Treatment of Latent TB Infection (LTBI)

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Summary of TB Trends in US

- Number of cases increased in 2015; case rate similar
- 2/3 of all cases are in people born outside the US, the majority of whom have been residing in US > 5 years
- HIV coinfection has decreased to < 6%
- TB cases among homeless individuals has also declined
- Resuming and intensifying progress to TB elimination (≤ 1 case/million) requires
  - Strengthening systems to prevent transmission of infectious TB
  - Increasing the effort to detect and treat latent TB infection in at-risk groups

(Latent) TB Infection in the US

- Infection with Mycobacterium tuberculosis without manifestations of active disease
  - Asymptomatic
  - Normal or stable chest radiography
- Up to 13 million people in US infected; ~ 4.5%
- 5-10% may go on to have active TB if untreated
- ~ 70% of LTBI in foreign born individuals
- 19% of US born with LTBI treated; 10% of foreign born
- Treatment 90% effective
- 80% active cases arise from prior infection
- No significant decline in TST or IGRA positivity over past decade

Mancuso et al, AJRCCM, 2016
(Latent) TB Infection in the US

- A large reservoir of LTBI remains, and continues to be a barrier to TB elimination
- Ramping up targeted testing and treatment is the path to TB elimination
- Clinicians, health care agencies, community organizations, esp those serving at-risk patients, are critical to success

2 Billion with LTBI
200 Million with TB Disease
> 80% contagious

LTBI Treatment Challenges

- Identification of those infected
- Lengthy treatment leading to limited adherence
- Adverse effects influencing patient and provider agreement
- Perception of risk
- Cost

Addressing Barriers: CDC & USPSTF

Targeted testing and treatment
- CDC and USPSTF recommend testing in those at increased risk
  - USPSTF
    - Those from countries with increased TB prevalence
    - Those in high risk congregate settings
    - Consult with L/SHD regarding populations at risk
  - CDC still recommends testing
    - HCW
    - Close contacts
    - Certain medical illnesses (HIV, DM etc)
    - Before starting medications such as TNFα blocker

Clinicians and community organizations critical to TB elimination
- Many at high risk not seen by HD
- TB disease may be missed by today’s clinician
- TB education/outreach
Addressing Barriers: CDC & USPSTF

- Cost
  - LTBI $500 versus TB Disease $18,000
  - USPSTF Grade “B” should allow for screening to occur without cost-sharing within those risk groups
  - Medicare/Medicaid
  - Treatment cost

LTBI Treatment Challenges

- Identification of those infected
- Lengthy treatment leading to limited adherence
- Perception of risk (high) and benefit (low)
- 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>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**

*Menzies et al., Indian Jnl of Medical Research, 2011*

LTBI Treatment Adverse Effects

**Isoniazid**

- Asymptomatic LFT elevation in 10-20% on INH
  - Generally return to normal even if medication continued
- Clinical hepatitis – 0.1% on INH
  - Can increase depending on other risk factors and medications
  - Severe/fatal very rare but have been reported
- Peripheral neuropathy <0.2%

**Rifamycin**

- Asymptomatic hyperbilirubinemia 0.6%
- Clinical hepatitis increases when INH + RIF
- Cutaneous – up to 6% of people, usually self limited
- Hypersensitivity reactions - rare
LTBI Treatment Challenges

- Identification of those infected
- Lengthy treatment leading to limited adherence
- Perception of risk (high) and benefit (low)
- Adverse effects influencing patient and provider agreement
- Cost

TB Infection Treatment and Duration: INH 9 months

- Completion of Isoniazid for 9 months (9H) is variable, but poor even in controlled situations
  - 53% in NJ (Lardizabal et al., 2006)
  - 69% in CDC INH – RPT trial

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>X</td>
<td></td>
</tr>
<tr>
<td>Lower overall cost</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Higher adherence</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>More effective against INH-resistant strains</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Shorter duration</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fewer drug-drug interactions</td>
<td>X</td>
<td></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.

Short course regimen: INH + Rifapentine 12 dose regimen

PROs
- INH + Rifapentine + B6 once a week x 12 weeks
- Adherence better

CONS
- Pill burden (10 pills)
- DOT
- Rifapentine information lacking for some groups
Treatment Adherence

- Treatment efficacy increases with amount of drug taken
- Many do not complete therapy, regardless of whether adverse effects are present
- Shorter course regimens may have better adherence

Trajman, JLTLD, 2010
Goswami, BMC Public Health, 2012

LTBI Treatment

1. Initiating treatment
2. Choosing a treatment regimen
3. Monitoring
4. Completion

Prior to treatment initiation:

- Rule out TB disease
  - Assess/evaluate for symptoms
  - CXR
  - Microbiology (AFB smear/culture) if suspicion for TB disease
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
  - E.g. active liver disease, alcoholism
- Ascertain current and previous drug therapy and side effects

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
  - Consider in older individuals with other chronic medical conditions/medications
High risk – CXR consistent with prior TB disease

- i.e., old fibrotic lesions consistent with prior tuberculosis – e.g. dense nodules, scar, volume loss, sharp margins, ‘hard’, bronchiectasis
- Lack of change from prior CXR
- TST reaction 5mm or greater

Lower risk – CXR consistent with healed primary TB

- i.e., calcified solitary pulmonary nodule, apical pleural capping, calcified hilar lymph node
- Not at increased risk of developing TB disease
  - Treat as though CXR normal
- Use other risk factors and appropriate TST size to determine treatment with standard regimen
Treatment Initiation: 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 and monitoring plan

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 9*</td>
<td>Daily</td>
<td>270</td>
<td></td>
</tr>
<tr>
<td>INH 6</td>
<td>Daily</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>RIF 4</td>
<td>Daily</td>
<td>120</td>
<td></td>
</tr>
<tr>
<td>INH-RPT 3</td>
<td>Weekly**</td>
<td>12</td>
<td></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 > 9-10 mos.

