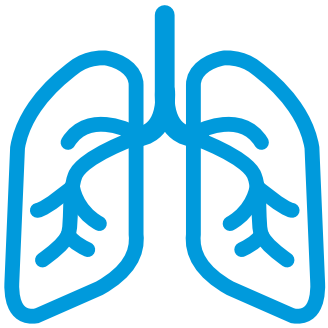


LATENT TB. ACTIVE CONCERN.

A GUIDE FOR PROVIDERS

Tuberculosis Program
Virginia Department of Health

This provider resource is intended to assist healthcare providers who work with patients and populations at risk for latent tuberculosis infection (LTBI). Designed to be a companion resource to Centers for Disease Control and Prevention (CDC) and the National Tuberculosis Controllers Association (NTCA) guidance, it will provide a background of LTBI, testing and treatment information, and guidance on talking to patients and their families about LTBI.

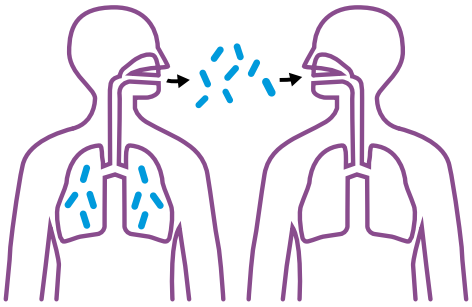
For additional information, please visit our website at https://www.vdh.virginia.gov/tuberculosis/.

I. BACKGROUND

WHAT IS LATENT TUBERCULOSIS INFECTION (LTBI)?

Latent tuberculosis infection (LTBI) is a condition where people are infected with a bacterium called *Mycobacterium tuberculosis* (*M. tuberculosis*) but do not have signs or symptoms, or bacteriologic or radiologic evidence of tuberculosis (TB) disease.

M. tuberculosis bacteria, which cause TB disease, are spread through the air from one person to another. TB disease is most often seen in the lungs, referred to as pulmonary TB, but can affect other parts of the body, including the brain, kidneys, or spine, which is known as extrapulmonary TB. Symptoms vary depending on the site of disease, but can include prolonged cough, weakness, fever, night sweats, chest pain, and hemoptysis. If untreated, TB disease can be fatal.



DIFFERENTIATING BETWEEN LTBI AND TB DISEASE:

A Person with LTBI	A Person with TB Disease
• Has no symptoms	• Symptoms may include one or more of the following: cough that lasts three weeks or more, fever, chest pain, weight loss, night sweats, fatigue, and decreased appetite
• Does not feel sick	• Usually feels sick
• Cannot spread TB bacteria to others	• Can spread TB bacteria to others
• Has a positive skin or blood test result for TB infection	• May have a positive skin or blood test result for TB infection.
• Has a normal chest x-ray and a negative sputum smear or culture	• May have an abnormal chest x-ray, or positive sputum smear or culture
• Needs treatment for LTBI to prevent TB disease	• Needs treatment for TB disease

Approximately 5-10% of people with LTBI will go on to develop TB disease if not treated for LTBI. The risk for progression from LTBI to TB disease is highest within the first two years post-infection. The progression of untreated LTBI to TB disease accounts for approximately 80% of U.S. TB cases. It is essential that we identify and treat people with LTBI in order to reach our TB elimination goals and prevent additional morbidity and mortality.

II. TARGETED TESTING

EXPANDING TESTING AND TREATMENT OF LTBI IS ESSENTIAL TO ELIMINATING TB IN THE U.S.

WHO SHOULD BE TESTED FOR TB:

The CDC and the U.S. Preventive Services Task Force (USPSTF) recommends targeted testing of people and populations who are at increased risk for LTBI. This targeted testing approach ensures that those most in need of treatment are provided access, while reducing waste of resources and preventing inappropriate treatment. During routine visits, healthcare providers are recommended to identify patients with increased risk and test them for LTBI, making sure to have a plan for follow-up care if a patient is diagnosed with LTBI or TB disease.

Those most at risk for developing TB disease include:

1. Those who have an increased likelihood of exposure to persons with TB disease; and
2. Those with conditions that increase their risk of progressing from LTBI to TB disease.

