Prevention of Tuberculosis: TB Screening, Diagnosis of Latent Tuberculosis Infection and Preventive Therapy

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Objectives

- Describe screening recommendations for TB in resource-constrained countries
- Frame the diagnosis and treatment of persons with Latent TB Infection (LTBI) in context of overall TB control strategies
- Understand diagnostic tools and treatment of LTBI-INH preventive therapy and other evidence-based regimens
- Understand best practices for adherence and monitoring during treatment of LTBI
Pathophysiology of Latent Infection with M. TB

- Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, travel to the alveoli, and multiply. A few bacilli enter the bloodstream and spread to other parts of the body.
- Within 2 - 8 weeks, immune cells (macrophages) ingest and surround the tubercle bacilli and form a barrier shell (granuloma), that keeps bacilli contained and under control for most people (LTBI).
- Granulomas may persist with dormant bacilli (LTBI), or may break down to produce TB disease.
- 2 to 8 weeks after infection, LTBI can be detected via tuberculin skin test (TST) or interferon-gamma release assay (IGRA)
## Latent TB Infection vs. TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection (LTBI)</th>
<th>TB Disease (in the lungs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive, contained tubercle bacilli in the body</td>
<td>Active, multiplying tubercle bacilli in the body</td>
</tr>
<tr>
<td>TST or IGRA blood test results usually positive</td>
<td>TST or IGRA blood test results usually positive</td>
</tr>
<tr>
<td>Chest x-ray usually normal</td>
<td>Chest x-ray usually abnormal</td>
</tr>
<tr>
<td>Sputum smears and cultures negative</td>
<td>Sputum smears and cultures may be positive</td>
</tr>
<tr>
<td>No symptoms</td>
<td>Symptoms such as cough, fever, weight loss</td>
</tr>
<tr>
<td>Not infectious</td>
<td>Often infectious before treatment</td>
</tr>
<tr>
<td>Not a case of TB</td>
<td>A case of TB</td>
</tr>
</tbody>
</table>

TST= tuberculin skin test; IGRA= Inferferon-gamma release assay
Note: HIV+ persons may have false-negative TST and IGRA, atypical symptoms or CXR pattern, etc.

CDC. Module 1 – Transmission and Pathogenesis of Tuberculosis
Risk of Developing Disease

• Normal Immune System
  – Untreated, 5% of infected persons with normal immunity develop TB in first 1–2 years post infection, another 5% later in life
  – Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

• Persons with weak immunity at increased risk of progressing to TB disease
  – Untreated HIV infection highest risk factor: risk of developing TB disease is 7%–10% each year;
  – Children <5 years of age also at increased risk
## Risk of TB and poor health outcomes in clinical risk groups.
(Increased risk of progression to TB once infected)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Risk of TB</th>
<th>Health outcomes related to risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight (BMI &lt;18.5)</td>
<td>Pooled relative risk estimate from meta-analysis: 3.2 (95% CI, 3.1–3.3)78</td>
<td>Increased risk of death and TB relapse; systematic reviews, no pooled estimate79,80</td>
</tr>
<tr>
<td>Gastrectomy or jejunoileal bypass</td>
<td>No pooled estimate</td>
<td>Increased risk of death associated with undernutrition (see &quot;Underweight&quot;), but no published data specifically on gastrectomy or jejunoileal bypass</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Pooled relative risk estimate from systematic review: 3.1 (95% CI, 2.3–4.3)81</td>
<td>Pooled relative risk of TB treatment failure or death from systematic review: 1.69 (95% CI, 1.36–2.12) and relapse: 3.89 (95% CI, 2.43–6.23)82</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>Pooled relative risk estimate from systematic review: 2.9 (95% CI, 1.9–4.6)83</td>
<td>Higher risk of TB treatment failure and relapse and death during treatment; systematic review, no pooled estimate84</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>Pooled relative risk estimate from systematic review: 2.0 (95% CI, 1.6–2.5)85</td>
<td>Increased risk of death; systematic review, no pooled estimate86</td>
</tr>
<tr>
<td>Chronic renal failure or haemodialysis</td>
<td>No pooled estimate; relative risk range, 10–2581</td>
<td>Increased risk of death; systematic review, no pooled estimate82</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>No pooled estimate; increased risk probably due to high prevalence of other risk factors, such as HIV</td>
<td>Increased risk of death; systematic review, no pooled estimate82</td>
</tr>
<tr>
<td>Solid organ transplantation</td>
<td>No pooled estimate; relative risk range, 20–7481</td>
<td>No published data</td>
</tr>
<tr>
<td>Old age</td>
<td>Not established; prevalence surveys report increased risk with age27,28</td>
<td>Increased risk of death; systematic review, no pooled estimate86</td>
</tr>
<tr>
<td>Previously treated TB</td>
<td>High incidence of TB due to relapse and reinfection; no systematic review</td>
<td>Retreatment cases have higher risk of poor outcomes and higher risk of MDR-TB</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Not established85</td>
<td>Infants of mothers with TB have increased risks of premature birth and perinatal death; pregnant women with TB are more likely to have complications during pregnancy; initiating TB treatment is associated with better maternal and infant outcomes than late initiation84,94,95,96,97,98</td>
</tr>
</tbody>
</table>

BMI, body mass index; CI, confidence interval; MDR-TB, multidrug-resistant TB.

Fig. 10  Principles for stopping tuberculosis (TB) transmission. TB control is based on preventing susceptible individuals from becoming infected using vaccination, preventing infected individuals from developing the disease using prophylactic treatment, preventing individuals with TB from having contact with susceptible individuals through early detection and cure, isolation, and infection control measures.

How Do We Reach TB Elimination Targets?

- The 2050 Stop TB target of TB elimination is most likely to be achieved if both latent infection and TB disease are treated.
TB Control Priorities

1. Detection and treatment of persons with active tuberculosis

2. Investigation of infectious cases to detect contacts with active TB or who are infected at risk of future TB

3. Prevent future TB through screening high risk groups and providing LTBI treatment to persons with M. tuberculosis infection (and no active disease)
Systematic Screening for Active TB

- **Passive case finding**: Diagnosing TB among people who actively seek medical care with TB symptoms (“self-referral”)

- **Systematic screening**: The systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly.
  
