**Treatment of Latent TB Infection (LTBI)**

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**Latent TB Infection (LTBI)**

- Infection with *Mycobacterium tuberculosis* without manifestations of active disease
  - Asymptomatic
  - Normal or stable chest radiography
- >80% TB disease in the US is due to reactivation of latent infection
- Reactivation is preventable
- TB elimination focuses on targeting people with a high risk of LTBI for screening and treatment

Horsburgh & Rubin, NEJM 2011; 364 (154): 1441-8

**LTBI Treatment**

- 2 Billion with LTBI
- 200 Million with TB Disease
- >80% Contagious
  - Another opportunity to diagnose and treat  
  - Good efficacy
  - Opportunity to intervene  
  - Up to 50% undiagnosed, untreated
LTBI Treatment Challenges

- Lengthy treatment leading to limited adherence
- Adverse effects influencing patient and provider agreement
- Cost

Why is there a debate about treating LTBI?

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Latent TB infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Asymptomatic condition</td>
<td>• Asymptomatic condition</td>
</tr>
<tr>
<td>• Very serious complications</td>
<td>• Very serious complications</td>
</tr>
<tr>
<td>– Death</td>
<td>– Death</td>
</tr>
<tr>
<td>– Major disability</td>
<td>– Major disability</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>• Treatment is for years</td>
<td>• Treatment is max 9 months</td>
</tr>
<tr>
<td>– Expensive medications</td>
<td>– Cheap medications</td>
</tr>
<tr>
<td>– Potential serious side effects</td>
<td>– Potential serious side effects</td>
</tr>
<tr>
<td>– Requires close monitoring and follow up</td>
<td>– Requires close monitoring and follow up</td>
</tr>
</tbody>
</table>
| **BUT – no debate about Treating** | **WHY the debate about Treating??**

LTBI Treatment

- Initiating treatment
- Choosing a treatment regimen
  - Short-course regimens
- Monitoring
- Cases

Pre-Treatment Evaluation

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
  - 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

**Baseline Laboratory Evaluation**

- Not indicated routinely
- Indicated for:
  - Persons with HIV infection
  - Pregnant & postpartum women (up to 2-3 mos. after delivery)
  - Individuals with 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
    - Consider in older individuals with other chronic medical conditions/medications prior to INH-RPT

**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></td>
<td>2x wkly**</td>
<td>76</td>
</tr>
<tr>
<td>INH</td>
<td>6</td>
<td>Daily</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2x wkly**</td>
<td>52</td>
</tr>
<tr>
<td>Rif</td>
<td>4</td>
<td>Daily</td>
<td>120</td>
</tr>
<tr>
<td>RIF</td>
<td>4</td>
<td>Daily</td>
<td>120</td>
</tr>
<tr>
<td>INH-RPT</td>
<td>3</td>
<td>Weekly**</td>
<td>12</td>
</tr>
</tbody>
</table>

*Preferred ** Intermittent treatment only with DOT
**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.


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**Isoniazid Regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Doses</th>
<th>Ideal Duration</th>
<th>Complete Within</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>270</td>
<td>9 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Twice weekly*</td>
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<td>52</td>
<td>6 months</td>
<td>9 months</td>
</tr>
</tbody>
</table>

*via Directly Observed Therapy

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**Rifampin Regimens**

- RIF 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
- 120 doses should be completed within 6 months
- Children should receive 6 months
- Be aware of predicable drug interactions
- Rif + ZA for 2 months

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**Comparison of INH vs. RIF for Treatment of LTBI**

**Comparison of Regimen Features: 9H and 4R**

<table>
<thead>
<tr>
<th>Regimen Feature</th>
<th>9H</th>
<th>4R</th>
</tr>
</thead>
<tbody>
<tr>
<td>High efficacy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lower hepatotoxicity</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Lower overall cost</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Higher adherence</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>More effective against INH-resistant strains (e.g., among foreign-born persons)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Shorter duration</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fewer drug-drug interactions</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

* Good evidence that 3R is at least as efficacious as 6H. Inferential reasoning from other evidence suggests that efficacy of 4R may approach that of 9H.
**Special Situations – 1**