Those with an increased likelihood of exposure to persons with TB disease include:

- People who have had close contact with a person with confirmed or suspected active TB disease.
- 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 Virginia, we see the highest incidence in persons from India, Vietnam, Ethiopia, the Philippines, Honduras, and Guatemala.
- People who work or live in large group settings where there is a high risk for TB transmission, such as homeless shelters, correctional settings, hospitals, nursing homes, and other long term care facilities.
- Locally defined populations at an increased incidence of LTBI or TB disease, including medically underserved populations, low-income populations, or people with substance use disorders.
- Infants, children, or adolescents exposed to adults that have an increased likelihood of exposure to TB disease.

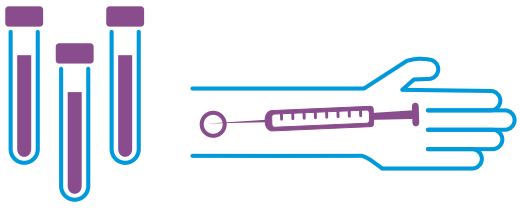
Those with conditions that increase the risk of progressing from LTBI to TB disease include:

- People living with HIV
- People with diabetes mellitus
- Children younger than 5 years of age
- People infected with *M. tuberculosis* within the last two years
- People with a history of untreated or inadequately treated TB
- People who are receiving immunosuppressive therapy, including tumor necrosis factor (TNF)-alpha antagonist, systemic corticosteroids equivalent to or greater than 15mg of prednisone/day, or immunosuppressive drug therapy following organ transplants
- People with certain medical conditions, including: cancer of the head, neck, or lung; chronic renal failure; gastrectomy or jejunoileal bypass; leukemia; silicosis
- People who are underweight or malnourished
- People who use drugs, particularly injection drugs

Conduct risk assessments to screen and identify patients at increased risk for LTBI or TB disease, using the risk assessment tools available on the VDH TB Program website (https://www.vdh.virginia.gov/tuberculosis/screening-testing/):

- Virginia TB Risk Assessment and User Guide
- Virginia TB Risk Assessment for Children Under 6 and User Guide
- CDC National Health Care Personnel (HCP) Baseline Individual TB Risk Assessment.

HOW TO TEST PEOPLE FOR TB:



There are two tests used to determine if a person has been infected with TB bacteria – TB blood tests (Interferon Gamma Release Assays [IGRAs]) and the Tuberculin Skin Test (TST). While these tests determine if a person has been infected with TB bacteria, a negative result does not exclude LTBI or TB disease. A diagnosis of LTBI requires additional follow up testing, including a chest radiograph and in certain circumstances a sputum culture, but should also include a complete evaluation of the patient's medical history, and a physical examination. **It is essential to exclude TB disease before initiating treatment for LTBI to ensure adequate and appropriate treatment.**

INTERFERON GAMMA RELEASE ASSAY (IGRA):

TB blood tests, more commonly known as IGRAs, test a person's blood in a laboratory to measure how the immune system reacts to the TB bacteria. For persons infected with *M. tuberculosis*, white blood cells will release interferon-gamma (IFN-γ) when mixed with antigens and controls. There are two IGRAs approved by the U.S. Food and Drug Administration (FDA) available in the United States: QuantiFERON®-TB Gold Plus (QFT-Plus) test and T-SPOT®. TB test (T-Spot).

The IGRA requires a single blood draw. It may be used in children ≥ 2. It is the preferred method for testing for TB infection in those who have received the bacille Calmette-Guérin (BCG) vaccine, or are unlikely to return to follow up appointments.

TUBERCULIN SKIN TEST (TST):

The Mantoux tuberculin skin test (TST) is conducted by a healthcare provider injecting 5 tuberculin units (0.1 cc) of purified protein derivative (PPD) intradermally into the lower part of the arm. After 2-3 days (48-72 hours), the patient returns to have a trained healthcare provider measure any induration, where the PPD was injected. A TST is the preferred test for children <2 years of age. TSTs are interpreted based on the size of the induration, the person's risk for TB infection, and their risk of progression to active TB disease.

It is important to note that people who have received the BCG vaccine may produce a false-positive TST reaction. False positive reactions can also occur when a person has certain non-tuberculosis mycobacteria infections, or when the test was improperly administered or interpreted. Thus, further evaluation is always needed for any positive TST reaction.

Additionally, false negative TST reactions are also possible. This may occur in the following populations: infants less than 6 months of age; immunosuppressed persons who are unable to mount an immune response; those who were recently infected with TB who are tested less than 8-10 weeks after exposure; those who received a recent live virus vaccination; those with a very remote infection; and those where the test was improperly administered or interpreted.

