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Southeastern National Tuberculosis Center
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sntc.medicine.ufl.edu

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

• Pts with HIV are at extremely high risk (10% per year) for developing TB disease.
• Test all HIV-infected pts for LTBI at time of entry into care
• All pts with (+) TST 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 with HIV should have TST done twice, with at least 72 hrs between tests.

Administration of TST

• Use 1/1000 5 mm-6 mm tuberculin purified antigen heptas (Fuji 10 mg, Lederle 6 mg, or MRC-Tennant 70 mg). 1 tuberculin should be 0.1 mL (0.1 mL/mL in diameter should be produced).
• If while not used, 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 5 days, (-) for 7 days
• 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 2.5 mm is considered (+) in HIV-infected persons
• False (+) may result from:
  • Infection with nontuberculous mycobacteria
  • Prior Bacillus Calmette-Guérin (BCG) vaccine reaction
  • Reactivity to other environmental antigens
  • Improper administration and/or interpretation of results
• Possible reasons for false (-) (not list all inclusive):
  • Anergy (inability to react to TST due to immune suppression; anergy testing with controls is not recommended)
  • Recent TB infection (2-6 weeks after exposure)
  • Extremes of age (newborns, elderly)
  • Concurrent infections (certain bacterial, fungal, or viral)
  • Overwhelming infection
  • Immune suppression due to meds, malignancy, or HIV
  • Recent live virus vaccine (wait 4-6 wks to administer)

Contraindications to a TST

• Only contraindicated for persons with a severe reaction to TST (e.g., necrosis, blistering, anaphylactic shock or ulceration)
• TST is NOT Done if pt is immunocompromised, e.g., has received chemotherapy, or persons previously vaccinated with BCG. Pts with (+) TST should not receive BCG vaccine (oral or cutaneous) 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 IGRAs ranges from 90% to 100%, sensitivity 50%-90% for TST. Three FDA approved assays are available:
  • QuantiFERON®-TB Gold (Cellestis Limited)
  • QuantiFERON®-TB Gold Plus (Cellestis Limited)
  • T-SPOT® TB Test (Oxford Immunotec Limited)
• It is important that test samples be drawn, transported, processed, and interpreted in accordance with each manufacturer’s recommendations.
• Blood samples must be processed within 8-16 hrs after collection (time of antigen exposure 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

IGRAs can be used in place of a TST in all situations when a TST is recommended with some preferences noted below.
• IGRA is preferred:
  • Persons who have received BCG whether as a vaccination or as cancer tx
  • Groups that have lower rates of return for TST read (e.g., homeless population, identification among assay groups) so that the white blood cells remain viable
• Additional information about IGRA can be found online at www.cdc.gov/tb/publications/factsheets/testing/IGRA.htm

Contraindications to IGRA

• Only contraindicated for persons with a severe reaction to prior TST (e.g., necrosis, blistering, anaphylactic shock or ulceration)
• TST is NOT Done if pt is immunocompromised, e.g., has received chemotherapy, or persons previously vaccinated with BCG. Pts with (+) TST should not receive BCG vaccine (oral or cutaneous) or symptomatic cough screen should be done annually

TREATMENT FOR LTBI

• All pts with (+) TST (or IGRA) for TB infection should have a CXR and clinical evaluation to rule out active TB disease

Tuberculosis infection for LTBI if any of the following conditions are met:
• (+) diagnostic test for LTBI or
• Close contact of person with infectious pulmonary TB or
• Inadequate LTBI treatment (e.g., old flares on chest radiography)

LTBI regimens:

• Isoniazid (INH) 5 mg/kg (max of 300 mg) daily for mos (All)
• INH 15 mg/kg (max of 900 mg) plus rifapentine (RPT) 900 mg (regimen also allows 400 mg of RIF) daily for 4 mos (All)
• Rifampin (RIF) 10 mg/kg (max of 600 mg) daily for 4 mos (All)
• 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 liver function (AST and ALT 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 hepatotoxicity (e.g., increased liver enzymes, fatigue)
• Instruct pt to seek medical evaluation for the following: fever, yellow eyes, dizziness, rash, or aches or > 1 day of nausea, vomiting, any abdominal pain, loss of аппети
• D/C INH/RIF-ALT if 5 x ULN (even if no symptoms) or ALT > 3 x ULN with symptoms

