CHAPTER 2: DIAGNOSIS AND TREATMENT OF LATENT TUBERCULOSIS INFECTION

INTRODUCTION

Evaluation, testing, and treatment for latent tuberculosis (TB) infection (LTBI) among persons at high TB risk are essential components of TB prevention and elimination efforts. Appropriate treatment of persons with LTBI can prevent progression to active TB disease and reduce morbidity and mortality. Although there are several options available for the testing and treatment of LTBI, the Bureau of TB Control (BTBC) prefers the use of blood-based tests and short-course treatment regimens for eligible persons whenever feasible. Routine clinical monitoring and case management can facilitate treatment completion and lead to improved health outcomes.
PRIORITY POPULATIONS FOR TUBERCULOSIS INFECTION SCREENING AND EVALUATION

TB screening refers to the identification of previously unrecognized TB disease or disease precursor in an asymptomatic population by history, examination, tests, or procedures. Prioritization for TB screening is based on research indicating that certain populations are at increased risk for becoming infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) or—if already infected—for progressing to active TB disease. Screening for TB risk among asymptomatic persons should be conducted to identify those for whom a screening test for TB infection is indicated.

Persons at increased risk for TB infection include those with close contact to a person diagnosed with infectious TB disease; those born in or having recently traveled or resided in a country with a high TB incidence (i.e., any country other than the U.S., Canada, Australia, New Zealand, or a country in Western or Northern Europe); and those who live or work in settings where TB exposure may be possible.

Persons at higher risk for progression to active TB disease include, but are not limited to: persons with recent TB infection (within the past two years); immunosuppression (e.g., human immunodeficiency virus [HIV] infection or taking immunosuppressive medications); history of untreated or inadequately treated TB disease; certain medical conditions (e.g., silicosis, end-stage renal disease); and young age (younger than five years of age). (See Table 2.1: Persons at High Risk for Tuberculosis Infection or Progression to Active Tuberculosis Disease.)

**BTBC has developed a TB RISK ASSESSMENT TOOL to help healthcare providers identify asymptomatic individuals at risk for TB for whom a test for TB infection is indicated. Persons at minimal risk for TB infection are not recommended for testing. (See Appendix B: Tuberculosis Risk Assessment Tool.)**

TESTS FOR TUBERCULOSIS INFECTION

There is no gold standard test to detect TB infection. Currently available tests for TB infection include interferon-gamma release assays (IGRA) or the tuberculin skin test (TST). Neither IGRA nor the TST can distinguish between LTBI and active TB. Neither test replaces clinical judgment, as either test may be falsely negative despite the presence of TB infection. The use of both IGRA and TST is not recommended for routine testing. However, it may be helpful in diagnosing TB infection when the first test is negative but clinical suspicion for TB is high or the risk of infection, progression to TB disease, or poor outcome is increased. In these circumstances, a positive result on either test would indicate TB infection.

When testing for TB infection, BTBC prefers an IGRA for persons two years of age and older and uses the TST for children younger than two years of age.
### TABLE 2.1: Persons at high risk for tuberculosis infection or progression to active tuberculosis disease

<table>
<thead>
<tr>
<th>PERSONS AT HIGH RISK FOR TB INFECTION</th>
<th>PERSONS AT HIGH RISK FOR PROGRESSION TO TB DISEASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Individuals with close contact to a person diagnosed with infectious TB disease</td>
<td>• Close contact to a person diagnosed with infectious TB disease</td>
</tr>
<tr>
<td>• Persons born in a country with a high TB incidence*</td>
<td>• Conversion of test for TB infection*</td>
</tr>
</tbody>
</table>
| • Persons who traveled or resided in a high TB incidence area* for one month or more consecutively | • Persons with immunosuppression, such as:  
  - HIV infection  
  - Immunosuppressive therapy†  
    - Prolonged corticosteroid use (equal to or more than 15 mg/day prednisone for one month or more)  
    - Use of other immunosuppressive medications (e.g., TNF-α inhibitors, JAK inhibitors, IL-1 receptor antagonists, chemotherapy, organ transplant medications)  
    - Some cancers (e.g., leukemias, lymphomas, head, neck, or lung cancers) |
| • Persons who live or work in settings where TB exposure may be possible:  
  - Healthcare facilities§  
  - Correctional facilities  
  - Homeless shelters  
  - Mycobacteriology laboratories  
  - Infants, children, and adolescents at risk (See Appendix B: Tuberculosis Risk Assessment Tool) | • Persons with previous TB disease  
  - Evidence of old, healed TB lesions on chest radiograph  
  - History of untreated or inadequately treated TB disease  
  - Persons with clinical conditions or procedures such as:  
    - Silicosis  
    - Diabetes mellitus  
    - End-stage renal disease  
    - Body weight greater than or equal to 10% below ideal body weight or body mass index less than 18.5 kg/m²  
    - Organ transplantation  
    - Gastrectomy  
    - Chronic malabsorption syndromes  
    - Jejunoileal bypass  
  - Persons who inject illicit drugs or smoke tobacco products  
  - Infants and children age younger than 5 years of age with a positive test for TB infection |


* Any country other than the United States, Canada, Australia, New Zealand, or outside Western or Northern Europe, is considered a high TB incidence area.

† Includes hospitals, long-term care facilities, and drug treatment centers

‡ Either by history or evidence of conversion of TB test result (change from negative to positive IGRA result or an increase of 10 mm or more in size of TST reaction) within a 2-year period

§ Persons with medical conditions which may require immunosuppressive therapy (e.g., rheumatoid arthritis, Crohn’s disease, ulcerative colitis, ankylosing spondylitis, psoriasis) should receive a screening test for TB infection prior to initiation of the immunosuppressant agent(s).

Abbreviations Used: HIV=human immunodeficiency virus; IGRA=interferon gamma release assay; IL-1=interleukin-1; JAK inhibitors=Janus kinase inhibitors; kg=kilograms; m²=meters²; mg=milligrams; mm=millimeters; TB=tuberculosis; TST=tuberculin skin test; TNF-α=tumor necrosis factor-alpha
INTERFERON-GAMMA RELEASE ASSAYS

IGRAs are a blood-based in-vitro immunologic assay designed to measure the interferon-γ response of T lymphocytes sensitized to specific *M. tuberculosis* antigens (ESAT-6, CFP-10) that are absent from all bacille Calmette-Guérin (BCG) strains and most nontuberculous mycobacteria (NTM), with the exception of *M. kansasii*, *M. marinum*, and *M. szulgai*. IGRAs have excellent sensitivity (i.e., test is positive when TB infection is present) and, unlike the TST, are unaffected by a person’s BCG vaccination status or by their prior sensitization to the majority of NTMs. IGRAs are thus more specific than the TST for *M. tuberculosis* infection (i.e., fewer false-positive results).

IGRAs have been available in the U.S. since 2001; the two IGRAs currently available are the QuantiFERON®-TB Gold Plus (QFT) and T-Spot®.TB (T-Spot). Available IGRAs may change, so current Centers for Disease Control and Prevention (CDC) recommendations should be referenced for the latest guidance. Laboratories report IGRA results according to the reporting algorithms established by the manufacturer. Laboratory results include both qualitative and quantitative data in the provider report.

**QFT**: QFT results are reported as either “positive,” “negative,” or “indeterminate.” Quantitative data are reported for TB Antigen Tube 1 antigens (TB1; ESAT-6, CFP-10), TB Antigen Tube 2 antigens (TB2; ESAT-6, CFP-10, additional peptides), positive (Mitogen) control, and negative (Nil) control values.

Both TB1 and TB2 antigen tubes contain the *M. tuberculosis* antigens ESAT-6 and CFP-10. The TB1 tube contains peptides from ESAT-6 and CFP-10 that are designed to elicit cell-mediated immune responses from CD4+ T-helper lymphocytes. The TB2 tube contains additional peptides targeted toward cell-mediated immune responses from CD8+ cytotoxic T cells, which have been shown to be more frequently detected in persons with active TB disease versus LTBI and may be associated with recent *M. tuberculosis* exposure.

A QFT result is positive if the Nil value is ≤ 8.0 IU/ml and either TB antigen tube minus Nil is ≥ 0.35 IU/ml and ≥ 25% of the Nil value. A negative QFT result requires both antigen tubes minus Nil to be < 0.35 IU/ml, or ≥ 0.35 and < 25% of Nil value, and the mitogen minus Nil to be ≥ 0.5 IU/ml.

Some QFT results may be indeterminate due to processing errors or the patient’s inability to respond to either control. If the results of the QFT are indeterminate, repeat the QFT. If two different QFT specimens yield indeterminate results, clinical judgment is used to determine if the patient has likely TB infection. (See Table 2.2: Interpretation of QuantiFERON-TB Gold Plus Results.)
**TABLE 2.2:** Interpretation of QuantiFERON-TB Gold Plus (QFT) results

<table>
<thead>
<tr>
<th>NIL (IU/ml)</th>
<th>TB1 MINUS NIL (IU/ml)</th>
<th>TB2 MINUS NIL (IU/ml)</th>
<th>MITOGEN MINUS NIL (IU/ml)*</th>
<th>QFT-PLUS RESULT</th>
<th>REPORT/INTERPRETATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 8.0</td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Any</td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>Any</td>
<td>Positive† M. tuberculosis infection likely</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>≥ 0.35 and ≥ 25% of Nil value</td>
<td>&lt; 0.35 or ≥ 0.35 and &lt; 25% of Nil value</td>
<td>≥ 0.5</td>
<td>Negative M. tuberculosis infection NOT likely</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.35 or ≥ 0.35 and &lt; 25% of Nil value</td>
<td>&lt; 0.35 or ≥ 0.35 and &lt; 25% of Nil value</td>
<td>&lt; 0.35 or ≥ 0.35 and &lt; 25% of Nil value</td>
<td>&lt; 0.5</td>
<td>Indeterminate‡ Likelihood of M. tuberculosis infection cannot be determined</td>
</tr>
<tr>
<td>&gt; 8.0†</td>
<td>Any</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


* Responses to the Mitogen positive control (and occasionally TB Antigens) can be outside the range of the microplate reader. This has no impact on test results. Values > 10 IU/ml are reported by the QFT-Plus software as > 10 IU/ml.

† Where M. tuberculosis infection is not suspected, initially positive results can be confirmed by retesting the original plasma samples in duplicate in the QFT-Plus ELISA. If repeat testing of one or both replicates is positive, the test result is considered positive.

‡ Refer to package insert for possible causes.

§ In clinical studies, less than 0.25% of subjects had interferon gamma levels of > 8.0 IU/ml for the Nil Value.

**Abbreviations Used:** IU=international units; ml=milliliters; M. tuberculosis=Mycobacterium tuberculosis; TB=tuberculosis
**T-SPOT:** T-Spot results are reported as “positive,” “negative,” “borderline,” or “invalid.” Quantitative data are reported for the Panel A (ESAT-6) and Panel B (CFP-10) TB antigens, positive (Mitogen) control, and negative (Nil) control spot counts. Results are interpreted by subtracting the spot count in the Nil control from the spot count in Panel A and Panel B. For a valid test, the Nil control has ≤10 spots; if Panel A or B minus Nil has ≤4 spots, then the Mitogen must also have ≥20 spots for a valid result. T-Spot is the only IGRA test that gives a borderline result.

