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of West Coast Infectious Diseases in Safety Harbor, FL

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of the Florida/Caribbean AETC

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Treatment of Tuberculosis (TB) in HIV/AIDS

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Editors:

Jeffrey Beal, MD, AAHIVS

Joanne J. Orrick, PharmD, AAHIVE

Jerry Jean Stambaugh, PharmD

Managing Editor:

Theresa C. Skipper, MPH

Layout:

Maximo Lora, BA

Ashley Vandonkelaar, BFA

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This convenient pocket-sized guide is intended to assist clinicians in managing HIV-infected patients (pts) with latent tuberculosis infection (LTBI) and drug-susceptible tuberculosis infection (TB). This guide summarizes the guidelines for the diagnosis and treatment (tx) of LTBI and TB and includes adult dosing, available dosage forms, drug-drug interactions, side effects, and important pt counseling points.

The information contained in this publication is intended for medical professionals. If a serious adverse event occurs please report the event to the FDA (www.fda.gov/Safety/MedWatch/HowToReport/default.htm), to help increase pt safety. Recognizing the rapid changes that occur in this field, clinicians are encouraged to consult with their local experts or research the literature for the most up-to-date information to assist with individual tx decisions for their pt.

In addition to the references listed below, consult www.cdc.gov/tb and www.aidsinfo.nih.gov for up-to-date information on the diagnosis and tx of LTBI and/or active TB.

- Centers for Disease Control and Prevention. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. MMWR 2009; 58(No. RR-4): [19-27, 145, 150, 167, 171, 179-182, 195-7]. Available at http://www.aidsinfo.nih.gov/contentfiles/Adult_OI.pdf
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- Centers for Disease Control and Prevention. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium tuberculosis Infection-United States, 2010. MMWR 2010; 59(No. RR-5):[1-24]. Available at <http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf>
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011; 1-167. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed February 6, 2012

TREATMENT FOR LTBI

- All pts with a (+) test (TST or IGRA) for TB infection should have a CXR and clinical evaluation to rule out active TB disease prior to initiating LTBI tx
- Treat HIV-infected pts for LTBI if any of the following conditions are met:
 - (+) diagnostic test for LTBI **or**
 - Close contact of person with infectious pulmonary TB **or**
 - Inadequately treated TB (e.g., old fibrotic changes on chest radiography)
- LTBI regimens:
 - Isoniazid (INH) 5 mg/kg (max of 300 mg) daily for 9 mos (All) **or**
 - (INH 15 mg/kg [max of 900 mg] **plus** rifapentine [RPT] 900 mg [if ≥ 50 kg] **or** 750 mg [if 32.1-49.9 kg]) once weekly **via directly observed tx (DOT)** for 12 wks **only if pt is otherwise healthy, is not pregnant, and is not on ART or**
 - INH 15 mg/kg (max of 900 mg) twice weekly **via DOT** for 9 mos (BII) **or**
 - Rifampin (RIF) 10 mg/kg (max 600 mg) daily for 4 mos (BIII)
 - Due to increased risk of hepatotoxicity, 2 mos RIF/PZA regimen is not recommended (DI)

Monitoring Patients Treated for LTBI

- Monitor all pts clinically at least monthly including physical exam and side effect assessment
- Perform baseline LFTs (AST or ALT and total bilirubin) in all pts and check monthly in pts with risk factors for hepatotoxicity (e.g., liver disease, regular alcohol use, receiving ART)
- Perform CBC with diff and platelets at baseline if rifampin used and repeat testing if results abnormal or pt has symptoms suggestive of hematologic adverse reaction
- Instruct pt to seek medical attention for the following: fever, yellow eyes, dizziness, rash, or aches or > 1 day of nausea, vomiting, weakness, abdominal pain, loss of appetite
- D/C INH-RPT if ALT ≥ 5x ULN (even if no symptoms) or ALT ≥ 3x ULN with symptoms

ACTIVE TUBERCULOSIS

Initiating ART in HIV-infected Patients with Active TB

- All HIV-infected pts with active TB should start ART
- The DHHS Guidelines provide the following recommendations regarding the timing of initiation of ART in pts with active TB:
 - CD4 < 200 cells/mm³: start ART within 2-4 wks of starting TB tx (AI)
 - CD4 200-500 cells/mm³: start ART within 2-4 wks, or at least by 8 wks after initiation of TB tx (AIII)
 - CD4 > 500 cells/mm³: start ART within 8 wks of starting TB tx (recommended by most panel members) (BIII)