  - Active strategy complementing the patient-initiated pathway to TB diagnosis
  
  - Should increase case detection rate
Systematic Screening for Active TB

• The primary objective of screening for active TB is to ensure that **active TB is detected early** and treatment is initiated promptly:

• Benefits:
  – **Individual**: Reducing the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences of TB
  – **Community**: Reduce TB transmission
Recommendations for Active TB Screening

• Must balance potential benefits against the risks and costs of screening.
  – Some risk groups should always be screened
  – But prioritization of other risk groups and the choice of screening approach depends on the epidemiology, the health-system context, and the resources available

• Target screening on 2 high risk groups:
  – Persons with increased risk of exposure to M. tuberculosis
  – Persons with conditions that are associated with increased risk of progression to active TB if infected

• “Indiscriminate mass screening should be avoided”

WHO, 2013: http://www.who.int/tb/tbscreening
Recommendations for Active TB Screening

Strong recommendations

• **Recommendation 1**: Household contacts and other close contacts should be systematically screened for active TB.
  – Especially children and People living with HIV (PLHIV)

• **Recommendation 2**: People living with HIV should be systematically screened for active TB at each visit to a health facility.

• **Recommendation 3**: Current and former workers in workplaces with silica exposure should be systematically screened for active TB.

WHO, 2013: http://www.who.int/tb/tbscreening
Recommendations for Active TB Screening

Conditional recommendations

- **Recommendation 4**: Systematic screening for active TB should be considered in prisons and other penitentiary institutions.

- **Recommendation 5**: Systematic screening for active TB should be considered in people with an untreated fibrotic chest X-ray lesion.

- **Recommendation 6**: In settings where the TB prevalence in the general population is $\geq 100/100,000$ population, systematic screening for active TB should be considered among people who are seeking health care or who are in health care and who belong to selected risk groups.

WHO, 2013: http://www.who.int/tb/tbscreening
Recommendations for Active TB Screening

• Recommendation 7:

  (a) Systematic screening for active TB may be considered for geographically defined subpopulations with extremely high levels of undetected TB (1% prevalence or higher).

  (b) Systematic screening for active TB may be considered also for other subpopulations that have very poor access to health care, such as people living in urban slums, homeless people, people living in remote areas with poor access to health care, and other vulnerable or marginalized groups including some indigenous populations, migrants and refugees.

WHO, 2013: http://www.who.int/tb/tbscreening
## Possible risk groups to consider for screening for TB

<table>
<thead>
<tr>
<th>Potential site of screening</th>
<th>Risk group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community</strong></td>
<td>Geographical areas with a high prevalence</td>
</tr>
<tr>
<td></td>
<td>Subpopulations with poor access to health care and with other associated risk factors (such as living in a poor area, an urban slum or a remote area; being a member of an indigenous or tribal population, or a migrant, refugee, homeless, or nomadic; being a sex worker)</td>
</tr>
<tr>
<td><strong>Hospital outpatient and inpatient departments, and primary health-care centres</strong></td>
<td>People previously treated for TB</td>
</tr>
<tr>
<td></td>
<td>People with an untreated fibrotic lesion identified by chest radiography</td>
</tr>
<tr>
<td></td>
<td>People living with HIV and people attending HIV testing</td>
</tr>
<tr>
<td></td>
<td>People with diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>People with chronic respiratory disease and smokers</td>
</tr>
<tr>
<td></td>
<td>Undernourished people</td>
</tr>
<tr>
<td></td>
<td>People with gastrectomy or jejunoleal bypass</td>
</tr>
<tr>
<td></td>
<td>People with an alcohol-use disorder and intravenous drug users</td>
</tr>
<tr>
<td></td>
<td>People with chronic renal failure</td>
</tr>
<tr>
<td></td>
<td>People having treatments that compromise their immune system</td>
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<tr>
<td></td>
<td>Elderly people</td>
</tr>
<tr>
<td></td>
<td>People in mental health clinics or institutions</td>
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<tr>
<td><strong>Residential institutions</strong></td>
<td>Prisoners and prison staff</td>
</tr>
<tr>
<td></td>
<td>People residing in shelters</td>
</tr>
<tr>
<td></td>
<td>Other congregate institutions (such as the military)</td>
</tr>
<tr>
<td><strong>Immigration and refugee services</strong></td>
<td>Immigrants from settings with a high prevalence of TB</td>
</tr>
<tr>
<td></td>
<td>People in refugee camps</td>
</tr>
<tr>
<td><strong>Workplaces</strong></td>
<td>Health-care workers</td>
</tr>
<tr>
<td></td>
<td>Miners or others who are exposed to silica</td>
</tr>
<tr>
<td></td>
<td>Other workplaces with a high prevalence of TB</td>
</tr>
</tbody>
</table>

Note: The list is not exhaustive and risk groups may be reachable in different places depending on the local epidemiological situation and health-system context.

Guidelines for Intensified Tuberculosis Case-finding and Isoniazid Preventive Therapy for People Living with HIV (PLHIV) in Resource-Constrained Settings

WHO
Intensive Case Finding and IPT in PLHIV

- HIV is strongest risk factor for TB disease in those with latent or new M. tuberculosis infection
- Undiagnosed TB common among PLHIV
- High mortality among HIV-TB co-infected individuals
- Intensive Case Finding (ICF) and treatment of TB among HIV-infected persons interrupts disease transmission by infectious cases, reduces morbidity and delays mortality
- Active screening for TB offers the opportunity to provide isoniazid preventive therapy (IPT) for those who do not have symptoms and signs of TB
Intensive Case Finding and IPT in PLHIV

• In response to dual epidemics of HIV and TB, WHO has recommended 12 collaborative TB/HIV activities to reduce morbidity, mortality and transmission

• April 2008, WHO convened Three I’s for HIV/TB Meeting to update new WHO/UNAIDS policy about HIV - TB prevention

  Three I’s for HIV/TB
  – Intensified case-finding of TB (ICF),
  – Isoniazid preventive therapy (IPT) and
  – Infection control for TB.
Principles for Stopping TB Transmission

**Fig. 10** Principles for stopping tuberculosis (TB) transmission. TB control is based on preventing susceptible individuals from becoming infected using vaccination, preventing infected individuals from developing the disease using prophylactic treatment, preventing individuals with TB from having contact with susceptible individuals through early detection and cure, isolation, and infection control measures.

The ID-TB/HIV Study

• CDC-DTBE led a cross-sectional study “Improving Diagnosis of TB in HIV-Infected Persons: The ID-TB/HIV Study”

• Enrolled more than 2,000 PLHIV from 8 anti-retroviral (ARV) clinics in Cambodia, Thailand, and Vietnam

• Goal was to determine the best method for screening and diagnosing TB in PLHIV.
The ID-TB/HIV Study

- Previously recommended screening approaches failed to detect >two-thirds of patients with TB ds.