SELECTING A TB TEST

The decision of which TB screening test to use should be made by an individual's healthcare provider, and should include a plan for follow-up care for persons diagnosed with TB and LTBI.

Please note, a TST or IGRA should not be used for a person with documentation of a previous positive TB test result or treatment for TB disease.

While routine testing using both an IGRA and TST is not recommended, there are certain situations where it may be useful:

- When the initial test is negative and the risk for infection and progression to disease is high, or there is a clinical suspicion of TB disease and confirmation of the presence of *M. tuberculosis* infection is desired.
- When 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.

INTERPRETING TB TEST RESULTS

INTERFERON GAMMA RELEASE ASSAY (IGRA):

Interpretation of an IGRA test will depend on the type of test that was performed. If a QuantiFERON®-TB Gold Plus test was used, the result will be based on the amount of IFN-γ that is released in response to the *M. tuberculosis* antigens and control substances. If the T-SPOT® TB test was used, results are based on the number of IFN-γ producing cells produced. Result reports should include both qualitative and quantitative results.

Qualitative results include the following categories: positive, negative, indeterminate (QuantiFERON®-TB Gold Plus), invalid (T-SPOT® TB), and borderline (T-SPOT® TB). The interpretation of these categories are described below:

Result	Interpretation
Positive	This result indicates *M. tuberculosis* infection is likely.
Negative	This result indicates *M. tuberculosis* infection is unlikely, but cannot be excluded if the patient has signs and symptoms consistent with TB disease, or the patient has a high risk of developing TB disease once infected with *M. tuberculosis*.
Indeterminate	This result is specific to the QuantiFERON®-TB Gold Plus test, and indicates that the test did not provide useful information as to the presence of *M. tuberculosis* infection. Repeating the IGRA or performing a TST may be useful following this result.
Invalid	This result is specific to the T-SPOT® TB test, and indicates that the test did not provide useful information as to the presence of *M. tuberculosis* infection. Repeating the IGRA or performing a TST may be useful following this result.
Borderline	This result is specific to the T-SPOT® TB test, and indicates an uncertain likelihood of *M. tuberculosis* infection. Repeating the IGRA or performing a TST may be useful following this result.

Quantitative results are reported as numerical values, including quantitative assay measures of the TB antigen and negative and positive controls, known respectively as nil and mitogen.

TUBERCULIN SKIN TEST (TST):

TSTs are interpreted based on the size of the induration, the person's risk for TB infection, and their risk of progression to TB disease. Measurement and interpretation of a TST should be done only by a trained healthcare provider. Induration interpretations which indicate a positive result are described below:

≥ 5 or more millimeters	10 or more millimeters	15 or more millimeters
• People living with HIV • People with chest radiograph findings consistent with prior untreated TB disease • People with organ transplants • Other immunosuppressed persons • Close contacts to an infectious TB disease case	• People born in high incidence TB countries (i.e., Mexico, the Philippines, Vietnam, India, China, Haiti, and Guatemala) • People with substance use disorders • Mycobacteriology laboratory workers • People who live or work in high-risk congregate settings • People with certain medical conditions putting them at higher risk for TB (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, or certain intestinal conditions) • People who are underweight • Children younger than five years of age • Infants, children, and adolescents exposed to adults in high-risk categories	• People with no known risk factors for TB

ADDITIONAL TESTING GUIDANCE FOR SELECT POPULATIONS

BOOSTER PHENOMENON FOR TST TESTING

The booster phenomenon occurs during TST testing when a person is tested after many years of being infected with TB, causing them to have a negative reaction to an initial TST, followed by a positive reaction to a subsequent TST given up to a year later. This occurs because the first TST will stimulate or boost the person's ability to react to the test, and does not represent a skin test conversion between the first and second TSTs. This is most commonly seen in older adults who were previously infected but who's ability to react to tuberculin has decreased over time.

To address these concerns, a person's healthcare provider can perform what is called two-step testing, which distinguishes between a boosted reaction and reactions due to recent infections. Two-step testing is most useful for persons who will be retested periodically, and should be used for initial skin testing. To perform two-step TST testing, a person should receive an initial baseline TST. If this initial test is positive, the person likely has LTBI and should be treated after additional evaluation to rule

out active TB disease. If this initial test is negative, they should receive another TST approximately 1-3 weeks after the initial test. If the second test is positive, this reaction represents a boosted reaction, and the person likely has LTBI and should be treated after additional evaluation to rule out active TB disease. If the second TST is negative, it is unlikely that the person has LTBI.