T-Spot results may be invalid due to inappropriate blood storage conditions, delay in sample transport, patient specific conditions, or laboratory error. In the case of borderline or invalid results, repeat the T-Spot test. If two different T-Spot specimens yield borderline or invalid results, clinical judgment is used to determine if the patient has likely TB infection. (See Table 2.3: Interpretation of T.Spot.TB Test Results.)

**TABLE 2.3: Interpretation of T-SPOT.TB test results**

<table>
<thead>
<tr>
<th>NIL (spots)</th>
<th>PANEL A MINUS NIL (spots)</th>
<th>PANEL B MINUS NIL (spots)</th>
<th>MITOGEN (spots)</th>
<th>T-SPOT.TB RESULT</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10</td>
<td>≥ 8</td>
<td>≥ 8</td>
<td>Any</td>
<td>Positive</td>
<td>8 spots or more in either Panel A-Nil or Panel B-Nil (Panel A-Nil or Panel B-Nil)</td>
</tr>
<tr>
<td>≤ 10</td>
<td>5, 6, or 7</td>
<td>5, 6, or 7</td>
<td>Any</td>
<td>Borderline*†</td>
<td>5, 6, or 7 spots (highest of Panel A-Nil or Panel B-Nil)</td>
</tr>
<tr>
<td>≤ 4</td>
<td>≥ 20</td>
<td>Any</td>
<td>Negative</td>
<td></td>
<td>Mitogen control has 20 spots or more and both Panel A-Nil and Panel B-Nil have 4 spots or fewer</td>
</tr>
<tr>
<td>≤ 4</td>
<td>&lt; 20</td>
<td>Any</td>
<td>Invalid*‡</td>
<td>Mitogen control has fewer than 20 spots and both Panel A-Nil and Panel B-Nil have 4 spots or fewer</td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>Any</td>
<td>Any</td>
<td>Invalid*‡</td>
<td>Nil control has more than 10 spots</td>
<td></td>
</tr>
</tbody>
</table>

*† Refer to package insert for possible causes.
*‡ Results where the highest of the Panel A or Panel B spot count is such that the (Panel minus Nil) spot count is 5, 6, or 7 spots should be considered Borderline (equivocal) and retesting by collecting another patient specimen is recommended.
* Invalid results should be reported as "Invalid" and it is recommended to collect another sample and re-test the individual.
TUBERCULIN SKIN TEST

The TST is an in-vivo test that measures cell-mediated immune response to a large number of mycobacterial proteins present in tuberculin (or purified protein derivative [PPD]).

BTBC staff are trained in the placement and reading of a TST in the Mantoux method. (See Appendix C: Administering the Tuberculin Skin Test.) In the Mantoux method, a trained healthcare provider injects 0.1 milliliter (ml) of tuberculin intradermally into the volar surface of the person’s forearm. The provider instructs the patient to return to the clinic 48 to 72 hours following the injection so that the provider can measure the induration (not erythema) of the skin reaction at the injection site.

BTBC does not accept or recommend self-reading of the TST. The size of the measured induration (a hard, dense, raised formation) and the patient’s individual risk factors define the interpretation of the TST. Based on the sensitivity and specificity of the TST and the prevalence of TB in different groups, three cut-points have been recommended for determining a positive tuberculin reaction. (See Table 2.4: Criteria for Determination of a Positive Tuberculin Skin Test Result.)

Providers can administer the TST to all persons at risk for TB infection, including pregnant persons and persons with HIV infection. Persons with a documented prior positive TST result (or reliable self-report) do not require repeat testing; additionally, repeat TST testing may cause a prominent local reaction resulting in necrosis of the skin and subcutaneous tissue.

TWO-STEP TUBERCULIN SKIN TESTING: Healthcare workers or others with occupational exposure to TB (e.g., employees or residents of nursing homes and other congregate settings) may be required to have baseline and annual screening for TB. When baseline screening includes the TST, a two-step testing process is performed. If the initial TST is negative, a second TST is administered, typically within one to three weeks after the initial (negative) test. The response to the second TST is recorded as the baseline result.

Some persons with remotely acquired TB infection may have a diminished immune response to the initial test. If a two-step baseline TST is not performed, those testing positive at the next annual testing may be incorrectly identified as being newly infected due to a “boosting” of their immune response by the initial test. Boosting is most common in persons older than 55 years of age and can also occur in BCG-vaccinated persons. Two-step testing is not performed when an IGRA is the initial TB test.
### TABLE 2.4: Criteria for determination of a positive tuberculin skin test result

<table>
<thead>
<tr>
<th>SIZE OF INDURATION</th>
<th>CRITERIA FOR DETERMINATION OF POSITIVE RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 5 mm</td>
<td>Persons who:</td>
</tr>
<tr>
<td></td>
<td>• have had recent contact to someone with infectious TB disease</td>
</tr>
<tr>
<td></td>
<td>• have HIV infection or other immunosuppressive conditions</td>
</tr>
<tr>
<td></td>
<td>• have fibrotic changes on chest radiograph consistent with old TB disease</td>
</tr>
<tr>
<td></td>
<td>• are currently taking certain medications that can cause immunosuppression, such as:</td>
</tr>
<tr>
<td></td>
<td>- anti-TNF-α inhibitor treatment (e.g., infliximab, etanercept), JAK inhibitors, Interleukin receptor antagonists</td>
</tr>
<tr>
<td></td>
<td>- medications after organ transplantation</td>
</tr>
<tr>
<td></td>
<td>- steroids (equivalent to 15 milligrams of prednisone or more/day for one month or more)</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>Persons who:</td>
</tr>
<tr>
<td></td>
<td>• were born in OR traveled/resided ≥ one month consecutively in a country with a high TB incidence rate*</td>
</tr>
<tr>
<td></td>
<td>• live or work in institutional settings where exposure to TB may be possible± (e.g., healthcare facilities, correctional facilities, homeless shelters, mycobacteriology laboratories)</td>
</tr>
<tr>
<td></td>
<td>• have medical conditions associated with increased risk of progression to active TB disease, including:</td>
</tr>
<tr>
<td></td>
<td>- silicosis</td>
</tr>
<tr>
<td></td>
<td>- diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>- end-stage renal disease</td>
</tr>
<tr>
<td></td>
<td>- gastrectomy</td>
</tr>
<tr>
<td></td>
<td>- jejunoileal bypass</td>
</tr>
<tr>
<td></td>
<td>- certain hematologic disorders (e.g., leukemias or lymphomas)</td>
</tr>
<tr>
<td></td>
<td>- specific malignancies (e.g., carcinoma of the head, neck, or lung)</td>
</tr>
<tr>
<td></td>
<td>• are younger than 5 years of age</td>
</tr>
<tr>
<td></td>
<td>• inject illicit drugs</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>Persons:</td>
</tr>
<tr>
<td></td>
<td>• at low risk for TB disease</td>
</tr>
<tr>
<td></td>
<td>• for whom testing is not generally indicated</td>
</tr>
</tbody>
</table>

* Countries with high TB incidence rates include any country other than the United States, Canada, Australia, New Zealand, or a country in Western or Northern Europe.

± As defined by local epidemiological risk and/or regulations. Healthcare facilities includes hospitals, long-term care facilities, and drug treatment centers.

**Abbreviations Used:** HIV=human immunodeficiency virus; JAK=Janus kinase; mm=millimeters; M. tuberculosis=Mycobacterium tuberculosis; TB=tuberculosis
**COMPARING INTERFERON GAMMA RELEASE ASSAYS AND TUBERCULIN SKIN TESTS**

There are advantages and disadvantages associated with each type of test for TB infection. (See Table 2.5: *Comparison of Interferon Gamma Release Assays and Tuberculin Skin Test*.)

**TABLE 2.5:** Comparison of interferon gamma release assays (IGRA) and tuberculin skin tests (TST)

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>IGRA</th>
<th>TST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antigens</td>
<td>• More specific to <em>M. tuberculosis</em> complex&lt;sup&gt;a&lt;/sup&gt;</td>
<td>• Less specific to <em>M. tuberculosis</em> complex</td>
</tr>
<tr>
<td>Boosting</td>
<td>• No; two-step testing not needed</td>
<td>• Yes, with serial testing; two-step testing is recommended at baseline in settings that require surveillance testing</td>
</tr>
<tr>
<td>False-positives</td>
<td>• Not with BCG, but with a few environmental mycobacteria&lt;sup&gt;b&lt;/sup&gt;</td>
<td>• With both BCG and some environmental mycobacteria</td>
</tr>
<tr>
<td>Interpretation</td>
<td>• Positive/negative result (may also have indeterminate or borderline results that require retesting)</td>
<td>• Based on size of induration (not erythema) and patient’s relative risk for TB exposure or development of disease</td>
</tr>
<tr>
<td></td>
<td>• Minimal inter-reader variability</td>
<td>• Subject to errors during implantation and interpretation</td>
</tr>
<tr>
<td>Time frame</td>
<td>• Blood samples must be processed within a manufacturer-determined time frame</td>
<td>• Test must be read between 48 and 72 hours after administration</td>
</tr>
<tr>
<td>Minimum number of visits</td>
<td>• One</td>
<td>• Two</td>
</tr>
</tbody>
</table>

<sup>a</sup> TB antigens ESAT-6 and CFP-10

<sup>b</sup> False-positive results may occur with *Mycobacterium sulgazi*, *Mycobacterium kansasii*, *Mycobacterium marinum*

**Abbreviations Used:** BCG=bacille Calmette-Guérin vaccine; *M. tuberculosis*= *Mycobacterium tuberculosis*; TB=tuberculosis; TST=Mantoux tuberculin skin test

**FALSE-NEGATIVE AND FALSE-POSITIVE RESULTS:** Certain medical conditions and other factors may affect the results of IGRAs and TSTs. (See Table 2.6: *Factors associated with false-negative or false-positive results for Interferon Gamma Release Assay and Tuberculin Skin Test.*)
### TABLE 2.6: Factors associated with false-negative or false-positive results for interferon-gamma release assays and tuberculin skin tests

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>FALSE-NEGATIVE*</th>
<th>FALSE-POSITIVE*</th>
</tr>
</thead>
</table>
| Infections | • Viral illnesses (HIV, measles, varicella)  
• Bacterial illnesses (typhoid fever, pertussis, brucellosis, typhus, leprosy)  
• Early TB infection (less than 8 weeks)  
• Severe TB disease (meningitis, disseminated)  
• Fungal disease | • Exposure to *M. kansasii*,  
*M. marinum*, and *M. szuligoi* (for IGRA)  
• Exposure to additional NTM (for TST) |
| Vaccines² | • Measles, mumps, rubella  
• Polio  
• Varicella  
• Smallpox | • BCG vaccine (for TST) |
| Concurrent clinical and/or demographic factors | • Metabolic abnormalities  
• Chronic renal failure  
• Primary immunodeficiencies  
• Malignancies (e.g., lymphomas, leukemia)  
• Sarcoidosis  
• Poor nutrition  
• Very young or elderly age  
• Protein deficiency | • Transfusion with whole blood from donors with known positive TST |
| Drugs and technical factors | • Corticosteroids, TNF-α blockers, JAK inhibitors, Interleukin receptor antagonists, or other immunosuppressive medications  
• Chemotherapy  
• Material—poor quality, inadequate dose (for TST), improper storage (exposure to heat/light), or expired  
• Administration—not injected intradermally (for TST)  
• Reading—inexperienced reader, recording error, read too early/late (TST) | • Reading—inexperienced reader (for TST) |
| Interpretative | • Misclassification of risk group or erroneous decrease in mm reading of induration (for TST) | • Misclassification of risk or erroneous increase in mm reading of induration (for TST) |