- CXR consistent with old TB disease:
  - i.e., old fibrotic lesions consistent with prior tuberculosis – e.g., dense nodules, scar, volume loss, sharp margins, ‘hard’, bronchiectasis
  - TST reaction 5mm or greater
  - In addition to standard LTBI regimens, some prefer INH + RIF for 4 months, if previously untreated

**Special Situations – 2**

- 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
**INH and Rifapentine for 12 weeks**

- Rifapentine (RPT) is a rifamycin with a long half-life
  - Used as part of weekly continuation phase regimen in selected patients with TB disease
- INH for 9 months vs. INH + RPT weekly for 12 weeks with DOT
- Completion: 11-12 doses within 16 weeks; >72 hours apart
- Study population (8000 patients)
  - TST+ close contacts (70%)
  - Converters (25%)
  - TST+ HIV or HIV with close contact (2%)
  - TST+ with fibrotic changes (2%)
  - Later expanded to include children 2-11

**INH and Rifapentine for 12 weeks**

- Efficacy was similar
  - 0.19% v 0.43% developed TB disease
- 82% in INH-RPT vs. 69% completion in standard therapy group
- Permanent drug discontinuation due to adverse effect higher in INH-RPT group, although overall fewer adverse events in INH-RPT
- More hepatotoxicity in INH alone group
- More ‘possible hypersensitivity’ reactions in INH-RPT

**INH-RPT Recommendations**

- Equal alternative to 9 months INH in otherwise healthy individuals ≥12 years old + high risk for TB disease:
  - Close contact
  - Converter
  - Fibrotic changes on CXR
  - HIV not on ART, otherwise healthy
- Others are considered on an individual basis if circumstances deem INH-RPT to be a better choice
- Children 2-11 years old can be considered especially if unlikely to complete 9 months + high risk to progress to TB disease

**INH-RPT NOT Recommended**

- Children < 2 years old
- HIV on ART
- Pregnancy, or likely to become pregnant during treatment
- Presumed INH or RIF resistance
- Prior AE with INH or rifamycin
Cautions with INH-RPT

- Ensure TB disease is not present
- Patients with fibrotic or 'old healed' lesions on CXR
- HIV infected patients
  - CXR may appear normal despite presence of TB disease
  - More extra-pulmonary disease

RPT Adverse Effects

- Reddening of secretions
- Uncommon
  - Hepatotoxicity
  - Leukopenia,
  - Thrombocytopenia
  - Hypersensitivity seen with other rifamycins
    - Fever, 'flu-like', pruritus, hypotension, headache, petechiae
- Hepatic induction of drug metabolism
- Be observant of other potential adverse effects as regimen more widely used
- Report: ltbidruevents@cdc.gov; MedWatch

Choosing INH-RPT

- DOT feasibility
- Drug availability and resources
- Program operations
- Expectance of treatment completion
- Patient/Provider preferences

Dosing

<table>
<thead>
<tr>
<th>Isoniazid (INH)</th>
<th>Rifapentine (RPT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mg/kg rounded up to the nearest 50 or 100 mg</td>
<td>900 mg maximum</td>
</tr>
<tr>
<td>10.0–16.0 kg</td>
<td>500 mg</td>
</tr>
<tr>
<td>16.1–25.0 kg</td>
<td>450 mg</td>
</tr>
<tr>
<td>25.1–32.0 kg</td>
<td>600 mg</td>
</tr>
<tr>
<td>33.1–49.0 kg</td>
<td>750 mg</td>
</tr>
<tr>
<td>≥50.0 kg</td>
<td>≥900 mg maximum</td>
</tr>
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</table>

Isoniazid (INH) is formulated as 300 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 350 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

INH-RPT Monitoring

- Assess for fever, dizziness, rash, jaundice, aches, abdominal pain, nausea, vomiting, loss of appetite at each encounter
- Educate patients to report above symptoms
- Monthly clinical assessment at a minimum