- Screening for TB using a combination of 3 symptoms detected almost all cases (93%) among PLHIV.
  - ≥1 symptom (cough, fever, night sweats) = positive screen
  - Absence of all symptoms = negative symptom screen
  - Positive symptom screen → evaluation for TB disease
  - Negative symptom screen have TB disease reliably ruled-out (97% without TB had no symptoms), allowing IPT to be started more quickly.
Development of a standardized screening rule for TB in PLHIV in resource-constrained settings

- CDC and WHO then collaborated on a meta-analysis of 12 observational studies involving over 8000 PLHIV

- Absence of all the symptoms of current cough, night sweats, fever or weight loss can identify a subset of PLHIV who have very low probability of TB disease
  - This screening rule has a **sensitivity of 79% and a specificity of 50%**.

- Led to a change in WHO’s international guidelines for screening for TB among PLHIV.

- “Adults and adolescents living with HIV should be screened for TB using a clinical algorithm at every visit to a health facility or contact with a health worker.”

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000391
Algorithm for TB screening in person living with HIV in HIV prevalent and resource-constrained settings.

http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1000391
Intensive Case Finding in PLHIV in Resource-Constrained Settings

Adults and adolescents living with HIV should be screened for TB with a clinical algorithm:

1. Those who **do not report any one of the symptoms** of current cough, fever, weight loss or night sweats are unlikely to have active TB and **should be offered IPT**.
   - **Strong recommendation, moderate quality of evidence**

2. Those who **report any one of the symptoms** of current cough, fever, weight loss or night sweats may have active TB and **should be evaluated for TB** and other diseases.
   - **Strong recommendation, moderate quality of evidence**

INH Preventive Therapy in PLHIV in Resource-Constrained Settings

3. Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least 6 months of IPT as part of a comprehensive package of HIV care.

- IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

- Strong recommendation, high quality of evidence

INH Preventive Therapy in PLHIV in Resource-Constrained Settings

4. Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT*.

- IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.

- Conditional recommendation, moderate quality of evidence

*The considerations for implementation should include the local context such as the epidemiology of TB and HIV, and settings with the highest rates of prevalence and transmission of TB among people living with HIV.
The Isoniazid Prevention Therapy Trial (IPTT)

- From 2004 - 2011, CDC conducted a trial in Botswana to determine whether 36 months of IPT is more effective in preventing TB disease among PLHIV than the routinely prescribed 6 month treatment regimen.

- Results:
  - IPT was highly effective (>90% reduction) in reducing TB in people with a positive tuberculin skin test
  - 36 months of IPT further reduced the risk 76% compared to 6 months of IPT in highly TB-endemic settings
  - ART in combination with IPT is beneficial
  - Use of the tuberculin skin test to determine IPT eligibility is more important than less important.
Testing for LTBI in Resource-Constrained Settings

5. TST is not a requirement for initiating IPT in people living with HIV
   – Strong recommendation, moderate quality of evidence

6. PLHIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals
   – Strong recommendation, high quality of evidence
IPT and Drug-resistant TB in Resource-Constrained Settings

7. Providing IPT to PLHIV does not increase the risk of developing INH-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.

- Strong recommendation, moderate quality of evidence
Intensified TB Case-finding and Prevention of TB in Children Living with HIV

8. Children living with HIV who do not have poor weight gain, fever or current cough are unlikely to have active TB.
   – Strong recommendation, low quality of evidence

9. Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.
   – Strong recommendation, low quality of evidence
Intensified TB Case-finding and Prevention of TB in Children Living with HIV

10. Children living with HIV who are >12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive 6 months of IPT (10 mg/kg/day with 25mgB6/day) as part of a comprehensive package of HIV prevention and care services.
   - Strong recommendation, moderate quality of evidence

11. In children living with HIV who are <12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive 6 months of IPT if the evaluation shows no TB disease.
   - Strong recommendation, low quality of evidence
Secondary IPT Prophylaxis in Children

12. All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.
   - Conditional recommendation, low quality of evidence
Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-income Countries.

WHO, 2012
TB Control Priorities

1. Detection and treatment of persons with active tuberculosis

2. Investigation of infectious cases to detect contacts with active TB or who are infected at risk of future TB

3. Prevent future TB through screening high risk groups and providing LTBI treatment to persons with M. tuberculosis infection (and no active disease)
Screening and Treating Contacts for LTBI

- Treat high-risk contacts with IPT without testing for LTBI once active TB is excluded by an appropriate clinical evaluation.

1. PLHIV who are household or close contacts of people with infectious TB
   - Strong recommendation, high-quality evidence

2. Children <5 years of age who are household or close contacts of people with TB
   - Strong recommendation, high-quality evidence

WHO. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries, 2012
Screening and Treating Contacts for LTBI

- Tests for LTBI, including TST and IGRA, can be used to identify people at increased risk for developing active TB and who are therefore candidates for treatment of LTBI.

- As the value of providing treatment for LTBI in low- and middle-income countries is not proven, it is not recommended as a broad program approach.
  - Ongoing risk of TB transmission in countries with higher burden of tuberculosis.

WHO. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries, 2012
Recommendations from WHO Contact Investigations Guidelines

- In caring for patients exposed to an infectious index case who are at increased risk for developing TB if infected, clinicians may, however, test them for LTBI with a TST or IGRA and treat them with IPT if LTBI is present.

- As the risks and benefits of treating LTBI, documented by a recent TST conversion or associated with other diseases (such as diabetes mellitus) and conditions, are quantified, the indications for treatment may be broadened.

- Unless a plan includes policies and procedures for treating LTBI, testing for LTBI should not be undertaken.

WHO. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries, 2012
TB Elimination Strategies and Tools in the United States
TB Control Priorities

1. Detection and treatment of persons with active tuberculosis

2. Investigation of infectious cases to detect contacts with active TB or who are infected at risk of future TB

3. Prevent future TB through screening high risk groups and providing LTBI treatment to persons with M. tuberculosis infection (and no active disease)
Targeted TB Testing and Treatment of Latent TB Infection

- As TB disease rates in the U.S. decrease, finding and treating persons at high risk for LTBI has become a priority.

- Treatment of LTBI substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease.
  - Individual reduction of morbidity & mortality
  - Decrease community transmission

- Targeted testing for LTBI
  - Purpose: To identify persons at high risk for TB who would benefit by treatment of LTBI if infected
  - Screening of low-risk persons not recommended (reduce the waste of resources, prevent inappropriate treatment)
The Scope and Impact of Treatment of LTBI in the United States and Canada.

- Tuberculosis Epidemiologic Studies Consortium (TBESC) Task Order 13

- Conducted a survey of clinics in the U.S. (n=19) and Canada (n=2) that initiated LTBI treatment for $\geq 10$ patients in 2002.