ACTIVE TUBERCULOSIS

Initiating ART in HIV-Infected Patients with Active TB

All HIV-infected patients with active TB should start ART

The DHHS Guidelines provide the following recommendations for the timing of initiation of ART in pts with TB:
• CD4 > 200 cells/mm3: start ART within 2-4 wks of starting TB tx
• CD4 ≤ 200 cells/mm3: start ART within 2-4 wks, or at least by 8 wks after initiation of TB tx
• CD4 ≤ 500 cells/mm3: start ART within 8 wks of starting TB tx (review panel recommendations)
Priftin®

All pts with presumed or confirmed active TB should be started

**Treatment of Drug-Susceptible Active Pulmonary TB**

- Pyrazinamide (PZA) 500 mg tab
- Rifapentine (RPT)
- Rifabutin (RBT) 150 mg cap
- Rifampin (RIF) 150, 300 mg cap;

**ACTIVE TUBERCULOSIS**

- 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 presentations 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 [+] or -)

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**

- 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 therefore be used in pts with impaired liver function
- Rifapentine is a long-acting rifamycin that is dosed once weekly, but should not be used in HIV-infected pts due to risk of acute hepatitis and relapse
- 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)
- Combination phase: INH + (RIF or RBT) 3x/wk via DOT for 4-7 mos
- Extended the combination 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)

**Drug Dosage Form**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hepatic/Renal Food Restrictions</th>
<th>Important Points</th>
</tr>
</thead>
</table>
| Isoniazid (INH) | 100, 300 mg tab; 50 mg/mL oral soln; injection (100 mg/mL) | • Do not use in pts with acute hepatic disease | Empty stomach (30 mins before or after INH)
| | | • Consider dosage adjustments in pts with CrCl < 10 mL/min | 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 | • No dosage adjustments appear to be necessary in pts with hepatic impairment | Empty stomach (1 hr prior to or 2 hrs after meal); may take with food, may consider cap and mix in food (applesauce)
| | | • With or without food, may consider cap and mix in food (applesauce) | Most common/severe AEs: distal dorsal edema, red-orange discoloration of body fluids (e.g., urine, sweat, tears), rashes, arthralgias, hematologic reactions (anemia, neutropenia, thrombocytopenia), uveitis (dose-related), hepatotoxicity
| Rifampin (RIF) | 150, 300 mg cap; injection (600 mg vial) | • Do not exceed 8 mg/kg/day in pts with hepatic impairment | Empty stomach (1 hr prior to or 2 hrs after meal); may take with food, may consider cap and mix in food (applesauce)
| | | • CrCl < 30 mL/min; RBT dose by 50% | Most common/severe AEs: distal dorsal edema, red-orange discoloration of body fluids (e.g., urine, sweat, tears), rashes, arthralgias, hematologic reactions (anemia, neutropenia, thrombocytopenia), hepatotoxicity, hypersensitivity reaction (dermatologic manifestations including urticaria, rash, and possible anaphylaxis, rare), laboratory abnormalities (including liver function test abnormalities in 15% of pts) |
| Rifapentine (RPT) | 150 mg tab | • No dosage adjustments appear to be necessary in pts with hepatic impairment | Take with food
| | | • Not studied in renal impairment (17% renal elimination) | Most common/severe AEs: distal dorsal edema, red-orange discoloration of body fluids (e.g., urine, sweat, tears), rashes, arthralgias, hematologic reactions (anemia, neutropenia, thrombocytopenia), hepatotoxicity
| Ethambutol (EMB) | 100, 400 mg tab | • Use with caution in pts with hepatic disease | Take with food to ↓ GI upset
| | | • CrCl < 30 mL/min; HD: 15-25 mg/kg per dose 3x/week | Most common/severe AEs: GI upset (nausea, vomiting, anorexia), optic neuritis, peripheral neuropathy, arthralgias, hepatotoxicity, hypersensitivity reaction, hyperuricemia, rash, hypersensitivity reaction
| Pyrazinamide (PZA) | 500 mg tab | • Contraindicated in pts with hepatic disease | Take with or without food
| | | • CrCl < 30 mL/min; HD: 25-35 mg/kg 3x/week | Most common/severe AEs: hepatotoxicity, arthralgias/myalgias, ↑ uric acid, rare hematologic reactions (anemia, neutropenia), peripartum, porphyria, sideroblastic anemia

