

# LATENT TUBERCULOSIS INFECTION

## A GUIDE FOR PRIMARY HEALTH CARE PROVIDERS



Centers for Disease  
Control and Prevention  
National Center for HIV/AIDS,  
Viral Hepatitis, STD, and  
TB Prevention



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# LIST OF ABBREVIATIONS

**AFB**

acid-fast bacilli

**AIDS**

acquired immunodeficiency syndrome

**ALT**

alanine aminotransferase

**ART**

antiretroviral therapy

**AST**

aspartate aminotransferase

**ATS**

American Thoracic Society

**BCG**

bacille Calmette-Guérin

**CDC**

Centers for Disease Control and Prevention

**DOT**

directly observed therapy

**FDA**

Food and Drug Administration

**HIV**

human immunodeficiency virus

**IFN- $\gamma$** 

interferon-gamma

**IGRA**

interferon-gamma release assay

**INH**

isoniazid

**LTBI**

latent tuberculosis infection

**MDR TB**

multidrug-resistant tuberculosis

**MMWR**

Morbidity and Mortality Weekly Report

**NTCA**

National Tuberculosis Controllers Association

**PPD**

purified protein derivative

**QFT-Plus**

QuantiFERON<sup>®</sup>-TB Gold Plus

**RIF**

rifampin

**RPT**

rifapentine

**SAT**

self-administered therapy

**TB**

tuberculosis

**TNF-alpha**

tumor necrosis factor-alpha

**T-Spot**

T-SPOT<sup>®</sup>.TB test

**TST**

tuberculin skin test

**USPSTF**

U.S. Preventive Services Task Force

**WHO**

World Health Organization

# INTRODUCTION

Tuberculosis (TB) is caused by a bacterium called *Mycobacterium tuberculosis* (*M. tuberculosis*). Not everyone infected with TB bacteria becomes sick. As a result, two TB-related conditions exist: latent TB infection (LTBI) and TB disease. It is estimated that up to 13 million people in the United States (U.S.) have LTBI. People with LTBI are infected with *M. tuberculosis*, but they do not have TB disease. People with LTBI do not have signs and symptoms of TB disease, and they cannot spread *M. tuberculosis* to others. While not everyone with LTBI will develop TB disease, about 5–10% of infected people will develop TB disease over their lifetimes if not treated for LTBI.

Progression from untreated LTBI to TB disease accounts for approximately 80% of U.S. TB cases. Identifying and treating people with LTBI is essential for controlling and eliminating TB disease in the U.S. LTBI treatment is effective for preventing TB disease. Primary care providers play a key role in achieving the goal of TB elimination because of their access to populations at high risk for TB.

This guide is intended for primary care providers who care for individuals and populations who may be at risk for infection with *M. tuberculosis*. **This document is not meant to be used as a substitute for CDC guidelines, but rather as a ready and useful reference.** For detailed information regarding the diagnosis and treatment of LTBI, please refer to the following CDC guidelines:

- [Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020](#)
- [American Thoracic Society/Infectious Diseases Society of America/ Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children](#)

Further guidance can be found in the **References** section, **Appendix F**, and **Appendix G**. Clinicians should contact their state and local TB control offices for additional information on diagnosing and treating LTBI. Contact information can be located on the [State TB Control Offices website](#).

# TARGETED TESTING FOR TUBERCULOSIS

Targeted testing is an essential TB prevention and control strategy that is used to identify and treat individuals with LTBI who are at high risk for developing TB disease. Identifying individuals with LTBI is essential to the goal of TB elimination because treatment of LTBI can prevent infected individuals from developing TB disease and thereby stop the further spread of TB to others.

The CDC and the U.S. Preventive Services Task Force (USPSTF) recommend testing people who are at increased risk for TB infection. During routine patient evaluations, health care providers should identify individuals who are at high risk for TB and test them for LTBI. A few simple questions will help health care providers assess a patient's risk (see **Appendix A** for a sample risk assessment tool). TB testing activities should be done only when there is a plan for follow-up care to evaluate and treat all individuals diagnosed with LTBI or TB disease.

People who are at low risk for LTBI generally should not be tested. Testing in low-risk populations can take resources away from other important activities. Also, positive test results in low-risk populations are sometimes inaccurate.

## Identifying People at High Risk for TB

Generally, groups at high risk fall into two broad categories (**Table 1**):

1

People who are at high risk for exposure to or infection with *M. tuberculosis*

2

People who are at high risk for developing TB disease once infected with *M. tuberculosis*



**TABLE 1.**  
**Groups at High Risk for TB Infection and TB Disease**

<b>People at High Risk for Exposure to or Infection with <i>M. tuberculosis</i></b>	<b>People at High Risk for Developing TB Disease after Infection with <i>M. tuberculosis</i></b>
<ul style="list-style-type: none"> <li>• Contacts of people known or presumed to have infectious TB disease</li> <li>• People who were born in or who frequently travel to countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala (see <b>Appendix B</b>)</li> <li>• People who currently live or used to live in large group settings where TB is more common, such as homeless shelters, prisons, jails, or nursing homes</li> <li>• Employees of high-risk congregate settings</li> <li>• Health care workers who serve patients with TB disease</li> <li>• Populations defined locally as having an increased incidence of LTBI or TB disease, including medically underserved populations, low-income populations, or people who abuse drugs or alcohol</li> <li>• Infants, children, and adolescents exposed to adults who are at increased risk for LTBI or TB disease</li> </ul>	<ul style="list-style-type: none"> <li>• People living with HIV</li> <li>• Children younger than 5 years of age</li> <li>• People recently infected with <i>M. tuberculosis</i> (within the last 2 years)</li> <li>• People with a history of untreated or inadequately treated TB disease</li> <li>• People who are receiving immunosuppressive therapy such as tumor necrosis factor (TNF)-alpha antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation</li> <li>• People with silicosis; chronic renal failure; leukemia; or cancer of the head, neck, or lung</li> <li>• People with diabetes mellitus</li> <li>• People who have had a gastrectomy or jejunioileal bypass</li> <li>• People who have low body weight</li> <li>• People who use substances (such as injection drug use)</li> <li>• Populations defined locally as having an increased incidence of disease due to <i>M. tuberculosis</i>, including medically underserved and low-income populations</li> </ul>

# DIAGNOSIS OF LATENT TB INFECTION (LTBI)

The diagnosis of LTBI is based on information gathered from the medical history, a TB test (i.e., a TB blood test [interferon-gamma release assay {IGRA}] or a tuberculin skin test [TST]), a chest radiograph, a physical examination, and sputum examinations in certain circumstances. TB disease must be excluded before initiating treatment for LTBI, because failure to do so may result in inadequate treatment and development of drug resistance. Key differences between LTBI and TB disease are listed in **Table 2**.

**TABLE 2.**  
**Differentiating Between LTBI and TB Disease**

Latent TB Infection (LTBI)	TB Disease
<ul style="list-style-type: none"><li>• No symptoms or physical findings suggestive of TB disease</li><li>• TB blood test or TST result usually positive</li><li>• Chest radiograph is typically normal</li><li>• If done, respiratory specimens are smear and culture negative</li><li>• Cannot spread TB bacteria to others</li><li>• Should consider treatment for LTBI to prevent TB disease</li></ul>	<ul style="list-style-type: none"><li>• Symptoms may include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite</li><li>• TB blood test or TST result usually positive</li><li>• Chest radiograph is usually abnormal, but may be normal in people with advanced immunosuppression or extrapulmonary TB disease</li><li>• Respiratory specimens are usually smear and/or culture positive, but may be negative in people with extrapulmonary TB disease or minimal/early pulmonary TB disease</li><li>• Can spread TB bacteria to others</li><li>• Needs treatment for TB disease</li></ul>



# Tests for TB Infection

Currently, the available methods of testing for *M. tuberculosis* infection are the TB blood tests (interferon-gamma release assays [IGRAs]) and the Mantoux tuberculin skin test (TST).



## TB Blood Tests (Interferon-Gamma Release Assays [IGRAs])

An IGRA is a type of blood test that is used to determine if a person is infected with *M. tuberculosis* by measuring the immune response to TB proteins in whole blood. Specimens are mixed with peptides that simulate antigens derived from *M. tuberculosis* and controls. In most people infected with *M. tuberculosis*, the white blood cells recognize the simulated antigens and release interferon-gamma (IFN- $\gamma$ ).

There are two U.S. Food and Drug Administration (FDA) approved TB blood tests commercially available in the U.S.:

- QuantiFERON®-TB Gold Plus (QFT-Plus)
- T-SPOT®.TB test (T-Spot)

A TB blood test should **not** be performed on a person who has written documentation of either a previous positive TB test result (TB blood test or TST) or treatment for TB disease.

See **Table 3** for advantages and limitations of TB blood tests.

**TABLE 3.**  
**Advantages and Limitations of TB Blood Tests**

Advantages of TB Blood Tests	Limitations of TB Blood Tests
<ul style="list-style-type: none"><li>• Requires only one patient visit to conduct the test</li><li>• Does not cause booster phenomenon (see <i>Special Considerations in Testing for TB Infection</i>)</li><li>• Not subject to the biases and errors associated with TST placement and reading</li><li>• Results can be available within 24 hours</li><li>• Unaffected by the bacille Calmette-Guérin (BCG) vaccine and most nontuberculous mycobacteria (NTM)</li></ul>	<ul style="list-style-type: none"><li>• Blood samples must be processed within 8 to 32 hours after collection</li><li>• Errors in collecting or transporting blood specimens or in running and interpreting the test can decrease the accuracy of TB blood tests</li><li>• Tests may be expensive</li></ul>

## Interpretation of TB Blood Test Results

Interpretation of TB blood test results depends on the test being used. QFT-Plus results are based on the amount of IFN- $\gamma$  that is released in response to the *M. tuberculosis* antigens and control substances. T-Spot results are based on the number of IFN- $\gamma$  producing cells (spots) produced. Laboratories should provide both the qualitative and quantitative results.

