LATENT TUBERCULOSIS INFECTION

- Latent tuberculosis infection (LTBI) is the presence of Mycobacterium tuberculosis in the body without signs and symptoms (e.g., the absence of bacteriologic evidence of tuberculosis (TB) disease)

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

- TST: This is the preferred test for LTBI in adults. It is contraindicated in those with a history of anaphylaxis to tuberculin or pregnant women.
- IGRA: This test requires blood draws and thus is contraindicated in those with a history of moderate to severe anaphylaxis.

Administration of TST

- Use 1/2 to 1/4 inch 25-gauge needle and tuberculin syringe
- Inject 0.1 mL of tuberculin purified protein derivative (PPD) in at least two different sites
- Read the test at 48 to 72 hours

Interferon Gamma Release Assay

- IGRA is an in vitro test that measures the production of interferon gamma in response to Mycobacterium tuberculosis-specific antigens

NOTE: TST is not contraindicated in infants, children, pregnant women, or persons previously vaccinated with BCG

TREATMENT OF LTBI

- Low risk: Continue daily activities as usual
- High risk: Consider treatment

Interferon Gamma Release Assay

- IGRA is in vitro test that measures the production of interferon gamma in response to Mycobacterium tuberculosis-specific antigens

- Specified of IGRA ranges 92%-97%, compared to 56%-95% for TST
- Two FDA-approved assays are available: QuantiFERON®-TB Gold In-Tube (Cellestis Limited) and T-SPOT.TB (Oxford Immunotec Limited)

- It is important that test samples be drawn, transported, processed, and interpreted according to each manufacturer’s recommendations

- Definite infection: Sputum or tissue cultures for M. tuberculosis
- Anergy (inability to react to TST due to immune suppression; e.g., neoplasms, HIV, or corticosteroids)
- Extremes of age (newborns, elderly)
- Problem with tuberculin used (e.g., improper storage), collection (time requirements differ among assays) so
- Poor admin technique (e.g., subcutaneous instead of intradermal), improper reading or result interpretation

Contraindications to a TST

- Contraindicated for persons with a severe reaction to TST
- M. tuberculosis disease
- Current or recent exposure to M. tuberculosis

NOTE: Treatment for LTBI should be supervised by a specialist

REFERENCES:

**ACTIVE TUBERCULOSIS Continued**

Monitoring Therapy for Pulmonary TB Continued

- Repeat CXR after 2 months of tx (not essential if cultures (+) at diagnosis and CXR showing, presumptive diagnosis of TB can be made). End of tx CXR should be reviewed by most to document end to tx of baseline.
- Repeat drug susceptibility testing if culture (+) after 3 months. Of tx. Consider tx failure if (+) culture at 4 months. Consider an expert specialist for pts who fail tx and also have drug resistance.

Monitoring for Drug Adverse Effects (AEs)

**Baseline:**
- Obtain tx for risk factors for AEs (e.g., diabetes, renal failure, ESR, albuminuria, use) and concurrent medications
- Obtain baseline labs - LFTs, TBili, uric acid, BUN/Cr, CBC, CD4 and percentage

**Monthly:**
- Interpreting pt results for AEs, medications in, and medication 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 + 4 mg PO 3x/day
- Persistent cases may require lorazepam 0.5 to 1 mg 30 min before TB meds
- Peripheral neuropathy (INH) - Ensure pt is receiving pyridoxine (vitamin B6) 25-50 mg po daily
- Fish, prevents arthralgia 30 min before initial TB Rx and pm
- If INH, do exam on day 1 and color. If decreased, stop the EMB. Check dose, renal function, serum drug levels, refer to hepatologist. Consult TB/HIV expert for tx of pts requiring 2-drug tx in the future.

**Drug Resistance:**

- Sputum smear and culture:
- Pts with HIV are more likely to have extrapulmonary disease (e.g., low Karnofsky score, low body mass index, disease (e.g., gouty arthritis). If symptomatic may add.
- All HIV-infected pts with active TB should start ART
- Do not combine RIF with Stivada® (elvitegravir/cobicistat/emeritab/cibalibine/tenofovir DF)