CHILDREN

Routine healthcare evaluations should include TB risk assessments for all children. Testing should be considered for children with an increased risk of acquiring LTBI or TB disease.

If a child is identified as being at increased risk for LTBI or TB disease, the preferred tests are:

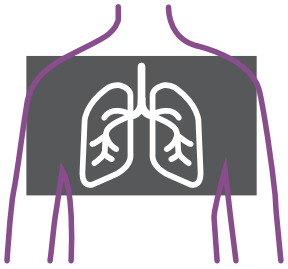
- An IGRA for asymptomatic children ≥2 years of age who have received the BCG vaccine or who are unlikely to return to have the TST read.
- A TST for children <2 years of age.

Please refer to the *Red Book: Report of the Committee on Infectious Diseases* which provides additional information on LTBI and TB testing and treatment for infants, children, and adolescents.

CONTACTS

Testing is recommended for all persons identified during a contact investigation as potential contacts to a person with known or presumptive infectious TB disease. When the initial TB test is negative, contacts should be retested 8-10 weeks after the last exposure using the same type of test as the infection may have been too recent to detect at the time of the first test.

Given their increased risk for rapid progression to TB disease, children younger than 5 years of age and persons who are immunosuppressed should receive a chest radiograph even if the initial TB test is negative and they are asymptomatic (see Completing the Clinical Workup section). If their chest radiograph is normal and their initial TB test is negative, they should still be started on treatment, which is known as window prophylaxis. This treatment is offered during what is known as the window period, which is the time it can take a TST or IGRA to become positive after a person has been exposed to another person with TB disease. Window prophylaxis can prevent early infection and progression to TB disease. Window prophylaxis should be continued until a second TB test is performed 8-10 weeks after their last exposure. If the second test is negative, treatment can usually be discontinued, but if it is positive, treatment should be continued and completed.



HEALTHCARE PERSONNEL

The CDC and National Tuberculosis Controllers Association (NTCA) recommend that all healthcare personnel be screened for TB upon hire. Annual TB testing is not recommended unless there is a known exposure, ongoing transmission, or they work in a high-risk setting. Screening should include a baseline TB risk assessment, TB symptom evaluation, a TB test, and additional evaluation for TB disease, as needed.

Please note, if a TST is used as the pre-placement testing method, personnel should be tested using the two-step TST process, but if an IGRA is used then the two-step is not required, as a single IGRA test will suffice.

PEOPLE LIVING WITH HIV

Given the significantly increased risk of progression from LTBI to TB disease amongst persons living with HIV (PLWH), it is recommended that all PLWH should be tested for LTBI at the time of their initial diagnosis, as well as annually for those with an increased risk for repeated or ongoing exposure to TB disease.

Given immunosuppression concerns amongst people living with advanced HIV or AIDS, a negative TB test, however, does not exclude the possibility of LTBI or TB disease. Further evaluation is necessary. Additionally, repeat testing is recommended for those previously known to have a negative TB test after initiating antiretroviral therapy (ART), as ART helps restore an immune response.

COMPLETING THE CLINICAL WORKUP

As previously mentioned, an IGRA or TST will only identify if a person has been infected with TB bacteria, but follow up testing and a complete physical examination and medical history review is required to determine if they have LTBI or TB disease. This testing should include a chest radiograph and in certain circumstances (e.g., PLWH or presence of respiratory symptoms) a sputum culture. It is essential to exclude TB disease before initiating treatment for LTBI to ensure adequate and appropriate treatment.

For chest radiographs, the CDC recommends the following:

- A chest radiograph is indicated in the absence of a positive IGRA or TST 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 a posterior-anterior and lateral chest radiograph, while all other ages should have at least posterior-anterior views. Other views or additional studies should be done at the provider's discretion.
- 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.

REPORTING REQUIREMENTS FOR LTBI

Beginning November 14, 2018, LTBI became a reportable condition in Virginia for people of any age. Results of a positive test for TB infection (IGRA or TST), as well as chest radiograph results, treatment information, and underlying conditions should be included in morbidity reports.