- Qualitative results are reported as positive, negative, indeterminate, invalid, or borderline (**Table 4**).
- Quantitative results are reported as numerical values that include responses to the TB antigen and two controls, nil and mitogen. Quantitative results may be useful for clinical decision-making in individual cases, in combination with risk factors.

**TABLE 4.**  
**Interpretation of TB Blood Test Results**

TB Blood Test Result	Interpretation
<b>Positive</b>	<i>M. tuberculosis</i> infection likely.
<b>Negative</b>	<i>M. tuberculosis</i> infection unlikely, but cannot be excluded, especially if <ol style="list-style-type: none"><li>1. Patient has signs and symptoms consistent with TB disease.</li><li>2. Patient has a high risk for developing TB disease once infected with <i>M. tuberculosis</i> (e.g., the patient is immunosuppressed).</li></ol>
<b>Indeterminate (QFT-Plus only) or Invalid (T-Spot only)</b>	The test did not provide useful information about the likelihood of <i>M. tuberculosis</i> infection. Repeating a TB blood test or performing a TST may be useful.
<b>Borderline (T-Spot only)</b>	Repeating a TB blood test or performing a TST may be useful.



## Tuberculin Skin Test (TST)

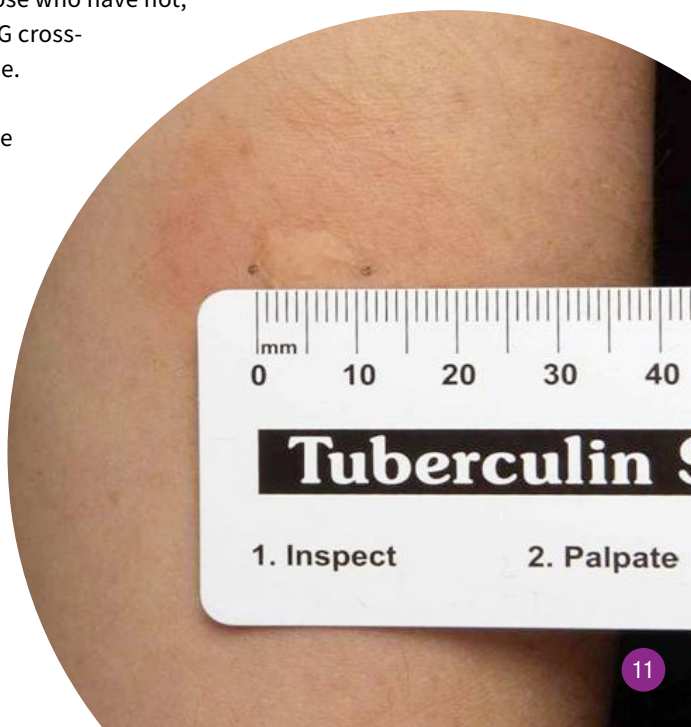
The Mantoux tuberculin skin test (TST) is also called the TB skin test. The TST is used to determine if a person has been infected with *M. tuberculosis*. If a person is infected, a delayed-type hypersensitivity reaction is detectable 2–8 weeks after infection. The skin test is administered intradermally using the Mantoux technique by injecting 0.1 ml of 5 tuberculin units of purified protein derivative (PPD) solution. The reading and interpretation of TST reactions should be conducted within 48–72 hours after administration. For more information about tuberculin skin testing, visit the CDC website for additional resources (see [Resources](#)) and refer to [Appendix C](#).

The TST should not be performed on a person who has written documentation of a previous positive TB test result (TB blood test or TST) or treatment for TB disease.

### Interpretation of Tuberculin Skin Test Reactions

Interpretation of TST results is based on the measurement of the reaction in millimeters (mm), the person's risk of acquiring TB infection, and the risk of progression to disease if infected ([Table 5](#)). A TST that was not measured and recorded in mm of induration must be repeated. Interpretation of the TST result is the same for people who have had BCG vaccination as it is for those who have not, because a majority of BCG cross-reactivity wanes with time.

TST results should only be read by a trained health care professional. Training is essential for health care professionals to gain proficiency in the administration and interpretation of the TST.



**TABLE 5.**  
**Interpretation of Tuberculin Skin Test (TST) Reactions**

**5 or more millimeters**

A TST reaction of **≥5 mm** of induration is considered positive for:

- People living with HIV
- Recent contacts of people with infectious TB
- People with chest x-ray findings suggestive of previous TB disease
- People with organ transplants
- Other immunosuppressed patients (e.g., patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone or those taking TNF-alpha antagonists)

**10 or more millimeters**

A TST reaction of **≥10 mm** of induration is considered positive for:

- People born in countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala
- People who abuse drugs
- Mycobacteriology laboratory workers
- People who live or work in high-risk congregate settings (e.g., nursing homes, homeless shelters, or correctional facilities)
- People with certain medical conditions that place them at risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, or certain intestinal conditions)
- People with a low body weight (<90% of ideal body weight)
- Children younger than 5 years of age
- Infants, children, and adolescents exposed to adults in high-risk categories

**15 or more millimeters**

A TST reaction of **≥15 mm** of induration is considered positive for:

- People with no known risk factors for TB

Although TB testing activities should generally be targeted towards groups or people at risk, certain individuals may be required to have testing for employment or school attendance independent of risk. CDC and the American Thoracic Society (ATS) do not recommend a testing approach that is independent of a risk assessment.



## Selecting a Test to Detect TB Infection

Health care providers are encouraged to use TB blood tests to screen for LTBI. There are a few preferences and special considerations when determining which test to use.

- TB blood tests are the preferred method of testing for the following:
  - Groups of people who might be less likely to return for TST reading and interpretation (e.g., homeless people or drug users)
  - People who have received the BCG vaccine
  - People who are likely to be infected with *M. tuberculosis* and are at a low to intermediate risk of progression to TB disease
  - People who are unlikely to be infected with *M. tuberculosis* (note: those who are unlikely to be infected generally should not be tested for TB; a confirmatory test is recommended if the initial test is positive in people unlikely to be infected)
- Current U.S. guidelines suggest the TST as the recommended method of testing for children younger than 5 years of age while noting that some experts use TB blood tests in younger children. Clinicians may also choose to consult the American Academy of Pediatrics (AAP) guidance on the use of the TB blood test in children.

In general, using either a TB blood test or a TST is acceptable medical and public health practice. Routine testing with both TST and TB blood tests is **NOT** recommended; however, there are certain situations where results from both tests may be useful (See **Appendix D**).

# Special Considerations in Testing for TB Infection

## Bacille Calmette-Guérin (BCG) TB Vaccine

In many parts of the world where TB is common, the BCG vaccine is used to protect infants and young children from serious, life-threatening disease (specifically miliary TB and TB meningitis). The World Health Organization (WHO) recommends that the BCG vaccine be administered during infancy in TB endemic countries. However, BCG is not generally recommended for use in the U.S. because of the low risk of infection with *M. tuberculosis*, the variable effectiveness of the vaccine against adult pulmonary TB, and the vaccine's potential interference with TST reactivity. The BCG vaccine should be considered in consultation with a TB expert only for select individuals who meet specific criteria.

The BCG vaccine may cause a false-positive TST reaction. There is no reliable way to distinguish a positive TST reaction caused by BCG vaccination from a reaction caused by true TB infection. When using the TST, people who have been vaccinated with BCG should always be further evaluated for LTBI or TB disease as if they were not vaccinated with BCG. TST reactivity caused by BCG vaccine generally wanes with the passage of time, but periodic skin testing may prolong (boost) reactivity in vaccinated people. TST reactions should be interpreted based on risk stratification regardless of BCG vaccination history.

TB blood tests use *M. tuberculosis* specific antigens that do not cross react with BCG and, therefore, do not cause false positive reactions in BCG recipients. TB blood tests are the preferred test for people who have received the BCG vaccine.

## HIV Infection

Worldwide, TB is a leading cause of death among people living with HIV. The risk of progression from LTBI to TB disease is 7% to 10% each year for those with both LTBI and untreated HIV infection. Those with LTBI who are not HIV infected have a 10% risk over their lifetime. Thus, the risk of progression to TB disease is 10 times greater for those who are HIV infected. This risk is substantially reduced with effective antiretroviral therapy (ART) for HIV, but the risk is still higher than it is for HIV-negative people with LTBI.

All people with HIV should be tested for LTBI at the time of HIV diagnosis, regardless of their epidemiological risk of TB exposure. A negative TB blood test or TST result does not exclude LTBI, particularly among people with advanced HIV infection or AIDS, as they may have a compromised ability to react to tests for TB infection. Annual testing for LTBI using TST is recommended for people with HIV who are at high risk for repeated or ongoing exposure to people with active TB disease.

After the initiation of ART, repeat testing for LTBI is recommended for HIV-infected people previously known to have negative TB blood test or TST results, because the immune response may be restored by ART.