*Applies to both IGRA and TST except where indicated

² The IGRA or TST may be falsely negative if performed after a recently-administered vaccine

Abbreviations Used: BCG=bacille Calmette-Guérin vaccine; HIV=human immunodeficiency virus; IGRA= interferon gamma release assay; JAK inhibitors=Janus kinase inhibitors; mm=millimeters; NTM=nontuberculous mycobacterium; TNF-α=tumor necrosis factor-alpha; TST=tuberculin skin test, TB=tuberculosis
TESTING AMONG PRIORITY POPULATIONS AND SPECIAL CONSIDERATIONS

CONTACTS

Contacts, or persons exposed to an individual with infectious TB disease, represent the group with the highest risk of being infected with TB. Approximately 16% of persons tested through contact investigation in NYC have a positive test result and 1% are diagnosed with active TB disease; thus evaluation of close contacts to persons with active TB disease is conducted as soon as feasible, in consultation with the NYC Health Department. (See Chapter 11: Contact Investigation.)

Since it can take up to eight weeks after exposure to M. tuberculosis (“window period”) for the immune system to mount a response, the initial (baseline) test may be falsely negative if conducted too soon after TB exposure. If the baseline test is negative, and the person has no symptoms or medical risk factors for TB, a repeat test is obtained shortly after the end of the window period, usually eight weeks after the last exposure. Using the same baseline and post-window period test for TB infection is preferred; if not feasible, providers should avoid using a less specific post-window test (i.e., TST) when a more specific baseline test (i.e., IGRA) was used at baseline.

Prompt medical evaluation is conducted for contacts with a positive baseline or post-window period test for TB infection or those with medical risks or symptoms consistent with active TB regardless of the TB infection test result. Contacts younger than five years of age and those who have HIV infection or another immunosuppressive condition are a priority for evaluation since they are at high risk for rapid progression to active TB disease if infected.

PERSONS WHO HAVE HUMAN IMMUNODEFICIENCY VIRUS INFECTION

People living with HIV infection who become infected with TB are at high risk for developing active TB disease. Thus, testing for TB infection occurs as soon as a person is diagnosed with HIV infection, regardless of their epidemiological risk of TB exposure.

Persons with HIV infection who have a positive test for TB infection require additional testing to rule out active TB disease. For those with a negative TB infection test result, clinical judgment is used to determine the need for further evaluation to rule out active TB disease. For those who have advanced HIV infection (CD4 cell count less than 200 cells/cubic millimeter [mm$^3$]), a negative TB infection test result, and no indications for initiating empiric LTBI treatment, retest for TB infection once anti-retroviral therapy (ART) is started and the CD4 count equals or exceeds 200 cells/mm$^3$. Annual testing for TB infection is recommended only for patients with HIV infection who are at high risk of repeated or ongoing exposure to persons with active TB disease. For persons living with HIV infection who are contacts to a person with infectious TB, empiric treatment for LTBI is recommended, regardless of CD4 count, previous LTBI treatment, or IGRA/TST result.
PERSONS WITH AN IMMUNOSUPPRESSIVE MEDICAL CONDITION OR TAKING IMMUNOSUPPRESSIVE THERAPY

Persons with an immunosuppressive condition other than HIV infection or who are on immunosuppressive therapy are tested for TB infection with IGRA or TST either 1) at the time of diagnosis of the condition; or 2) before starting immunosuppressive therapy. Persons receiving treatment for various dermatological, rheumatological, and gastrointestinal disorders (e.g., certain forms of arthritis [rheumatoid, juvenile idiopathic, or psoriatic], lupus, inflammatory bowel disease [Crohn’s, ulcerative colitis], psoriasis, ankylosing spondylitis, and non-infectious uveitis), certain cancers (e.g., leukemia, lymphoma, head, neck, or lung cancer), or pre- and post-organ transplantation may have impairment of their immune response. A positive IGRA or TST result is indicative of TB infection in all such persons. (See Table 2.4: Criteria for Determination of a Positive Tuberculin Skin Test Result for definition of a positive TST result.)

TST or IGRA results in immunosuppressed persons may be falsely negative, either due to the drug therapy or to the underlying medical condition; two-step testing may be indicated if TST is used. The patient is treated for LTBI if any of the tests are positive or if they are a recent contact to a person with infectious TB (once active TB is ruled out). If the IGRA or TST is negative, clinical judgment is used to determine if empiric LTBI treatment is required. Annual testing for TB infection is recommended for persons who are at high risk for repeated or ongoing exposure to persons with active TB disease.

PERSONS WHO LIVE OR WORK IN SETTINGS WHERE TUBERCULOSIS EXPOSURE IS MORE LIKELY

Persons who live or work in settings where TB exposure is more likely may be at risk for TB infection based on local TB epidemiology and risk of transmission. Such settings include healthcare facilities (e.g., hospitals, long-term care facilities, drug treatment centers), correctional facilities, mycobacterial laboratories, and homeless shelters. TB infection testing recommendations or requirements are based on institutional guidelines, as well as state and local laws and regulations. Baseline and annual testing for TB infection is often recommended or required. Updated recommendations from the National TB Controllers Association and CDC for screening and testing healthcare personnel include: individual baseline (preplacement) risk assessment, symptom evaluation and testing of persons without prior TB or latent TB infection (LTBI), no routine serial testing in the absence of exposure or ongoing transmission, treatment for healthcare personnel diagnosed with LTBI, annual symptom screening for persons with untreated LTBI, and annual TB education of all healthcare personnel. Persons undergoing serial testing receive either a two-step TST or a single IGRA as part of their baseline evaluation; the test used for subsequent screening should be the same as the one used at baseline.

The New York State Department of Health (NYSDOH) requires a medical evaluation of all healthcare workers prior to employment in hospitals and diagnostic and treatment centers in New York State, which must include TB screening. Requirements are subject to change. Current guidelines for healthcare facilities and employee TB screening can be found at: www.health.ny.gov
PERSONS WHO WERE BORN, RESIDED, OR TRAVELED IN AREAS WITH HIGH RATES OF TUBERCULOSIS

Regardless of the duration of residence in the U.S., persons who were born or resided/traveled (for one month or longer) in countries with high TB incidence should be screened for TB infection, preferably with an IGRA. Countries with high TB incidence rates include any country other than the U.S., Canada, Australia, New Zealand, or a country in Western or Northern Europe. Some individuals born in high TB incidence countries may have been screened for TB disease with a chest radiograph (CXR) for permanent legal residence in the U.S., but may not have received a test for TB infection. Similarly, persons who resided in or traveled to a country with a high TB incidence for one consecutive month or longer should be screened for TB infection after returning to the U.S.

CHILDREN YOUNGER THAN 18 YEARS OF AGE

Children younger than 18 years of age are tested for TB infection based on individual risk factors following completion of a TB risk assessment. (See Appendix B: Tuberculosis Risk Assessment Tool.) Administrative or mandated tests for TB infection for entry to daycare, school, camp, or college are discouraged in the absence of risk factors. The consumption of raw milk or cheese products from outside the U.S. has also been associated with TB infection. Children with known exposure to such products are tested for TB infection and offered treatment if indicated.

PERSONS WHO PREVIOUSLY RECEIVED BACILLE CALMETTE-GUÉRIN VACCINATION

Tests for TB infection can be used among persons who previously received the BCG vaccination. A history of BCG vaccination does not influence the decision to test for TB infection. Since IGRAs do not cross-react with BCG, they are the preferred test for persons with a history of BCG vaccination. Although BCG vaccination can cause a false-positive cross-reaction to the TST (especially within the first 12 months after vaccination), sensitivity to tuberculin is highly variable and decreases over time. The presence or size of a TST reaction does not predict whether BCG vaccination will provide protection against TB disease or whether the reaction is due to BCG vaccination or TB infection. Thus, a positive reaction to the TST in BCG-vaccinated persons is interpreted as indicating TB infection when the person tested is at increased risk of TB infection or progression to active TB disease.

PERSONS RECEIVING LIVE VIRUS VACCINATIONS

Although the TST and IGRAs can be administered in conjunction with all vaccines, the measles, mumps, and rubella (MMR) vaccine and other live attenuated vaccines (e.g., varicella, nasal influenza vaccines) may transiently suppress the immune response to either type of test. When timing TB testing with the administration of the MMR or other live virus vaccines, one of the following three administration sequences may be used:

- The TST or IGRA is performed at the same visit as the MMR/live virus vaccine.
- The TST or IGRA is delayed at least four to six weeks if the MMR/live virus vaccine is given first.
The TST or IGRA is performed first and results are obtained (e.g., 48-72 hours after TST placement) and then the MMR/live virus vaccine is given.

**MEDICAL EVALUATION**

Once a person has tested positive for TB infection, the provider must conduct further clinical and radiologic evaluation and rule out active TB disease before an LTBI diagnosis can be established or LTBI treatment can be initiated. All persons who have a current or prior positive test for TB infection are examined by a clinical provider and receive a medical history and physical examination, CXR, and relevant laboratory testing if clinically indicated. In some instances, patients not testing positive should also receive medical evaluation. (See Table 2.7: Recommended Clinical Evaluation Based on Test for Tuberculosis Infection Results.)

**TABLE 2.7: Recommended clinical evaluation based on test for tuberculosis infection results**

<table>
<thead>
<tr>
<th>RESULT</th>
<th>RECOMMENDED CLINICAL EVALUATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative IGRA or TST</td>
<td>• No further evaluation is needed unless indicated by clinical judgment (e.g., clinical suspicion of active TB, immunosuppression, new TB risk factor, live or work in high-risk setting)</td>
</tr>
<tr>
<td>Positive IGRA or TST</td>
<td>• Rule out active TB disease with clinical evaluation, CXR, and other diagnostics as clinically indicated</td>
</tr>
</tbody>
</table>
| Indeterminate\(^a\) or invalid\(^b\) IGRA  | • Result could be due to error in specimen collection or laboratory processing or to the patient’s reduced immune response to the TB antigens (i.e., anergy)  
• Repeat the IGRA. If 2 separate specimens from a patient yield indeterminate or invalid results, do not repeat IGRA; consider medical evaluation and CXR to rule out active TB |
| Borderline IGRA\(^b\)                      | • Indicates an uncertain likelihood of *M. tuberculosis* infection  
• Repeat IGRA. If 2 separate specimens from a patient yield borderline results, do not repeat IGRA; consider medical evaluation and CXR to rule out active TB |

\(^a\) QFT-TB Gold Plus only  
\(^b\) T-SPOT.TB only  

**Abbreviations Used:**  
CXR = chest radiograph; IGRA = interferon gamma release assay; *M. tuberculosis* = *Mycobacterium tuberculosis*; TB = tuberculosis; TST = tuberculin skin test
CLASSIFICATION OF THE PATIENT AND IMPLICATIONS FOR CLINICAL FOLLOW-UP

After a clinical evaluation, patients are initially classified according to the INTERNATIONAL CLASSIFICATION OF TUBERCULOSIS. (See Appendix A: International Classification of Tuberculosis.) Further evaluation may require re-classification.