**Monitoring for Drug Effectiveness (ADE)**

- **Baseline**: Obtain tx for risk factors for ADEs (diabetes, renal failure, hepatic, alcohol use) and concurrent medications
- Obtain baseline labs - LFTs, TBili (INH, RIF/RBT, PZA)
- Prolonged productive cough (usually > 3 wks), chest pain, hemoptysis, fever/chills, night sweats, decreased appetite/weight loss, fatigue
- If it is to be on EMB, obtain baseline eye exam for both acuity and color discrimination
- 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
- Vital signs - (increases risk for drug resistance)
- Change time of TB Rx dose, have pt eat 2 hrs before next dose
- Add metoclopramide 5 to 10 mg or promethazine 25 mg 30 min before TB drugs
- Persistent cases may require krasnoprax 0.5 to 1 mg 30 min before TB meds
- Peripheral neuropathy (INH) - Ensure pt is receiving vitamin B6 (dose-related), hepatotoxicity
- 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 TB regimen management
- If on EMB, do eye exam for acuity and color. If decreased, stop EMB and refer to ophthalmologist. Consult TB/HIV expert for TB regimen modification
- If initially smear (+), test more frequently (e.g., every 2 mos) to assess tx response
- Repeat CXR after 2 mos of tx [not essential if cultures (+) wks) to assess tx response
- If pt is to be on EMB, obtain baseline eye exam for both acuity and color discrimination
- Encourage pt to immediately report symptoms of hepatitis or changes in vision

**Monitoring for Drug Effectiveness (ADE) (Continued)**

- Periodically during tx:
- Stop the EMB. Check dose, renal fx, serum drug levels, refer to ophthalmologist. Consult TB/HIV expert for TB regimen management
- If initially smear (+), test more frequently (e.g., every 2 mos) to assess tx response
- If pt is to be on EMB, obtain baseline eye exam for both acuity and color discrimination
- Encourage pt to immediately report symptoms of hepatitis or changes in vision

**Immune Reconstitution Inflammatory Syndrome (IRIS)**

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

**Therapeutic Drug Monitoring**

- Interactions and complexities in drugs and interactions
- Consider whether therapeutic drug monitoring is needed for each tx
- Pts who are switching from LAM to another tx or those with complex tx regimens

**Drug-drug Interactions with Rifamycins and ARVs**

- Rifampin (RIF)-based Regimen with ARVs
- Rifabutin (RBT)-based Regimen with ARVs

**Protease Inhibitors**

- Due to significant interactions and/or need for high doses of ritonavir to overcome the interactions, it is impractical to use rifampin with protease inhibitors (boostered or unboosted) and it is not recommended

**Integrase Inhibitor**

- Increase ritonavir (RAL) to 800 mg bid

**CCR5 Inhibitor**

- Not recommended, but if used: maraviroc (MVC) 300 mg bid or etravirine (ETV) 200 mg bid
- MVC 600 mg bid (without CYP3A inhibitor)

**Rifapentine**

- Do not use RIF with etravirine, nevirapine, or rifampirine

**Protease Inhibitors**

- ritonavir-boosted PIs
- ATV/r
- DRV/r
- FPV/r
- LPV/r
- SQV/r
- TPV/r
- Unboosted PIs
- ATV
- RPV
- FPV
- Integrase Inhibitor
- No dosage adjustments recommended for RAL or RBT
- MCV 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 TBD)

**Drug-drug Interactions**

- Interactions and complexities in drugs and interactions
- Consider whether therapeutic drug monitoring is needed for each tx
- Pts who are switching from LAM to another tx or those with complex tx regimens
- TDM should be considered for most pts with renal insufficiency or or complex drug-drug interactions
- Consider TDM in pts on cyclodextrin
- Consult an TB/HIV expert for assistance in managing these pts
- Pts and TB drugs are available through many commercial labs as well as the Infectious Disease Pharmacokinetic Laboratory at the University of Florida in Gainesville (http://idpl.cof.ufl.edu)

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