NOTE: Recent data from CROI 2011 (www.natap.org/2011/CROI/croi_138.htm) suggest that pts with CD4 < 50 cells/mm³ should start ART within 2 wks of starting TB tx

Contraindications to a TST¹

- Only contraindicated for persons with a severe reaction to prior TST (e.g., necrosis, blistering, anaphylactic shock or ulceration)
- 1. TST is NOT contraindicated in infants, children, pregnant women, or persons previously vaccinated with BCG. Pts with prior (+) TST should not receive TST; chest x-ray (CXR) or symptomatic cough screen should be done annually**

Interferon (IFN)-Gamma Release Assays (IGRAs)

- IGRAs are *in vitro* assays that detect IFN-gamma release in response to Mycobacterium tuberculosis specific antigens. Specificity of IGRA ranges 92%-97%, compared to 56%-95% for TST. Three FDA approved assays are available:
 - QuantiFERON® - TB Gold (Cellestis Limited)
 - QuantiFERON® - TB Gold In-Tube (Cellestis Limited)
 - T-SPOT® TB Test (Oxford Immunotec Limited)
- It is important that test samples be drawn, transported, processed, and interpreted according to each manufacturer's recommendations
 - Blood samples must be processed within 8-16 hrs after collection (time requirements differ among assays) so that the white blood cells remain viable
- Additional information about IGRAs can be found online at www.cdc.gov/tb/publications/factsheets/testing/IGRA.htm

Recommendations on the Use of IGRA

- IGRA can be used in place of a TST in all situations when a TST is recommended with some preferences noted below.
- IGRA is preferred in:
 - Persons who have received BCG whether as a vaccination or as cancer tx
 - Groups that have low rates of return for TST read (e.g., homeless persons, drug-users, and those who failed to return within 72 hrs for TST read in the past)

Repeat Testing for LTBI Recommended When:

- CD4 increases to > 200 cells/mm³ in response to ART since may have false (-), TST or IGRA, when severely immunocompromised
- Exposed to an active TB case; retest at the time of exposure and again in 8-10 wks
- Pt is identified to have a risk factor for infection with *M. tuberculosis* (incarcerated or lived in a congregate setting)
- Abused IV drugs, been homeless, or living in a shelter
- Traveled to a country where active TB disease is common (most countries in Latin American, the Caribbean, Africa, Asia, Eastern Europe and Russia)
- Worked in a migrant farm camp
- Been in close contact with recent immigrants from high-prevalence countries
- Had symptoms suggestive of active TB disease

NOTE: Annual testing is recommended for pts who have ongoing risks such as those listed. Pts with a hx of (+) TST or IGRA should have annual CXR or symptomatic cough screen.

DIAGNOSIS OF LTBI: Tuberculin Skin Test (TST) or Interferon Gamma Release Assay (IGRA)

- Pts with HIV are at extremely high risk (10% risk per yr) for developing active TB if infected with TB
- Test all HIV-infected pts for LTBI at time of entry into care
- All pts with (+) test for LTBI should be evaluated for active TB (i.e. chest x-ray and clinical evaluation) before starting tx for LTBI

Tuberculin Skin Test

- The Mantoux tuberculin skin test (TST) method is recommended and each step must be properly performed to increase accuracy of results
- Pts who will have repeat TST should have two-step testing done initially. Pts with (-) initial TST should have 2nd test 1-3 wks later; a (+) 2nd test indicates prior infection (booster effect)

Administration of TST

- Use ¼ to ½ inch 27-gauge needle and tuberculin syringe
- Inject 0.1 mL of tuberculin purified protein derivative (PPD) intradermally into the inner surface of the forearm
- When done correctly, a wheal (pale elevation of skin), 6-10 mm in diameter should be produced
- If wheal not produced, repeat placement on opposite arm or on same arm ≥ 2 inches from original site

Reading of TST

- Reaction measured in 48 to 72 hrs (must be done by properly trained health professional)
 - (+) reaction can be measured accurately for ≤ 7 days, (-) for ≤ 72 hrs
 - Schedule repeat TST or IGRA if pt does not return within 72 hrs
- Measure area of induration (raised palpable, hardened area), not areas of redness, across the forearm
- Report results in mm (not as "positive" or "negative")