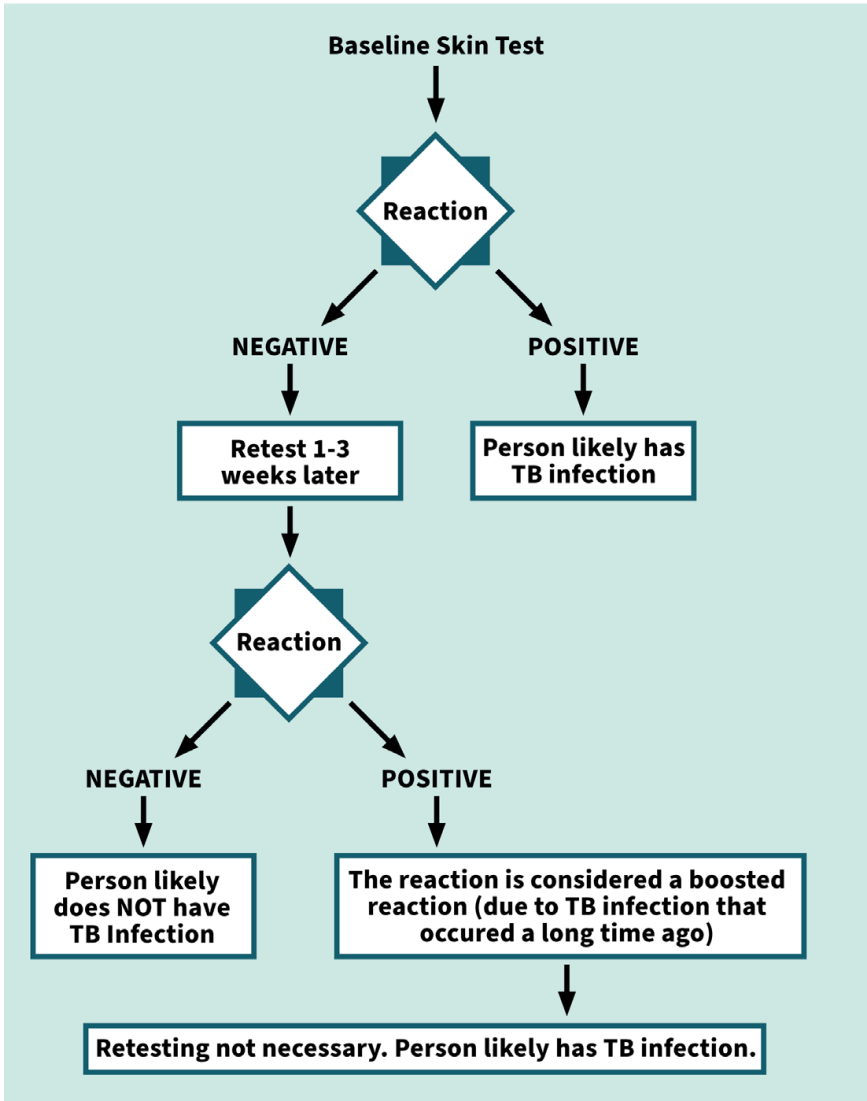
## Booster Phenomenon

One factor that can affect the accuracy of the baseline TST is the booster phenomenon. Some people infected with *M. tuberculosis* may have a negative reaction to the TST if many years have passed since they became infected. However, if they are tested again within a year of the first test, they may have a positive reaction indicating likely TB infection. This is because the first test stimulates, or boosts, their ability to react to the test. This is commonly referred to as the “booster phenomenon” and may incorrectly be interpreted as a skin test conversion (going from negative to positive). It may appear that these people were infected between the first and second skin tests; however, the second reaction is actually a boosted reaction (due to TB infection that occurred a long time ago). These people should still be considered for LTBI treatment after ruling out TB disease, particularly if they have risk factors for progression to disease.

To avoid misinterpretation, a strategy called two-step testing has been developed for telling the difference between boosted reactions and reactions caused by recent infection. For people who will be retested periodically, two-step testing should be used for the initial skin test. If the first TST result in the two-step baseline testing is positive, consider the person infected and evaluate and treat the person accordingly. If the first test result is negative, the TST should be repeated in 1–3 weeks. If the second test result is positive, consider the person infected and evaluate and treat the person accordingly. If both tests are negative, consider the person uninfected and classify the TST as negative at baseline testing (see **Figure 1**).

When TB blood tests are used, there is no need for a second test because boosting does not occur. TB blood tests do not boost subsequent test results because, unlike the TST, the patient is not exposed to the *M. tuberculosis* antigens. However, the TST can boost a subsequent TB blood test. Therefore, if a person will be tested with both the TST and a TB blood test, it is recommended to conduct the TB blood test either before or at the same time as the TST.

**Figure 1.**  
**Two-Step TST Testing**





## TB Screening and Testing of Health Care Personnel

In 2019, the Centers for Disease Control and Prevention (CDC) and the National Tuberculosis Controllers Association (NTCA) released updated recommendations for TB screening, testing, and treatment of health care personnel. These recommendations state that all U.S. health care personnel should be screened for TB upon hire (i.e., pre-placement). Annual TB testing of health care personnel is **not** recommended unless there is a known exposure or ongoing transmission. The screening process includes a baseline individual TB risk assessment, TB symptom evaluation, TB test (TB blood test or TST), and additional evaluation for TB disease as needed.

If the TST is used to test health care personnel upon hire (pre-placement), the “two-step method” is recommended.

If a TB blood test is used for baseline testing, two-step testing is not required.

The local health department should be notified immediately if TB disease is suspected.

### Contacts

Contacts are people who have been exposed to a person with known or presumptive infectious TB (e.g., pulmonary or laryngeal TB with a positive sputum smear). For contacts of a person with infectious TB disease, retesting 8–10 weeks after the end of exposure is indicated when the initial TB blood test or TST result is negative. In contact investigations, retesting is not called two-step testing. The second test is needed to determine if infection occurred but was too recent to be detected at the time of the first test. This is because it can take 2–8 weeks after being infected with *M. tuberculosis* for the body’s immune system to mount a response detectable by the tests.

Children younger than 5 years of age and immunosuppressed contacts (e.g., persons living with HIV) who have negative TB blood test or TST results should have a chest radiograph. If the chest radiograph is normal, treatment should be started for LTBI and the contact should be retested 8 to 10 weeks after their last exposure to the person with TB.

If testing is repeated, the same type of test (TB blood test or TST) should be used. If the repeat test result is **positive**, treatment should be continued. If the repeat test result is **negative**, treatment can usually be discontinued.

## Pregnancy

Pregnant women should be targeted for TB testing only if they have a specific risk factor for *M. tuberculosis* infection or for progression from LTBI to TB disease.

The TST is both safe and reliable throughout the course of pregnancy. TB blood tests are also safe to use during pregnancy, but they have not been fully evaluated for diagnosing TB infection in pregnant women. Therefore, the test results should be interpreted with caution and with the help of a TB expert.

If a TB blood test or TST reaction is positive in a pregnant woman, obtain a chest radiograph using proper shielding.

## Other Diagnostic Considerations

### Chest Radiograph

Chest radiographs (x-rays) help differentiate between LTBI and pulmonary TB disease in individuals with positive tests for TB infection. The following guidelines are recommended:

- A chest radiograph should be ordered as part of a medical evaluation for a person who has a positive TB blood test or TST result.
- A chest radiograph is indicated in the absence of a positive test result for TB infection when a person is a close contact of an infectious TB patient and treatment for LTBI will be started (e.g., “window prophylaxis” in a young child or immunocompromised person).
  - Children younger than 5 years of age should have both posterior-anterior and lateral views; all others should have at least posterior-anterior views.
- Other views or additional studies should be done based on the health care provider’s judgment.
- People with nodular or fibrotic lesions consistent with old TB are high-priority candidates for treatment of LTBI after TB disease is excluded.
- People with fully calcified, discrete granulomas on chest radiograph do not have an increased risk for progression to TB disease.

## Sputum Examination for Acid-Fast Bacilli (AFB) Smear and Culture

Sputum examination is indicated for people with positive test results for TB infection and either an abnormal chest radiograph or the presence of respiratory symptoms (even when the chest radiograph is normal).

For people with HIV infection, sputum examination should be considered even with a normal chest radiograph. In the context of advanced HIV, chest radiographs can appear normal.

## Physical Examination and Medical History

Physical examination and medical history (which includes obtaining information about previous positive tests for TB infection, previous treatment for LTBI or TB disease, and a risk assessment for liver disease) are indicated for individuals with positive TB test results. Written documentation of a previous positive TB blood test or TST result is required; a patient's verbal history is not sufficient. **Appendix E** provides an example of a documentation form.



# TREATMENT OF LATENT TB INFECTION (LTBI)

## Overview

There are several treatment regimens available for the treatment of LTBI (see **Table 6** and **Appendix F**). Providers should work with patients to choose the appropriate regimen based on the following:

- Drug-susceptibility results of the presumed source case (if known)
- Coexisting medical conditions
- Potential for drug-drug interactions

In 2020, CDC and NTCA released updated guidelines on the treatment of LTBI. While all the regimens are effective, short-course rifamycin-based 3- or 4-month regimens are the preferred treatment options for LTBI. Short-course LTBI treatment regimens are effective, are safe, and have higher completion rates than longer 6- to 9-month regimens of isoniazid (INH) monotherapy. If short-course treatment is not an option (e.g., due to drug interactions with rifamycins), CDC and NTCA recommend 6 or 9 months of daily INH as effective alternative LTBI treatment regimens. It is important for clinicians and pharmacists to know the difference between rifampin (RIF) and rifapentine (RPT). RIF and RPT are not interchangeable, and clinicians and pharmacists should ensure that patients receive the correct medication for the prescribed treatment regimen.

Clinicians should contact their state and local TB control offices for additional information on diagnosing and treating LTBI. Contact information can be located on the [State TB Control Offices website](#).

## Treatment Regimens



### **Three Months of Once-weekly Isoniazid (INH) plus Rifapentine (RPT) Regimen (3HP)**

The 3-month regimen of 12 once-a-week doses of INH and RPT is also known as the 3HP regimen. The regimen can be given under directly observed therapy (DOT) or self-administered therapy (SAT). Health care providers should choose the mode of administration (DOT or SAT) based on local practice, individual patient attributes and preferences, and other considerations (including risk of progression to severe forms of TB disease).

