



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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TUBERCULOSIS
INFECTION:
A GUIDE FOR PRIMARY
HEALTH CARE
PROVIDERS

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LIST OF ABBREVIATIONS

ART	antiretroviral therapy
AFB	acid-fast bacilli
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
APHL	American Public Health Laboratories
AST	aspartate aminotransferase
ATS	American Thoracic Society
BCG	bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
DTH	delayed-type hypersensitivity
DOT	directly observed therapy
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assay
IFN- γ	interferon-gamma
INH	isoniazid
LTBI	latent TB infection
MDR TB	multidrug-resistant tuberculosis
MMWR	<i>Morbidity and Mortality Weekly Report</i>
NNRTIs	nonnucleoside reverse transcriptase inhibitors
PI	protease inhibitors
PPD	purified protein derivative
QFT-G	QuantiFERON [®] -TB Gold
QFT-GIT	QuantiFERON [®] -TB Gold In-tube
RIF	rifampin
TB	tuberculosis
TNF- α	tumor necrosis factor-alpha
T-Spot	T-SPOT [®] .TB
TST	tuberculin skin test
USPHS	U.S. Public Health Service
WHO	World Health Organization

INTRODUCTION

This guide is intended for primary care providers who care for individuals and populations who may be at risk for infection with *Mycobacterium tuberculosis*. Latent tuberculosis infection (LTBI) is the presence of *Mycobacterium tuberculosis* in the body without signs and symptoms, or radiographic or bacteriologic evidence of tuberculosis (TB) disease.

Approximately one-third of the world's population is infected with *M. tuberculosis*. In the United States, an estimated 9–14 million people have LTBI. Without treatment, approximately 5–10% of persons with LTBI will progress to TB disease at some point in their lifetime. Identifying and treating those at highest risk for TB disease will help move toward elimination of the disease. Primary care providers play a key role in achieving the goal of TB elimination because of their access to high-risk populations.

Guidelines for testing and treating LTBI were released by the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS). They can be found in the June 9, 2000 issue of *Morbidity and Mortality Weekly Report (MMWR)*, entitled *Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection*. Most recently, recommendations for the use of interferon-gamma release assays (IGRAs) were released in the June 25, 2010 issue of *Morbidity and Mortality Weekly Report (MMWR)*, entitled *Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium Tuberculosis Infection*. References for these guidelines and updates can be found on page 32.

This document is not meant to be used as a substitute for the guidelines, but rather as a ready and useful reference that highlights the main points of those guidelines.

TARGETED TESTING FOR TUBERCULOSIS

Targeted testing is an essential TB prevention and control strategy. This strategy entails finding and treating persons with LTBI who are at the highest risk for progressing to TB disease, and thus would benefit from treatment. Treatment of these high-risk individuals also benefits society by reducing the number of future TB cases. Unfocused population-based testing is not cost-effective or useful and leads to unnecessary treatment. TB testing activities should be conducted only among high-risk groups, with the intent to treat if LTBI is detected. Once TB disease has been excluded, treatment of LTBI should be offered to patients regardless of their age.

However, there may be instances in which health care providers are asked to test individuals who are not necessarily regarded as high risk (e.g., daycare center workers, teachers, and U.S.-born students). A few simple questions will help health care providers assess a patient's risk for LTBI. Appendix A (p. 24) contains a sample risk assessment tool.

Currently, there are two testing methods available for the detection of *M. tuberculosis* infection in the U.S. The tests include:

- Mantoux tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs)

Three U.S. Food and Drug Administration (FDA) approved IGRAs are commercially available in the U.S.:

- QuantiFERON®-TB Gold test (QFT-G)
- QuantiFERON®-TB Gold-in-Tube test (QFT-GIT)
- T.SPOT®.TB test

IDENTIFYING PERSONS AT RISK FOR DEVELOPING TB DISEASE

Generally, persons at risk for developing TB disease fall into two broad categories: those who **have an increased likelihood of exposure to persons with TB disease** and those with **clinical conditions or other factors associated with an increased the risk of progression from LTBI to TB disease**.