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>
<td>76</td>
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<td>52</td>
<td>6 months</td>
<td>9 months</td>
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*via Directly Observed Therapy
Rifampin Regimens

• RIF daily for 4 months is an acceptable alternative
  – 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 predictable drug interactions (opiates, corticosteroids, oral contraceptives, PI, warfarin etc)
• Orange discoloration urine, tears etc; may stain contact lenses
• Rif + PZA for 2 months

12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)

- 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 + RPT for 3 months v Standard INH for 9 months

12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)

Study Population (n = 7731)

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST+ close contacts</td>
<td>71%</td>
</tr>
<tr>
<td>Converters</td>
<td>25%</td>
</tr>
<tr>
<td>TST+ HIV or HIV+ close contact</td>
<td>2%</td>
</tr>
<tr>
<td>TST+ with fibrotic changes</td>
<td>2%</td>
</tr>
</tbody>
</table>

Sterling et al., NEJM, 2011
12 Dose Regimen INH + RPT
PREVENT TB (TBTC Study 26)

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

12 Dose INH + RPT (3HP) 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 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
**RUTGERS**

**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
- Reporting: ltbidugevents@cdc.gov; MedWatch
  [http://www.fda.gov/safety/medwatch/howtoreport/default.htm](http://www.fda.gov/safety/medwatch/howtoreport/default.htm)
- Post-marketing surveillance study

**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

**Dosing for INH-RPT with DOT**

<table>
<thead>
<tr>
<th>Dosing</th>
<th>Dosage</th>
</tr>
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<tbody>
<tr>
<td>Isoniazid</td>
<td>15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>10.0–16.0 kg 300 mg&lt;br&gt;14.1–25.0 kg 450 mg&lt;br&gt;25.1–32.0 kg 600 mg&lt;br&gt;32.1–49.9 kg 750 mg&lt;br&gt;&gt;50.0 kg 900 mg maximum</td>
</tr>
</tbody>
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Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 150 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.

**Choosing INH-RPT**

- DOT feasibility
- Drug availability and resources
- Cost of regimen vs cost-effectiveness
- Program operations
- Expectance of treatment completion
- Patient/Provider preferences

**Recommendations for Use of an INH-RPT Regimen with DOT to Treat LTBI**

[MMWR / December 9, 2011 / Vol. 60 / No. 48](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a1.htm)

Treatment regimens...stay tuned..

- 3HP
  - Post – marketing surveillance data
  - iAdhere: self administered therapy (+/- text messaging) v DOT
    - SAT is comparable to DOT in the US
    - DOT still recommended by CDC
  - HIV on or soon to start ART (currently not recommended)
- 4R versus 9H
- 9H versus 1 month daily INH and Rifapentine

Belnap et al., CROI 2015

Monthly Monitoring During LTBI Treatment

- 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

- 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>Regimen</th>
<th>Duration</th>
<th>Doses</th>
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<tr>
<td>Rifampin</td>
<td>4 months</td>
<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>
</tbody>
</table>

### Summary

- 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

- 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
- The patient agrees to treatment for LTBI

### 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 with DOT is an option
B. The risk of hepatotoxicity is higher with INH-RPT
C. Higher prednisone does may be necessary
D. None of the above
Case #2

- A 47 y.o. household contact to a patient with active TB is found to be QFT Gold positive. She is known to be TST negative in the past. She is on no medications and is otherwise healthy. She works from home and lives with the index case.

- Which regimen is best for this patient?

A. INH daily for 9 months
B. RIF daily for 4 months
C. INH twice weekly for 9 months
D. INH + Rifapentine weekly x 12 weeks via DOT
E. No treatment

Case #3

- A 55 y.o. woman with Rheumatoid Arthritis about to start etanercept presents to you with a positive T-SPOT.TB test.
- She notes vague night sweats and a 5 pound weight loss over the past 4 weeks
- She has diffuse, severe pain and swelling in her hands, feet, wrists and knees
- The patient had a CXR 4 months ago and it was reportedly normal

What is the next best option?

A. Repeat CXR
B. Start Rifampin 600 mg x 4 months and inform rheumatologist etanercept can be started in 2 weeks
C. Place a PPD and have patient return in 2 days for reading
D. Start Isoniazid 300 mg x 9 months and inform rheumatologist that etanercept could be started in 1 month
Each patient below has a TST of 6mm. Which CXR is consistent with old, healed pulmonary tuberculosis?

A. A  
B. B  
C. C  
D. D

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

A. A  
B. B  
C. C  
D. D