The 3HP regimen is recommended for people older than 2 years of age, including people with HIV/AIDS who are taking antiretroviral medications that have acceptable drug-drug interactions with RPT, such as efavirenz and raltegravir.\*

The 3HP regimen of INH and RPT is NOT recommended for the following individuals:

- Children younger than 2 years of age
- People with HIV/AIDS who are taking antiretroviral medications with clinically significant or unknown drug interactions with once-weekly RPT\*
- People presumed to be infected with INH- or RIF-resistant *M. tuberculosis*
- Pregnant women or women expecting to become pregnant during the 3-month regimen



## Four Months of Daily Rifampin (RIF) Regimen (4R)

A 4-month regimen of RIF, also known as 4R, is recommended for HIV-negative adults and children of all ages. The 4R regimen is especially recommended for people who cannot tolerate INH or who have been exposed to INH-resistant TB. LTBI treatment with RIF should be given daily for 4 months.

RIF should not be used to treat HIV-infected people taking some combinations of ART.\* In situations where RIF cannot be used, sometimes another drug, rifabutin (RBT), may be substituted.



## Three Months of Daily Isoniazid (INH) and Rifampin (RIF) Regimen (3HR)

The 3-month regimen of INH and RIF, also known as 3HR, is given daily. 3HR is one of the three preferentially recommended short-course rifamycin-based regimens for adults and children of all ages, including HIV-negative and HIV-positive patients as drug interactions\* allow.

\* Information about drug-drug interactions between specific anti-mycobacterial agents, including rifamycins (rifampin, rifabutin, and rifapentine) and antiretroviral agents, is available from [Department of Health and Human Services, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV](#).



## Six or Nine Months of Daily Isoniazid (INH) Regimens (6H or 9H)

If short-course treatment is not an option (e.g., due to drug interactions with rifamycins), regimens of 6 or 9 months of daily INH are considered alternative treatment regimens. Six months of daily INH, also known as 6H, is strongly recommended for HIV-negative adults and children of all ages and is a treatment option for HIV-positive adults and children of all ages. Nine months of daily INH, also known as 9H, is another treatment option for both HIV-negative and HIV-positive adults and children of all ages. Patients can be treated daily or twice weekly with INH. Patients being treated twice weekly should receive DOT.

It is important to note that although efficacious, treatment regimens of 6 or 9 months of daily INH have higher liver toxicity risk and lower treatment completion rates than shorter rifamycin-based regimens.



**TABLE 6.**  
**LTBI Treatment Regimens**

Drug(s)	Duration	Dose and Age Group	Frequency	Total Doses
<b>Isoniazid (INH)* and Rifapentine (RPT)†</b>	3 months	<b>Adults and children aged &gt;12 years</b> INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum 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 maximum <b>Children aged 2–11 years:</b> INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly	12
<b>Rifampin (RIF)*</b>	4 months	<b>Adults:</b> 10 mg/kg <b>Children:</b> 15-20 mg/kg** Maximum dose: 600 mg	Daily	120
<b>Isoniazid (INH)* and Rifampin (RIF)*</b>	3 months	<b>Adults</b> INH*: 5 mg/kg; 300 mg maximum RIF*: 10 mg/kg; 600 mg maximum <b>Children</b> INH*: 10-20 mg/kg††; 300 mg maximum RIF*: 15-20 mg/kg; 600 mg maximum	Daily	90
<b>Isoniazid (INH)*</b>	6 months	<b>Adults:</b> 5 mg/kg <b>Children:</b> 10-20 mg/kg†† Maximum dose: 300 mg	Daily	180
		<b>Adults:</b> 15 mg/kg <b>Children:</b> 20-40 mg/kg†† Maximum dose: 900 mg	Twice weekly <sup>§</sup>	52
<b>Isoniazid (INH)*</b>	9 months	<b>Adults:</b> 5 mg/kg <b>Children:</b> 10-20 mg/kg†† Maximum dose: 300 mg	Daily	270
		<b>Adults:</b> 15 mg/kg <b>Children:</b> 20-40 mg†† Maximum dose: 900 mg	Twice weekly <sup>§</sup>	76

\* Isoniazid is formulated as 100-mg and 300-mg tablets.

† Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

§ Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication). DOT or self-administered therapy (SAT) may be used for the 3-month regimen of INH and RPT.

\*\* Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.

†† The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (Source: American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–53).

†† The American Academy of Pediatrics recommends an isoniazid dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice-weekly regimen.\*

# Special Considerations for LTBI Treatment

## Directly Observed Therapy (DOT)

DOT for LTBI treatment should be considered for people who are at especially high risk for TB disease (e.g., young children) and are either taking an intermittent regimen or who may have difficulty with treatment adherence. Because of the importance of each dose, DOT must be used for patients on INH regimens given twice weekly.

## Contacts

Contacts should be evaluated immediately for LTBI and TB disease. If a contact's TB blood test (interferon-gamma release assay [IGRA]) or TST result is positive and TB disease is excluded, the contact should be considered high priority for LTBI treatment (see the guidance below). Contacts who have negative test results should be retested 8–10 weeks after their last exposure to infectious TB. This is because it can take 2–8 weeks after being infected with *M. tuberculosis* for the body's immune system to mount a response detectable by the tests.

LTBI treatment is sometimes given to people who are at high risk for rapidly developing TB disease, even if they have a negative TB blood test or TST result and less than 8–10 weeks have passed since they were last exposed to TB. These contacts include:

- Immunosuppressed people, including those who are HIV infected
- Children younger than 5 years of age

Treatment should be continued until the results of the second test and other medical evaluation are known. For contacts at high risk of TB disease, such as people with HIV/AIDS, a full course of LTBI treatment may be recommended even in the absence of a positive TB blood test or TST result. Consult with your local TB control program about the management of such contacts.

Providers should choose the appropriate LTBI regimen based on drug-susceptibility results of the presumed source case (if known).



- If a person is exposed to known drug-susceptible TB or drug susceptibility is unknown:
  - Positive TB blood test or TST result → Treat with a short-course rifamycin-based regimen (*note: if short-course treatment is not an option, 6 or 9 months of daily INH is an alternative option*)
- If a person is exposed to known INH-resistant TB:
  - Positive TB blood test or TST result → Treat with RIF for 4 months (*note: before starting treatment, it is important to confirm that the source case's M. tuberculosis isolate is susceptible to RIF*)
- If a person is exposed to known RIF-resistant TB:
  - Positive TB blood test or TST result → Treat with INH (*note: before starting treatment, consult an expert in the treatment of drug-resistant TB*)
- If a person is exposed to known multidrug-resistant (MDR) TB:
  - Positive TB blood test or TST result → Treat with later-generation fluoroquinolone (*note: before starting treatment, consult an expert in the treatment of MDR TB*)

In general, contacts with a positive TB blood test or TST who can provide written documentation of prior adequate treatment for LTBI do not need to be retreated. Retreatment may be indicated for people at high risk of becoming re-infected and progressing to TB disease (e.g., young children and immunosuppressed people). In complicated situations, a TB expert should be consulted.

## People with HIV/AIDS

- For information about drug-drug interactions between specific anti-mycobacterial and antiretroviral agents, see [Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV](#).
- LTBI treatment for people with HIV/AIDS should be provided in consultation with an expert in the management of HIV and TB coinfection.
- If the test for TB infection is negative, consider LTBI treatment if the person has had recent exposure to infectious TB, as discussed above.

## Pregnancy

- For most pregnant women, LTBI treatment can be delayed until 2–3 months post-partum to avoid administering unnecessary medication during pregnancy.
  - There is potential for an increased risk of hepatotoxicity during pregnancy and the first 2–3 months of the post-partum period.
- For women who are at high risk for progression from LTBI to TB disease, especially those who are a recent contact of someone with infectious TB disease, LTBI treatment should not be delayed on the basis of pregnancy alone, even during the first trimester.
- Before starting LTBI treatment, TB disease must be excluded through a symptom review and chest radiograph. For pregnant women at high risk for progression to TB disease, careful clinical monitoring or laboratory monitoring should be conducted.
- Pregnant women can take any of the following regimens for the treatment of LTBI:
  - 4-month daily regimen of RIF (4R)
  - 3-month daily regimen of INH and RIF (3HR)
  - 6- or 9-month daily regimen of INH (6H or 9H)
- Supplementation with 25–50 mg/day of pyridoxine (vitamin B6) is recommended for pregnant women taking INH to ameliorate possible adverse effects of the drug.
- For women in the post-partum period (within 3 months of delivery), baseline liver function tests should be conducted.

- The 3HP regimen is **not** recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety during pregnancy has not been studied.

## Breastfeeding Women

- Breastfeeding is not contraindicated in women taking INH or RIF separately.



- Breastfeeding women who are taking INH must be given a vitamin B6 supplement.
- However, there currently is not enough data to indicate whether the 3HP regimen is safe for women to take while breastfeeding.
- Supplementation of pyridoxine (vitamin B6) is recommended for nursing women and for breastfed infants.
- The amount of INH or RIF in breast milk is inadequate for treatment of infants with LTBI.
- RIF can cause orange discoloration of body fluids, including breast milk. Orange discoloration of body fluids is expected and harmless.