A patient who has a positive test for TB infection and a normal CXR and no signs or symptoms of TB disease is classified as CLASS II. Class II patients are further classified as either contact, medical risk (e.g., immunosuppression), population risk (e.g., from high TB incidence country), or administrative risk (e.g., employment or school requirement) and are treated for LTBI as indicated.

A patient who has a positive test for TB infection and a CXR with calcified granuloma and no signs or symptoms of TB disease can be classified as CLASS II and is treated for LTBI. Sputum does not need to be collected to rule out active TB disease.

A patient who has a positive test for TB infection and an abnormal CXR consistent with active TB disease is classified as CLASS V (high or low, based on presence of symptoms or degree of CXR abnormalities), and is evaluated for active TB disease and managed accordingly. (See Chapter 2: Diagnosis and Treatment of Tuberculosis Disease in Adults.)

A patient who has a positive test for TB infection and CXR showing fibrotic lesions suggestive of old, healed TB disease requires a medical evaluation for current symptoms of TB disease and need for treatment. Providers order a complete blood count (CBC), chemistry panel, viral hepatitis screen, and three consecutive sputum samples for smear, nucleic acid amplification (NAA) testing (if sputum is AFB smear-positive), culture, and susceptibility testing. If prior CXRs are not available for comparison, repeat CXR may be obtained after two months to assess stability or changes in radiologic findings.

• If there are no symptoms of TB disease, providers classify the individual as CLASS V (low) and evaluate and treat for active TB disease as indicated.
• If there are TB disease symptoms, providers classify the individual as CLASS V (high) and evaluate and treat for active TB disease as indicated.

If the patient has a history of treatment for pulmonary TB, patients can be classified based on clinical judgment as:

• CLASS V (high or low, based on symptoms). Providers are recommended to evaluate the patient with sputum testing to rule out active TB disease, decide whether to re-treat, and re-classify based on final evaluation.
• CLASS IV if the patient is asymptomatic and has a detailed history or documentation of treatment. Providers are recommended to evaluate to determine whether to re-treat based on re-exposure and other factors.
MEDICAL HISTORY

A comprehensive medical history is obtained, which includes the following:

- Risk factors for TB infection or, if already infected, progression to TB disease
- Previous testing for TB infection
- Previous treatment for LTBI or TB disease
- Previous or current exposure to a person with infectious TB disease
- Other coexisting medical conditions (e.g., HIV or other immunosuppressive conditions, diabetes)
- Use of prescription and over-the-counter medications, supplements, or herbal products
- Allergic or adverse reactions to medications
- History of liver disease or hepatitis
- Social history including substance use (e.g., drug, alcohol, tobacco) and homelessness
- Test results of prior HIV testing

PHYSICAL EXAMINATION

After obtaining a thorough medical history, providers perform a directed physical examination to assess the possibility of TB disease in specific sites (e.g., cardiac, pulmonary, lymph nodes).

CHEST RADIOGRAPH

All persons with a positive test for TB infection or symptoms consistent with TB disease receive a posterior-anterior CXR to rule out pulmonary TB disease. Children younger than five years of age must have both a posterior-anterior and lateral CXR. In some instances, other views (e.g., apical lordotic) or additional studies (e.g., computed tomography [CT] scans) may be necessary.

If there is documentation of a normal CXR and medical evaluation in the electronic medical record (EMR) within the previous month, a repeat CXR is not necessary unless the patient is currently symptomatic, immunosuppressed, younger than five years of age, or a contact to a person with infectious TB. For all others, clinical judgment is used to determine the need for a repeat CXR.

For persons who are referred or present to a NYC Health Department TB clinic with a report of a positive test for TB infection and a normal CXR, the CXR report is reviewed by a NYC Health Department TB clinic provider who determines whether a repeat CXR is indicated. In general, a repeat CXR is obtained if:

- The patient has symptoms consistent with active TB disease.
- The original CXR was taken more than one month ago in patients with HIV infection, other immunosuppressive conditions, age younger than five years, or those who are contacts to a person with infectious TB disease.
- The language in the CXR report is ambiguous, regardless of the date the CXR was taken.
LABORATORY TESTS FOR PERSONS BEING CONSIDERED FOR LATENT TUBERCULOSIS INFECTION TREATMENT

Routine baseline laboratory studies are indicated for certain persons before initiating LTBI treatment. These studies include: a baseline complete blood count (CBC), a viral hepatitis screen, and a chemistry panel, which consists of serum glucose, creatinine, liver function tests (LFTs), such as aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, and total bilirubin. Baseline laboratory studies are obtained for patients with the following conditions or situations:

- HIV infection
- Pre-existing liver disease (e.g., alcoholic hepatitis, cirrhosis)
- Viral hepatitis (e.g., hepatitis B or C)
- History of chronic alcohol ingestion or intravenous drug use
- Pregnant or postpartum (up to three months after delivery) patients
- Taking drugs for other medical conditions that may be hepatotoxic or have drug-to-drug interactions with LTBI treatment (See Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications.)
- At the provider’s discretion

LTBI treatment can be initiated the same day the baseline laboratory tests are drawn to save the patient a visit back to the clinic, as long as the patient can be contacted in the event of an abnormal blood test result that requires follow-up. Abnormal test results are evaluated by a provider as soon as possible or, at the latest, within three business days of starting treatment for LTBI. The provider documents follow-up actions in the EMR. All critical laboratory results are reported to a NYC Health Department on-call physician for timely follow-up.

HUMAN IMMUNODEFICIENCY VIRUS SCREENING

NYC Health Department TB clinics employ opt-out HIV testing for all patients being evaluated for LTBI or active TB disease unless there is a documented prior positive test result or recent negative HIV test result within the past 12 months.

Parental consent for HIV testing of children younger than 18 years of age is not required in New York State. (See Chapter 17: Laws Governing Tuberculosis Care in New York City.) Since HIV infection is an important risk factor for progression of LTBI to active TB disease, HIV testing is particularly important for persons meeting the following criteria:

- Previous or current positive test for TB infection
- Previous or current diagnosis of LTBI or TB disease
- Close contact to a person with infectious TB disease
- CXR with abnormalities consistent with old, healed TB disease
In addition, the CDC recommends opt-out HIV screening for the following persons:

- All patients 13 to 64 years of age at least once as part of routine healthcare, regardless of presence or absence of HIV risk factors
- All pregnant persons as part of routine prenatal screening
- Annual HIV screening of asymptomatic persons with risk factors for HIV infection
- More frequent screening (e.g., once every three or six months) as clinically indicated

TREATMENT OF LATENT TUBERCULOSIS INFECTION

Treatment of LTBI in high-risk persons is essential for TB prevention efforts. Completion of an appropriate LTBI treatment regimen can reduce the risk of TB disease by approximately 90%.

All high-risk persons who test positive for TB infection are offered one of the approved treatment regimens for LTBI once active TB disease is ruled out, regardless of age or time since immigration to the U.S. Regimens for contacts initiating LTBI treatment may be modified based on results of drug-susceptibility testing (DST) of the isolate obtained from the source case (index patient); however, LTBI treatment should not be delayed if these results are not known. High-risk contacts (e.g., younger than five years of age or immunosuppressed) are promptly started on LTBI treatment, often during the window period after an initial negative test for TB infection, once active TB is ruled out.

Patients who completed LTBI therapy but are re-exposed to another person with TB disease are evaluated again for the new exposure. For recent contacts to patients with infectious TB, a new CXR is taken and, if normal, a repeat course of LTBI treatment is strongly recommended, especially if:

- The patient has HIV infection or is otherwise immunosuppressed
- The patient has medical risk factors for progression to TB disease
- The patient is younger than 18 years of age
- There is evidence of recent TB transmission around the index patient (e.g., documented IGRA or TST conversions among contacts, additional close contacts with active TB disease)

Likewise, close contacts who have a prior positive test for TB infection but did not receive prior LTBI treatment are advised to receive treatment for the recent exposure.

Clinical providers may have concerns about initiating LTBI treatment, particularly among older persons due to potential side effects of medications; however, advanced age itself is not a contraindication to treatment. As with any treatment, clinical providers weigh the risks and benefits for each individual, based on TB risk factors and results of the clinical evaluation.
### TABLE 2.8: Recommended drug regimens for the treatment of latent tuberculosis infection in adults and children