Persons at risk for exposure to persons with TB disease include the following:

- Known close contacts of a person with infectious TB disease
- Persons who have immigrated from TB-endemic regions of the world (see Appendix B, p. 25)
- Persons who work or reside in facilities or institutions with people who are at high risk for TB, such as hospitals that care for TB patients, homeless shelters, correctional facilities, nursing homes, or residential facilities for patients with AIDS

Also at risk are those with certain **conditions and other factors associated with progression from LTBI to TB disease**. These conditions and factors include:

- HIV infection
- Injection drug use
- Radiographic evidence of prior healed TB
- Low body weight (10% below ideal)
- Other medical conditions, such as:
 - silicosis
 - diabetes mellitus
 - chronic renal failure or on hemodialysis
 - gastrectomy
 - jejunioileal bypass
 - solid organ transplant
 - head and neck cancer
 - conditions that require prolonged use of corticosteroids or other immunosuppressive agents such as TNF-antagonists
- Recent TST converters (persons with baseline testing results who have an increase of 10 mm or more in the size of the TST reaction within a 2-year period. The risk of progression is greatest in the first 1 or 2 years after infection.)
- Infants and children under the age of five years who have a positive TB test result

DIAGNOSIS OF LATENT TB INFECTION

The diagnosis of LTBI is based on information gathered from the medical history, TST or IGRA result, chest radiograph, physical examination, and in certain circumstances, sputum examinations. The presence of TB disease must be excluded before treatment for LTBI is initiated (i.e., waiting for culture results if specimens are obtained) because failure to do so may result in inadequate treatment and development of drug resistance (see Table 1).

CDC discourages use of diagnostic tests for LTBI among individuals and populations at low risk for infection with *M. tuberculosis*. Despite CDC recommendations to the contrary, testing is sometimes done to meet administrative or legal requirements for groups who are not considered to have an increased possibility of infection in the absence of other factors cited above, such as persons meeting entrance requirements for certain schools and workplaces.

**TABLE 1:
Differentiating Between LTBI and TB Disease**

LTBI

- No symptoms or physical findings suggestive of TB disease
- Positive TST or IGRA result
- Chest radiograph normal
- If done, respiratory specimens are smear and culture negative

TB Disease

- Symptoms *may* include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite.
- TST or IGRA result usually positive
- Chest radiograph is usually abnormal. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease.
- Respiratory specimens are usually smear or culture positive. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease.

TESTS FOR TB INFECTION

Tuberculin Skin Test (TST)

The tuberculin skin test (TST) is used to determine if a person is infected with *M. tuberculosis*. The skin test is administered intradermally using the Mantoux technique by injecting 0.1ml of 5 TU purified protein derivative (PPD) solution. If a person is infected, a delayed-type hypersensitivity reaction is detectable 2–8 weeks after infection. The reading and interpretation of TST reactions should be conducted within 48 to 72 hours of administration by a trained health care professional. For more information about tuberculin skin testing, visit the CDC website for additional resources (see Resources, p. 30) and refer to Appendix C on p. 26.

Key Points

- The TST should not be performed on a person who has written documentation of either a previous positive TST result or treatment for TB disease.
- Patients or family members should never measure TST results; this should only be done by a trained health care professional.
- Interpretation of the TST result is the same for persons who have had BCG vaccination.
- A TST that was not measured and recorded in mm of induration must be repeated.

CLASSIFICATION OF TUBERCULIN SKIN TEST REACTIONS

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

- HIV-infected persons
- Recent contacts of a person with infectious TB disease
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Organ transplant recipients
- Persons who are immunosuppressed for other reasons (e.g., taking equivalent of ≥15 mg/day of prednisone for 1 month or more or those taking TNF-α antagonists)

- A TST reaction of **≥10 mm of induration** is considered positive in
- Recent immigrants (within last 5 years) from high-prevalence countries
 - Injection drug users
 - Residents or employees of high-risk congregate settings (prisons, jails, long-term care facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with AIDS, and homeless shelters)
 - Mycobacteriology laboratory personnel
 - Persons with clinical conditions previously mentioned (see p. 7)
 - Children younger than 4 years of age
 - Infants, children, or adolescents exposed to adults at high risk for TB disease (see p. 7)

- A TST reaction of **≥15 mm of induration** is considered positive in
- Persons with no known risk factors for TB

Although skin testing activities should be conducted only among at-risk groups, certain individuals may be required to have testing for employment or school attendance independent of risk. CDC and ATS do not recommend an approach independent of risk assessment.