Interpretation of TST Results

- Reaction of ≥ 5 mm is considered (+) in HIV-infected persons
- False (+) may result if:
 - Infection with nontuberculous mycobacteria
 - Prior Bacillus Calmette-Guérin (BCG) vaccine (reactivity wanes over time; use of IGRA preferred)
 - Improper admin and/or interpretation of results
- Possible reasons for false (-) (list is not all inclusive):
 - Anergy (inability to react to TST due to immune suppression; anergy testing with "controls" is not recommended)
 - Recent TB infection (2-8 wks after exposure)
 - Extremes of age (newborns, elderly)
 - Concurrent infections (certain bacterial, fungal, or viral)
 - Overwhelming TB disease
 - Immune suppression due to meds, malignancy, or HIV
 - Recent live virus vaccine (wait 4-6 wks to admin TST)
 - Problem with tuberculin used (e.g., improper storage), poor admin technique (e.g., giving subcutaneous instead of intradermally), improper reading and/or interpretation of results

ACTIVE TUBERCULOSIS

Diagnosis of Active Tuberculosis Infection

- Evaluate all pts with a (+) TB test (TST or IGRA) for active TB
- Test for TB in all pts suspected of having active TB; a (-) test does not rule out active TB, particularly in immunocompromised pts
- Symptoms of active pulmonary TB:
 - Prolonged productive cough (usually > 3 wks), chest pain, hemoptysis, fever/chills, night sweats, decreased appetite/weight loss, fatigue
- Pts with HIV are more likely to have extra-pulmonary TB compared to those without HIV. Symptoms and clinical presentation depend on the site of infection
- CXR: Abnormalities usually seen in upper lobe. Pts with HIV may have atypical CXR appearance
- Sputum smear and culture:
 - 3 sputum specimens (8-12 hrs apart) should be sent for smear examination (AFB stain and nucleic acid amplification test [NAAT]) and culture (even if smear is [-])

NOTE: In extra-pulmonary TB, sputum smear and culture are usually (-) until late in disease

Treatment of Drug-Susceptible Active Pulmonary TB in HIV-infected patients

*Consult a TB/HIV expert for the management of extra-pulmonary and/or drug resistant TB

- All HIV pts should receive directly observed tx (DOT)
- All pts with presumed or confirmed active TB should be started on a 4-drug regimen of isoniazid (INH), rifampin [RIF] or rifabutin [RBT], pyrazinamide (PZA), and ethambutol (EMB)
 - Rifabutin is often substituted for rifampin in HIV-infected pts since it is a less potent inducer of drug metabolism and can be used with most ARVs (see drug interaction table)
 - Rifapentine is a long-acting rifamycin that is dosed once weekly, but **should not be used** in HIV-infected pts due to higher rates of relapse and resistance
- Initial phase:** INH + (RIF or RBT) + PZA + EMB daily for 2 mos (discontinue EMB prior to 2 mos if susceptible to INH, RIF/RBT, PZA)
- Continuation phase:** INH + (RIF or RBT) 3x/wk via DOT for 4-7 mos
 - Extend the continuation phase from 4-7 mos if the sputum culture remains (+) at 2 mos (send repeat sputum for susceptibility testing and consult an expert if resistant to INH and/or RIF)

Adult Dose of Agents for Active TB

| | | INH | RIF ² | RBT ² | PZA | EMB |
|-------|-------|-----|------------------|------------------|-------|-------|
| Daily | mg/kg | 5 | 10 | 5 | 15-30 | 15-25 |
| | max | 300 | 600 | 300 | 2000 | 1600 |
| 3x/wk | mg/kg | 15 | 10 | 5 | 50-70 | 30 |
| | max | 900 | 600 | 300 | 3000 | 2400 |

2. See Drug Interactions table for interactions and dosing recommendations with ART

Monitoring Therapy for Pulmonary TB

- Monitoring pt clinically at least monthly
- Sputum for smear and culture monthly until 2 consecutive (-) culture results
 - If initially smear (+), test more frequently (e.g., every 2 wks) to assess tx response
- Repeat CXR after 2 mos of tx [not essential if cultures (+) at diagnosis but if (-) at diagnosis and CXR improving, presumptive diagnosis of TB can be made]. End of tx CXR recommended by most to document baseline.
- Repeat drug susceptibility testing if culture (+) after 3 mos of tx. Consider tx failure if (+) culture at 4 mos. Consult a TB/HIV specialist for pts who fail tx and/or have drug resistance.