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTERVAL AND DURATION</th>
<th>DOSAGE</th>
<th>COMPLETION CRITERIA</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIF</td>
<td>Daily for 4 months</td>
<td>Adults (max.)</td>
<td>10 mg/kg (600 mg)</td>
<td>120 doses within 6 months • Recommended for people of all ages • Preferred treatment for people who have been exposed to INH-resistant, RIF-susceptible TB • Use of rifamycins may be limited by potential drug-to-drug interactions† • Some antiretroviral drugs, such as the PIs, NNRTIs, and INSTIs have interactions with rifamycins. Clinicians must consult web-based updates or clinical experts for the latest specific recommendations§ • Children &lt; 2 years require dosing closer to 20 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Children (max.)</td>
<td>10–20 mg/kg (600 mg)</td>
<td></td>
</tr>
<tr>
<td>INH and RPT</td>
<td>Once weekly for 12 weeks</td>
<td>Adults and children 2 years of age and older (max.)</td>
<td>INH: Adults and children age 12 years and older: 15 mg/kg rounded up to the nearest 50 or 100 mg (900 mg) Children age 2-11 years: 25 mg/kg rounded up to the nearest 50 or 100 mg (900 mg) RPT: 10.0–14.0 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 max.)</td>
<td>≥ 11 doses within 16 weeks • Administration by DOT is preferred. • Use of rifamycins may be limited by potential drug-to-drug interactions† • Can be used by person with HIV infection taking antiretroviral medications with acceptable drug-to-drug interactions with RPT (e.g., efavirenz- or raltegravir-containing regimens)§ • Pyridoxine (vitamin B6) supplementation (50 mg once per week) may be recommended*</td>
</tr>
</tbody>
</table>
### TABLE 2.8: Recommended drug regimens for the treatment of latent tuberculosis infection in adults and children (continued)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>INTERVAL AND DURATION</th>
<th>DOSAGE</th>
<th>COMPLETION CRITERIA</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| **INH** | Daily for 6 months† | Adults (max.) | 5 mg/kg (300 mg) | 182 doses within 9 months | • For patients with HIV infection, INH may be administered concurrently with NRTIs, PIs, NNRTIs, or INSTIs  
• Pyridoxine (vitamin B6) supplementation (25 mg/day) may be recommended*  
• Aluminum-containing antacids reduce INH absorption  
• Acetaminophen, cimetidine, phenytoin, disulfiram, carbamazepine, valproate, clopidogrel, and citalopram levels may be increased with concomitant INH use*  
• Avoid tyramine-containing foods (e.g., cheese, red wine, certain types of fish) |
| | Children† (max.) | 10–20 mg/kg (300 mg) | | |
| **INH** | Daily for 9 months‡ | Adults (max.) | 5 mg/kg (300 mg) | 270 doses within 12 months | • For patients with HIV infection, INH may be administered concurrently with NRTIs, PIs, NNRTIs, or INSTIs  
• Pyridoxine (vitamin B6) supplementation (25 mg/day) may be recommended*  
• Aluminum-containing antacids reduce INH absorption  
• Acetaminophen, cimetidine, phenytoin, disulfiram, carbamazepine, valproate, clopidogrel, and citalopram levels may be increased with concomitant INH use*  
• Avoid tyramine-containing foods (e.g., cheese, red wine, certain types of fish) |
| | Children† (max.) | 10–20 mg/kg (300 mg) | | |
| **INH** | Twice weekly for 6 months‡ | Adults (max.) | 15 mg/kg (900 mg) | 52 doses in 9 months | • DOT must be used  
• Pyridoxine (vitamin B6) supplementation (50 mg twice per week) may be recommended*  
• Avoid tyramine-containing foods (e.g., cheese, red wine, certain types of fish) |
| | Children† (max.) | 20–40 mg/kg (900 mg) | | |
| **INH** | Twice weekly for 9 months‡ | Adults (max.) | 15 mg/kg (900 mg) | 76 doses in 12 months | • DOT must be used  
• Pyridoxine (vitamin B6) supplementation (50 mg twice per week) may be recommended*  
• Avoid tyramine-containing foods (e.g., cheese, red wine, certain types of fish) |
| | Children† (max.) | 20–40 mg/kg (900 mg) | | |

† Use of rifamycins may be limited by potential drug-to-drug interactions (e.g., methadone, certain oral hypoglycemic agents, oral contraceptives)  
‡Pyridoxine (vitamin B6) supplementation (25 mg/day) may decrease peripheral and central nervous system effects of INH and is used in patients who are using alcohol, pregnant, nursing infants, malnourished or who have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy.  
§Treatment may be considered as complete at six months for healthy persons older than 18 years of age who have no risk for progression to TB disease and no HIV infection or other immunosuppressive conditions.  
¶The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.  
§Visit http://aidsinfo.nih.gov for the latest guidelines and complete list of contraindicated medications.  
*For more information, check a drug interaction (https://www.rxlist.com/drug-interaction-checker.htm) website.  
Abbreviations Used: DOT=directly observed therapy; HIV=human immunodeficiency virus; INH=isoniazid; INSTIs=integrase strand transfer inhibitor; kg=kilograms; mg=milligrams; NNRTI=non-nucleoside reverse transcriptase inhibitors; NRTI=nucleoside reverse transcriptase; PIs=protease inhibitors; Rif=rifampin; RPT=rifapentine
LATENT TUBERCULOSIS INFECTION TREATMENT REGIMENS

Several LTBI treatment regimens are available in NYC Health Department TB clinics and are listed below. Short-course regimens are preferred for eligible patients as they have been demonstrated to have efficacy, high treatment completion rates, and are generally well-tolerated.

LTBI treatment regimens are generally well-tolerated. However, adverse reactions can occur and close clinical monitoring during treatment is essential in mitigating the risk. Treatment indications, options, duration, methods of administration (i.e., self-administered and directly observed therapy [DOT]), and potential adverse effects are discussed with patients so that an informed decision about the optimal regimen can be made; the discussion and decisions are documented in the EMR. Potential drug-to-drug interactions and individual patient characteristics are considered when selecting a regimen. (See Appendix J: Recommendations for Patients to Assist with Taking Tuberculosis Medications and Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications.)

RIFAMYCINS

Rifamycins are a class of drugs (e.g., rifampin [RIF], rifapentine [RPT], and rifabutin [RBT]) that have been used for many years in the treatment of both LTBI and active TB disease. Rifamycins are generally well-tolerated, and RIF is a commonly used short-course medication for LTBI treatment at NYC Health Department TB clinics. In addition, for contacts of a person with infectious isoniazid- (INH) resistant, RIF-susceptible TB, RIF is the LTBI treatment of choice. RIF is recommended for daily use by self-administration for four months (4R) to treat LTBI in adults and children.

Side Effects

Possible side effects of rifamycins include the following (see Table 2.9: Monitoring for Side Effects and Adverse Reactions During Latent Tuberculosis Infection Treatment):

- Gastrointestinal symptoms such as nausea, vomiting, anorexia, abdominal pain
- Cutaneous reactions such as pruritus (with or without rash)
- Hepatotoxicity, particularly with elevated bilirubin
- Rare hypersensitivity reactions such as fever, headache, dizziness, musculoskeletal pain, and petechiae
- Orange discoloration of body fluids (e.g., tears, saliva, sweat, urine, stool) is expected with use of RIF and is harmless; however, permanent discoloration of contact lenses may occur

Contraindications

Contraindications to the use of RIF include:

- History of severe RIF-induced reaction, including hepatic, skin, and allergic reactions
- Thrombocytopenia
• Severe chronic liver disease
• Current treatment with certain protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI), and integrase strand transfer inhibitors (INSTI)

Due to drug interactions, RIF must not be used to treat persons living with HIV infection who are taking certain combinations of antiretroviral therapy (ART). In such cases, another rifamycin, such as RBT, can be substituted for RIF. RBT is considered equally effective to RIF in treating LTBI, but has less effect on the metabolism of other drugs given concurrently. RBT may be used with regimens containing NNRTI, PI, and certain INSTI. RBT may also be given to patients on methadone as generally the dose of methadone does not need to be increased. It may also cause less gastrointestinal distress and liver function abnormalities.

**Drug-to-Drug Interactions**

Use of RIF and other rifamycins can also be limited by the potential for drug-to-drug interactions. RIF increases the metabolism of many medications when given concurrently and can decrease their efficacy (e.g., certain oral hypoglycemic agents, anticoagulants, antidepressants, certain antihypertensives, methadone). In addition, rifamycins decrease the efficacy of hormonal contraceptives and alternative forms of contraception are advised for patients wishing to avoid pregnancy during treatment. (See *Appendix F: Potential Drug Interactions with Isoniazid and Rifamycin Medications*.)

**ISONIAZID AND RIFAPENTINE**

A once-weekly, 12-dose regimen of INH and RPT (3HP) is indicated for use in the treatment of LTBI among the following persons requiring LTBI treatment:

• Patients two years of age and older; data on safety and pharmacokinetics of RPT in children younger than two years of age are not available
• Persons living with HIV infection who are taking ART with acceptable drug-to-drug interactions with RPT (e.g., efavirenz- or raltegravir-containing regimens) (see aidsinfo.nih.gov/guidelines)
• Contacts to a person with infectious TB if isolate is susceptible to both INH and RIF
• Persons who are not currently or planning to be pregnant or breastfeeding

The 3HP regimen can be given by DOT, including electronic DOT (eDOT) using video technology and smart phones. In 2017, a published clinical trial demonstrated that self-administration of 3HP was non-inferior to DOT and could also be used. The decision to use DOT vs. self-administration is based on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease. In the absence of additional efficacy data supporting self-administration of 3HP, BTBC policy still recommends the use of DOT, when possible, for patients taking 3HP.

**Side Effects**

While 3HP is generally well-tolerated, possible side effects include those for INH and RPT, in addition to hypersensitivity syndrome (fever, chills, headache, fatigue, uveitis, urticaria, pruritus, or petechiae). This
syndrome typically presents around the third to fourth week of treatment. (See Table 2.9: Monitoring for Side Effects and Adverse Reactions During Latent Tuberculosis Infection Treatment.)

Contraindications

Contraindications to the use of 3HP include:

- Children younger than two years of age
- Persons living with HIV infection who are receiving ART with drug-to-drug interactions with RPT
- Pregnancy (current or planned) or breastfeeding during treatment

ISONIAZID

INH was the standard treatment for LTBI for many years due to its established efficacy in preventing progression to TB disease among those with TB infection. However, with shorter and equally efficacious LTBI regimens now available, such as 4R and 3HP, NYC Health Department TB clinics primarily use INH when the short course regimens cannot be used due to either resistance or intolerance to rifamycins. For contacts, 3HP or INH can be used when the person with infectious TB has INH-susceptible TB.

If INH monotherapy must be used, a 6-month regimen (6H) is recommended, including for children and persons living with HIV; a 9-month regimen (9H) may be used based on clinical judgment. INH is recommended for daily use by self-administration and may be administered concurrently with any ART used to treat HIV infection.

Side Effects

INH is generally well-tolerated. Possible side effects include the following:

- Gastrointestinal symptoms (e.g., nausea, vomiting, anorexia, abdominal pain)
- Jaundice
- Fatigue
- Arthralgias
- Rash
- Elevation of serum liver enzyme concentrations
- Clinical hepatitis
- Peripheral neuropathy

Contraindications

Contraindications to use of INH include:

- History of severe INH-induced reaction, including hepatic, skin, or allergic reactions, or neuropathy
- Severe chronic liver disease
### TABLE 2.9: Monitoring for side effects and adverse reactions during latent tuberculosis infection treatment

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SIDE EFFECTS/ADVERSE REACTIONS</th>
<th>MONITORING*</th>
<th>COMMENTS*</th>
</tr>
</thead>
</table>
| RIF  | • Anorexia  
• Nausea, vomiting  
• Icterus  
• Abdominal pain  
• Hepatitis  
• Rash and/or pruritus  
• Fever or flu-like symptoms  
• Easy bruising or bleeding  
• Renal failure  
• Red discoloration of urine and other secretions  | • CBC, LFTs (AST, ALT, and serum bilirubin), and serum creatinine at baseline if clinically indicated  
• Baseline hepatitis screen for any patient having blood drawn  
• Repeat monthly labs if baseline results are abnormal, patient has risk factors for toxicity, or patient has symptoms of adverse reactions  | • Normal red or orange discoloration of body fluids (e.g., tears, saliva, sweat, urine, stool)  
• May permanently discolor soft contact lenses or dentures  
• May develop neutropenia or thrombocytopenia  
• Hepatitis risk increases with age; underlying liver disease, chronic alcohol ingestion, or intravenous drug use; use of other potentially hepatotoxic drugs; and if pregnant or up to three months postpartum  
• Many potential drug interactions§  
• Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, ketoconazole, coumadin derivatives, hormonal contraceptives, oral hypoglycemic meds (except metformin), digitalis, sulfonylureas, diazepam, ß-blockers; consult with providers prescribing these agents  
• Methadone dosage may need to be increased; monitor for withdrawal symptoms and consult with methadone maintenance program as needed  
• May impair glucose control in people with diabetes  
• Advise patients to use barrier contraception in addition to oral or non-hormonal contraceptives  
• Contraindicated in patients taking most PIs, NNRTIs, and INSTIs  |
| INH and RPT | • Anorexia  
• Nausea, vomiting  
• Flu-like symptoms  
• Polyarthralgia  
• Hypersensitivity syndrome including fever, chills, headache, fatigue, uveitis, urticaria, pruritus, or petechiae  | • CBC, LFTs (AST, ALT, and serum bilirubin), and serum creatinine if clinically indicated  
• Baseline hepatitis screen for any patient having blood drawn  | • See RIF and INH sections  
• If present, hypersensitivity syndrome is typically seen around third to fourth weeks of treatment |
### TABLE 2.9: Monitoring for side effects and adverse reactions during latent tuberculosis infection treatment (continued)

