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 Challenges
• Lengthy treatment leading to limited adherence
• Adverse effects influencing patient and provider agreement
• Perception of risk
• 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>Very serious complications</td>
<td>Asymptomatic condition</td>
</tr>
<tr>
<td>– Death</td>
<td>– Asymptomatic condition</td>
</tr>
<tr>
<td>– Major disability</td>
<td>– Major disability</td>
</tr>
<tr>
<td>– AND transmission</td>
<td>– AND transmission</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>
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</tr>
</tbody>
</table>

BUT – no debate about Treating

WHY the debate about Treating??

Menezes et al., Indian Jntl of Medical Research. 2011

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
  – E.g. 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></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>INH-RPT</td>
<td>3 Weekly**</td>
<td></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 > 9-10 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>
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<td>12 months</td>
</tr>
<tr>
<td>Daily</td>
<td>180</td>
<td>6 months</td>
<td>9 months</td>
</tr>
<tr>
<td>Twice weekly*</td>
<td>52</td>
<td>6 months</td>
<td>9 months</td>
</tr>
</tbody>
</table>

*Isoniazid Treatment

- 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
- Why?
  - Hepatotoxicity
  - Provider preferences
  - Duration and pill burden

*via Directly Observed Therapy
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 predictable drug interactions (opiates, corticosteroids, oral contraceptives, PI, warfarin etc)
- RIF + PZA for 2 months

Treatment of LTBI: Comparison of INH vs. RIF

<table>
<thead>
<tr>
<th>Comparison of Regimen Features: 9H and 4R</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</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(e.g., among foreign-born persons)</td>
<td></td>
<td></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.

PREVENT TB (TBTC Study 26): INH + 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 + RPT for 3 months vs Standard INH for 9 months

PREVENT TB (TBTC Study 26): INH + Rifapentine for 12 weeks
- Efficacy was similar
  - 0.19% vs 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

Study Population (n = 7731)

| TST+ close contacts | 71% |
|------------------------------------------|
| Converters | 25% |
| TST+ HIV or HIV+close contact | 2% |
| TST+ with fibrotic changes | 2% |

Sterling et al., NEJM, 2011
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 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
- Reporting: ltbidrugevents@cdc.gov; MedWatch 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

Choosing INH-RPT

- DOT feasibility
- Drug availability and resources
- Program operations
- Expectance of treatment completion
- Patient/Provider preferences
Dosing for INH-RPT with DOT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>15 mg/dl up to 50 or 100 mg</td>
</tr>
<tr>
<td>RIF</td>
<td>300 mg maximum</td>
</tr>
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</table>

**In Connecticut**

- 55% Male
- Median age at start of treatment: 38 years
  - Range 10 – 90 years
  - Median age at start of treatment: 38 years
  - Range 10 – 90 years

- 58% Foreign Born
  - Top countries of birth include: Peru, Haiti, Dominican Republic, and China
  - 41% arrived in the US within the past year (56% within the last 5 years)

**Provider Type**

- Private: 78%
- Public: 13%
- Schools: 9%

**Risk Factors**

- 3% (10) diagnosed in long-term care
- 5% (17) reported a history of homelessness in the past year
- Substance use in the past year
  - 2.5% (9) reported excess alcohol use
  - 2.0% (7) reported injection drug use
  - 3.6% (13) reported non-injection drug use
- 19% (69) unemployed
- 5% (19) contact to a known case
- 11% report a known medical risk factor
Treatment outcome of patients who started INH-RPT
March 2012–December 2014

357 patients started INH-RPT
287 with final disposition data
244 (85%) successfully completed
43 discontinued
24 (8%) adverse event
12 (4%) lost to follow-up or refused
7 (2%) other reason

Symptoms and Adverse Drug Reactions

- 50% of patients reported at least one symptom while receiving treatment
- Despite symptoms, only 24 (8%) patients experienced an adverse event which caused treatment to be stopped
- 3 hospitalizations

Symptom | Number of Complaints
---------|---------------------
Nausea   | 38 (15%)
Fatigue  | 31 (12%)
Soreness | 28 (11%)
Numbness/Tingling | 20 (8%)
Fever    | 20 (8%)
Diarrhea | 17 (7%)
Appetite Loss | 13 (5%)
Rash     | 13 (5%)
Abnormal Labs | 8 (3%)
Yellowing skin/eyes | 2 (<1%)
Other    | 63 (24%)

Percentages do not add up to 100%; patients can report more than 1 symptom

Predictors of Treatment Discontinuation

- Controlling for other factors, elevated liver transaminases (OR = 57.1) and fever (OR = 19.3) are strong predictors of treatment discontinuation

Treatment regimens...stay tuned..

- 3HP
  - Post – marketing surveillance data
  - iAdhere: self administered therapy (+/- text messaging) v DOT
- Prelim - SAT does not seem to be inferior to DOT in the US
- DOT still recommended
- HIV
- 4R versus 9H
- 9H versus 1 month daily INH and Rifapentine

Belnap et al., CROI 2015

Short-Course Treatment for LTBI

- 15 regimens indirectly compared from 53 studies and > 130,000 subjects
- Rifamycin containing regimens (without PZA) are as, if not more, effective as 9H or 6H and safer
- Rifampin alone for 3-4 months rated lowest for hepatotoxicity
- PZA containing regimens are not preferred due to hepatotoxicity


Treatment of LTBI: 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

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
Compliance 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-RFT</td>
<td>3 months</td>
<td>11-12</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

Treatment Adherence
- Treatment efficacy increases with amount of drug taken
- Overall only 50-65% complete therapy, regardless of whether adverse effects are present
- Shorter course regimens may have better adherence

Trajman, LTLID, 2010
Goswami, BMC Public Health, 2012
Factors Associated with Treatment Adherence

- Adherence
  - Non US birthplace
  - Recent exposure to active case
- Non-adherence
  - Perception of low risk of progression to TB disease
  - Dislike of venipuncture
  - Fear of side effects
  - Lower educational level
  - Unstable housing
  - Side effects

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

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

- 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
Case #1

- Transaminases were monitored off INH and slowly improved to baseline values (ALT 2x ULN)
- Seen by Hepatology
- Presented to clinic after a 4 month gap for re-initiation of LTBI treatment

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

A. Repeat QFT
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 with DOT is an option
B. The risk of hepatotoxicity is higher with INH-RPT
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

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

Thank you!