LTBI Treatment

Stacey Rizza, MD, FIDSA
Associate Director, Mayo Clinic Center for Tuberculosis
Chair, Mayo HIV Clinic
Associate Professor of Medicine
Mayo Clinic, Rochester, MN
Disclosures

• No financial disclosures
Objectives

• Describe guidelines for LTBI treatment

• Describe monitoring recommendations for patients on LTBI therapy
Latent TB Infection (LTBI) Treatment

• Rationale
  • To prevent the development of active disease
  • Component of TB control
  • Durability of protection against reactivation depends on regional prevalence of TB and risk for reexposure

• A decision to test for LTBI is a decision to treat
# Targeted Testing for LTBI

<table>
<thead>
<tr>
<th>High Likelihood of Exposure to TB</th>
<th>High Risk of Progression to Active TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Close contacts</strong> of a person with infectious TB disease</td>
<td>HIV Infection</td>
</tr>
<tr>
<td>Persons who have <strong>immigrated</strong> from areas of the world with high rates of TB</td>
<td><strong>Recent LTBI test conversion</strong> (within past 2 years)</td>
</tr>
<tr>
<td>Residents/employees of high-risk <strong>congregate settings</strong> (correctional facilities, homeless shelters, healthcare facilities)</td>
<td><strong>History of prior, untreated TB</strong> or fibrotic lesions on chest radiograph</td>
</tr>
<tr>
<td></td>
<td>Those receiving <strong>TNF-α antagonists</strong> for treatment of autoimmune diseases</td>
</tr>
<tr>
<td></td>
<td>Solid organ <strong>transplant</strong>, lymphoma, leukemia, head and neck cancer, chemotherapy</td>
</tr>
<tr>
<td></td>
<td>Chronic kidney disease requiring <strong>hemodialysis</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Children</strong> who have positive LTBI test</td>
</tr>
</tbody>
</table>
Prior to Treatment

- Rule out active disease
  - Symptom screen
  - Chest X-ray

- Assess for medical conditions and medications that may affect treatment choices

- Determine whether patient has ever been treated for LTBI or TB disease

- Establish rapport with patient; explain therapy and adverse effects
Which LTBI treatment regimens require directly observed therapy (DOT)?

A) Daily isoniazid x 9 months  
B) Twice weekly isoniazid x 9 months  
C) Daily rifampin x 4 months  
D) Weekly isoniazid + rifapentine  
E) B & D
# LTBI Treatment Regimens

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration</th>
<th>Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>Preferred treatment for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Persons living with HIV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Children aged 2-11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pregnant Women (with pyridoxine/vitamin B6 supplements)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly*</td>
<td></td>
<td>Preferred treatment for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Pregnant Women (with pyridoxine/vitamin B6 supplements)</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Twice weekly*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid and Rifapentine</td>
<td>3 months</td>
<td>Once weekly*</td>
<td>Treatment for:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Persons 12 years or older</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not recommended for persons who are:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Younger than 2 years old,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Living with HIV/AIDS taking antiretroviral treatment,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Presumed infected with INH or RIF-resistant M. tuberculosis, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Women who are pregnant or expect to become pregnant within the 12-week regimen</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td></td>
</tr>
</tbody>
</table>

[cdc.gov- 2/2017]
LTBI Treatment Programs

INH

• 9-month regimen
  • The 9-month regimen is preferred - more efficacious

• 6-month regimen
  • 6 months may be more cost-effective and result in greater adherence by patients

• Every effort should be made to ensure that patients adhere to LTBI treatment for at least 6 months

• The preferred regimen for children aged 2 to 11 years is 9 months of daily INH.
Isoniazid Adverse Effects

- Transient *asymptomatic elevation* of AST/ALT in 10-15% (usually in 1st 4-8 weeks of therapy) – usually resolves

- Hepatotoxicity / hepatitis
  - Increased in HIV (4x), HCV (5x) or both HIV-HCV (14x) co-infections
  - Usually in 1st 4-8 weeks of therapy) – typically 0.1-1% risk without underlying liver disease
  - *Rapid improvement* (AST/ALT) after stopping drugs - clue to INH toxicity