Interferon–Gamma Release Assays (IGRAs)

IGRAs are used to determine if a person is infected with *M. tuberculosis*. The QuantiFERON®-TB Gold test (QFT-G), QuantiFERON®-TB Gold In-Tube test (QFT-GIT), and T-SPOT®-TB are blood tests that measure a person’s immune reactivity to specific mycobacterial antigens. Specimens are mixed with peptides that simulate antigens derived from *M. tuberculosis* and controls. In a person infected with *M. tuberculosis*, the white blood cells recognize the simulated antigens and release interferon-gamma (IFN-γ); results are based on the amount of IFN-γ released.

Key Points

- Advantages of IGRAs include the following:
 - Requires a single patient visit
 - Does not cause booster phenomenon (see p. 13)
 - Less subject to reader bias than TST
 - Unaffected by BCG and most environmental mycobacteria

- Limitations of IGRAs include the following:
 - Blood sample must be processed within 8-16 hours
 - Limited data exist on use in groups such as children younger than 5 years of age, persons recently exposed to TB, immunocompromised persons, and those who will be tested repeatedly (serial testing)

Selecting a Test to Detect TB Infection

- IGRAs are the preferred method of testing for:
 - Groups of people who have a poor rates of returning to have TST read
 - Persons who have received BCG vaccine
- TST is the preferred method for testing for:
 - Children under the age of 5 years
- Either TST or IGRA may be used without preference for other groups that are tested for LTBI.

Key Point

- Routine testing with *both* TST and IGRAs is **NOT** recommended.

TABLE 2:
Interpretation of IGRA Results

IGRA test	Results reported as:
• QuantiFERON® - TB Gold	• Positive, negative, indeterminate
• QuantiFERON® - TB Gold In-Tube	• Positive, negative, indeterminate
• T-SPOT® .TB	• Positive, negative, indeterminate, borderline

Note: Laboratory should provide both quantitative and qualitative test results

SPECIAL CONSIDERATIONS IN TESTING FOR TB INFECTION

BCG Vaccine

The BCG (bacillus Calmette-Guerin) vaccine is currently used in many parts of the world where TB is common to protect infants and young children from serious, life-threatening disease, specifically miliary TB and TB meningitis. The World Health Organization (WHO) recommends that **BCG** vaccine be administered during infancy in TB endemic countries. BCG vaccination is not recommended in the U.S. The question of the effect of BCG vaccine on TST results often causes confusion. TST reactivity caused by BCG vaccine generally wanes with the passage of time, but periodic skin testing may prolong (boost) reactivity in vaccinated persons. A history of BCG vaccine is not a contraindication for tuberculin skin testing or treatment for LTBI in persons with positive TST results. TST reactions should be interpreted regardless of BCG vaccination history (see pages 9-10).

IGRAs use *M. tuberculosis* specific antigens that do not cross react with BCG and therefore, do not cause false positive reactions in BCG recipients.

HIV Infection

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 and who are HIV negative only have a 10% risk over their lifetime.

HIV-infected persons should be tested for LTBI as soon as their HIV status becomes known. A negative TST or IGRA result does not exclude LTBI as they may have a compromised ability to react to tests for TB infection. Annual testing should be considered for HIV-infected persons who are TST or IGRA negative on initial evaluation and who have a risk for exposure to *M. tuberculosis*. Because the usefulness of anergy testing in HIV-infected individuals or others has not been demonstrated, it is not recommended.

After the initiation of antiretroviral therapies (ART), repeat testing for LTBI is recommended in HIV-infected persons previously known to have negative TST or IGRA results as immune reconstitution may result in restoration of immune response.