Monitoring for Adverse Drug Effects (ADE)

Baseline:

- Obtain hx for risk factors for ADEs (diabetes, renal failure, hepatitis, alcohol use) and concurrent medications
- Obtain baseline labs - LFTs, TBili, uric acid, BUN/Cr, CBC with differential
- If pt is to be on EMB, obtain baseline eye exam for both acuity and color discrimination
- Educate pt on the signs and symptoms of hepatitis
- Encourage pt to immediately report symptoms of hepatitis or changes in vision

Monthly:

- Interview pt for ADEs, changes in medications, and screen for possible drug interactions
 - Vomiting - (increases risk for drug resistance)
 - Change time of TB Rx dose, have pt eat 2 hrs before dosing
 - Add metoclopramide 5 to 10 mg or promethazine 25 mg 30 min before TB drugs
 - Persistent cases may require lorazepam 0.5 to 1 mg 30 min before TB meds
 - Peripheral neuropathy (INH) - Ensure pt is receiving vitamin B6 25-50 mg po once daily
 - Itching - add antihistamine 30 min before TB Rx and prn
- If on EMB, do eye exam for acuity and color. If decreased, stop the EMB. Check dose, renal fx, serum drug levels, refer to ophthalmologist. Consult TB/HIV expert for TB regimen modification.
- LFTs, TBili (INH,RIF/RBT,PZA) - Continue Rx unless AST > 3x ULN and symptomatic, AST ≥ 5x ULN and asymptomatic, or significant increases in bilirubin and/or alkaline phosphatase. Consult a TB/HIV expert for management of these cases.

Periodically during tx:

- Uric acid levels do not need to be followed unless symptomatic. (e.g., gouty arthritis). If symptomatic may add allopurinol, NSAIDS.
- If at risk or otherwise indicated, do lab work for renal function, CBC with differential

Monitoring for Adverse Drug Effects (ADE)

(Continued)

Periodically during tx: (continued)

- Consider therapeutic drug monitoring for TB, HIV (NNRTI, PI, integrase inhibitor, maraviroc) and other interacting drugs if signs of ADE, renal or hepatic disease or possible tx failure
- If severe reaction occurs, consult an TB/HIV expert, or call TB Hotline 1-800-4TB-INFO (1-800-482-4636) for assistance**

Immune Reconstitution Inflammatory Syndrome (IRIS)

- Pts may have worsening or new onset symptoms of active TB following initiation (more common in pts with CD4 < 50 cells/mm³ and pts with higher pre-ART HIV viral load)
- Continue both ART and anti-TB tx while managing IRIS
- Mild cases can be treated with NSAIDs while more severe cases may require corticosteroid tx

Drug-drug Interactions with Rifamycins and ARVs

Rifampin (RIF)⁴-based Regimen with ARVs

| NNRTIs | |
|--|---|
| Efavirenz 600 mg every night (standard) or consider ↑ to 800 mg every night (pts > 60 kg) | |
| Do not use RIF with etravirine, nevirapine, or rilpivirine | |
| Protease Inhibitors | |
| Due to significant interactions and/or need for high doses of ritonavir to overcome the interactions, it is impractical to use RIF with a PI-containing regimen (boosted or unboosted) and it is not recommended | |
| Integrase Inhibitor | |
| Increase raltegravir (RAL) to 800 mg bid | |
| CCR5 inhibitor | |
| Not recommended, but if used: maraviroc (MVC) 300 mg bid (with potent CYP3A inhibitor); MVC 600 mg bid (without potent CYP3A inhibitor) | |
| Rifabutin (RBT)-based Regimen with ARVs | |
| NNRTIs | |
| NNRTI | RBT |
| Efavirenz (standard dose) | 450-600 mg daily or 600 mg 3x/wk if no PI in the regimen ⁵ |
| Etravirine standard dose (do not combine with RBT if used with RTV-boosted PI) | 300 mg daily or 3x/wk (standard dose) |
| Nevirapine (standard dose) | 300 mg daily or 3x/wk (standard dose) |
| Rilpivirine | Do not use RBT with rilpivirine |
| Protease Inhibitors | |
| Ritonavir-boosted PIs | |
| ATV/r | RBT 150 mg every other day or 3x/wk. Some recommend RBT 150 mg daily or 300 mg 3x/wk. TDM recommended since LPV/r with RBT 150 mg 3x/wk has been shown to result in sub-therapeutic RBT levels in some pts. |
| DRV/r | |
| FPV/r | |
| LPV/r | |
| SQV/r | |
| TPV/r | |
| Unboosted PIs | |
| ATV | RBT 150 mg every other day or 3x/wk |
| FPV | RBT 150 mg daily or 300 mg 3x/wk |
| Integrase Inhibitor | |
| No dosage adjustments recommended for RAL or RBT | |
| CCR5 inhibitor | |
| MVC 150 mg bid (with potent CYP3A inhibitor); MVC 300 mg bid (without potent CYP3A inhibitor or inducer); Dose RBT based on other drugs in regimen (consider TDM) | |

4. All are with RIF standard dose

5. Some experts recommend 450 mg 3x/wk;

Hollender E, Stambaugh J, Ashkin D, Akinlabi O, Narita M. (2003). The Concomitant Use of Rifabutin and Efavirenz in HIV/ TB Co-infected Patients. 10th Conference on Retroviruses and Opportunistic Infections, abstract 785.