## Infants and Children

- Because of their young age, infants and young children with LTBI are known to have been recently infected and are at high risk for progressing to TB disease.
- Infants and young children are also more likely than older children and adults to develop life-threatening forms of TB disease.
- Testing adults who have been in close social contact with the child may be warranted to determine whether a person with infectious TB disease can be found. Consult with your local TB control program.
- Children under 5 years of age who are contacts of an adult with infectious TB disease should receive treatment for LTBI even if the initial TST or blood test result is negative and less than 8–10 weeks have passed since their last exposure to infectious TB; this is called *window prophylaxis*. Before starting window prophylaxis, TB disease should be excluded by chest radiograph and symptom review.
  - A second TST or blood test should be administered 8–10 weeks after the last exposure to someone with infectious TB disease. If testing is repeated, the same type of test (TB blood test or TST) should be used. If the repeat test result is **positive**, treatment should be continued. If the repeat test result is **negative**, treatment can usually be discontinued. Window prophylaxis can be discontinued if **all** of the following conditions are met:
    - i. The infant is 6 months of age or older.
    - ii. Second TST or blood test result is also negative.
    - iii. Second TST or blood test was performed 8 or more weeks after the child was last exposed to an adult with infectious TB disease.

- In certain instances, medical providers might decide to prescribe a complete course of LTBI treatment even if the second TST or blood test is negative, particularly if the exposure to someone with TB disease is substantial.
- Although all of the LTBI regimens are effective, health care providers should prescribe the more convenient shorter treatment regimens, when possible.
- The following regimens are recommended for the treatment of LTBI in children:
  - 3-month once weekly regimen of INH and RPT (3HP)
  - 4-month daily regimen of RIF (4R)
  - 3-month daily regimen of INH and RIF (3HR)
  - 6- or 9-month daily regimen of INH (6H or 9H)
- 3HP is recommended for children older than 2 years of age and may be given via DOT or SAT.
- 4R and 3HR treatment regimens are recommended for children of any age. 6H or 9H regimens are recommended alternative treatment regimens for children of any age.
- DOT for LTBI treatment should be considered for people who are at especially high risk for TB disease (e.g., young children) and are either taking an intermittent regimen or who may have difficulty with treatment adherence. Because of the importance of each dose, DOT must be used for patients on INH regimens given twice weekly.
- Risk of INH-related hepatitis in infants, children, and adolescents is minimal.
- Routine monitoring of serum liver enzymes is not necessary unless the child has risk factors for hepatotoxicity.

## Additional Notes of Importance

- Old fibrotic lesions can represent previous TB disease. Persons with old fibrotic lesions with TST results of  $\geq 5$  mm of induration or a positive TB blood test result and negative culture should be treated for LTBI.
- Calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping represent healed primary *M. tuberculosis* infection and do not increase the risk of TB disease. The decision to treat for LTBI would be the same as for a person with a normal chest radiograph.

- Treatment must be modified if the patient is a contact of an individual with drug-resistant TB disease. Consult a TB expert if the known source of TB infection has drug-resistant TB.

## Adverse Effects of Drugs Used to Treat LTBI

Some health care providers have concerns about treating patients for LTBI. These concerns have traditionally been related to the length of treatment and the potential side effects of medications. For patients without drug intolerance or drug-drug interactions, short-course (3–4 months) rifamycin-based treatment regimens are preferred over the longer-course (6–9 months) INH monotherapy for treatment of LTBI. Short-course LTBI treatment regimens are effective, are safe, and have higher completion rates than longer 6- or 9-month regimens of INH monotherapy. Shorter, rifamycin-based treatment regimens generally have a lower risk of hepatotoxicity than longer 6- or 9-month regimens of INH monotherapy.

As with any treatment, the health care provider must weigh the risks and benefits for each individual. Obtaining a detailed and accurate medical history and updating information at frequent intervals will identify persons who require close monitoring; this will aid in determining the most appropriate course of action. CDC guidelines, drug package inserts, and other authoritative medical sources should be consulted whenever there is a question about side effects or drug-drug interactions.

To ensure safe and efficacious treatment for LTBI, the health care provider should periodically assess the patient's progress. The sections that follow discuss some of the adverse effects of INH and rifamycins, as well as recommendations for monitoring during treatment and for assessing and ensuring adherence.

### Possible Adverse Effects of INH

- **Elevated serum liver enzyme concentrations:** Asymptomatic elevation of serum liver enzyme concentrations occurs in 10%–20% of people taking INH; liver enzyme concentrations usually return to normal even when treatment is continued.
  - It is generally recommended that INH be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms, or 5 times the upper limit of normal if the patient is asymptomatic.

- **Clinical hepatitis:** Clinical hepatitis occurs in less than 1% of people taking INH and is more common when INH is combined with other hepatotoxic agents. Factors that may increase either of these rates or the severity of hepatitis include daily alcohol consumption, underlying liver disease or risks for liver disease, and the concurrent use of other medications that are metabolized in the liver. Symptomatic hepatitis is rare in patients younger than 20 years of age, but severe and fatal cases have been reported.
  - Patients of all ages with underlying risk factors for liver disease should be monitored clinically.
- **Peripheral neuropathy:** Peripheral neuropathy occurs in less than 1% of people taking INH at conventional doses. It is more likely in the presence of other conditions associated with neuropathy. Persons with risk factors for neuropathy (e.g., pregnant women; breastfeeding infants; persons infected with HIV; those with diabetes, alcoholism, malnutrition, or chronic renal failure; or those who are of advanced age) are given pyridoxine (vitamin B6). Vitamin B6 can be administered at 25–50 mg/day with 6H, 9H, or 3HR, and at 50 mg/week with 3HP to prevent neuropathy.

## Possible Adverse Effects of Rifampin (RIF) and Rifapentine (RPT)

- **Hepatotoxicity:** Shorter, rifamycin-based treatment regimens generally have a lower risk of hepatotoxicity than longer 6- or 9-month regimens of INH monotherapy. Evidenced by transient asymptomatic hyperbilirubinemia, hepatotoxicity may occur in 0.6% of persons taking RIF.
- **Cutaneous reactions:** Pruritus/itching (with or without a rash) or other cutaneous reactions may occur in some persons taking RIF. The reactions are generally self-limited and may not be a true hypersensitivity; continued treatment may be possible.
- **Hypersensitivity reactions:** Rarely, rifamycins can be associated with hypersensitivity reactions, including hypotension, anaphylaxis, nephritis or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/lightheadedness, musculoskeletal pain, petechiae, and pruritus.
- **Gastrointestinal symptoms:** Symptoms such as nausea, anorexia, and abdominal pain are rarely severe enough to discontinue treatment.
- **Discoloration of body fluids:** Orange-red discoloration of body fluids, such as urine and breast milk, is expected and harmless, but patients should be advised beforehand. Soft contact lenses and dentures may be permanently stained.

- **Drug-drug interactions:** RIF and RPT have drug-drug interactions with numerous medications. They are known to reduce concentrations of methadone, warfarin, hormonal contraceptives, tricyclic antidepressants, haloperidol, diazepam, and phenytoin. Dose adjustment of the companion medication may be necessary. Women using hormonal contraceptives should be advised to consider an alternative method of contraception (e.g., a barrier method).
- **Contraindication with certain antiretroviral therapy (ART) medications:** Rifampin (RIF) should not be used in HIV-infected individuals being treated with certain antiretroviral medications, such as protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors, and the CCR5 antagonist maraviroc. Substitution of rifabutin (RBT) for RIF in the 4-month regimen may be considered for such patients. Rifapentine (RPT) should not be used in HIV-infected persons taking antiretroviral medications that have clinically significant or unknown drug interactions with RPT. Clinicians are referred to the AIDSinfo guidelines, [\*Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV\*](#), that present the most current recommendations for TB treatment for persons with HIV infection and LTBI.

## Patient Monitoring and Education During Treatment

To ensure safe and efficacious treatment for LTBI, the health care provider should periodically assess the patient's progress. This evaluation involves clinical monitoring, laboratory testing, and patient education.

### Clinical Monitoring

- All patients receiving LTBI treatment should be evaluated at least monthly for the following:
  - Adherence to the prescribed regimen
  - Signs and symptoms of TB disease
  - Adverse reactions (such as signs and symptoms of hepatitis)
- Patients being treated for LTBI who experience possible adverse reactions should be advised to stop medication and consult their health care provider immediately.

## Laboratory Testing

- Baseline laboratory testing (measurements of serum AST, ALT, and bilirubin) is not routinely indicated for all patients at the start of LTBI treatment.
  - Baseline testing can be considered on an individual basis, especially for patients taking other medications for chronic medical conditions.
- Laboratory testing at the start of LTBI therapy is recommended for patients with any of the following factors:
  - Liver disorders
  - History of liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis)
  - Regular use of alcohol or injection drugs
  - Risks for chronic liver disease
  - HIV infection
  - Pregnancy or the immediate post-partum period (i.e., within 3 months of delivery)
- After baseline testing, routine periodic retesting (e.g., monthly) is recommended for persons who had abnormal initial results and other persons at risk for hepatic disease.
- At any time during treatment, whether or not baseline tests were done, laboratory testing is recommended for patients who have symptoms suggestive of hepatitis (e.g., fatigue, weakness, malaise, anorexia, nausea, vomiting, abdominal pain, pale stools, brown urine, chills) or who have jaundice.
- It is generally recommended that medication be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms, or 5 times the upper limit of normal if the patient is asymptomatic.

## Patient Education

- Explain the disease process and rationale for medication in the absence of symptoms or radiographic abnormalities.
- Review the importance of completing treatment for LTBI.
- Inform patients that RIF and RPT may cause urine or other body fluids to turn orange. This side effect is harmless.



- Instruct patients at the start of treatment to stop taking their medication and seek medical attention immediately if they experience any of the following medication side effects:
  - Dizziness or lightheadedness
  - Loss of appetite
  - Flu-like symptoms
  - Severe diarrhea or light-colored stools
  - Shortness of breath
  - Feelings of sadness or depression
  - Fever
  - Unexplained anorexia
  - Brown urine (color of coffee or cola)
  - Icterus (jaundice)
  - Rash
  - Persistent paresthesia (tingling or prickling sensation) of hands and feet
  - Persistent fatigue or weakness lasting 3 or more days
  - Abdominal tenderness, especially in right upper quadrant
  - Easy bruising or bleeding
  - Arthralgia (joint pain)
  - Nausea
  - Vomiting
- Discuss management of common side effects and the need to report to health care provider.