- Extrapolated study data to the entire U.S. population
  - Used an estimated 20-60% treatment effectiveness and 5% lifetime risk of active TB without treatment,

- Results: Targeted screening and treatment of LTBI likely prevented between 4,000 and 11,000 active TB cases in the U.S.

Who should be tested for LTBI? (CDC 2000)

2 Groups:

- Persons with Risk for Recent TB Infection (Exposure Risk)

- Persons with Risk of Progression to Active TB if Infected with *M. tuberculosis*
Diagnosis of Latent TB Infection
Testing for *M. tuberculosis* Infection

- Two testing methods available for the detection of *M. tuberculosis* infection:
  - Mantoux tuberculin skin test (TST)
  - Interferon-gamma release assays (IGRA) (if available)

- These tests *do not* exclude LTBI or TB disease

- Decisions about medical and public health management should include other information, and not rely only on TST or IGRA results
Diagnosis of TB Infection: Tuberculin Skin Test (TST)

Interpretation of TST reaction depends on size of induration and person’s risk factors for TB
Mantoux Tuberculin Skin Test
Interpreting the Reaction

• Induration of $\geq 5$ mm is considered positive for:
  
  – People living with HIV
  
  – Recent close contacts of people with infectious TB
  
  – People with chest x-ray findings suggestive of previous TB disease
  
  – People with organ transplants
  
  – Other immunosuppressed patients
**Mantoux Tuberculin Skin Test**

**Interpreting the Reaction**

- Induration of \( \geq 10 \text{ mm} \) is considered a positive reaction for:
  - Recent immigrants to the U.S. from areas where TB is common
  - People who inject drugs
  - People who live or work in high-risk congregate settings
  - Mycobacteriology laboratory workers
Mantoux Tuberculin Skin Test
Interpreting the Reaction

• Induration of \( \geq 10 \text{ mm} \) is considered a positive reaction for:
  
  – People with certain medical conditions that increase risk for TB
  
  – Children younger than 4 years old
  
  – Infants, children, or adolescents exposed to adults in high-risk categories
Mantoux Tuberculin Skin Test
Interpreting the Reaction

- Induration of $\geq 15$ mm is considered a positive reaction for people who have no known risk factors for TB
Mantoux Tuberculin Skin Test
False-Positive Reaction

- Factors that can cause people to have a positive reaction even if they do not have TB infection:
  - Infection with nontuberculous mycobacteria
  - BCG vaccination
  - Administration of incorrect antigen
  - Incorrect measuring or interpretation of TST reaction
Mantoux Tuberculin Skin Test
BCG Vaccine

- People who have been vaccinated with BCG may have a false-positive TST reaction
  - However, there is no reliable way to distinguish between reaction caused by TB infection or by BCG vaccine

- Individuals should always be further evaluated if they have a positive TST reaction
Mantoux Tuberculin Skin Test False-Negative Reaction

- Factors that can cause false-negative reactions:
  - Anergy
  - Recent TB infection (within past 8 – 10 weeks)
    - It can take 2 – 8 weeks after TB infection for body’s immune system to react to tuberculin
  - Younger than 6 months of age
  - Recent live-virus (e.g., measles or smallpox) vaccination
  - Incorrect method of giving the TST
  - Incorrect measuring or interpretation of TST reaction
Mantoux Tuberculin Skin Test
Anergy

• Inability to react to skin tests due to weakened immune system

• Anergy testing is no longer routinely recommended
**Two-step Testing**

- Strategy used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection.

- Should be used for initial skin testing of persons who will be retested periodically, such as health care workers exposed to TB patients.

- If the reaction to the first test is negative, a second test should be repeated 1-3 weeks later.

- A positive reaction to the second test probably indicates a boosted reaction and the person is classified as “previously infected” (NOT a new conversion)

- LTBI treatment should be considered according to the person’s risk of TB, likelihood of adherence, etc.
Interferon-Gamma Release Assays (IGRA)
Whole Blood Gamma Interferon Assay

- IGRAs use purified antigens from MTB to stimulate peripheral-blood lymphocytes to produce gamma interferon
- QFT measures gamma interferon in the supernatant of the cell suspension
- TSPOT measures cells producing gamma interferon using ELISpot assay
Interferon Gamma Release Assays (IGRAs)

- Three IGRAs approved by the U.S. FDA and are commercially available in the U.S.:
  - QuantiFERON®-TB Gold test (QFT-G);
  - QuantiFERON®-TB Gold In-Tube test (QFT-GIT);
  - T-SPOT®.TB test (T-Spot)

Note: Latest guidelines: CDC guidelines for QFT-GIT and T-SPOT published June 2010
www.cdc.gov/mmwr Vol. 59, No. RR-5
<table>
<thead>
<tr>
<th></th>
<th>QFT-Gold</th>
<th>QFT-Gold In Tube (QFT-GIT)</th>
<th>T-Spot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Format</strong></td>
<td>Process whole blood within 12h</td>
<td>Process whole blood within 16h</td>
<td>Process peripheral blood mononuclear cells (PBMCs)</td>
</tr>
<tr>
<td><strong>M. Tuberculosis antigen</strong></td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</td>
<td>Single mixture of synthetic peptides representing ESAT-6 &amp; CFP-10, and TB 7.7</td>
<td>Separate mixtures of synthetic peptides representing ESAT-6 &amp; CFP-10</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td>IFN-γ concentration</td>
<td>IFN-γ concentration</td>
<td># of IFN-γ producing cells (spots)</td>
</tr>
<tr>
<td><strong>Possible Results</strong></td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate</td>
<td>Positive, negative, indeterminate, borderline</td>
</tr>
</tbody>
</table>

IGRA: General Points

- IGRAs are highly specific (~95%)
  - Both commercially available tests (QFT and T-SPOT TB) are substantially more specific than the TST since they are not impacted by BCG
- IGRAs have a moderate to high sensitivity compared to TST
  - QFT being as sensitive as PPD (70-80%) in immunocompetent
  - T-SPOT TB is more sensitive (~90%) than QFT and PPD in the immunocompromised
**IGRA: Advantages**

- Requires a single patient visit to conduct the test.
- Results can be available within 24 hours.
- Does not boost responses measured by subsequent tests.
- Prior BCG (bacille Calmette-Guérin) vaccination does not cause a false-positive IGRA test result.
- Use of an IGRA may increase acceptance of LTBI treatment
IGRA: Disadvantages

- Blood samples must be processed within 8-16 hours after collection while white blood cells are still viable.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease accuracy.
- Limited data on the use of IGRAs to predict who will progress to TB disease in the future.
- Limited data on the use of IGRAs for:
  - Children younger than 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons (including HIV); and
  - Serial testing (test-retest variability)
  - Discordant test results
- Tests may be expensive.
Specific CDC Recommendations