- Peripheral neuropathy – give vitamin B6 (10-50 mg/day) to prevent
  - Hypersensitivity (fever, rash)
    - (+) ANA (< 20%)
    - Lupus-like reaction (≤10%)
LTBI Treatment Program
12-Dose (Isoniazid and Rifapentine) Regimen

• An equal option to the standard INH 9-month daily regimen otherwise healthy people, 12 years of age and older,

• The 12-dose regimen can be considered for other groups on a case by case basis when it offers practical advantages:
  • Completion within a limited timeframe
  • HIV-infected persons
  • 12 years of age and older, who are not on antiretroviral medications
  • Children aged 2-11 years if completion of 9 months of INH is unlikely and hazard of TB disease is great.
LTBI Treatment Program
12-Dose (Isoniazid and Rifapentine) Regimen

• The 12-dose regimen is **NOT** recommended for the following individuals:
  • Children younger than 2 years of age
  • People with HIV/AIDS who are taking antiretroviral therapy (ART)
  • People presumed to be infected with INH or rifampin-resistant *M. tuberculosis*
  • Pregnant women, or women expecting to become pregnant while taking this regimen
LTBI Treatment Program
12-Dose (Isoniazid and Rifapentine) Regimen

- The choice between the 12-dose regimen and other recommended LTBI treatment regimens depends on several factors, including:
  - Feasibility of DOT
  - Resources for drug procurement and patient monitoring
  - Considerations of medical and social circumstances that could affect patient adherence
  - Preferences of the patient and prescribing health care provider
Current CDC recommendations state isoniazid + rifapentine weekly x 12 weeks is an acceptable alternative LTBI regimen for which groups with high risk of developing active TB?

A) Persons ≥ 12 years old with recent LTBI test conversion, recent exposure to contagious TB, CXR consistent with healed pulmonary TB, or HIV infection but not on antiretrovirals

B) Pregnant females

C) HIV-infected individuals on antiretroviral therapy

D) A & C

E) A & B

MMWR. 2011;60(48):1650-3.
Isoniazid (INH) + Rifapentine (RPT)

- INH/RPT weekly x 3 mo (DOT) non-inferior to 9 mo daily INH (self-administered) in randomized open label trial
  - N=7731, mostly HIV(-) in Brazil, Canada, Spain, and US
  - ≥ 12 years old (later ≥ 2 yo) + 1 of 4 high-risk groups (recent LTBI test conversion, recent exposure to contagious TB, CXR consistent with healed pulmonary TB, HIV infection and not on ARVs with + LTBI test or close TB contact)

- Completion rate was 82% for INH/RPT and 69% for INH (p<0.01)
- Hepatotoxicity greater in INH than INH/RPT (2.7% vs 0.4%; p<0.001)
- Higher rates of permanent drug discontinuation due to an adverse event in the rifapentine/INH group (4.9 % vs. 3.7 %; p=0.009)

Isoniazid + Rifapentine

• Further study is needed for:

  • Completion /efficacy without DOT
  • Durability of protection/ efficacy/toxicity in those with HIV (also with antiretrovirals)
  • Efficacy/toxicity in other groups without recent infection (prior to TNF-α inhibitors)
  • Utility where the incidence of TB is high
LTBI Treatment Program
Rifampin

• A 4-month regimen of RIF can be considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB.

• It should not be used to treat HIV-infected persons taking some combinations of ART.
Rifampin Adverse Effects

• **Most Common:**
  - Rash, generally self-limited (true hypersensitivity rare)
  - Nausea/vomiting
  - Hepatotoxicity: *(usually cholestatic; ↑ bilirubin is a clue)*
  - Orange discoloration of body fluids

• **Less Common:**
  - Influenza-like syndrome
  - Cytopenias - ↓ WBC, ↓ platelets
  - Nephrotoxicity; interstitial nephritis
  - Hypersensitivity reactions
Rifampin Drug Interactions

• Rifampin induces its own metabolism during the first 2 weeks

• Induces cyt p450 system & decreases levels of:
  • Steroids, OCP/estrogen
  • Protease inhibitors
  • Warfarin
  • Antiepileptics
    • Methadone, morphine
    • Digoxin, calcium channel blockers, β-blockers
      • Azoles + many others
Pyridoxine and Isoniazid – Who Needs It?

