Latent Tuberculosis Infection: Screening, Evaluation, and Treatment

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Statement of Interest

- Presenter *Stepheni Appleby, RN* does not have any personal or financial conflicts of interest to list

Objectives

- **Discuss Latent Tuberculosis Infection**
  - Screening
  - Evaluation
  - Treatment

Latent Tuberculosis Infection

- **Diagnosis of Latent TB Infection**
  - The diagnosis of LTBI is based on information gathered from the medical history, TST or IGRA result, chest radiograph, physical examination, and in certain circumstances, sputum examinations.
  - Tuberculosis Disease must be ruled out before LTBI treatment can begin to ensure adequate treatment and decreased risk of resistance. This means waiting on final cultures if sputum specimen were collected and if necessary, delaying the start of LTBI if person reports new symptoms at start of LTBI.

Latent TB Infection (LTBI) Quick Facts

- 2 to 8 weeks after infection, LTBI can be detected via TST or interferon-gamma release assay (IGRA)
- The immune system is usually able to stop the multiplication of bacilli
- Persons with LTBI are not infectious and do not spread organisms to others
- about 5 to 10% of infected persons will develop TB disease at some time in their lives.

Testing for Tuberculosis

Who Should Be Screened?

- Contacts to People with Active TB disease
- Foreign-born people from endemic countries
- Healthcare personnel
- Laboratory personnel
- People who live or work in Jails/prisons
- People who live/work in homeless shelters
- People who live/work in other congregate settings like nursing homes and group homes
- Patients with HIV, DM, chronic kidney disease, or other conditions requiring immunosuppressive drug therapy

Methods for Detecting *M. tb* Infection in U.S.

- **Mantoux tuberculin skin test (TST)**
- **IGRAs:**
  - QuantiFERON-TB Gold In-Tube (QFT-GIT)®, and
  - T-Spot.*TB*®
- **These tests do not exclude LTBI or TB disease**
- **Decisions about medical/public health management should include other info/data, and not rely only on TST/IGRA results**

Mantoux Tuberculin Skin Test (TST)

- Purified protein derivative (PPD), derived from tuberculin, is injected between skin layers using the Mantoux technique
- Infected person's immune cells recognize TB proteins in PPD, respond to site, causing wheal to rise
- Takes 2-8 weeks after exposure and infection for the immune system to react to PPD
- Reading and interpretation of TST reaction must be done within 48–72 hours

TB Test Interpretation Center for Disease Control **A tuberculin skin test should be considered positive and reported IF:**		
≥ 5 mm induration AND any of the following:	≥ 10 mm induration AND any of the following:	≥ 15 mm induration:
• HIV infection • Recent contacts with TB infected persons • Chest x-ray findings suspicious for TB • Organ transplant recipient • Persons with immunosuppression	• Recent immigrants from high-prevalence countries (within 5 years) • Injection drug users/needle sharing • Residents or employees of high-risk congregate settings (long term care, shelters, prisons) • Mycobacteriology lab personnel • Children less than 4 years old • Persons with OR children/infants exposed to persons at high-risk for TB	• Any person with NO known risk factors for TB

https://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm

Interferon Gamma Release Assays (IGRAs)

- IGRAs detect *M. Tb* infection by measuring immune response in blood
- Cannot differentiate between TB and LTBI; other tests needed
- May be used for surveillance/screening, or to find those who will benefit from treatment
- FDA-approved IGRAs are QFT Gold In-Tube and T-Spot.*TB* test

Medical Evaluation for TB

- Medical history: symptoms (pulmonary and extra-pulmonary), exposure, previous treatment, comorbidities, demographic risks
- Physical examination: What does the patient present with that you can see, touch, hear?
- Test for TB infection: TST/ IGRA results
- Chest radiograph: Nodules, lesions, granulomas, calcifications
- Bacteriologic examination: smear for AFB, Culture (gold standard), NAA testing

- "Put the puzzle pieces together"

Treatment for Latent Tuberculosis Infection

Treatment for Latent TB Infection (LTBI)

- **Approximately 13 million persons in U.S. estimated to have LTBI**
  - 5%-10% of otherwise healthy persons will develop TB disease if untreated
  - About half of those healthy persons will develop TB within first 2 years of infection
- **Treatment of LTBI essential to preventing and eliminating TB disease**
- **Reduces risk of LTBI to TB disease progression**
- **Use targeted testing to find persons at high risk for TB who would benefit from LTBI treatment**
- **Several treatment regimens available**

Updated 2020 LTBI Treatment Guidelines

- **Clinical question: Which regimens for treatment of latent tuberculosis infection have greatest effectiveness and least toxicity?**
- **More effective treatment of LTBI will facilitate TB elimination**
- **Prioritized recommended regimens as either preferred or alternative**
- **Preferred regimens: Excellent tolerability and efficacy, shorter treatment duration, and higher completion rates**
- **Alternative regimens: Excellent efficacy, longer treatment duration and lower completion rates**
- **Rationale for prioritizing regimens:**
  - Treatment completion rates are higher with shorter regimens
  - Determination on similarity of efficacy and safety
  - Shorter regimen is more effective because completion rates are higher

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020
https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm

Preferred Regimens

- **Three months of Once-Weekly INH Plus Rifapentine (3HP)**
  - "12 Dose Regimen" Strongly recommended for adults and children aged >2 years, including HIV-positive persons
  - Treatment completion rates higher with 3-month regimen
  - Potential disadvantages: cost of medications, need to take numerous pills simultaneously (10 pills once weekly), and association with systemic drug reaction
- **Four months of Daily Rifampin**
  - Strongly recommended for HIV-negative adults and children of all ages
  - No evidence available for effectiveness in HIV-positive persons
  - Potential disadvantages of rifamycin-based regimens including drug interactions with warfarin, OCP, azole antifungals, and HIV ART. Rifabutin has fewer drug interactions and may be used in place of rifampin when rifampin is contraindicated due to drug-drug interactions and isoniazid cannot be used

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Preferred Regimens

- **Three months of Daily INH Plus Rifampin**
  - Regimen of 3 months daily isoniazid plus rifampin is conditionally recommended for adults and children of all ages and for HIV-positive persons as drug interactions allow
  - HIV-negative adults and children with a positive TST who

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)

LTBI Treatment Regimens

Isoniazid (INH) -rifapentine (RPT) Regimen (12-dose regimen, 3HP)

- INH and RPT given in 12 once-weekly doses under DOT
- Offers equal option to 9 months daily INH. High completion rates.
- Recommended for treating LTBI in otherwise healthy people ≥2 years of age
- Can be used for people living with HIV who are taking antiretroviral medications with acceptable drug-drug interactions with Rifapentine.

LTBI Treatment Recommendations (3HP dosages)

- Adults and Children aged 12 years and older:
  INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum
  RPT:
  10–14.0 kg 300 mg
  14.1–25.0 kg 450 mg
  25.1–32.0 kg 600 mg
  32.1–49.9 kg 750 mg
  ≥50.0 kg 900 mg maximum
- Children aged 2–11 years:
  INH*: 25 mg/kg; 900 mg maximum
  RPT†: as above

https://www.cdc.gov/tb/topic/treatment/ltbi.htm

Rifampin (4R)

- **4 months daily Rifampin: 120 doses within 4 months**
- This regimen should not be used in people with HIV who are taking some combinations of antiretroviral therapy.
- Adult: 10 mg/kg
- Children: 15–20 mg/kg‖
  Maximum dose: 600 mg
- Side Effects: monitor for s/s of hepatotoxicity (ADB Pain, jaundice, persistent n/v, dark colored urine, lethargy, fatigue)

Alternative Regimens

- **6 month Regimen of Daily INH (6H)**
  - Strongly recommended for HIV-negative adults and children of all ages
  - Conditionally recommended for HIV-positive adults and children of all ages

- **9 month Regimen of Daily INH (9H)**
  - Conditionally recommended for adults and children of all ages, both HIV-negative and HIV-positive

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Alternative	6 mos isoniazid given daily	Strong[§]	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

LTBI Treatment Regimens

Isoniazid (INH)

- **6-month regimen: 180 doses within 6 months (6H)**
  - Can be given daily via DOT: 180 doses within 6 months
  - Adult: 5 mg/kg
    Children: 10–20 mg/kg
    Maximum dose: 300 mg

  - Can be given twice weekly via DOT: 52 doses within 6 months
  - Shorter regimen not recommended for children, immunosuppressed persons, persons whose x-rays suggest previous TB
  - Adult:15 mg/kg
  - Children: 20–40 mg/kg
  - Maximum dose: 900 mg

LTBI Treatment Regimens

Isoniazid (INH)

- **9-Month daily regimen: 270 doses within 9 months (9H)**
  - Effective for otherwise healthy individuals
  - Effective for HIV-infected as well as HIV-uninfected persons
  - Adult: 5 mg/kg
    Children: 10–20 mg/kg
    Maximum dose: 300 mg
- **Can be given Twice Weekly via DOT: 76 doses within 9 months**
  - Adult:15 mg/kg
  - Children: 20–40 mg/kg
  - Maximum dose: 900 mg

Adverse Reactions to INH

Use of INH is associated with some adverse reactions:

- **Peripheral neuropathy – give vitamin B_6 if patient has risk factors, or if signs/symptoms develop**
- **Fatal hepatitis – pregnant/postpartum women at increased risk; monitor closely**
- **Elevated liver enzymes – discontinue INH if liver enzyme levels exceed 3X normal with symptoms, or 5X upper limit of normal with no symptoms**
  - Closely monitor if signs/symptoms of liver injury, or liver enzyme levels are elevated but less than above

LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

Special Considerations for Treatment of LTBI

- **People living with HIV:**
  - Recently guidelines changed and people taking certain ARTs can also take 3HP
  - Treatment Priority as people living with HIV are at greater risk of development of disease
- **Pregnant Women: 3HP not recommended, INH safe to use during pregnancy and whilst breastfeeding**
- **Children: children are priority especially if from an endemic country or contact to a person with active TB**

Sources

- https://www.cdc.gov/tb/topic/treatment/tbhiv.htm
- https://www.cdc.gov/tb/topic/treatment/pregnancy.htm
- https://www.cdc.gov/tb/topic/treatment/ltbi.htm
- https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w
- https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm#T3_down