## Assessing Patient Adherence

Many variables affect a patient's adherence to LTBI treatment. Using shorter treatment regimens can help patients complete treatment. Health care providers should prescribe the more convenient shorter regimens when possible.

Episodes of non-adherence should be recognized and addressed as soon as possible. See **Table 7** for examples of barriers to adherence.

**TABLE 7.**  
**Examples of Barriers to Patient Adherence to LTBI Treatment**

<b>Clinic-Related Variables</b>
<ul style="list-style-type: none"><li>• Long waiting time for appointment and referrals</li><li>• Long waiting time in provider’s office</li><li>• Inconvenient office hours</li><li>• Complicated telephone system (not user friendly)</li><li>• Cost</li></ul>
<b>Patient-Related Barriers</b>
<ul style="list-style-type: none"><li>• Misinformation or confusion about certain issues, such as<ul style="list-style-type: none"><li>• The meaning of test results</li><li>• Differences between injections, vaccines, TST, and blood tests</li><li>• The words “positive” and “negative” as they relate to test results</li><li>• Modes of TB transmission and prevention</li><li>• Exposure vs. becoming infected</li><li>• Safety of family and friends around someone with LTBI</li></ul></li><li>• Residential instability</li><li>• Lack of financial resources</li><li>• Poor access to health care</li><li>• Stigma associated with TB</li><li>• Co-existing medical conditions</li><li>• Culture and language</li><li>• Religious practices (e.g., fasting from food)</li></ul>
<b>Treatment Barriers</b>
<ul style="list-style-type: none"><li>• Complexity and duration of treatment</li><li>• Medication side effects</li><li>• Obtaining refills</li><li>• Frequency of office visits</li><li>• Cost, including insurance co-payment</li></ul>

# Techniques to Improve Adherence

- Collaborate with the local health department to provide treatment.
- Provide DOT if the patient is high risk (e.g., HIV infected, young child, or TB contact).
- Use case management principles to coordinate care and services.
- Consider free or low-cost medication.
- Offer rewards for adherence (incentives), such as grocery store or restaurant vouchers, nutritional supplements, cell phone credits, or movie tickets.
- Provide enablers to overcome barriers, e.g., free transportation or public transportation vouchers.
- Provide patient education and instructions in patient's primary language at every visit.
- Ensure confidentiality.
- Suggest or provide patient reminders, such as pill box, calendar, or timer.

# Post-Treatment Follow Up

- Patients should receive documentation that includes TB blood test or TST results, chest radiograph results, names and dosages of medication, and duration of treatment. Patients should be instructed to present this document any time future TB testing is required.
- Providers should re-educate patients about the signs and symptoms of TB disease and advise them to contact their medical provider if they develop any of these signs or symptoms.
- Among patients who have documented completion of LTBI treatment, serial or repeat chest radiographs are not indicated unless the patient develops signs or symptoms suggestive of TB disease.



# SAMPLE TB RISK ASSESSMENT TOOL

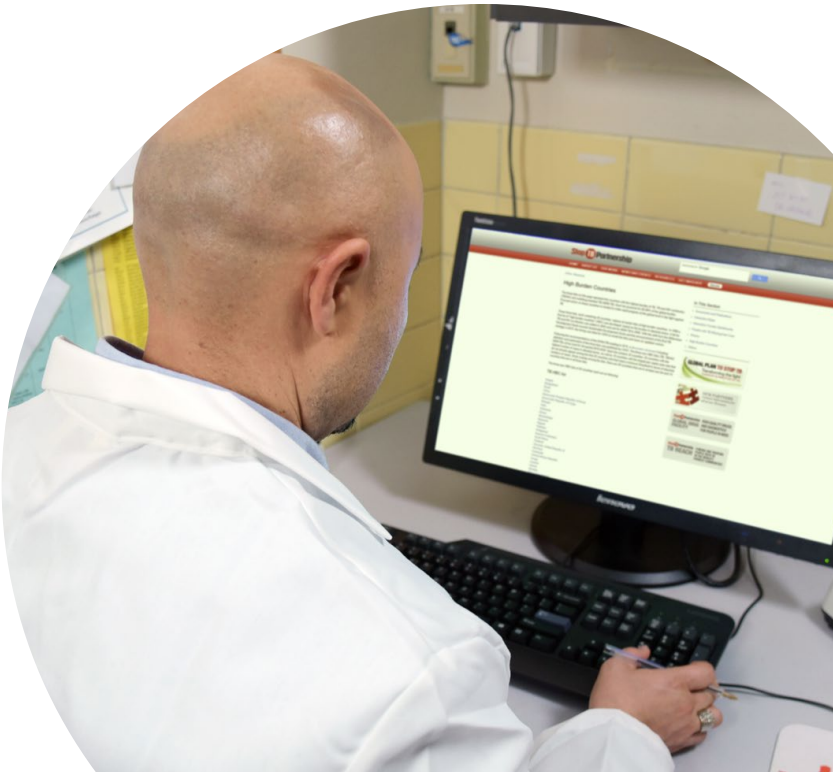
Persons should be considered at increased risk for TB if any of the following statements are marked “Yes.”

Risk Factor	Yes	No
<p><b>Temporary or permanent residence of ≥1 month in a country with a high TB rate.</b></p> <p>Any country other than the United States, Canada, Australia, New Zealand, and those in northern Europe or western Europe.</p>		
<p><b>Current or planned immunosuppression, including</b> human immunodeficiency virus (HIV) infection, organ transplant recipient, treatment with a TNF-alpha antagonist (e.g., infliximab, etanercept, or other), chronic steroids (equivalent of prednisone ≥15 mg/day for ≥1 month), or other immunosuppressive medication (e.g., cancer chemotherapy).</p>		
<p><b>Close contact during lifetime with someone who has had infectious TB disease.</b></p>		

*Adapted from: Risk assessment form developed by the California Department of Health, Tuberculosis Control Branch*

# IDENTIFYING PERSONS FROM HIGH BURDEN COUNTRIES

- Local epidemiologic profiles are the most useful resource to identify countries of highest risk. Health care providers should base testing and treatment decisions on local immigration patterns and epidemiology.
- In 2019, approximately 70% of TB cases in the United States occurred in non-U.S.-born persons.
- The top five countries of birth of non-U.S.-born persons with TB were Mexico, the Philippines, Vietnam, India, and China.
- For a list of high burden countries and profiles of these countries, see the [Stop TB Partnership website](#).



# ADMINISTRATION AND MEASUREMENT OF THE TST\*

## Administration

The Mantoux test is the recommended tuberculin skin test (TST). It is administered by injecting 0.1 ml of 5 tuberculin units of purified protein derivative (PPD) solution intradermally into the volar surface of the forearm using a 27-gauge needle with a tuberculin syringe.

- Obtain results of all previous TSTs or TB blood tests. Ask patient to describe what the test area looked like 2–3 days after administration. Written documentation must be obtained for history to be applicable.
- Avoid areas of skin with veins, rashes, or excess hair.
- Cleanse the area with alcohol swab, allow area to dry, and inject all antigen just below the surface of the skin on the volar surface of the forearm, forming a 6–10 mm wheal (a pale, raised area with distinct edges; has orange-peel appearance and does not disappear immediately).
- If no wheal forms, or if a wheal forms that is less than 6 mm of induration, the test should be repeated immediately, approximately 2 inches from original site or on the other arm.
- If minor bleeding occurs, dab the injection site with a cotton swab.
- Avoid covering the area with a bandage or applying pressure to the injection site.
- Record the date, time, and location of TST administration.
- Instruct patient not to scratch the site, but to use a cool compress to relieve any itching or swelling.
- Inform patient that they will need to return for a reading of their TST within 48–72 hours (2–3 days).
- Give written appointment card for their TST reading.
- Provide written information about the TST (pamphlet or brochure).

## Measurement

- Measure the induration (hard bump) rather than erythema (area of redness).
- Palpate area with fingertips, measuring the diameter of induration perpendicular to the long axis of the arm.
- Use ballpoint pen to mark edges of induration.
- Use a TST ruler or ruler with millimeters to measure the distance between the 2 points.

## Recording and Documentation

- Record date TST was administered.
- Record the brand name of the PPD solution, lot number, manufacturer, and expiration date on the patient record.
- Record results in millimeters of induration (0 mm if there is no induration) rather than as positive or negative.
- Record date and time of reading and name of person reading TST.
- Provide written documentation to patient and ordering health care provider.

## Storage and Handling

- PPD solution must be kept refrigerated at 36°– 46° F.
- Avoid fluctuations in temperature; do not store on the refrigerator door.
- Syringes must be filled immediately prior to administration.
- Store and transport the tuberculin in the dark as much as possible; avoid exposure to light.
- Tuberculin testing solution should not be stored with other vials, such as Tdap, that could be mistaken for PPD.

\* Contact the local health department TB program for training on the Mantoux tuberculin skin test. Contact information can be located at <https://www.cdc.gov/tb/links/tboffices.htm>.