- IGRAs preferred
  - Person not likely to return for test reading (homeless, drug users, etc.)
  - Persons who received BCG for vaccine or cancer treatment
- TST preferred: Children <5 years
- TST or IGRA
  - Contacts; periodic screening of health care workers

Specific CDC Recommendations

- Consider TST AND IGRA
  - Increased risk of infection, progression to TB, poor outcome (e.g., HIV)
  - Clinical suspicion of TB and confirmation of infection desired
  - Additional confirmation of LTBI will help with compliance
  - Healthy low risk persons with positive test
    - (single pos. test not reliable evidence of infection in low risk person)

LTBI Testing Summary: Comparison of Quantiferon and TST

**Quantiferon:**
- In vitro test
- Specific antigens
- No boosting
- 1 patient visit
- Minimal inter-reader variability
- Results in 1 day
- Requires blood test
- Not affected by BCG, most atypical mycobacteria

**TST**
- In vivo test
- Single antigen
- Boosting phenomenon
- 2 patient visits
- Inter-reader variability
- Results in 2-3 days
- No phlebotomy
- Cross-reacts with BCG, atypical mycobacteria
LTBI TREATMENT REGIMENS IN LOW TB BURDEN COUNTRIES
## LTBI Treatment in Low TB Burden Countries

### Recommended regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily</td>
<td>9 months (6 months)</td>
<td>Long duration, poor adherence</td>
<td>9H</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Twice weekly</td>
<td>9 months (6 months)</td>
<td>Directly-observed, long duration</td>
<td>9H-DOT</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Daily</td>
<td>4 months</td>
<td>Drug interactions</td>
<td>4R</td>
</tr>
<tr>
<td>Isoniazid + rifapentine</td>
<td>Once weekly</td>
<td>3 months</td>
<td>DOT</td>
<td>3HP</td>
</tr>
</tbody>
</table>

### Other regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Frequency</th>
<th>Duration</th>
<th>Issues</th>
<th>Abbrev</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid + rifampin</td>
<td>Daily</td>
<td>3 months</td>
<td>Not in U.S. recommendations</td>
<td>3HR</td>
</tr>
<tr>
<td>Rifampin + pyrazinamide</td>
<td>Daily or 2x/week</td>
<td>2 months</td>
<td>Potentially fatal: <strong>NOT RECOMMENDED</strong></td>
<td>2RZ</td>
</tr>
</tbody>
</table>
Treatment of LTBI: Isoniazid (INH)

- More than 20 randomized, placebo-controlled trials of LTBI treatment with INH have been conducted involving more than 100,000 subjects.

- The combined average reduction in TB reported in these studies was 60% during the period of observation.
  - These results were based on the total study populations treated, regardless of how regularly medication was taken.
  - Reduction highest during year of treatment

- When analyses were limited to participants who took INH for most of their treatment year, efficacy approximated 90%.

- Protection demonstrable nearly 20 years after treatment.


How Much Isoniazid is Needed for the Prevention of Tuberculosis?

- Longer durations of therapy corresponded to lower TB rates among those who took 0-9 months.
- Subgroup analysis, no extra increase in protection among those who took > 9 months.

*Figure.* Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months that isoniazid was taken in the combined programs.

INH in Patients with HIV

- Meta-analysis of 7 randomized controlled trials
  - Mexico, Haiti, the United States, Zambia, Uganda and Kenya
  - Conducted between 1985 and 1997
  - INH more effective than placebo in preventing active TB among HIV-infected persons with +TST, reducing the TB incidence by 60-80%

- Some (not all) found association between INH and improved survival

- Preferred regimen for HIV+ persons is 9 months INH

- If known exposure, treat regardless of TST result

INH: Safety, Tolerability, Completion

• Dose:
  – Daily INH:
    • Adults: 300mg (5mg/kg)
    • Kids: 10-20mg/kg not to exceed 300mg
  – Twice-weekly INH:
    • Adults: 15mg/kg adults
    • Kids: 20-40mg/kg, not to exceed 900mg
    • Must be given by DOPT

• Adherence for 6-9 months 30-60%
• Monthly clinical assessments (does not mean routine LFT’s)
INH: Safety, Tolerability, Completion

- **Adverse events:**
  - 10-20% will develop liver enzyme abnormalities (most are transient and not clinically significant)
  - Hepatotoxicity ~0.1%-0.5%
    - Increased risk with age, liver disease, HCV, alcohol use, prior INH hepatotoxicity, other hepatotoxic medications
  - Peripheral neuropathy is uncommon at doses of 5 mg/kg.
    - Persons with risk factors for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection), pregnant women, and persons with seizure disorder may be given pyridoxine (vitamin B\(^6\)) 10-50 mg/day with INH, as this may prevent neuropathy.
    - Patients who develop signs and symptoms of peripheral neuropathy may also be started on vitamin B\(^6\).
  - Mortality rate 0.3/1000 (increases with age and alcohol use)
Rifamycins

• Inhibit DNA-dependent RNA polymerase
  – Active against dormant and semi-dormant bacteria that characterize LTBI
  – Isoniazid only active against replicating bacteria
• Active against a broad array of bacteria (including *M. Tuberculosis*)

• Examples:
  – Rifampin
  – Rifabutin
  – Rifapentine
Rifampin – Efficacy

• One randomized clinical trial

• From 1981 to 1987, a cohort of older Chinese men with silicosis (n=679) randomized to one of three groups:
  – Rifampin for three months (3R)
  – Rifampin plus INH for three months (3HR)
  – Isoniazid for six months (6H)
  – Placebo

Rifampin – Efficacy

- Development of active TB:

- The effectiveness of 3 months of rifampin vs. placebo was calculated at 50% among persons who completed the 5-year study and at 46% among all persons who initiated treatment

- (Patients all had silicosis, so TB rates were much higher)

So where do we get “4 months” from?

- $6H < 12H \sim 9H$, so $9H$ is the recommendation
- $3R \sim 6H < 9H$, so….
- $4R$ is the recommendation

In other words, we have no direct efficacy data (yet) for four months of rifampin.

- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted (though not studied for LTBI treatment)
Other Evidence for Rifampin

- 2 small observational studies suggesting efficacy
  - Homeless persons who developed a TST conversion during an epidemic of INH-resistant TB
    - No patients treated with Rifampin monotherapy for an average of 6 months developed TB disease compared to 8.6% of untreated persons.
  - 157 adolescent contacts to an INH-resistant source case who developed TST conversions after *M. tuberculosis* exposure
    - None developed active TB during the 2 years following completion of 6 months of rifampin therapy.