Providers can report LTBI electronically using the Virginia Department of Health's Confidential Morbidity Report on the VDH website (https://www.vdh.virginia.gov/tuberculosis/), or download a morbidity report form (Epi-1) if you prefer to fax a report of TB infection to your local health department.

LTBI TREATMENT REGIMENS OVERVIEW

Fortunately, there are several treatment options available to treat LTBI. Selecting the appropriate regimen should be based on the following:

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

The CDC and NTCA recommend short-course, rifamycin based treatments, as they are demonstrated to be safe, effective, and have higher completion rates than traditional six or nine month treatment regimens. If short-course treatments are not clinically appropriate, CDC and NTCA still recommend 6 or 9 months of daily isoniazid (INH) monotherapy. An electronic copy of these guidelines are available online at: http://www.tbcontrollers.org/resources/tb-infection/. Additionally, please consult the companion document, *Testing and Treatment of Latent Tuberculosis Infection in the United States: Clinical Recommendations*, which serves as a practical guide reflecting current best practice. The companion document may be accessed here: http://www.tbcontrollers.org/resources/tb-infection/

In summary, here are the recommended treatment regimens:

- Three months of once-weekly isoniazid plus rifapentine (3HP)
  - This regimen is recommended for those older than 2 years of age, including PLWH on ART that do not have drug-drug interactions with rifapentine (RPT), and should be given under directly observed therapy (DOT).
  - This regimen should not be used by those less than 2 years of age, PLWH with drug-drug interactions to RPT, people presumed to be infected with INH- or RIF-resistant *M. tuberculosis*, and pregnant women or those expecting to become pregnant during the 3-month treatment period.
- Four months of daily rifampin (4R)
  - This regimen is recommended for HIV-negative people of all ages, and those who cannot tolerate INH or have been exposed to INH-resistant *M. tuberculosis*. This regimen can be given by self-administered therapy (SAT).
  - This regimen should not be given to PLWH taking some combinations of ART.
- Three months of daily isoniazid plus rifampin (3HR)
  - This regimen is recommended for persons of all ages, including HIV-negative and HIV-positive patients as drug-drug interactions allow.
- Six or nine months of isoniazid (6H or 9H, respectively)
  - Both regimens are recommended for HIV-negative and HIV-positive persons of all ages, and can be given daily or twice weekly. If given twice weekly, then it should be given under DOT.

Please see the resources section of this document for additional information on the preferred and alternative LTBI treatment regimens, including dosage guidance.

Additionally, please refer to the CDC's guidance document, *Latent Tuberculosis Infection: A Guide for Primary Health Care Providers* https://www.cdc.gov/tb/publications/ltbi/default.htm for additional information on recommended treatment regimens for select populations, including pregnant women, PLWH, and infants and children.

LTBI TREATMENT REGIMENS SIDE EFFECTS

While all recommended treatment regimens are safe and effective, the medications do have some known adverse effects which providers and their patients should be aware of and know how to address. Ensuring providers have an accurate and complete medical history and list of current medication will help identify the most appropriate treatment, while also identifying those in need of close monitoring during their treatment course.

Below is a summary of possible side effects of INH, RIF and RPT:

INH	RIF and RPT
• Elevated serum liver concentrations • Clinical hepatitis • Peripheral neuropathy	• Hepatoxicity • Cutaneous reactions • Hypersensitivity reactions • Gastrointestinal symptoms • Discoloration (orange-red) of body fluids • Drug-drug interactions - including methadone, warfarin, hormonal contraceptives, tricyclic antidepressants, haloperidol, diazepam, and phenytoin • Contraindication with certain ART medications

In addition to sharing information on possible adverse effects, providers should share the following list of symptoms, and inform their patients to seek immediate medical attention if any of these should occur:

- Dizziness or lightheadedness
- Loss of appetite
- Flu-like symptoms (e.g., fever, chills, headaches, dizziness, musculo -skeletal pain)
- Severe diarrhea or light-colored stools
- Shortness of breath
- Feelings of sadness or depression
- Fever
- Unexplained weight loss
- Brown urine (color of coffee or cola)
- Yellowish skin or eyes
- Rash
- Persistent tingling or prickling sensation of hands and feet
- Persistent tiredness or weakness lasting 3 or more days
- Stomach pain
- Easy bruising or bleeding
- Joint pain
- Nausea
- Vomiting
- Itching

Please see the resources section of this document for additional information on possible adverse effects of LTBI medications.