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SIDE EFFECTS/ADVERSE REACTIONS</th>
<th>MONITORING*</th>
<th>COMMENTS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>• Anorexia</td>
<td>• LFTs (AST, ALT, and serum bilirubin) at baseline if clinically indicated</td>
<td></td>
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<td></td>
<td>• Nausea, vomiting</td>
<td>• Baseline hepatitis screen for any patient having blood drawn</td>
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<tr>
<td></td>
<td>• Abdominal pain</td>
<td>• Repeat monthly LFTs if baseline results are abnormal, patient has risk factors for toxicity, or patient has symptoms of adverse reactions</td>
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<td></td>
<td>• Dark urine</td>
<td>• Asymptomatic elevation of hepatic enzymes can occur. Mild and transient elevation of serum transaminases occurs in 10-20% of patients taking INH, usually in the first one to three months of treatment but can occur at any time. Most enzyme levels return to normal and generally there is no need to discontinue INH</td>
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<td></td>
<td>• Rash</td>
<td>• Hepatitis risk increases with age; underlying liver disease, heavy alcohol ingestion, or intravenous drug use; use of other potentially hepatotoxic drugs; and if pregnant or up to three months postpartum</td>
<td></td>
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<tr>
<td></td>
<td>• Hepatitis</td>
<td>• Pyridoxine (vitamin B6, 25 mg/day) may prevent peripheral neuropathy and should be used in patients who have chronic alcohol use, HIV, cancer, chronic renal or liver disease, malnutrition, diabetes or pre-existing peripheral neuropathy, or are pregnant or breastfeeding infants</td>
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<tr>
<td></td>
<td>• Peripheral neuropathy</td>
<td>• Lupus-like syndrome—may consider checking anti-histone antibody</td>
<td></td>
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<td></td>
<td>• Jaundice</td>
<td>• Aluminum-containing antacids reduce INH absorption</td>
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<td></td>
<td>• Persistent fatigue</td>
<td>• Acetaminophen toxicity can occur with concurrent INH use</td>
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<td></td>
<td>• Weakness</td>
<td>• Cimetidine, theophylline, phenytoin, carbamazepine, valproate, clopidogrel, disulfiram, and tizanidine levels may be increased with concurrent INH use. Measure serum concentrations of theophylline, phenytoin, carbamazepine, and valproate in patients receiving INH and adjust dosing if necessary, in consultation with prescribing providers</td>
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<td></td>
<td>• Arthralgia</td>
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<td></td>
<td>• Mild CNS effects including headache, poor memory or concentration, depression</td>
<td></td>
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<tr>
<td></td>
<td>• Acne</td>
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</tbody>
</table>

*Select patients may not need baseline labs done

Abbreviations Used: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CBC=complete blood count; CNS=central nervous system; HIV=human immunodeficiency virus; INH=isoniazid; LFTs=liver function tests; LTBI=latent tuberculosis infection; mg=milligrams; NNRTI=nonnucleoside reverse transcriptase inhibitors; PI=protease inhibitor; RIF=rifampin; RPT=rifapentine

For more information, check a drug interaction website (e.g., https://www.rxlist.com/drug-interaction-checker.htm)
CLINICAL MONITORING DURING LATENT TUBERCULOSIS INFECTION TREATMENT

While LTBI treatment regimens are generally well-tolerated, side effects and adverse reactions can occur and may negatively impact treatment adherence and completion. Patients on LTBI treatment are educated about the signs and symptoms of adverse drug reactions and the need for prompt cessation of treatment should such symptoms occur. Educational information and materials are provided in the patient’s preferred language and documented in the EMR.

Persons taking LTBI treatment are evaluated by monthly clinical monitoring until treatment completion and are evaluated more frequently if clinically indicated. (See Chapter 8: Clinical Monitoring and Follow-Up for Tuberculosis Treatment.)

Persons on monotherapy with RIF or INH who are at low risk for hepatotoxicity or who have started treatment and are tolerating it well may be candidates for monthly nursing follow-up visits, either in clinic or remotely, with referrals to a physician as clinically indicated. Persons on 3HP receive monthly physician evaluations until treatment completion; select patients may have monthly nursing follow-up at the physician’s discretion. The monthly monitoring plan is documented in the EMR.

Serum chemistries, CBC, LFTs, or other tests based on specific drugs are performed periodically as needed. Persons taking treatment for LTBI are monitored for signs or symptoms of adverse reactions, including hepatotoxicity, and managed accordingly. (See Figure 2.1: Latent Tuberculosis Infection (LTBI) Clinical Evaluation and Counseling and Figure 2.2: Monitoring for and Management of Hepatotoxicity during Treatment for Latent Tuberculosis Infection.)

Monthly LFTs are obtained for the patients with the following conditions:

- HIV infection
- Pre-existing liver disease (e.g., alcoholic hepatitis, cirrhosis)
- Viral hepatitis (e.g., hepatitis B or C)
- History of chronic alcohol ingestion or intravenous drug use
- Pregnant or postpartum (up to two to three months after delivery)
- Taking other drugs that may be hepatotoxic or interact with LTBI treatment
- Baseline abnormal LFTs

Mild adverse effects are managed by treating the symptoms without interrupting therapy; whereas, with more severe adverse effects, the offending drug(s) are discontinued and additional clinical and laboratory evaluation are conducted before attempting to restart treatment.
**FIGURE 2.1:** Latent tuberculosis infection (LTBI) clinical evaluation and counseling


---

Patient is eligible for taking LTBI treatment

Does the patient have risk factors for hepatotoxicity?*
- HIV infection
- Pre-existing liver disease (e.g., cirrhosis)
- Viral hepatitis (e.g., hepatitis B or C)
- Chronic alcohol ingestion or intravenous drug use
- Up to 2-3 months post-partum
- Starting treatment with two or more anti-TB drugs
- Baseline ALT/AST or total bilirubin abnormal
- Concomitant medications that are hepatotoxic or interact with LTBI treatment

---

Pregnant?

YES

Assess TB risk.
Is the patient:
- Living with HIV infection or other immunosuppression?
- A close contact of a person with TB?
- A documented new converter?

HIGHER

Check ALT/AST and bilirubin
- ALT/AST or bilirubin ≥ 3x ULN if symptomatic
- ALT/AST or bilirubin ≥ 5x ULN if asymptomatic

YES

Conduct clinical evaluation and consider hepatology referral

DEFER TREATMENT

NO

DEFER TREATMENT UNTIL 2-3 MONTHS POSTPARTUM

DECREASED RISK

INITIATE TREATMENT

---

NO

YES

---

*Age is a risk factor for hepatotoxicity with INH; consider baseline and periodic LFT monitoring monthly, every other month, or at 1, 3, and 6 months as clinically indicated.

**Abbreviations Used:** ALT=alanine aminotransferase; AST= aspartate aminotransferase; LFT=liver function test; LTBI=latest tuberculosis infection; TB=tuberculosis; ULN=upper limit of normal
**FIGURE 2.2:** Monitoring for and management of hepatotoxicity during treatment for latent tuberculosis infection (LTBI)


---

**Patient is currently taking LTBI treatment**

**Does the patient have risk factors for hepatotoxicity?**

- HIV infection
- Pre-existing liver disease (e.g., cirrhosis)
- Viral hepatitis (e.g., hepatitis B or C)
- Chronic alcohol ingestion or intravenous drug use
- Pregnant or up to 2-3 months post-partum
- Starting treatment with two or more anti-TB drugs
- Baseline ALT/AST or total bilirubin abnormal
- Concomitant medications that are hepatotoxic or interact with LTBI treatment

**YES**

- Check ALT/AST and total bilirubin at 2-4 weeks

**NO**

**Does the patient have symptoms of hepatotoxicity?**

- Fever
- Nausea
- Vomiting
- Abdominal pain
- Jaundice
- Unexplained fatigue

**YES**

- Conduct clinical evaluation; hepatology referral if indicated

**NO**

**CONTINUE TREATMENT**

**Check ALT/AST and total bilirubin**

**ALTERNATIVES**

- ALT/AST change of >3x baseline or increase in bilirubin
- **HOLD TREATMENT**

**HOLD TREATMENT**

- Conduct hepatitis screen:
  - IgM anti-HAV
  - HBsAg (if positive, check HBeAg and hepatitis B DNA)
  - IgM HBcAb
  - Anti-HCV (if positive, check HCV RNA)
  - Exclude other liver problems

**LFTs normal**

**HOLD TREATMENT**

- If on RIF:
  - Can rechallenge with RBT or
  - Can switch to INH

- If on INH:
  - Can rechallenge with INH or
  - Can switch to RIF

- If on INH and RPT:
  - Can switch to RIF

**LFTs abnormal**

**Check ALT/AST and total bilirubin**

**ALT/AST >3x ULN and symptomatic or ALT/AST > 5x ULN and asymptomatic**

**HOLD TREATMENT**

**Abbreviations:** ALT=alanine aminotransferase; AST=aspartate aminotransferase; HAV=hepatitis A virus; HBcAb=hepatitis B core antibody; HBeAg=hepatitis B core antigen; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INH=isoniazid; INR=international normalized ratio; LFT=liver function test; LTBI=latent tuberculosis infection; RIF=rifampin; RNA=ribonucleic acid; RPT=rifapentine; TB=tuberculosis; ULN=upper limit of normal

---

*Age is a risk factor for hepatotoxicity with INH; consider baseline and periodic LFT monitoring monthly, every other month, or at 1, 3, and 6 months as clinically indicated.

**When ALT< 2x ULN or at new baseline**

**LFTs normal**

**Patient is currently taking LTBI treatment**

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45 New York City Bureau of Tuberculosis Control Program Manual, 5th Edition
SPECIAL CONSIDERATIONS FOR LATENT TUBERCULOSIS INFECTION DIAGNOSIS AND TREATMENT DURING PREGNANCY

Patients at high risk of TB infection or for progressing to active disease if infected require TB testing during pregnancy. Routine testing for TB infection in all pregnant patients is not necessary, as pregnancy itself does not increase the risk for TB infection; however all pregnant patients should be screened for TB risk and tested accordingly. Either IGRA (preferred) or TST may be used to test patients with TB risk factors, both of which are safe and reliable during pregnancy. A TB risk assessment tool (see Appendix B: Tuberculosis Risk Assessment Tool) is used to identify pregnant patients at high risk for TB infection. Pregnant patients are evaluated for TB infection or disease as described below.