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. They may have a positive reaction to a subsequent TST because the initial test stimulates their ability to react to the test. This is commonly referred to as the “booster effect” and may incorrectly be interpreted as a skin test conversion (going from negative to positive). For this reason, the “two-step method” is recommended at the time of **initial** testing for individuals who may be tested periodically (e.g., health care workers). If the first TST result in the two-step baseline testing is positive, consider that the person is 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 that the person is infected and evaluate and treat the person accordingly; if both steps are negative, consider the person uninfected and classify the TST as negative at baseline testing (see Figure 1).

When IGRAs are used for serial testing, there is no need for a second test because boosting does not occur.

FIGURE 1:
Two-Step Tuberculin Skin Test (TST) Method

1st TST	Negative	Repeat TST in 1–3 weeks
2nd TST	Negative	Person probably does not have infection
	Positive	Boosted reaction due to infection in the past

Contacts

- For contacts of a person with infectious TB disease, retesting in 8–10 weeks is indicated when the initial TST or IGRA result is negative.
- Children under the age of 5 years and immunosuppressed persons (e.g., HIV infected) who have a negative results should have a chest radiograph. If normal, treatment should be started for LTBI and another test performed 8–10 weeks after contact has ended.

- If a repeat test result is positive, treatment should be continued. If it is negative, treatment can usually be discontinued. However, for some contacts at very high risk a full course of LTBI treatment may be recommended even in the absence of a positive TST or IGRA result. Consult with your local TB control program about the management of such contacts.
- In contact investigations, retesting is not called two-step testing. The second test is needed to determine if infection occurred but was too early in onset to be detected at the time of the first test.
- If testing is repeated, the same type of test (TST or IGRA) should be used.

Pregnancy

- Test only if specific risk factors are present. (see p. 7).
- If a TST or IGRA reaction is positive, obtain a chest radiograph using proper shielding.

OTHER DIAGNOSTIC CONSIDERATIONS

Chest Radiograph

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

- Order a chest radiograph as part of a medical evaluation for a person who has a positive TST or IGRA result.
- A chest radiograph is also 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 (i.e., “window prophylaxis” in a young child or immunocompromised person).
- Children less 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.
- Persons with nodular or fibrotic lesions consistent with old TB are high-priority candidates for treatment.
- Persons with calcified granulomas only are not at increased risk for progression to TB disease.
- Periodic follow-up radiographs are not indicated regardless of whether treatment is completed except in unusual circumstances (e.g., contacts to patients with MDR TB).

Sputum Examination for AFB Smear and Culture

Sputum examination is indicated for persons 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).

Physical Examination and Medical History

Physical examination and medical history, which includes obtaining information about previous positive results of a test for TB, previous treatment for LTBI or TB disease, and a risk assessment for liver disease, are indicated for an individual with positive test results. Written documentation of a previously positive TST or IGRA result is required; a patient’s verbal history is not sufficient. Appendix D (p. 28) provides an example of a documentation form.

TREATMENT OF LATENT TB INFECTION

TREATMENT REGIMENS

Using an adaptation of the U.S. Public Health Service (USPHS) rating system, CDC and ATS have rated LTBI treatment regimens based on the strength of recommendation and the quality of the evidence that supports that recommendation (see Table 3).

**TABLE 3:
Treatment Regimens**

Drug/Dose	Frequency/ Duration (Doses)	Rating*(Evidence)†	
		HIV negative	HIV positive
Preferred Regimen			
Isoniazid Adult: 5 mg/kg Children: 10-20 mg/kg Maximum dose 300 mg	Daily x 9 months (270 doses)	A (II)	A (II)
Alternate Regimens			
Isoniazid Adult: 15 mg/kg Children: 20-40 mg/kg Maximum dose 900 mg	Twice weekly x 9 months§ 76 doses)	B (II)	B (II)
Isoniazid Adults: 5 mg/kg Children: Not recommended Maximum dose 300 mg	Daily x 6 months (180 doses)	B (I)	C (I)
Isoniazid Adults: 15 mg/kg Children: Not recommended Maximum dose 900 mg	Twice weekly x 6 months§ (52 doses)	B (II)	C (I)
Rifampin Adults: 10 mg/kg Children: 10-20 mg/kg Maximum dose 600 mg	Daily x 4 months (120 doses) Daily x 6 months (180 doses)	B (II)	B (III)

