of HBV-HIV Co-infection:

- HIV/HBV-co-infected pts initiating ART should be treated for HBV, regardless of the level of HBV DNA, either with antiviral agents active against both HIV and HBV or with antiviral agents with independent activity against each
- If not initiating ART, anti-HBV therapy is indicated for HBeAg (+) pts with abnormal ALT levels and HBV DNA levels $>20,000$ IU/mL ($>10^5$ copies/mL) and for HBeAg (-) pts with abnormal ALT levels and HBV DNA levels $>2,000$ IU/mL ($>10^4$ copies/mL)
- Due to risk of liver disease progression, some experts recommend tx at any level of detectable HBV DNA, especially with \uparrow ALT levels or significant histological inflammatory activity and/or fibrosis on liver biopsy

Tx of HIV-HBV Co-infection:

- Lamivudine, emtricitabine, or tenofovir should not be used for tx of HBV in co-infected pts not treated with combination HIV ART
- PegIFN alfa suppresses HIV replication and does not select for resistance mutations that will influence future HIV tx. PegIFN alfa-2a might be considered for tx of HBV infection in HIV co-infected pts irrespective of need for HIV ART.
- Adefovir is active in both HBeAg (+) and HBeAg (-) pts with chronic HBV. Studies have not demonstrated K65R or K70E mutations after up to 4 yrs of tx with adefovir. Adefovir might be considered for tx of HBV in HIV co-infected pts irrespective of the need for tx of HIV.
- Entecavir should not be used as monotherapy for tx of HBV in HIV co-infected pts who are not also receiving combination ART due to HIV-associated mutation (M184V)
- Emergence of HBV resistance is common with telbivudine monotherapy and it is not recommended

Tx of HBV in HIV-infected Pts Who Are Not Receiving ART:

- Agents with sole activity against HBV only must be selected (i.e. adefovir or pegIFN alfa-2a) X 48 wk
- Early initiation of ART should also be considered

Tx of HBV in HIV-infected Pts Who Require ART:

- Emtricitabine and tenofovir (available as Truvada[®]) is recommended due to ease of administration, tolerability, and dual HBV and HIV activity
- Entecavir can be considered for pts with HIV control who do not demonstrate YMDD motif (M204V/I) mutations (close monitoring of HBV DNA needed if these mutations present since \uparrow risk of entecavir resistance)

HBV, HCV and HIV Infected Pts:

- Need for ART should be the first priority
- If ART is not required IFN based therapy, which suppresses both HCV and HBV, should be considered

Duration of Anti-HBV Therapy:

- HIV/HBV-coinfected individuals who are HBeAg (+) and who become HBeAg (-) and anti-HBe (+) on lamivudine therapy should be treated for a minimum of 6–12 months beyond HBeAg seroconversion. If receiving ART, continue HBV therapy, even if seroconverted to anti-HBe
- Viral suppression without HBeAg seroconversion, tx with anti-HBV agents should be continued indefinitely

Lamivudine-resistant HBV:

- If fully suppressed HIV: consider the addition of adefovir or pegIFN to lamivudine, or exchange tenofovir for one of the other nucleoside agents in the ART regimen.
- Lamivudine or emtricitabine should be continued as this may \downarrow development of mutations to other anti-HBV drugs

Risk of Hepatocellular Carcinoma (HCC):

- Optimal screening strategy is unknown. AFP screening should be confirmed with liver imaging. In pts with documented cirrhosis hepatic ultrasound imaging is recommended at 6–12 month intervals.
- Co-infected persons with well-controlled HIV infection found to have liver decompensation [defined as Child-Pugh-Turcotte (CPT) score ≥ 7 and/or Model for End-stage Liver Disease (MELD) score >10] or evidence of early HCC should be referred for orthotopic liver transplantation. Post-transplant HBV tx is required.

Special considerations for pregnancy and Opportunistic Infections are available at http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf

[Click here to access a supplemental document containing a summary of additional infections included in the OI Prevention and Tx Guidelines](#) (e.g. *Pneumocystis jirovecii*, *Toxoplasma gondii*, Mycobacterium Avium Complex Disease, Histoplasmosis, and others).

The complete collection of previous issues of HIV CareLink are available online.

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