MEDICAL HISTORY AND PHYSICAL EXAMINATION

All pregnant patients with a positive test for TB infection are examined by a provider to rule out active TB disease and make recommendations for LTBI treatment. Medical evaluation includes:

- Medical history including TB risk factors, prior TB history and treatment, history of recent exposure to a person with infectious TB disease, and coexisting medical conditions (e.g., HIV or other immunosuppressive conditions, liver disease, hepatitis) and medications
- Social history including substance use (e.g., drug, alcohol, tobacco), risk factors for HIV, homelessness
- Physical examination
- Laboratory tests as indicated
- Test for HIV infection during pregnancy, unless there is prior documentation of a positive HIV test or recent negative test done as part of their obstetrical care

CHEST RADIOGRAPH

A CXR is obtained to assist with ruling out active TB for any pregnant patient with a positive IGRA or TST. The CXR is prioritized for patients with either of the following, even during the first trimester of pregnancy:

- Symptoms suggestive of TB disease (e.g., fever, cough, chills, night sweats, chest pain)
- HIV infection or other immunosuppressive conditions

For pregnant patients with recent close contact to a person with infectious TB, CXR may be obtained in the first trimester based on epidemiologic risk (e.g., evidence of TB transmission among contacts) and clinical judgment. Pregnant patients with HIV infection or other immunosuppressive conditions who are a recent close contact to a person with infectious TB require a CXR in the first trimester even if the IGRA or TST is negative. (See Figure 2.2: Evaluation of Pregnant Patients at Risk for Tuberculosis.) For all other pregnant patients with a positive test for TB infection, including a documented IGRA or TST conversion within two years, a CXR can be obtained after the first trimester.
A lead shield must be used to cover the abdomen and pelvis for all pregnant patients receiving a CXR. Pregnant patients may be hesitant to receive a CXR due to concerns about radiation exposure. The amount of radiation exposure from a CXR is very small (0.1 millisievert [mSv], equivalent to 2.4 days of natural background radiation). The risk of untreated active TB disease in a pregnant patient and the possible consequences of congenital TB in the infant far outweigh the theoretical risk from a CXR.

If the CXR is abnormal, prompt evaluation is required to rule out active TB disease, including collecting three sputum samples for acid-fast bacilli (AFB) smear and culture, determining the need for empiric therapy, and reporting the patient to BTBC as potentially having active TB (Class V, high or low). (See Chapter 3: Diagnosis of Tuberculosis Disease in Adults.)

If the CXR is normal, LBTI treatment initiation is based on the individual’s risk factors as described below.

**TREATMENT FOR LATENT TUBERCULOSIS INFECTION**

The need to treat active TB disease during pregnancy is well-established. The decision to treat LTBI in pregnant patients must weigh the risk of developing active TB disease against the possible risk of hepatotoxicity from the medications. LTBI therapy is initiated according to the stratification outlined below.

**DURING THE FIRST TRIMESTER:**

Persons with HIV infection or other immunosuppressive conditions may be considered for treatment during the first trimester. If, at the provider’s discretion, treatment is delayed until after the first trimester, close observation for development of symptoms consistent with active TB disease is required.

**AFTER THE FIRST TRIMESTER:**

Persons with documented IGRA or TST conversion in the past two years may be considered for treatment after the first trimester. Close contacts may also be treated after the first trimester. However, if they are a recent close contact of persons with infectious TB, treatment may be initiated in the first trimester based on epidemiological risk factors (e.g., evidence of transmission to contacts) and clinical judgment.

**POST-PARTUM:**

For all other pregnant patients, LTBI treatment is started two to three months after delivery, including those with population risk or radiographic evidence of old, healed TB disease, once active TB has been ruled out.

**REGIMENS FOR PATIENTS WHO BECOME PREGNANT WHILE TAKING TREATMENT FOR LATENT TUBERCULOSIS INFECTION**

In general, LTBI treatment is discontinued in patients who become pregnant, unless they have HIV infection or are otherwise immunosuppressed, were a recent converter when LTBI treatment was started, or were a contact to a person with infectious TB disease. If discontinued, to reduce the risk of peripartum hepatitis, LTBI treatment is restarted two to three months after delivery. When treatment is restarted, a full course is given (e.g., previous doses ignored).
FIGURE 2.3: Evaluation of pregnant persons at risk for tuberculosis (TB)

1. A CXR may be obtained in any person with HIV or other immunosuppressive conditions at the discretion of the provider, even if the TB test is negative; 2. Contacts who have a negative test for TB infection require a repeat test after the window period (8 weeks after last exposure ended); 3. Based on epidemiological risk factors and clinical judgment, CXR may be recommended in the 1st trimester for pregnant contacts without HIV infection; 4. Elevated alkaline phosphatase is not an indication to hold LTBI treatment as it may be due to placental origin; 5. Treatment for LTBI includes either RIF or INH. Labs include CBC and LFTs if patient is taking RIF, and only LFTs if giving INH. INH with rifapentine is contraindicated in pregnancy.

Abbreviations Used: CBC=complete blood count; CXR=chest radiograph; HIV=human immunodeficiency virus; IGRA=interferon gamma release assay; INH=isoniazid; LFT=liver function test; LTBI=latent tuberculosis infection; RIF=rifampin; TST= tuberculin skin test
INH has been commonly used for LTBI treatment in pregnant patients. Although INH readily crosses the placental barrier, it is not teratogenic, even when given during the first trimester of pregnancy. Pyridoxine (vitamin B6) is given to pregnant patients taking INH to prevent peripheral neuropathy.

RIF crosses the human placenta and appears in cord blood. Reports of the use of RIF during pregnancy generally involve patients on multiple TB drug therapy, so the sole contribution of RIF to maternal and fetal outcomes is difficult to determine. Though there have not been any controlled data on the use of RIF in pregnancy, extensive use of RIF for the treatment of TB disease in pregnant patients suggests that it is safe to use in most circumstances.

For pregnant persons who were exposed to persons with multidrug-resistant TB (MDR-TB), providers can call the TB HOTLINE at 844-713-0559 for consultation. LTBI treatment may be delayed in such cases to avoid possible adverse effects of the medications on the developing fetus. In such cases, pregnant persons receive close clinical follow-up with initial CXR and repeat CXR at regular intervals or if TB symptoms develop (see Special Considerations for Contacts of Persons with Multidrug-Resistant Tuberculosis).

BREASTFEEDING

Breastfeeding can be initiated or continued during LTBI treatment of the mother. The drug concentrations in breast milk are typically too low to create toxicity in the infant. However, infants should be monitored for signs of hepatotoxicity or peripheral neuritis. Similarly, the amount of LTBI medication provided by breast milk is inadequate for LTBI treatment (if relevant) of the infant. Infants requiring INH treatment must also receive supplemental vitamin B6.

SPECIAL CONSIDERATIONS FOR DIAGNOSIS AND TREATMENT OF LATENT TUBERCULOSIS INFECTION IN INFANT AND CHILD CONTACTS

All child contacts to persons with infectious TB require evaluation to determine if they have TB infection or disease. BTBC prioritizes the evaluation of children younger than five years of age, as they are at high risk for TB infection and, if infected, progression to TB disease.

MEDICAL EVALUATION, TESTING FOR TUBERCULOSIS INFECTION, AND CHEST RADIOGRAPH

All child contacts to persons with infectious TB receive an evaluation, including the following:

- Medical history
- Physical examination
- Baseline test for TB infection
  - TST is used for children younger than two years of age
  - IGRA is preferred for children two years of age and older
- CXR
• Children five years of age or older: posteroanterior (PA) view, if test for TB infection is positive; other views (e.g., lateral, lordotic) are obtained as clinically indicated.

• Children younger than five years of age require CXR regardless of test for TB infection result and require both PA and lateral views.

For infants younger than six months of age, providers may use their discretion with respect to performing a TST. A negative TST is not considered reliable until infants are at least six months of age due to their immature immune response. All infant and child contacts with a negative baseline TST receive a repeat test when they are at least six months of age and when at least eight weeks have passed since their last exposure to a person with active TB disease. All other aspects of the evaluation are as noted above.

If children younger than five years of age live in the same household as a person with infectious TB disease, the infectious patient and children are kept separated until one of the following conditions are met:

• The person with infectious TB is taking appropriate treatment and has demonstrated an adequate clinical response to treatment (e.g., AFB-negative smears and improvement in symptoms), or

• The child has started LTBI treatment, including window period prophylaxis.

If the index patient remains infectious despite initiation of therapy (e.g., due to extensive MDR-TB), BCG vaccine can be considered for the child if the test for TB infection is negative (least desirable option). BTBC only uses BCG vaccine for children who are contacts to MDR-TB patients. (See Appendix D: The Use of Bacille Calmette-Guérin Vaccine.)

WINDOW PERIOD PROPHYLAXIS OF INFANT AND CHILD CONTACTS

If active TB disease has been ruled out, treatment to prevent TB is initiated during the window period, even if the first IGRA or TST is negative among:

• Contacts younger than five years of age

• Contacts between five to 15 years of age, at the provider’s discretion

Window prophylaxis is discontinued if the post-window period IGRA or TST remains negative and the patient:

• Does not have HIV infection or other immunosuppressive conditions

• Is older than six months of age

Some providers may decide to complete a full course of preventive treatment if only a few months are remaining.

A full course of LTBI treatment is completed if the initial CXR is normal and:

• The baseline or post-window period IGRA or TST is positive
• The baseline or post-window period IGRA or TST is negative, but the patient has HIV infection or other immunosuppressive conditions
• There is ongoing exposure to a person with infectious TB or evidence of TB transmission in the household, at the provider’s discretion

As with adults, short-course treatment of LTBI is preferred for eligible infants and children whenever feasible. In addition, choice of LTBI treatment depends on DST results of the isolate obtained from the infectious person who is believed to have infected the child.

›› Use RIF for any child, even those younger than two years of age, when the isolate is susceptible to RIF.
›› Use 3HP in children older than two years of age, when the isolate is susceptible to both INH and RIF.
›› Use INH when the isolate is susceptible to INH and other regimens either cannot be tolerated or are contraindicated.
›› If the isolate demonstrates multi-drug resistance, base the regimen on DST results.

Infants are likely to require frequent dose adjustments while on window prophylaxis due to their rapid weight gain. Avoid using sorbitol-containing medications (e.g., INH syrup formulation) since these may cause diarrhea and decrease the parent’s motivation to continue the child’s prophylaxis. As an alternative to syrup, crush INH tablets and mix with small amounts of soft food (e.g., yogurt, pudding, jam). Based on the dosing, RIF may need to be compounded; for infant and child contacts being seen at NYC Health Department TB clinics, this service is available through the clinic pharmacy by prescription.