Rifampin – Dose, Adherence and Toxicity

- Dose 600 mg daily x 4 months
  - 6 months in children
- Completion rates much higher, 60-91%
- Well-tolerated
  - Mild skin reactions, GI symptoms, orange body fluids
- Low rates of hepatotoxicity
  - 0.3% versus 1.4% for INH in one study
- Other
  - Hypersensitivity syndrome
    - “Flu-like” symptoms (fever, malaise, myalgias); Not well-defined
  - Anemia, thrombocytopenia
  - Both more common with intermittent doses
  - Use with extreme caution to rule out TB if used in HIV, avoid with ART.
Rifamycins – Drug Interactions

- Oral anticoagulants
- Oral contraceptives
- Cyclosporine
- Glucocorticoids
- Itraconazole
- Ketoconazole
- Methadone
- Midazolam or triazolam
- Phenytoin
- Quinidine
- Theophylline
- Verapamil
- β-Adrenergic blocking agents
- Chloramphenicol
- Clarithromycin
- Dapsone
- Diazepam
- Digoxin (oral)
- Diltiazem
- Disopyramide
- Doxycycline
- Fluconazole
- Haloperidol
- Losartan potassium
- Nifedipine
- Nortriptyline
- Sulfonylureas
- Tacrolimus
- Tocainide

Check everything for potential Drug-drug interactions! (Especially HIV medications)
Rifapentine

• Similar to rifampin, but a longer half-life

• Initially approved for once-weekly therapy of active TB in the continuation phase

• Three studies of efficacy for treatment of LTBI (once per week in combination with isoniazid)
  – 399 household contacts in Brazil
    • (Schechter M. Am J Respir Crit Care Med. 2006 Apr 15;173(8):922-6.)
  – 1150 HIV+ patients in South Africa
    • (Martinson N et al. 39th IUATLD World Conference on Lung Health, late breaker abstract, Paris, 2008.)
  – TB Trials Consortium “PREVENT-TB” Trial (TBTC study 26)
TB Trials Consortium Study 26 (PREVENT-TB)

- 8,053 “high-risk” patients in U.S., Brazil, Spain
  - Contacts, converters
  - HIV+ (very few)
  - Children 2 years and older

- Two arms:
  - Rifapentine/isoniazid weekly for 3 months by DOT (3HP-DOT)
    - Rifapentine (RPT) 900 mg (Graduated dosing for persons ≤50 kg)
    - Isoniazid 15-25 mg/kg; 900 mg max.
  - Isoniazid daily for 9 months self-administered (9H-SAT)
    - Isoniazid 5-15 mg/kg; 300 mg max.
  - Vitamin B6 (pyridoxine) 50 mg with each INH dose
Study 26 – results

• Both arms similar efficacy
  – 15 cases (0.43%) in 9H arm
  – 7 cases (0.19%) in 3HP arm

• Completion much higher with 3HP (80%)

• Toxicity slightly higher with 3HP (5% vs. 3% in 9H)
  – Hepatotoxicity the same
  – “Excess” toxicity was hypersensitivity
    • (There is some evidence that it may have been over-reported.)
Study 26 – Some caveats

• DOT was used in the study, so there is no data on completion rates for self-administered therapy
  – Ten pills once per week – adherence could be very different

• Limited data on HIV+ patients

• No data yet on children <2 years
INH-Rifapentine (3HP) – CDC Recommendations (Dec. 2011)

- Rifapentine 900 mg plus INH 900 mg once per week for 3 months (12 doses)
- 3 HP equal alternative to 9H for the following:
  - Contacts
  - Recent converters
  - Old, healed (Class IV) TB *(rule out active TB)
- Adults and children ≥12 years
  - Can be used in children 2-11y on a “case by case” basis
- HIV+ if healthy and on no ARVs

*MMWR*. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
3HP – CDC Recommendations (Dec. 2011)

- Choice between INH and INH-RPT depends on feasibility of DOT, ability to obtain drugs, ability to monitor side effects, ability to complete tx, preference of patient and physician
- Practical advantages: corrections, shelters, clinics for recent immigrants
- INH-RPT NOT recommended for:
  - Children under 2y
  - HIV patients on ART
  - Pregnant women or women wanting to become pregnant
  - Contacts to INH or Rif-resistant TB

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection. [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w)*
3HP – CDC Recommendations (Dec. 2011)

• Precautions:
  – Rifapentine (RPT) rarely can cause neutropenia, increased liver enzymes, hypersensitivity reactions (fever, dizziness, MSK pain, rash, pruritus)
  – RPT induces increased metabolism of many medications, particularly those metabolized by cytochrome P450 enzymes – avoid with methadone, coumadin and hormonal birth control
  – Women who use any form of hormonal birth control should be advised to add, or switch to a barrier method

*MMWR. Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
3 months INH-Rifampin

- Rifampin 600 mg plus INH 300 mg for 3 months
- *Not* included in the ATS/CDC guidelines for treatment of LTBI in the United States
  - Recommended in UK and Canada
- Can be self-administered, No intermittent option
- Limited data on efficacy, toxicity/side effects
- Recent randomized, controlled trial of 3 mos. RH compared to 6 mo INH in 590 immigrants to Spain:
  - Better adherence in 3 RH vs. 6R (72% vs. 52.4%, P=0.001)
  - Similar effectiveness, liver toxicity, and side effects
LTBI Treatment Regimens for Patients Exposed to Multidrug-Resistant TB

Contacts of Persons with Multidrug-Resistant TB

- Consider risk for progressing to MDR disease before recommending LTBI treatment
- When prescribing treatment for these contacts, consult an MDR TB expert
- Limited data on most effective treatment regimens
  - Use at least 2 anti-TB drugs, usually PZA and a quinolone or ethambutol, depending on resistance pattern of source case and patient’s ability to tolerate drugs.
  - Monotherapy with levofloxacin or ofloxacin has also been recommended

## LTBI Treatment Regimens for Patients Exposed to Multidrug-Resistant TB

<table>
<thead>
<tr>
<th>Drug resistance pattern of source case isolate</th>
<th>Recommended regimen†</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH, RIF</td>
<td>FQN monotherapy or</td>
</tr>
<tr>
<td></td>
<td>PZA and EMB or</td>
</tr>
<tr>
<td></td>
<td>FQN and PZA or</td>
</tr>
<tr>
<td></td>
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</tr>
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<tr>
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</tr>
<tr>
<td></td>
<td>FQN and ethionamide</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA</td>
<td>FQN monotherapy or</td>
</tr>
<tr>
<td></td>
<td>FQN and ethionamide</td>
</tr>
<tr>
<td>INH, RIF, EMB, PZA, ethionamide</td>
<td>FQN monotherapy or</td>
</tr>
<tr>
<td></td>
<td>FQN and cycloserine</td>
</tr>
<tr>
<td>INH, RIF, PZA, EMB, and FQN</td>
<td>Cycloserine and PAS or</td>
</tr>
<tr>
<td></td>
<td>PAS and ethionamide or</td>
</tr>
<tr>
<td></td>
<td>ethionamide and</td>
</tr>
<tr>
<td></td>
<td>cycloserine</td>
</tr>
</tbody>
</table>

† Recommendations are not evidence-based; there have been no clinical trials for the use of these regimens in contacts of patients with MDR TB. Recommendations are based on expert opinion.