Therapeutic Drug Monitoring

- Interactions can be complex and difficult to predict in individual pts
- Consider therapeutic drug monitoring in pts who are slow to respond to tx or have complex drug-drug interactions
- TDM should be considered for most pts with renal insufficiency or on dialysis
- Consider TDM in pts on cycloserine
- Consult an TB/HIV expert for assistance in managing these pts
- HIV and TB drug levels are available through many commercial labs as well as the Infectious Disease Pharmacokinetic Laboratory at the University of Florida in Gainesville (<http://idpl.cop.ufl.edu/>)

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Drugs Used for Treatment of Drug-Susceptible Active TB and LTBI

| Drug | Dosage Form | Hepatic/Renal | Food Restrictions | Important Points |
|--------------------------------|--|--|--|--|
| Isoniazid (INH) | 100, 300 mg tab; 50 mg/5 mL oral soln; injection (100 mg/mL) | <ul style="list-style-type: none"> Do not use in pts with acute hepatic disease Consider dosage ↓ in pts with CrCl < 10 mL/min | Empty stomach (30 mins before or 2 hrs after a meal) | <ul style="list-style-type: none"> Avoid antacids for 2 hrs before and after INH Most common/severe AEs: hepatotoxicity, peripheral neuropathy, optic neuritis, rare hematologic or dermatologic reactions Co-admin pyridoxine (vitamin B6) 25-50 mg once daily to prevent neuropathy |
| Rifabutin (RBT) | 150 mg cap | <ul style="list-style-type: none"> No dosage adjustments appear to be necessary in pts with hepatic impairment CrCl < 30 mL/min: ↓ RBT dose by 50% | With or without food, may open cap and mix in food (applesauce) | <ul style="list-style-type: none"> Most common/severe AEs: red-orange discoloration of body fluids (e.g., urine, sweat, tears), rash, arthralgias, hematologic reactions (anemia, neutropenia, thrombocytopenia), uveitis (dose-related), hepatotoxicity |
| Rifampin (RIF) | 150, 300 mg cap; injection (600 mg vial) | <ul style="list-style-type: none"> Do not exceed 8 mg/kg/day in pts with hepatic impairment CrCl < 10 mL/min: ↓ RIF dose by 50% | Empty stomach (1 hr prior to or 2 hrs after meal); may open cap and mix in food (applesauce) | <ul style="list-style-type: none"> Most common/severe AEs: GI disturbances, red-orange discoloration of body fluids (e.g., urine, sweat, tears), rash, flu-like syndrome, hematologic reactions (hemolytic anemia, leukopenia, thrombocytopenia), hepatotoxicity, hypersensitivity reaction (dermatologic manifestations including urticaria, rash, and possible serious reactions; renal manifestations including ↑ BUN, ↑ uric acid, acute renal failure) |
| Rifapentine (RPT) ³ | 150 mg tab | <ul style="list-style-type: none"> No dosage adjustments appear to be necessary in pts with hepatic impairment Not studied in renal impairment (17% renal elimination) | Take with food | <ul style="list-style-type: none"> Most common/severe AEs: red-orange discoloration of body fluids (e.g., urine, sweat, tears), rash, pyuria, hematologic reactions (anemia, neutropenia, thrombocytopenia), hepatotoxicity |
| Ethambutol (EMB) | 100, 400 mg tab | <ul style="list-style-type: none"> Use with caution in pts with hepatic disease CrCl < 30 mL/min or HD: 15-25 mg/kg per dose 3x/week | Take with food to ↓ GI upset | <ul style="list-style-type: none"> Most common/severe AEs: GI upset (nausea, vomiting, anorexia), optic neuritis, peripheral neuropathy, arthralgias, hepatotoxicity, hyperuricemia, rash, hypersensitivity reaction |
| Pyrazinamide (PZA) | 500 mg tab | <ul style="list-style-type: none"> Contraindicated in pts with hepatic disease CrCl < 30 mL/min or HD: 25-35 mg/kg 3x/week | With or without food | <ul style="list-style-type: none"> Most common/severe AEs: hepatotoxicity, arthralgias/myalgias, ↑ uric acid, rare hematologic reactions (thrombocytopenia, porphyria, sideroblastic anemia) |

3. Prifitin® [package insert]. Bridgewater, NJ: Sanofi-Aventis; 2010.