Monthly Monitoring During LTBI Treatment – 1

- 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

Monthly Monitoring During LTBI Treatment – 2

- 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 the Patient Who Misses Doses

- Extend or re-start treatment for frequent or prolonged interruptions that preclude completion within recommended time frame
- Examine patients to rule out TB disease when treatment interruption > 2 months
- Recommend and arrange for DOT as needed

**Completion of therapy is based on the total number of doses administered, not on duration alone**
### Completion of Therapy

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<th>Doses</th>
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<td>120</td>
<td>6 months</td>
</tr>
<tr>
<td>INH-RPT</td>
<td>3 months</td>
<td>11-12</td>
<td>16 weeks</td>
</tr>
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### Re-treatment of LTBI

- Re-infection can occur and is especially of concern in immunocompromised individuals
- Re-treatment should be considered based on underlying medical conditions, severity of exposure and age

### Take Home Points

- Prior to initiating LTBI treatment, assess for presence of TB disease
- Choose treatment regimen based on individualized evaluation of each patient
- Monthly clinical assessments and ongoing patient education important
- Use DOT for high-priority patients
- DOT for INH-RPT

### Case #1

- 49 y.o. man emigrated from Nigeria 1 year ago
- History of daily alcohol use until 6 months ago, abstinent since
- Hypertension, Hypercholesterolemia
- Hepatitis B core antibody positive
- No known TB contacts
- QFT-Gold – positive
- Asymptomatic
- CXR normal
Which of the following is the best indication to recommend LTBI treatment to the patient?

A. Alcoholism
B. Recent emigration from a country with high TB prevalence
C. Hepatitis B
D. Cardiac co-morbidities

Case #1

- Baseline LFTs:
  - AST was at ULN
  - ALT was 2x ULN
- Repeat hepatitis markers revealed only HBV core Ab+
- He reported abstaining from alcohol
- INH 300 mg and vitamin B6 were started
- Patient discontinued INH 3 weeks later due to epigastric pain but did not seek medical attention
- 2 weeks later, symptoms improved, presents to clinic
  - AST 2x ULN; ALT 3x ULN

Aside from repeating LFTs, what else must be done prior to initiating treatment for LTBI?

A. Repeat QFT-Gold
B. Check sputum for AFB x 3
C. Re-interview the patient and assess for signs or symptoms of TB disease
D. Perform a liver ultrasound
Case #2

- 56 y.o. woman from Jamaica
- Emigrated 22 years ago
- TST 14 mm
- TST 1 year ago “negative”
- Contact of an active case
- Medical history: Autoimmune hepatitis, SLE
- Medications include prednisone 7.5 mg daily, Azathioprine 50 mg daily, Abatacept monthly
- Weight 48 kg, Height 152 cm, BMI = 20
- CXR normal
- AST, ALT are slightly above ULN

Based on available guidelines, which of the following is not a reason to recommend LTBI treatment in this patient?

A. Recent TST conversion
B. Immigrant from an endemic country
C. Contact of an active case
D. Use of immunosuppressants

The patient wishes to discuss alternatives to INH for 9 months. Which of the following discussion points should be raised regarding treatment with RIF for 4 months or INH-RPT for 12 weeks?

A. Twice weekly RIF for 4 months with DOT is an option
B. The risk of hepatotoxicity is higher with INH-RPT
C. A higher prednisone dose may be necessary
D. None of the above

The patient wishes to discuss alternatives to INH x 9 months. Which of the following discussion points should be raised regarding alternative treatment regimens?

A. Twice weekly RIF with DOT is an option
B. The duration of treatment is 9 months
C. Higher prednisone dose may be necessary
D. None of the above
Case #3

- 25 y.o. HIV infected, pregnant woman
- Presents with a TST reaction of 8 mm
- Known contact to an active case
- Asymptomatic and has a normal CXR

What is the best course of action?

A. Repeat the TST in 8-10 weeks
B. Begin INH and B6
C. Defer treatment until she is 2 months post delivery
D. Perform an IGRA

Each patient below has a TST of 6mm. Which one should be treated for LTBI, based on radiograph as sole risk factor?