# SITUATIONS WHERE RESULTS FROM BOTH A TB BLOOD TEST AND TST MAY BE USEFUL

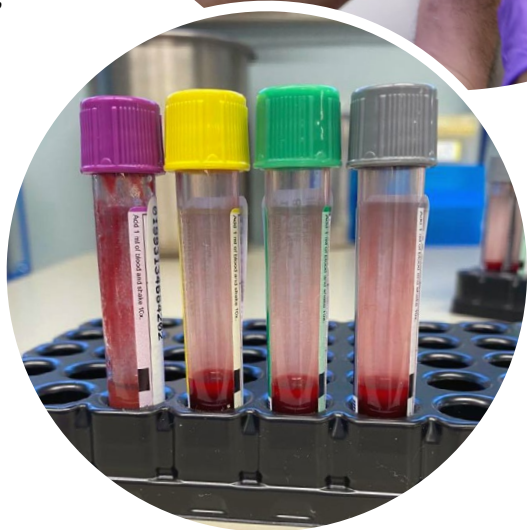
Routine testing with both a TB blood test and a TST is **not** recommended. However, results from both tests might be useful in the following situations:

- When the initial test is **negative** and:
  - The risk for infection, progression to disease, and/or a poor outcome is high (e.g., HIV-infected persons or children younger than 5 years of age who are exposed to a person with infectious TB).
  - There is clinical suspicion for TB disease (e.g., signs, symptoms, or radiographic evidence suggestive of TB disease) and confirmation of *M. tuberculosis* infection is desired.
  - Taking a positive result from a second test as evidence of infection increases detection sensitivity.
- When the initial test is **positive** and:
  - Additional evidence of infection is desired to encourage acceptance and adherence to treatment. For example, when counseling a BCG-immunized person who has a positive TST, a subsequent positive TB blood test, the results of which are not affected by BCG immunization, might be meaningful to the patient in accepting LTBI diagnosis and treatment. *Note: TB blood tests are the preferred method of testing for persons who have received the BCG vaccine.*
  - The person has a low risk of both infection and progression from infection to TB disease. Requiring a positive result from the second test as evidence of infection in a person at low risk increases the likelihood that the test reflects *M. tuberculosis* infection.



In addition, repeating a TB blood test or performing a TST should occur when the initial TB blood test result is indeterminate, borderline, or invalid, and a reason for testing persists.

Multiple negative results from any combination of these tests cannot exclude *M. tuberculosis* infection. Steps should be taken to minimize unnecessary and misleading testing of persons at low risk. Selection of the most suitable test or combination of tests for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost of testing.



# SAMPLE DOCUMENTATION FORMS

## Record of TB Blood Test

To Whom It May Concern:

The following is a record of TB blood test results:

Name: \_\_\_\_\_

Date of birth: \_\_\_\_\_

Type of test: \_\_\_\_\_ Date blood collected: \_\_\_\_\_

Laboratory: \_\_\_\_\_

### For QFT-Plus\*:

Nil: \_\_\_\_\_ IU/mL

TB1: \_\_\_\_\_ IU/mL

TB1 minus Nil: \_\_\_\_\_ IU/mL

TB2: \_\_\_\_\_ IU/mL

TB2 minus Nil: \_\_\_\_\_ IU/mL

Mitogen: \_\_\_\_\_ IU/mL

Mitogen minus Nil: \_\_\_\_\_ IU/mL

QFT-Plus Interpretation \_\_\_\_\_

### For T-SPOT®.TB:

Nil: \_\_\_\_\_ spots

TB Panel A: \_\_\_\_\_ spots

TB Panel A minus Nil: \_\_\_\_\_ spots

TB Panel B: \_\_\_\_\_ spots

TB Panel B minus Nil: \_\_\_\_\_ spots

Mitogen: \_\_\_\_\_ spots

T-Spot Interpretation \_\_\_\_\_

*\*also known as QuantiFERON®-TB Gold Plus*

For more information consult manufacturers' websites and package inserts.

### Record of Tuberculin Skin Test

To Whom It May Concern:

The following is a record of Mantoux tuberculin skin test (TST) results:

Name: \_\_\_\_\_ Date of birth: \_\_\_\_\_

Date and time test administered: \_\_\_\_\_

Administered by: \_\_\_\_\_

Manufacturer of Purified Protein Derivative (PPD): \_\_\_\_\_

Expiration date: \_\_\_\_\_ Lot number: \_\_\_\_\_

Time test read: \_\_\_\_\_ Read by: \_\_\_\_\_

Date: \_\_\_\_\_ Induration: \_\_\_\_\_ mm

TST interpretation: \_\_\_\_\_

### Record of Treatment Completion

To Whom It May Concern:

The following is a record of evaluation and treatment for *M. tuberculosis* infection:

Name: \_\_\_\_\_ Date of birth: \_\_\_\_\_

Tuberculin skin test (TST): Date: \_\_\_\_\_

Results (in millimeters of induration): \_\_\_\_\_

TB blood test: Date: \_\_\_\_\_ Type of test: \_\_\_\_\_ Result: \_\_\_\_\_

Chest radiograph: Date: \_\_\_\_\_ Result: \_\_\_\_\_

Date medication started: \_\_\_\_\_ Date completed: \_\_\_\_\_

Medication(s): \_\_\_\_\_

This person is not infectious. He/she may always have a positive TB test, so there is no reason to repeat the test. If you need any further information, please contact this office.

### Provider Contact Information

Name: \_\_\_\_\_

Phone Number: \_\_\_\_\_

Address: \_\_\_\_\_

Signature of Provider: \_\_\_\_\_ Date: \_\_\_\_\_

# LATENT TB INFECTION TREATMENT REGIMENS

	DRUG	DURATION	FREQUENCY
Preferred	<b>ISONIAZID<sup>†</sup></b> <b>AND</b> <b>RIFAPENTINE<sup>††</sup></b> <b>(3HP)</b>	3 months	Once weekly
	<b>RIFAMPIN<sup>§</sup></b> <b>(4R)</b>	4 months	Daily
	<b>ISONIAZID<sup>†</sup></b> <b>AND</b> <b>RIFAMPIN<sup>§</sup></b> <b>(3HR)</b>	3 months	Daily
Alternative	<b>ISONIAZID<sup>†</sup></b> <b>(6H/9H)</b>	6 months	Daily Twice weekly <sup>¶</sup>
		9 months	Daily Twice weekly <sup>¶</sup>

\*For persons with HIV/AIDS, see Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/overview>.

<sup>†</sup>Isoniazid is formulated as 100-mg and 300-mg tablets.

<sup>††</sup>Rifapentine is formulated as 150-mg tablets in blister packs that should be kept sealed until use.

<sup>¶</sup>Intermittent regimens must be provided via directly observed therapy (i.e., a health care worker observes the ingestion of medication).

Treatment regimens for latent TB infection (LTBI) use isoniazid (INH), rifapentine (RPT), or rifampin (RIF). **CDC and the National Tuberculosis Controllers Association preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy.** Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV\*), and potential for drug–drug interactions.

TOTAL DOSES	DOSE AND AGE GROUP
12	<b>Adults and children aged ≥12 yrs</b> INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg; 300 mg 14.1–25.0 kg; 450 mg 25.1–32.0 kg; 600 mg 32.1–49.9 kg; 750 mg ≥50.0 kg; 900 mg maximum
	<b>Children aged 2–11 yrs</b> INH <sup>†</sup> : 25 mg/kg; 900 mg maximum RPT <sup>††</sup> : See above
120	<b>Adults:</b> 10 mg/kg; 600 mg maximum
	<b>Children:</b> 15–20 mg/kg <sup>  </sup> ; 600 mg maximum
90	<b>Adults</b> INH <sup>†</sup> : 5 mg/kg; 300 mg maximum RIF <sup>§</sup> : 10 mg/kg; 600 mg maximum
	<b>Children</b> INH <sup>†</sup> : 10–20 mg/kg <sup>#</sup> ; 300 mg maximum RIF <sup>§</sup> : 15–20 mg/kg; 600 mg maximum
180	<b>Adults</b>
52	Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
270	<b>Children</b>
76	Daily: 10–20 mg/kg <sup>#</sup> ; 300 mg maximum Twice weekly: 20–40 mg/kg <sup>#</sup> ; 900 mg maximum

<sup>§</sup>Rifampin (rifampicin) is formulated as 150-mg and 300-mg capsules.

<sup>||</sup>The American Academy of Pediatrics acknowledges that some experts use rifampin at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (**Source:** American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–53).

<sup>\*</sup>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.

# LATENT TB INFECTION



TESTING



TREATMENT



## SUMMARY OF U.S. RECOMMENDATIONS



**Eliminating tuberculosis (TB) in the United States requires expanding testing and treatment of latent TB infection.**

The [Centers for Disease Control and Prevention \(CDC\)](#) and the [U.S. Preventive Services Task Force \(USPSTF\)](#) recommend testing people that are at increased risk for TB infection. Clinicians, health care agencies, and community organizations, especially those serving populations at risk, have a critical role in TB elimination.

# WHO SHOULD BE TESTED FOR TB INFECTION?



**CDC and the USPSTF recommend testing populations that are at increased risk for TB infection.**



**Anyone can get TB. However, some people have a higher risk of getting infected with TB bacteria. CDC supports the USPSTF recommendation to test certain groups at risk for TB infection. These groups include:**

- People who were born in or who frequently travel to countries where TB disease is common, including Mexico, the Philippines, Vietnam, India, China, Haiti, Guatemala, or other countries with high rates of TB. *(In general, people born in Canada, Australia, New Zealand, western European countries, or northern European countries are not considered at high risk for TB infection unless they spent time in a country with a high rate of TB.)*
- People who currently live or used to live in large group settings where TB is more common, such as homeless shelters, prisons, or jails.



**CDC also recommends testing for TB infection for other groups at risk. These groups include:**

- [Health care workers](#) and others who work in places with high risk for TB transmission, such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV.
- Anyone who has spent time with a person who has infectious TB disease.