FQN in vitro activity against *M. Tuberculosis* strains: Moxifloxacin = Gatifloxacin > Levofloxacin >> Ofloxacin > Ciprofloxacin. Selection of FQN should take this activity into consideration (More active preferred).

EMB, ethambutol; FQN, fluoroquinolone; INH, isoniazid; PAS, para-aminosalicylate; PZA, pyrazinamide; RIF, rifampin; TB, tuberculosis.

---

ADHERENCE AND MONITORING DURING LTBI TREATMENT
Clinical and Laboratory Evaluation

- Routine baseline laboratory tests (e.g., AST, ALT, and bilirubin) not required, except for:
  - HIV-infected persons
  - Pregnant women or those in early post-partum period
  - Persons with chronic liver disease; use alcohol regularly
  - Liver enlargement or tenderness during examination

- In the U.S., patients asked to come monthly for refills of LTBI treatment to enable frequent evaluation of adherence, signs/symptoms of TB disease, and potential adverse effects of meds

- Dispensing one month at a time facilitates clinical reassessment
Clinical Monitoring - 1

Instruct patient to immediately report signs and symptoms of adverse drug reactions (and stop treatment):

- Fever
- Headache
- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet
Follow-up (monthly) visits should include a brief physical exam and a review of:

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment
Laboratory Monitoring

- Follow-up lab testing if patient has conditions above, abnormal labs at baseline, or signs or symptoms of adverse drug reaction

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of therapy

- Discontinue treatment if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic
LTBI Pretreatment Clinical Evaluation and Counseling

- Identify TB DILI risks:
  - Chronic ethanol consumption?
  - Viral hepatitis?
  - Pre-existing liver disease?
  - Within 3 months post-partum?
  - Concomitant hepatotoxic medication?
  - Previous ALT or bilirubin abnormal?

- Assess TB risk:
  - Low
  - High

- Deferral of LTBI treatment:
  - Yes
  - No

- Pregnant?
  - Yes
  - No

- Hepatology evaluation:
  - Yes
  - No

- Check ALT, bilirubin (INR, PTT):
  - ALT ≥ 3 x ULN, Bilir >2, liver-related coagulopathy
  - No

Regimen selection according to indication and TB DILI risks:
- Isoniazid x 9 months, 6 months acceptable
- Rifampin x 4 months
  - e.g. if ALT 2-3 x ULN, isoniazid-resistance or -hepatotoxicity
- Isoniazid with rifampin x 4 months

Monitoring plan in medical record

Patient education:
- Use patient’s preferred language
- Hepatitis symptoms and signs
- Discontinue treatment at symptom onset & contact clinic

Monitoring for Hepatotoxicity During LTBI Treatment

Identify liver risk factors:
- Chronic ethanol consumption?
- Viral hepatitis?
- Pre-existing liver disease?
- Pregnant /3 months post-partum?
- Other hepatotoxic medications?
- ALT/AST or bilirubin abnormal?
- Chronic medical conditions?

No

Nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue?
Continue treatment

No

Baseline: ALT > 3 X ULN

During treatment:
- ALT 5 x ULN,
- ALT 3 x ULN with nausea, vomiting, abdominal pain, jaundice, or unexplained fatigue.

Or
- Change of 2-3 x baseline, if latter > 3 x ULN.

Yes

Check:
ALT (AST, bil): Baseline & q 2-4 weeks,
If biochemical monitoring desired for age >35:
baseline, then options include q 4-8 weeks, or at 1, 3, & 6 m

- IgM anti-HAV
  - HepBsAg (if +, \$BeAg)
  - IgM HepBcAb,
- Anti-HCV (if +, \$HCV RNA)
- Exclude other liver problems.

No, age >35 y
Hold treatment

Yes

Treatment option:
Rifampin x 4 m

Yes
Isoniazid rechallenge? (when ALT < 2 X ULN)

Yes
Halt treatment

Completion of LTBI Therapy

• Completion of therapy (in the U.S.) is based on the total number of doses administered, not on duration alone

• Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion

• When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease

• Recommend and arrange for DOT as needed (if resources allow)
## Treatment Completion for LTBI Regimens

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Duration</th>
<th>Interval</th>
<th>Minimum Doses for completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>9 months</td>
<td>Daily</td>
<td>270 within 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>76 within 12 months</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>Daily</td>
<td>180 within 9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Twice weekly</td>
<td>52 within 9 months</td>
</tr>
<tr>
<td>Isoniazid &amp; Rifapentine</td>
<td>3 months</td>
<td>Once weekly</td>
<td>12 within 16 weeks</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>Daily</td>
<td>120 within 6 months</td>
</tr>
</tbody>
</table>

Note: INH preventive therapy in HIV+ may be given for longer periods (36 months)
Identifying Barriers to Initiation and Adherence

- Physician perceptions and knowledge
- LTBI patient has no symptoms, low perceived risk of TB
  - Misinformation about TB or HIV
  - Health beliefs and practices
  - Limited financial resources
  - Competing priorities-food, transportation, housing, caring for family
  - Co-existing medical conditions
  - Medication side effects (or fear of side effects)
  - Cultural and language barriers
  - Real or perceived stigma related to LTBI diagnosis or treatment
  - Other fears (doctors, government, loss of confidentiality)
Measures to Improve Adherence

- DOT (directly observed therapy)
- Pill boxes, timers, calendars, etc.
- Case management
- Culturally-sensitive education and counseling
- Peer support from community agencies
- Incentives: small rewards that encourage or motivate patients (grocery store vouchers, nutritional supplements, or restaurant coupons)
- Enablers: free van transportation, bus tickets, reminder letters or phone calls, other assistance that makes it easier to keep appointments
- “Cues” as reminders (notes on coffee pot, mirror, etc.)
Questions?

Tuberculosis is Curable and Preventable

If you are rundown or have a cough, get a medical examination.