**Prodrug Monotherapy for Drug-Susceptible Active Pulmonary TB in HIV-infected Patients**

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Food Restrictions</th>
<th>Important Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>300, 600 mg tab</td>
<td>Food Avoidance</td>
<td>- Avoid alcohol for 2 hrs before and after INH</td>
</tr>
<tr>
<td></td>
<td>150 mg cap</td>
<td>- Avoid alcohol for 2 hrs before and after INH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>120, 200 mg soln</td>
<td>- Most common/severe AEs: hepatotoxicity, peripheral neuropathy, optic atrophy, rash, hematologic or dermatologic reactions</td>
<td></td>
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<tr>
<td>Rifabutin (RFB)</td>
<td>150 mg cap</td>
<td>With or without food, may open</td>
<td>- Most common/severe AEs: red-orange discoloration of body fluids (e.g., urine, sweat, tears), rash, flu-like syndrome, arthralgias, hemolytic anemia, neutropenia, thrombocytopenia, liver function test abnormalities (dose-related, rash; renal function test abnormalities including BUN, uric acid, acute renal failure)</td>
</tr>
<tr>
<td></td>
<td>300 mg cap</td>
<td>cap and mix in food (applesauce)</td>
<td>- Co-admin pyridoxine (vitamin B6) 25-50 mg po daily to prevent neuropathy</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>300 mg cap</td>
<td>With or without food, may open</td>
<td>- Most common/severe AEs: GI disturbances, red-orange discoloration of body fluids (e.g., urine, sweat, tears), rash, flu-like syndrome, arthralgias, hemolytic anemia, neutropenia, thrombocytopenia, liver-function abnormalities (dose-related, rash; renal function test abnormalities including BUN, uric acid, acute renal failure)</td>
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<tr>
<td></td>
<td>600 mg soln (600 mg/8 ml)</td>
<td>1 h prior to or 2 hrs after meal</td>
<td>- Most common/severe AEs: GI disturbances, red-orange discoloration of body fluids (e.g., urine, sweat, tears), rash, flu-like syndrome, arthralgias, hemolytic anemia, neutropenia, thrombocytopenia, liver-function abnormalities (dose-related, rash; renal function test abnormalities including BUN, uric acid, acute renal failure)</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>500 mg tab</td>
<td>With or without food</td>
<td>- Most common/severe AEs: nausea and vomiting, anorexia, optic neuropathy (neuropathy should report test results; peripheral neuropathy, arthralgias, hepatotoxicity, hyperbilirubinemia, hyperglycemia, hyperuricemia, hyperkalemia, decreased appetite, increased liver function tests)</td>
</tr>
<tr>
<td></td>
<td>300 mg soln (30 mg/ml)</td>
<td></td>
<td>- Most common/severe AEs: nausea and vomiting, anorexia, optic neuropathy (neuropathy should report test results; peripheral neuropathy, arthralgias, hepatotoxicity, hyperbilirubinemia, hyperglycemia, hyperuricemia, hyperkalemia, decreased appetite, increased liver function tests)</td>
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</table>

**RIFABUTIN (RFB) : Baseline**

**Drug Interactions**

**NOTE:** See Drug Interactions table for interactions and dosing recommendations before Rx.

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

**NOTE:** Consult a TB/HIV expert for assistance in managing these pts

**Therapeutic Drug Monitoring (TDM)**

- Interactions can be complex and difficult to predict in individual pts
- Consider TDM 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
- Consult an TB/HIV expert for assistance in managing these pts

**Immune Reconstitution Inflammatory Syndrome (IRIS)**

- Pts may have worsening or new onset sxs of active TB following tx initiation (more common with CD4 < 50 cells/mm3 and pts with higher pre-ART HIV viral load)
- Stop the EMB. Check dose, renal function, serum drug levels, refer to hepatologist. Consult TB/HIV expert for management of these cases.

**UnBoosted PIs**

- Lopinavir/ritonavir (LPV/r) (standard dose) RAL 300 mg po once daily (standard dose). Do not combine RIF with LPV/r boosted PIs
- ETR 300 mg po 3 times per week (standard dose) RPV Increase RRV to 500 mg po once daily* Pls

**NeA1**

- raltegravir (RAL) to 800 mg po bid. Use definitive alternative to INSTI (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.

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**Adult Dose of Agents for Active TB**

**INH = isoniazid** | **RIF = rifampin** | **RFB = rifabutin** | **PZA = pyrazinamide** | **EMB = ethambutol**
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</thead>
<tbody>
<tr>
<td><strong>mg/kg</strong></td>
<td><strong>30</strong></td>
<td><strong>150-200</strong></td>
<td><strong>600</strong></td>
<td><strong>300-2400</strong></td>
</tr>
<tr>
<td><strong>mg/kg</strong></td>
<td><strong>10</strong></td>
<td><strong>15</strong></td>
<td><strong>50-70</strong></td>
<td><strong>30</strong></td>
</tr>
<tr>
<td><strong>3 times per week</strong></td>
<td><strong>max 300</strong></td>
<td><strong>300</strong></td>
<td><strong>2000</strong></td>
<td><strong>1600</strong></td>
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<tr>
<td><strong>max 900</strong></td>
<td><strong>600</strong></td>
<td><strong>3000</strong></td>
<td><strong>2400</strong></td>
<td></td>
</tr>
</tbody>
</table>

**NOTE:** See Drug Interactions table for interactions and dosing recommendations before Rx.

**Monitoring Therapy for Pulmonary TB**

- Monitor pt clinically at least monthly
- Sputum for smear and culture monthly until 2 consecutive (-) cultures
- If initially smear (+), test more frequently (e.g., every 2 weeks) to assess tx response

**NOTE:** Adult/Adolescent OI Guidelines indicate to start ART in ART-naive pts within 2 weeks of stopping INH if CD4 < 50 and by 8-12 weeks for all others (AI) (accessed July 25, 2014) for recommendations regarding timing of ART initiation (all CD4 cell counts are in cells/ml)