Note: In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

* Strength of the recommendation: A = preferred regimen; B = acceptable alternative; C = offer when A and B cannot be given

† Quality of the supporting evidence: I = randomized clinical trials data; II = data from clinical trials not randomized or from other population; III = expert opinion

§ Intermittent regimen must be provided via directly observed therapy (DOT), i.e., health care worker observes the ingestion of medication

SPECIAL CONSIDERATIONS IN THE TREATMENT OF LTBI

Contacts

Contacts are those with recent exposure to a person with known or suspected infectious TB (e.g., pulmonary or laryngeal TB with positive sputum smear). They should be evaluated immediately for LTBI and TB disease. If the TST or IGRA result is positive, the guidelines below should be followed. Those who have negative results should be retested in 8–10 weeks. **However, if the chest radiograph is normal, LTBI treatment should be initiated in TST-negative children ≤ 5 years of age (note: some TB control programs may use a different age cutoff) and in immunocompromised persons of all ages who have negative TST or IGRA results. Treatment should be continued until the results of the second test and other medical evaluation are known.** For some contacts at very high risk a full course of LTBI treatment may be recommended even in the absence of a positive TST or IGRA result. Consult with your local TB control program about the management of such contacts.

- If person is exposed to known *drug-susceptible* TB or drug susceptibility is unknown:
 - Positive TST or IGRA result → treat regardless of age with isoniazid (INH) for 9 months preferred
- If person is exposed to known *isoniazid-resistant* TB:
 - Positive TST or IGRA result → treat for 4 months with rifampin (RIF)
- If person is exposed to known *multidrug-resistant* TB (MDR TB):
 - Positive TST or IGRA result → Consult an expert in the treatment of multidrug-resistant TB
- In general, TST or IGRA-positive contacts who can provide written documentation of prior adequate treatment for LTBI do not need to be retreated. Retreatment may be indicated for persons at high risk of becoming reinfected and progressing to TB disease (e.g., young children and immunosuppressed persons)

HIV-Infected Individuals

- HIV-infected individuals should be treated with a 9-month regimen of INH.

- **Rifampin** (RIF) is contraindicated in HIV-infected persons being treated with certain combinations of antiretroviral drugs. In those cases, rifabutin may be substituted for RIF (see CDC website at <http://www.cdc.gov/tb> for guidelines for the use of rifamycins and protease inhibitors or nonnucleoside reverse transcriptase inhibitors).
- If TB test result is negative, treat if HIV-infected person had recent exposure to infectious TB as discussed above.

Pregnancy

- After TB disease is excluded, consider immediate treatment for LTBI if the woman is HIV-infected or a recent contact, and monitor.
- In the absence of risk factors, wait until after the woman has delivered to avoid administering unnecessary medication during pregnancy.
- INH daily or twice weekly (using DOT) is the preferred regimen.
- Supplementation with 10-25 mg/d of pyridoxine (vitamin B6) is recommended.
- There is potential for an increased risk of hepatotoxicity during pregnancy and the first 2-3 months of the post-partum period.
- Consider delaying treatment for LTBI until 2–3 months post-partum unless there is a high risk of progression to TB disease (e.g., HIV infected, recent contact).

Breastfeeding

- Breastfeeding is not contraindicated in women taking INH.
- Supplementation with 10-25 mg/d of pyridoxine (vitamin B6) is recommended for nursing women and for breastfed infants.
- The amount of INH in breast milk is inadequate for treatment of infants with LTBI.

Infants and Children

- Infants and children under 5 years of age with LTBI have been recently infected and, therefore, are at high risk for progression to disease.
- Testing of adults 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.
- 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 (see below).
- DOT should be considered.

Additional Notes of Importance

- Old fibrotic lesions can represent previous TB disease. Persons with TST result of ≥ 5 mm of induration or a positive IGRA result and no active disease 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.

ADVERSE EFFECTS OF DRUGS USED TO TREAT LTBI

Some health care providers have concerns about treating patients for LTBI. These concerns are generally related to the length of treatment and the potential side effects of isoniazid (INH). 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 the health care provider in determining the most appropriate course of action. In addition, 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.