Maritime Tuberculosis Educational Committee.
Additional Resources

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection  *MMWR* 2000; 49 (No. RR-6)  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm)

- Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection  
  [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w)

  [http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.e.htm?s_cid=rr5905a1_e](http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.e.htm?s_cid=rr5905a1_e)
Additional Resources

  [http://ajrccm.atsjournals.org/content/174/8/935.full.pdf+html]

  [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5908a3.htm?s_cid=mm5908a3_e]

- Latent Tuberculosis Infection: A Guide for Primary Health Care Providers  
Additional Resources

- Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis

- CDC TB Website  [http://www.cdc.gov/tb](http://www.cdc.gov/tb)

- Southeastern National TB Center
  [http://sntc.medicine.ufl.edu/](http://sntc.medicine.ufl.edu/)


- CDC’s Morbidity and Mortality Weekly Report

- American Thoracic Society
  [http://www.thoracic.org/statements/](http://www.thoracic.org/statements/)
Risk Factors for Recent TB Infection
(U.S. guidelines, CDC 2000)

- Close contact to person with infectious TB
- Skin test conversion (within past 2 y)
- Foreign-born persons from areas that have a high incidence of active tuberculosis (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- Persons who visit areas with a high prevalence of active TB, especially if visits are frequent, prolonged
- Residents and employees of congregate settings whose clients are at increased risk for active TB
  - E.g., correctional facilities, long-term care facilities, and homeless shelters
Risk Factors for Recent TB Infection (U.S. guidelines, CDC 2000)

- Health-care workers who serve clients who are at increased risk for active TB
- Populations defined locally as having an increased incidence of latent M. tuberculosis infection or active TB, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol
- Infants, children, and adolescents exposed to adults who are at increased risk for latent M. tuberculosis infection or active tuberculosis
Risk of Progression from LTBI to TB Disease (U.S. guidelines, CDC 2000)

- HIV infection
- Infants and children aged <5 years
- Persons who were recently infected with *M. tuberculosis* (contacts within the past 2 years)
- Persons with a history of untreated or inadequately treated active TB, including persons with fibrotic changes on chest radiograph consistent with prior active tuberculosis
- Injection drug use
Risk of Progression from LTBI to TB Disease (U.S. guidelines, CDC 2000)

- Certain medical conditions such as
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure or on hemodialysis
  - Solid organ transplantation (e.g., heart, kidney)
  - Carcinoma of head, neck, or lung
  - Gastrectomy or jejunoilial bypass
  - Other immunosuppressive conditions or therapy (including use of TNF-α antagonists)
  - <90% of ideal body weight
BOX 2. Guidance for early detection and management of adverse effects during treatment of LTBI with a combination regimen of INH and RPT in 12 once-weekly doses under direct observation

- Education of patients to seek medical attention upon the first symptom of a possible adverse event.
- Clinical assessment upon the first sign or symptom of a possible adverse event.
- Monthly interview and brief physical examination for the findings of treatment-associated adverse events (e.g., icterus, tenderness of the liver, or rash).
- Baseline hepatic chemistry blood tests (at least aspartate aminotransferase [AST]) for patients with specific conditions:
  - HIV
  - Liver disorders
  - Women in the immediate postpartum period (≤3 months after delivery)
  - Regular alcohol usage
- Consideration of a baseline hepatic chemistry blood test for older patients on an individual basis, especially for those taking medications for chronic medical conditions.
- Blood tests at subsequent clinical encounters for patients whose baseline testing is abnormal and for others at risk for liver disease.
- Discontinuance of INH-RPT if a serum aminotransferase concentration is ≥5 times the upper limit of normal even in the absence of symptoms or ≥3 times the upper limit of normal in the presence of symptoms.
- Vigilance for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia.
  - Severe condition (e.g., hypotension requiring intravenous fluid support): discontinuance of INH-RPT; supportive medical care
  - Mild to moderate condition (e.g., dizziness treated with rest or oral fluids): conservative management of constitutional symptoms, clinical and laboratory monitoring, the option for continuing treatment under observation
Screening for Active TB

- **Systematic screening for active TB** is defined as the systematic identification of people with suspected active TB, in a predetermined target group, using tests, examinations or other procedures that can be applied rapidly.

- The screening tests, examinations or other procedures should efficiently distinguish people with a high probability of having active TB from those who are unlikely to have active TB.

- Among those whose screening is positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments, which together have high accuracy.
WHO Recommendations on Risk Groups to Screen

- The following risk groups should always be screened for active TB, in all settings
  - Close contacts with active TB
  - People living with HIV
  - Workers in silica exposed workplaces

WHO, 2013: http://www.who.int/tb/tbscreening
WHO Recommendations on Risk Groups to Screen

- The following risk groups may be prioritized for screening based on local TB epi, health systems capacity, resource availability, and feasibility of reaching groups
  - People living in prisons and other penitentiary institutions, and prison staff
  - People with untreated fibrotic CXR lesions
  - People in high TB burden settings (~TB prev >100,000 in gen pop) who are seeking care or who are care and belong to selected risk groups, and health care workers (Table next slide)
  - Geographically defined sub-populations with extremely high levels of undetected TB (>1%) and other sub-pops with very poor health care access

WHO, 2013: http://www.who.int/tb/tbscreening
What test to use in HIV? TST vs IGRA

- Optimal test for identifying HIV-infected individuals who would benefit most from IPT is uncertain
- Recent national and international guidelines differ in recommended LTBI screening strategies in HIV+
- Pai et.: Systematic review that addressed:
  1) Are IGRAs better than TST at predicting which HIV-infected individuals are at highest risk of progression to active TB; and
  2) Are IGRAs more sensitive than TST for diagnosis of MTB infection, particularly in HIV-infected individuals with advanced immunosuppression?

JAIDS: Volume 56(3), 1 March 2011, pp 230-238
37 studies that included 5,736 HIV-infected individuals.

In three longitudinal studies, the risk of active TB was higher in HIV + individuals with (+) versus (-) IGRA results.

However, the risk difference was not statistically significant in the two studies that reported IGRA results according to manufacturer-recommended criteria.

In persons with active TB (a surrogate reference standard for LTBI), pooled sensitivity estimates were heterogeneous but higher for TSPOT (72%; 95% confidence interval [CI], 62-81%) than for QFT-GIT (61%; 95% CI, 47-75%)
How Should Patients with LTBI be Treated?

- Randomized controlled trials have shown that up to 12 months of daily IPT for treatment of latent infection confers 25 to 92% protection against developing active TB
  - Results toward the upper end of this range when patients adhere fully to the treatment regimen.

- INH is a relatively safe drug (main side-effect is hepatitis, occurs in around 1% of patients)

- To date, however, IPT is not widely used.
  - In 2011, only a small proportion of HIV-positive people without active TB were treated with IPT.