• Those at increased risk for peripheral neuropathy
  • Diabetes mellitus
  • Alcohol dependence
  • HIV
  • Chronic kidney disease
  • Malnutrition
  • Pregnant/breastfeeding women
Monitoring of LTBI Therapy

- Everyone should have initial clinical evaluation prior to starting therapy with monthly clinical monitoring for signs/symptoms of hepatitis and adherence to medication while on therapy.

- For weekly INH/RPT, ask about signs/symptoms with each dose.

- Baseline liver enzyme testing in those with:
  - Underlying liver disease
  - HIV infection
  - Pregnant /postpartum (≤ 3 mo after delivery)
  - Regular alcohol consumption
  - Medication(s) with potential hepatotoxicity

- Routine lab monitoring during treatment for those whose baseline liver function tests are abnormal or those at risk for hepatic disease.

When Should LTBI Therapy be Stopped?

- Liver enzymes are:
  - ≥ 3 times upper limit of normal range and patient has symptoms
  - ≥ 5 times upper limit of the normal range and patient has no symptoms
Pregnant Women

- For most LTBI treatment can be delayed until after delivery, unless they have significant immunocompromising conditions, HIV, or recent TB contact
  - INH is safe during pregnancy
  - Preferred LTBI treatment regimen is 9 months of INH with pyridoxine
  - INH is safe for breastfeeding, give with pyridoxine
Biologics

Used for RA, Crohn’s disease, Psoriasis and a variety of other immune mediated diseases

• Remicaid (inflixamab)
• Embril (entanercept)
• Humira (adalimumab)

• Block TNFα activity required for containment of MTB

• Patients should be evaluated for LTBI
• Treatment of LTBI should be initiated prior to Rx
LTBI Treatment Key Points

- Test and treat those at high risk for TB exposure and/or progression to active disease

- Isoniazid daily x 9 months or Isoniazid + rifapentine weekly x 3 months with DOT (with caveats) are preferred regimens

- LTBI treatment regimens that include weekly or bi-weekly dosing require DOT

- Prior to treatment for LTBI, patients need clinical evaluation + CXR to rule out active TB disease

- While on therapy patients need monthly clinical monitoring; baseline liver enzymes for those at risk
Which LTBI treatment regimens require directly observed therapy (DOT)?

A) Daily isoniazid x 9 months
B) Twice weekly isoniazid x 9 months
C) Daily rifampin x 4 months
D) Weekly isoniazid + rifapentine
E) **B & D**

JAMA 2005; 293:2776
MMWR. 2011 Dec 9;60(48):1650-3.
Current CDC recommendations state isoniazid + rifapentine weekly x 12 weeks is an acceptable alternative LTBI regimen for which groups with high risk of developing active TB?

A) **Persons ≥ 12 years old with recent LTBI test conversion, recent exposure to contagious TB, CXR consistent with healed pulmonary TB, or HIV infection but not on antiretrovirals**

B) Pregnant females

C) HIV-infected individuals on antiretroviral therapy

D) A & C

E) A & B

MMWR. 2011;60(48):1650-3.
Review Cases
Case #1

- 36-year-old Native American female
- History of diabetes
- 35 weeks pregnant
- TST = 18 mm of induration
- No symptoms of TB disease
- CXR, CBC, LFTs normal
- No HIV
- No known contact with TB patient
Which of the following statements regarding this case is correct?

a) She has no known contact with TB. Therefore, this is likely a false-positive result due to pregnancy, therefore retest for LTBI after pregnancy

b) She has LTBI; as pregnancy is a risk factor for progression of TB, she should be treated immediately

c) She has LTBI but treatment can be deferred until post partum

d) Check IGRA as TST tends to be falsely positive in pregnancy

e) T-SPOT TB is the best test for LTBI in pregnancy
Questions?