**Some people with weaker immune systems, such as those with certain health conditions or who take certain medications, have a higher risk of developing TB disease once infected. Testing for TB infection should be part of their regular medical care. Health conditions that increase a person's risk of developing TB disease once infected include:**

- HIV infection
- Recent infection with *M. tuberculosis* (*within the last two years*)
- History of untreated or inadequately treated TB disease
- Medical treatments that suppress the immune system (*such as tumor necrosis factor-alpha [TNF] antagonists, corticosteroids, or drug therapy following organ transplants*)
- Silicosis; chronic renal failure; leukemia; or cancer of the head, neck, or lung
- Diabetes mellitus
- A gastrectomy or jejunioileal bypass
- Low body weight (*<90% of ideal body weight*)
- Substance use (*such as injection drug use*)



**Children, especially those under age 5, have a higher risk of developing TB disease once infected. Therefore, testing for TB infection in children is important if they are in one of the risk groups noted above.**



# RECOMMENDED TESTS FOR TB INFECTION:

*Testing for TB infection should be a routine and integral part of health care for patients with increased risk for TB. Health care providers are encouraged to use newer TB blood tests to screen for TB infection.*



**There are two kinds of tests that are used to determine if a person has been infected with TB bacteria: the TB blood test and the TB skin test.**



## **TB Blood Tests (Interferon Gamma Release Assays [IGRAs])**

TB blood tests (sometimes called IGRAs) use a blood sample to find TB infection. The tests measure the response of TB proteins when they are mixed with a small amount of blood. Only one visit is required to draw blood for the test.

TB blood tests are the preferred method of TB testing for people 5 years of age and older who have received the bacille Calmette-Guérin (BCG) vaccine.



## TB Skin Test (TST)

The TB skin test is also called the Mantoux tuberculin skin test (TST). With a TB skin test, a health care provider injects a small amount of testing fluid (called tuberculin or PPD) into the skin on the lower part of the arm.

After 2-3 days, the skin test reaction must be examined by a trained health care worker. The health care worker measures any swelling where the tuberculin was injected to determine if the reaction to the test is positive or negative.

TB skin tests are an acceptable alternative in situations where a TB blood test is not available, is too costly, or is too burdensome.



**A positive reaction to a TB blood test (IGRA) or TB skin test (TST) usually means TB infection. More tests, such as a chest x-ray, are needed to rule out TB disease.**



**A diagnosis of latent TB infection is made if a person has a positive TB blood test (IGRA) or TST result and a medical exam does not indicate TB disease.**

# RECOMMENDED TREATMENT REGIMENS FOR LATENT TB INFECTION:



**Treating latent TB infection is effective in preventing TB disease and less costly than treating TB disease.**

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**There are several [treatment regimens](#) for the treatment of latent TB infection.**

- These regimens use the drugs isoniazid, rifampentine, or rifampin.
- 

**CDC and the National Tuberculosis Controllers Association (NTCA) preferentially recommend short-course, rifamycin-based, 3- or 4-month latent TB infection treatment regimens over 6- or 9-month isoniazid monotherapy (6H or 9H, respectively).**

- Short-course regimens include:
  - Three months of once-weekly isoniazid plus rifampentine (3HP)
  - Four months of daily rifampin (4R)
  - Three months of daily isoniazid plus rifampin (3HR)
- Short-course latent TB infection treatments are effective, are safe, and have higher completion rates than longer treatments.
- If a short-course treatment regimen is not an option, 6H or 9H is an effective alternative latent TB infection treatment regimen.



## Shorter regimens help patients finish treatment.

**All treatment must be modified if the patient is a contact of an individual with drug-resistant TB disease. Consultation with a TB expert is advised if the known source of TB infection has drug-resistant TB.**

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**Clinicians should choose the appropriate treatment regimen based on drug susceptibility results of the presumed source case (if known), coexisting medical conditions (e.g., HIV infection), and potential for drug- drug interactions.**

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**Clinicians may choose to administer latent TB infection treatment through directly observed therapy (DOT) or self-administered therapy (SAT) based on local practice, individual patient attributes, and provider preferences.**





# LATENT TB INFECTION ONLINE RESOURCE HUB

*CDC's One-stop Shop for Information,  
Guidance, and Education*



The Latent TB Infection Online Resource Hub is a collection of downloadable materials for informing and educating the public, health care providers, policy makers, and other partners about the importance of expanded latent TB infection testing and treatment.

Available resources include:

- Guidance Documents
- Fact Sheets for Clinicians & Patients
- Communication Templates
- Key Messages & Social Media Content
- Slide Sets
- Images & Videos
- Infographics
- Helpful Links & More

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# RESOURCES

## Websites

- [Centers for Disease Control and Prevention \(CDC\) Division of Tuberculosis Elimination](#)
- [State TB Control Offices](#)
- [Find TB Resources](#)
- [World Health Organization](#)

## TB Centers of Excellence for Training, Education, and Medical Consultation

The CDC's Division of Tuberculosis Elimination funds four TB Centers of Excellence for Training, Education, and Medical Consultation (TB COEs). The TB COEs are regionally assigned to cover all 50 states and the U.S. territories.

The TB COEs support domestic TB control and prevention efforts with a focus on two major activities:

- Increasing knowledge, skills, and abilities for TB prevention and control through communication, education, and training activities
- Improving sustainable, evidence-based TB clinical practices and patient care through the provision of expert medical consultation

To view all of the educational materials developed by the TB COEs, visit the [TB COE's Products website](#).

For the most current information about the TB COEs, visit the [CDC website](#).

## Educational Materials for Health Care Providers\*

### Online Resources

- [Latent TB Infection Online Resource Hub](#) (CDC)
- [Mantoux Tuberculin Skin Test Training Resources](#) (CDC)
- [Latent TB Infection Treatment Regimens – Treatment Table](#) (CDC)
- [Latent TB Infection Treatment – FAQs for Clinicians](#) (CDC)
- [Latent TB Infection Testing and Treatment: Summary of U.S. Recommendations](#) (CDC)

## Booklets and Pocket Cards

- [Management for Latent Tuberculosis Infection in Children and Adolescents: A Guide for the Primary Care Provider](#) (Global Tuberculosis Institute at Rutgers)
  - [“Addendum 2014”](#)
- [Diagnosis and Treatment of Latent Tuberculosis Infection Pocket Drug Card](#) (Global Tuberculosis Institute at Rutgers)
- [TB Screening Tests in Children](#) (Heartland National TB Center)

## Fact Sheets

- [Targeted Tuberculin Testing and Interpreting Tuberculin Skin Test Results](#) (CDC)
- [Treatment of Latent Tuberculosis Infection: Maximizing Adherence](#) (CDC)
- [Interferon-Gamma Release Assay \(IGRAs\)](#) (CDC)
- [BCG Vaccine](#) (CDC)

## Slide Set

- [Targeted TB Testing and Treatment of Latent Tuberculosis Infection](#) (CDC)

## Videos

- [Latent TB Videos for Healthcare Providers](#) (Curry International TB Center and TB Free California)
- [TB Personal Stories](#) (CDC)

*\*View and download CDC education and training materials at the [TB publications and products website](#). Select materials are available in print and can be ordered from the [CDC-INFO On Demand publications system](#).*

## Educational Materials for Patients

### Brochures

- [12-Dose Regimen for Latent TB Infection \(English, Chinese, Haitian Creole, Marshallese, Spanish, Tagalog, Vietnamese\)](#) (CDC)
- [Questions and Answers About Tuberculosis \(English, Spanish\)](#) (CDC)
- [Patient Education Series \(English, Spanish, Tagalog, Vietnamese\)](#) (CDC)

## Medication Trackers

- [12-Dose Regimen for Latent TB Infection-Medication Tracker \(English, Chinese, Haitian Creole, Marshallese, Spanish, Tagalog, Vietnamese\)](#) (CDC)
- [4R Regimen for Latent TB Infection-Medication Tracker](#) (CDC)
- [3HR Regimen for Latent TB Infection-Medication Tracker](#) (CDC)

## Fact Sheets

- [What You Need to Know About Your Medicine for Latent Tuberculosis \(TB\) Infection – Fact Sheet Series](#) (CDC)
- [You Can Prevent TB](#) (CDC)

## Videos

- [TB Personal Stories](#) (CDC)

*\*CDC education and training materials may be viewed and downloaded online at the [patient & general public materials website](#). Select materials are available in print and can be ordered from the [CDC-INFO On Demand publications system](#).*



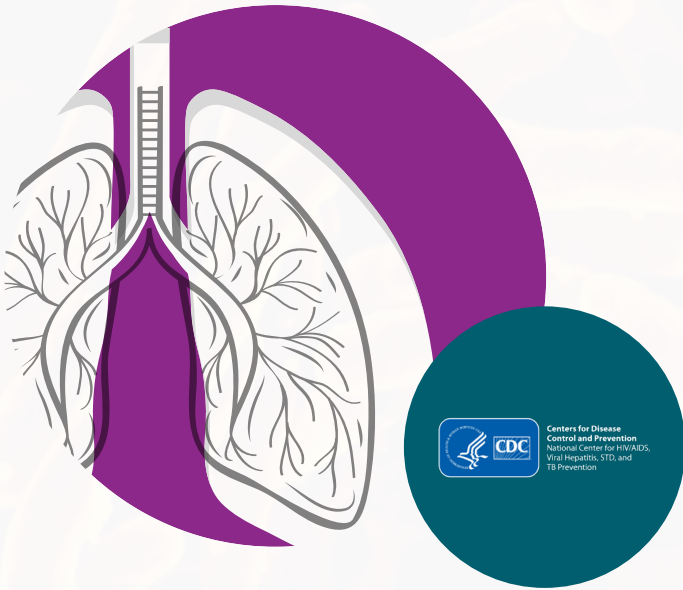


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Division of Tuberculosis Elimination

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