In addition to clinical monitoring, baseline laboratory testing at the start of LTBI treatment is recommended for certain people with the following risk factors:

- History of liver disease
- Liver disorders
- Regular use of alcohol or injection drugs
- Risks for chronic liver disease
- HIV infection
- Pregnancy - including up to 3 months following delivery

Following initial baseline testing, routine laboratory testing is recommended for any persons with abnormal initial results, as well as those at risk for hepatic disease. Additionally, regardless of baseline testing, laboratory testing is recommended for any person who develops signs of hepatitis throughout the course of treatment or persons who develop jaundice. According to CDC, it is recommended that medication be held in instances where a person's transaminase levels exceed 3 times the upper limit of normal if the person is symptomatic, and 5 times the upper limit of normal if the person is asymptomatic.

PATIENT EDUCATION AND ENCOURAGING TREATMENT ADHERENCE

One of the most important factors in positive patient outcomes is ensuring patients are provided with appropriate and comprehensive LTBI education. One resource that may be helpful is our *Latent Tuberculosis Infection Patient Resource Guide*, but we also have many other resources available through our website (https://www.vdh.virginia.gov/tuberculosis/). Patient education should always be delivered in a culturally competent manner and should include:

- LTBI disease overview - including differences between LTBI and TB disease, how LTBI is acquired, how LTBI can progress to TB disease, how TB tests work and are interpreted, including for those who have received the BCG vaccine, and addressing any misconceptions around LTBI
- LTBI treatment overview - including importance of completing treatment, use of medication trackers and other reminder techniques, possible side effects and how to manage them, and when and how patients should contact their care team.

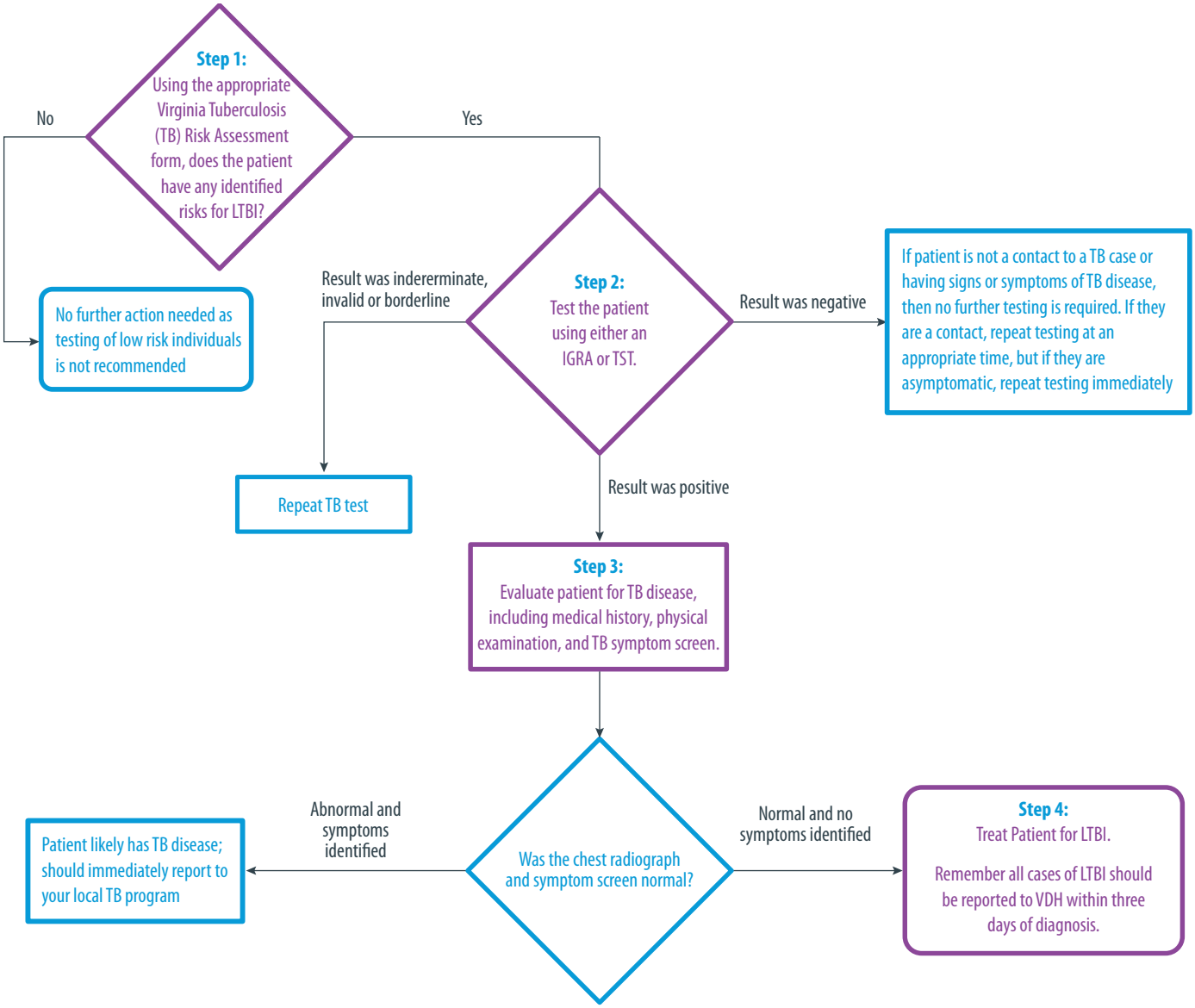
Providers should be mindful of the stigma associated with TB, and should work with their patients to address and unpack this stigma, including providing patients with suggestions on how to discuss their diagnosis with friends and family. Additionally, ensuring education and care plans are developed and provided in a culturally competent manner is essential. Important elements to consider include cultural practices, language accessibility and accommodations, and religious practices, particularly fasting. Lastly, providers should identify and collaboratively develop strategies to address any barriers to treatment completion, including individual barriers, such as coexisting medical conditions, clinic-based barriers, such as inconvenient hours, and treatment barriers, such as medication side effects. While some barriers will be easier to identify solutions for than others, addressing barriers before treatment will help improve patient adherence.