SPECIAL CONSIDERATIONS FOR CONTACTS OF PERSONS WITH MULTIDRUG-RESISTANT TUBERCULOSIS

To date, there have not been any published, controlled trials of LTBI treatment after exposure to a person with MDR-TB. Thus treatment protocols for close contacts to persons with MDR-TB are largely based on empirical data and must be individualized based on the drug susceptibility patterns of the index patient’s MDR-TB strain. There is well known toxicity with pyrazinamide (PZA)-containing regimens, as well as poor tolerability of most second-line drugs used to treat MDR-TB. The length of treatment may be influenced by age, immune status, and other epidemiological risk factors (e.g., evidence of transmission to other contacts). The decision of whether to provide LTBI treatment for contacts to persons with MDR-TB is therefore complex and must be made in consultation with BTBC experts.

Many experts recommend treatment of such contacts with a fluoroquinolone (FQN) such as levofloxacin (LFX) or moxifloxacin (MFX) if the index patient’s MDR-TB strain is sensitive to it. FQNs are recommended even in children since the potential benefit of preventing MDR-TB outweighs the potential risk of toxicity.

Persons receiving two or more anti-TB drugs receive baseline chemistry including glucose and creatinine, LFTs, CBC, and hepatitis profile, as well as HIV testing.
TREATMENT OPTIONS

Current LTBI treatment options for close contacts of persons with MDR-TB include the following:

1. **FQN monotherapy**: It is BTBC policy to use this option if the index patient’s TB isolate is susceptible to one or more FQN.
   - Use LFX or MFX in adults.
   - BTBC prefers the use of LFX in children due to a greater body of supporting literature and availability of a liquid formulation of the medication.

2. **Two drugs to which the index patient’s TB isolate is susceptible**.
   - A FQN plus a second drug; ethambutol (EMB) is preferred; other options include: ethionamide (ETA), cycloserine (CS), para-aminosalicylic acid (PAS).
     - Use of EMB requires monitoring of vision.
     - Avoid PZA if possible due to potential hepatotoxicity.
     - May use another two-drug regimen for children and adults if there is resistance to FQN, (i.e., pre-extensively drug-resistant TB [pre-XDR-TB]).

3. **No treatment with close monitoring for two years**.
   - Not preferred for patients with a recent documented IGRA or TST conversion or a high risk for progression to active TB disease.
   - Patient requires clinical evaluation and CXR at four, eight, 12, 18, and 24 months.

If the contact is treated, the duration of treatment ranges from six to 12 months. Contacts are treated for nine to 12 months if they either have HIV infection or another immunosuppressive condition or are children younger than five years of age. For patients who are immunosuppressed, consideration may be given to use of a single FQN for a longer duration (nine to 12 months) OR the use of two drugs (for six to 12 months). For all treatment regimens, providers discuss the risks/benefits/potential side effects of the medications with the patient and document in the patient’s EMR.

BCG vaccine is rarely used and is only considered for infants (younger than one year of age) exposed to an infectious person with MDR-TB. (See Special Considerations for Latent Tuberculosis Infection Diagnosis and Treatment of Infant and Child Contacts and Appendix D: The Use of Bacille Calmette-Guérin Vaccine.)

SPECIAL CONSIDERATIONS FOR TREATMENT OPTIONS OF PERSONS WITH RADIOGRAPHIC EVIDENCE OF OLD, HEALED TUBERCULOSIS

For asymptomatic persons with a positive IGRA or TST reaction ≥ 5 mm, along with a CXR that shows fibrotic lesions suggestive of old, healed TB disease, the classification and treatment decision is based on symptoms, clinical exam, and prior LTBI or TB disease treatment. Three sputa are obtained for AFB smear and culture. For patients with an abnormal CXR consistent with TB, a classification of Class V is given if three sputa are collected. If sputa are AFB smear-positive, active TB must be ruled out. (See Chapter 3:
Diagnosis of Tuberculosis Disease in Adults.) If sputa are AFB smear-negative and there is no evidence of adequate prior treatment for active TB disease, treatment may be started with INH and RIF, along with PZA and EMB for two months. The patient is classified as Class V (high). Pyridoxine is given to prevent peripheral neuropathy from INH. Monthly clinical follow-up is required. This approach has several advantages: it can be used to treat patients who may have INH-resistant organisms and it allows patients to start treatment at the first medical visit, rather than waiting for the final result of sputum cultures.

RECLASSIFICATION OF THE PATIENT

If sputum cultures are positive for *M. tuberculosis*, or if sputum cultures are negative for *M. tuberculosis* and if the follow-up CXR at two months shows improvement with empiric treatment, or if the patient responds clinically to medications, providers reclassify the individual as Class III and treat for active TB disease.

If all sputum cultures are negative for *M. tuberculosis* by two months, assess the follow-up CXR:

- If the CXR shows no change, the lesions are presumed to be inactive. Reclassify the patient as having old TB disease (Class IV) and treat as follows:
  - If the patient has no history of TB treatment and does not come from an area with high rates of drug-resistant TB, continue with two additional months of INH and RIF only.
  - If there is a history of TB treatment or the patient comes from an area with high rates of drug-resistant TB, continue all four drugs for an additional two months.
  - Patients with extensive fibrotic disease, HIV infection, or other immunosuppression may be candidates for an additional four months of treatment per provider’s discretion.
  - Other diagnoses should also be considered as clinically indicated and the patient may require referral to a pulmonologist.

If clinical symptoms or CXR show improvement, the lesions presumably were active. Reclassify the patient as having culture-negative active TB disease (Class III) and treat as follows:

- If the patient has no history of TB treatment and does not come from an area of high rates of drug-resistant TB, continue with two additional months of INH and RIF only. Some physicians may continue all four drugs if the patient is tolerating the regimen, due to high rates of INH resistance worldwide.
- If there is a history of TB treatment, continue all four drugs for an additional two months.

After four months of therapy, an end-of-treatment CXR is obtained, which will serve as a baseline for future reference. Some patients classified as having old TB disease (Class IV) or high suspicion of TB (Class V) may show improvement on the four-month CXR. These patients are reclassified as having culture-negative active TB disease (Class III).

If there is low clinical suspicion of active TB disease (Class V, low), and initial AFB smears are negative, an additional option is not to treat until the cultures are finalized. If cultures are negative, there are three
possible regimens for LTBI for persons with evidence of old, healed TB disease and no history of treatment: 4R, 3HP, or 6H.

**CASE MANAGEMENT OF PATIENTS WITH LATENT TUBERCULOSIS INFECTION**

Patients with LTBI do not feel sick and may face challenges in trying to complete therapy. Monthly clinical monitoring evaluations are scheduled for all patients receiving LTBI treatment. In addition, contacts to persons with infectious TB who are being treated for LTBI at a NYC Health Department TB clinic are assigned a case manager within one month of starting LTBI treatment. Various techniques are utilized to facilitate treatment adherence including: educating patients about the importance of adherence to treatment and about potential side effects, discussing barriers to adherence, and using incentives and enablers when feasible. The patient’s preferred language is used for these discussions. Patients are referred for assistance with social services as needed.

To promote treatment adherence and success, DOT is mandatory for persons receiving intermittent LTBI treatment with biweekly INH. DOT is preferred, when possible, for patients receiving 3HP. NYC Health Department TB clinics provide numerous DOT options. In-person DOT is offered to household contacts at the same time the person with infectious TB disease receives DOT. Video DOT has been found to be both cost saving and patient-centered. Video DOT (live [LVDOT] or recorded [RVDOT]) is offered to patients on the 3HP regimen to accommodate their schedules and preferences. Educational materials are provided in the patient’s preferred language.

**MANAGING INTERRUPTIONS IN TREATMENT AND DETERMINING COMPLETION OF THERAPY**

Decisions regarding completion of treatment are based on the total number of medication doses administered, as well as on the duration of therapy. (See Table 2.8: Recommended Drug Regimens and Dosages for Treatment of Latent Tuberculosis Infection in Adults and Children.)

- Patients taking RIF must complete 120 doses within six months.
- Patients taking 3HP must complete ≥ 11 weekly doses within 16 weeks.
- If there are interruptions in treatment with INH, patients can be given two to three additional months to complete the regimen.
- If there is a gap greater than three months, the entire course of INH treatment is restarted.
- Children and adults without HIV infection, other immunosuppressive conditions, or other medical risk factors can be considered to have completed treatment after six or more months of INH.

When treatment has been interrupted for more than three months, patients are reevaluated to rule out active TB disease. Patients with lapses in therapy, but who are still able to complete the recommended number of doses in the allotted time frame are encouraged to complete therapy. Patients who do not complete their LTBI treatment within the allotted time frame are evaluated to determine whether or not to restart treatment. If the decision is made to re-treat the patient, the entire LTBI regimen is restarted (e.g., previous
doses are not counted). Specific factors to consider when determining whether to restart treatment include the following:

- Individual’s risk for developing active TB disease
- Total number of doses of LTBI treatment administered
- Time elapsed since the last dose of treatment for LTBI
- Patient adherence issues (e.g., previous attempts at completion, willingness to continue)

Patients are encouraged to adhere to the LTBI treatment regimen; however, if a patient has failed three attempts to complete treatment, further attempts may not be indicated. Patients who are at high risk of progression to TB disease (e.g., contacts of persons with infectious TB disease, persons with HIV infection) are advised to return to the clinic if symptomatic to rule out active TB disease.

**DISCHARGE OF THE PATIENT FROM CLINIC**

Patients receiving LTBI treatment generally may be discharged from NYC Health Department TB clinic care when they return for the final month’s supply of medication (e.g., after the third month for patients taking a four-month treatment regimen). The provider performing the monthly evaluation notes in the EMR that the patient:

- Received enough medication for the last month of LTBI treatment; and
- Was discharged from the NYC Health Department TB clinic.

Contacts of persons with MDR-TB who are not treated for LTBI are recommended to have follow-up for two years, including clinical and radiological examinations at four, eight, 12, 18, and 24 months.

Documentation of the test for TB infection results, CXR results, and the LTBI treatment completion is provided to the patient in writing and patients are informed that repeat testing and treatment is generally not indicated except in specific circumstances (e.g., contact to person with infectious TB). The patient is educated to return to the NYC Health Department TB clinic if they develop symptoms consistent with TB.

**RE-TREATMENT OF LATENT TUBERCULOSIS INFECTION**

Repeat treatment for LTBI in the future should be considered for persons who have subsequently been in close contact with a person with infectious TB disease, including persons who:

- Have HIV infection, are otherwise immunosuppressed, or are at risk for progressing to TB disease
- Are younger than 18 years of age
- Do not have HIV infection, but had close contact to a person with highly infectious TB (e.g., presence of secondary cases or documented conversions of tests for TB infection in other contacts)

When LTBI treatment is repeated, a full course is given based on the assumption that exogenous reinfection may have occurred.
SUMMARY

Diagnosis and treatment of persons with LTBI is essential, particularly among those at highest risk for progression to active TB disease. Among eligible patients, BTBC prefers the use of an IGRA to detect TB infection and short-course regimens to treat LTBI. Routine follow-up and monitoring are used to facilitate treatment adherence and completion and ensure optimal health outcomes. Appropriate LTBI diagnosis and treatment are vital components of BTBC’s TB prevention and elimination efforts.
KEY SOURCES


Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf


