Treatment of Latent TB Infection (LTBI)

Amee Patrawalla, MD
Assistant Professor, New Jersey Medical School
Attending Physician, NJMS Global TB Institute
Before initiating treatment for LTBI:

• Rule out TB disease
  – Wait for culture result if specimen obtained
  – Assess/evaluate for symptoms

• Determine prior history of treatment for LTBI or TB disease

• Assess risks and benefits of treatment
  – Active liver disease

• Ascertain current and previous drug therapy and side effects
Initiating Treatment: Patient Education

- Counsel and educate patient
  - Discuss patient’s risk for progressing to TB disease
  - Emphasize benefits of treatment
  - Assess whether patient willing to be treated for full treatment period
- Review common side effects
- Establish treatment plan
Baseline Medical Evaluation

• Medical history
  – History of TB or HIV treatment
  – TB exposure
  – Risks for drug toxicity
    • e.g., alcoholism, liver disease, pregnancy
  – Complete medication list

• Chest x-ray
  – Rule out TB disease

• Laboratory tests
  – CBC and chemistry panel, if indicated
  – 3 sputum samples for AFB smear, culture, & DST if TB symptoms or findings on chest x-ray
# Treatment Regimens for LTBI

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Months of Duration</th>
<th>Interval</th>
<th>Minimum Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>9*</td>
<td>Daily</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>2x wkly**</td>
<td></td>
<td>76</td>
</tr>
<tr>
<td>INH</td>
<td>6</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>2x wkly**</td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>RIF</td>
<td>4</td>
<td>Daily</td>
<td>120</td>
</tr>
</tbody>
</table>

*Preferred  ** Intermittent treatment only with DOT

INH=isoniazid; RIF=rifampin
How Much INH Needed for Prevention of TB?

- Longer duration corresponded to lower TB rates if took 0 – 9 mos.
- No extra increase in protection if took > 9 mos.

## Isoniazid Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Doses</th>
<th>Ideal Duration</th>
<th>Complete Within</th>
<th>Special Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>270</td>
<td>9 months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Twice weekly*</td>
<td>76</td>
<td>9 months</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>180</td>
<td>6 months</td>
<td>9 months</td>
<td>Avoid: HIV infected, fibrotic lesion on CXR, children</td>
</tr>
<tr>
<td>Twice weekly*</td>
<td>52</td>
<td>6 months</td>
<td>9 months</td>
<td></td>
</tr>
</tbody>
</table>

*via Directly Observed Therapy*
Rifampin Regimens

• Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible
  – INH resistant or intolerant
  – Patient unlikely to be adherent for longer treatment period

• In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted

• Children should receive 6 months

• RIF + PZA for 2 months
Children and adolescents (<18 years old):
- 9 mo INH
- 6 mo RIF

Pregnant women:
- INH preferred
- May defer past the early post-partum period, except for HIV-infected women & recently infected with \textit{M. tb}

See lecture on pediatric TB
CXR consistent with old TB:
- i.e. Fibrotic lesion consistent with untreated TB disease
- TST reaction 5mm or greater
- In addition to standard LTBI regimens, some prefer INH + RIF for 4 months, after ruling out active disease

CXR with evidence of old healed primary TB:
- i.e. Calcified solitary pulmonary nodule, apical pleural capping, calcified hilar lymph node
- Not at increased risk of developing TB disease
- Use other risk factors and appropriate TST size to determine treatment with standard regimen
Special Situations – 3

• Persons exposed to INH-resistant TB:
  • 4 mo RIF - adults
  • 6 mo RIF - children

• Persons likely infected with multidrug-resistant TB:
  • 6-12 mo PZA and EMB, or PZA and quinolone (i.e., ≥ 2 drugs to which organism is susceptible)

See lecture on MDR-TB
LTBI Treatment for HIV-Positive Individuals

• HIV-positive patients in close contact to infectious TB should receive treatment for LTBI regardless of age, TST results or history of previous treatment for LTBI

• If Rifampin contraindicated (i.e. protease inhibitor), should receive Rifabutin

See lecture on TB/HIV co-infection
LTBI and Tumor Necrosis Factor-alpha Inhibitors

- TNF alpha is a pro-inflammatory cytokine, often implicated in autoimmune diseases
- Necessary for host response to mycobacterial infections
- TNF alpha blockers increasingly used for Rheumatoid Arthritis, Inflammatory Bowel Disease, Psoriatic arthritis, Ankylosing Spondylitis
- One of the major complications is reactivation of *M.tb*
LTBI and TNF alpha inhibitor: Management

- Rigorous screening for TB risk factors (e.g. country of origin, exposure, radiographic evidence of prior TB) prior to TNF alpha blocker

- Can use multiple modalities to increase sensitivity of recognizing LTBI (TST, IGRA, CXR)

- LTBI treatment is effective

- Concurrent LTBI treatment and TNF alpha inhibitor initiation is generally accepted

- Consider periodic re-testing
Prioritizing treatment based on reactivation risk

Table 1. Annual Risk of Reactivation Tuberculosis.*

<table>
<thead>
<tr>
<th>Size of Induration on Tuberculin Skin Test</th>
<th>Age</th>
<th>0–5 Yr</th>
<th>6–15 Yr</th>
<th>16–35 Yr</th>
<th>36–55 Yr</th>
<th>≥56 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent (95 percent confidence interval)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persons with nonconversion positive result</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9 mm</td>
<td></td>
<td>0.06</td>
<td>0.04</td>
<td>0.12</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>(0.03–0.11)</td>
<td>(0.03–0.06)</td>
<td>(0.05–0.32)</td>
<td>(0.03–0.19)</td>
<td>(0.03–0.16)</td>
<td></td>
</tr>
<tr>
<td>10–14 mm</td>
<td></td>
<td>0.19</td>
<td>0.08</td>
<td>0.15</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>(0.12–0.28)</td>
<td>(0.06–0.11)</td>
<td>(0.08–0.29)</td>
<td>(0.05–0.19)</td>
<td>(0.06–0.17)</td>
<td></td>
</tr>
<tr>
<td>≥15 mm</td>
<td></td>
<td>0.24</td>
<td>0.14</td>
<td>0.19</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>(0.19–0.30)</td>
<td>(0.12–0.17)</td>
<td>(0.10–0.34)</td>
<td>(0.07–0.21)</td>
<td>(0.08–0.20)</td>
<td></td>
</tr>
<tr>
<td>Persons with recent conversion or contacts of patients with active tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5–9 mm</td>
<td></td>
<td>0.29</td>
<td>0.06</td>
<td>0.30</td>
<td>0.23</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>(0.08–0.74)</td>
<td>(0.02–0.18)</td>
<td>(0.18–0.50)</td>
<td>(0.10–0.44)</td>
<td>(0.02–0.44)</td>
<td></td>
</tr>
<tr>
<td>10–14 mm</td>
<td></td>
<td>0.37</td>
<td>0.12</td>
<td>0.37</td>
<td>0.28</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>(0.16–0.71)</td>
<td>(0.05–0.25)</td>
<td>(0.26–0.53)</td>
<td>(0.17–0.45)</td>
<td>(0.04–0.39)</td>
<td></td>
</tr>
<tr>
<td>≥15 mm</td>
<td></td>
<td>0.54</td>
<td>0.12</td>
<td>0.56</td>
<td>0.42</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>(0.27–0.95)</td>
<td>(0.07–0.23)</td>
<td>(0.41–0.76)</td>
<td>(0.28–0.62)</td>
<td>(0.05–0.42)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Relative Risk of Reactivation Tuberculosis among Persons with Medical Conditions That Impair Immune Control of M. tuberculosis.*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced HIV infection</td>
<td>Pablos-Mendez et al.²⁷ Moss et al.²⁶</td>
<td>9.9 (8.7–11.3) †</td>
</tr>
<tr>
<td>Old, healed tuberculosis</td>
<td>Ferebee,¹³ Ferebee et al.²⁰</td>
<td>5.2 (3.4–8.0)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>Pablos-Mendez et al.²⁷</td>
<td>2.4 (2.1–2.8) †</td>
</tr>
<tr>
<td>Infliximab therapy</td>
<td>Keane et al.²⁸</td>
<td>2.0 (0.7–5.5) †</td>
</tr>
<tr>
<td>Poorly controlled diabetes</td>
<td>Pablos-Mendez et al.²⁷</td>
<td>1.7 (1.5–2.2) †</td>
</tr>
<tr>
<td>Silicosis</td>
<td>Cowie²⁹ Corbett et al.³⁰ Kleinschmidt and Churchyard³¹</td>
<td>1.7 (1.3–2.1) †</td>
</tr>
<tr>
<td>Underweight (≤10 percent below normal)</td>
<td>Palmer et al.,²² Edwards et al.²³</td>
<td>1.6 (1.1–2.2)</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>Thorn et al.³² Steiger et al.³³</td>
<td>1.4 (1.1–1.9) †</td>
</tr>
</tbody>
</table>

* † Denotes statistically significant result.
Vitamin B₆ Supplementation

- Uremia
- Malnutrition
- Alcoholism
- Diabetes
- Seizure disorder
- HIV infection
- Pregnancy
Baseline Laboratory Evaluation

• Not indicated routinely

• Is indicated in:
  – Persons with HIV infection
  – Pregnant & postpartum women (up to 2-3 mos. after delivery)
  – History/risk of liver disease
    • Heavy alcohol use
    • Chronic hepatitis
    • History of injection drug use
    • On two or more meds
    • On medications for other medical conditions
Adverse Effects on Liver

• Incidence of hepatitis in persons taking INH is lower than previously thought (0.1 to 0.15%)

• Hepatitis risk increases with age
  – Uncommon in persons < 20 years old
  – Nearly 2% in persons 50 to 64 years old

• Risk increased with underlying liver disease or heavy alcohol consumption

• Abnormal laboratory results should be further investigated prior to medication initiation

See lecture on Managing Adverse Drug Effects
Adverse Effects on Liver

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of treatment

- Some experts recommend withholding INH if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic

See lecture on Medication Side Effects
• Reinforce patient’s understanding of LTBI and its treatment

• Evaluate for **signs and symptoms** of active TB and drug reactions

• Monitor **adherence** to prescribed regimen

• **Educate** patient about signs and symptoms of hepatotoxicity

• Review all medications and assess for potential **drug interactions**
• Repeat liver function tests for
  – Patients with abnormal baseline
  – Persons with HIV infection
  – Pregnant and post-partum women
  – History/risk of liver disease
    ▪ Heavy alcohol ingestion
    ▪ Chronic hepatitis
    ▪ History of injection drug use
    ▪ On two or more meds
Management of Patient Who Missed Doses

• Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion within recommended time frame

• When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease

• Recommend and arrange for DOT as needed

• Completion of therapy is based on the total number of doses administered, not on duration alone
Retreatment of LTBI

• Re-infection can occur and is especially of concern in immunocompromised individuals.

• Retreatment should be considered based on underlying medical conditions, severity of exposure and age.
Summary

• Rule out TB disease

• Choose treatment regimen based on individualized evaluation of each patient

• Importance of monthly clinical assessments and ongoing patient education

• Use DOT for high-priority patients