TREATMENT COMPLETION AND NEXT STEPS

Healthcare providers should provide completion documentation, including TB test results, chest radiograph results, names, dosage, and duration of treatment medications, and the contact information of the treating provider to their patients upon completion of treatment. Patients should be instructed to present this documentation when any future TB screening is requested, and reminded that any future TB test will likely always be positive, so there is no need to repeat testing. Patients should also be reminded of the signs and symptoms of TB disease, and advised to inform their healthcare provider should they develop any signs or symptoms of TB disease.

LTBI PROVIDER DECISION TREE

Adapted from a similar tool developed by the California Department of Health, please refer to the decision tree below, which overviews the LTBI screening, testing, and treatment process.



LATENT TUBERCULOSIS INFECTION TREATMENT REGIMENS

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. https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_w

	DRUG	DURATION	FREQUENCY	TOTAL DOSES	DOSE AND AGE GROUP
Preferred	ISONIAZID† AND RIFAPENTINE†† (3HP)	3 months	Once weekly	12	**Adults and children aged ≥12 yrs** 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 k g; 900 mg maximum
					Children aged 2–11 yrs INH†: 25 mg/kg; 900 mg maximum RPT††: See above
	RIFAMPIN§ (4R)	4 months	Daily	120	**Adults:** 10 mg/kg; 600 mg maximum
					Children: 15–20 mg/kg‖; 600 mg maximum
	ISONIAZID† AND RIFAMPIN§ (3HR)	3 months	Daily	90	**Adults** INH†: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum
					Children INH†: 10-20 mg/kg#; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum
Alternative	ISONIAZID† (6H/9H)	6 months	Daily	180	**Adults** Daily: 5 mg/kg; 300 mg maximum Twice weekly: 15 mg/kg; 900 mg maximum
			Twice weekly¶	52	
		9 months	Daily	270	**Children** Daily: 10-20 mg/kg#; 300 mg maximum Twice weekly: 20–40 mg/kg#; 900 mg maximum
			Twice weekly¶	76	

* 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.

†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).

§ 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 INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

ADVERSE EFFECTS OF DRUGS USED TO TREAT LTBI

CDC LATENT TUBERCULOSIS INFECTION: A GUIDE FOR PRIMARY HEALTH CARE PROVIDERS

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 intolerability 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.

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.

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Tuberculosis Program

The Virginia Department of Health TB Program aims to prevent, treat, and eliminate TB to protect the health and promote the well-being of all people in Virginia.

For additional information, please visit our website at https://www.vdh.virginia.gov/tuberculosis/ or contact us at 804-864-7906 or tuberculosis@vdh.virginia.gov

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