The sections that follow discuss some of the adverse effects of INH and RIF, as well as recommendations for monitoring during treatment and for assessing and ensuring adherence.

Possible adverse effects of INH

- Asymptomatic elevation of serum liver enzyme concentrations occurs in 10%–20% of people taking INH. Increased enzyme concentrations can be accepted at up to 5 times the upper limit of normal for patients who are free of hepatitis symptoms, if the serum bilirubin concentration is in the normal range. Liver enzyme concentrations usually return to normal even when treatment is continued.
- Clinical hepatitis occurs in about 0.1% of people taking INH, and is more common when INH is combined with other agents. Factors that may increase either these rates or the severity of hepatitis include alcohol consumption, underlying liver disease or risks for liver disease, and the concurrent use of other medications which 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, and younger patients should be monitored clinically with the same precautions as older patients.

- Peripheral neuropathy occurs in less than 0.2% of people taking INH at conventional doses, and is more likely in the presence of other conditions associated with neuropathy such as diabetes, HIV, renal failure, and alcoholism. Pyridoxine (vitamin B6) supplementation is recommended in such conditions or to prevent neuropathy in pregnant or breastfeeding women.

Possible adverse effects of rifampin (RIF)

- Hepatotoxicity, evidenced by transient asymptomatic hyperbilirubinemia, may occur in 0.6% of persons taking RIF. Hepatitis is more likely when RIF is combined with INH.
- Cutaneous reactions, such as pruritis (with or without a rash), may occur in 6% of persons taking RIF. It is generally self-limited and may not be a true hypersensitivity; continued treatment may be possible.
- Gastrointestinal symptoms such as nausea, anorexia, and abdominal pain are rarely severe enough to discontinue treatment.
- Orange discoloration of body fluids is expected and harmless, but patients should be advised beforehand. Soft contact lenses may be permanently stained.
- RIF interacts with a number of drugs, causing drug-drug interactions. It is known to reduce concentrations of methadone, warfarin, oral contraceptives, and phenytoin. Women using oral contraceptives should be advised to consider an alternative method of contraception.
- RIF is contraindicated, or should be used with caution, in HIV-infected individuals being treated with certain protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs). In this situation, rifabutin may be substituted.

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 the following:

Clinical Monitoring

- Patients should visit the health care provider who is managing treatment on a monthly basis for
 - Brief physical assessment for signs of hepatitis
 - Assessment of adherence
 - Review of symptoms of possible adverse drug reactions or interactions

- Patients taking INH or RIF who experience possible adverse reactions should be advised to stop medication and consult their health care provider immediately.

Patient Education

- Explain the disease process and rationale for medication in absence of symptoms or radiographic abnormalities.
- Review the importance of completing treatment for LTBI.
- Discuss possible side effects of LTBI medications such as
 - Fever
 - Unexplained anorexia
 - Dark urine (color of coffee or cola)
 - Icterus
 - Rash
 - Persistent paresthesia 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
 - Nausea
 - Vomiting
- Discuss management of common side effects and the need to report to health care provider.

Laboratory Testing

- Baseline laboratory testing (measurements of serum AST, ALT, and bilirubin) are not routinely necessary
- 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
 - Risks for chronic liver disease
 - HIV infection
 - Pregnancy or the immediate postpartum period (i.e., within 3 months of delivery)
- Baseline testing can be considered on an individual basis, especially for patients taking other medications for chronic medical conditions.
- After baseline testing, routine periodic retesting 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, dark urine, chills) or who have jaundice. Patients should be instructed, at the start of treatment and at each monthly visit, to stop taking treatment and to seek medical attention immediately if symptoms of hepatitis develop and not to wait until a clinic visit to stop treatment.
- AST or ALT elevations up to 5 times normal can be accepted if the patient is free of hepatitis symptoms, and up to 3 times normal if there are signs or symptoms of liver toxicity.

ASSESSING ADHERENCE

Many variables affect a patient's adherence to the medication regimen for treatment of LTBI. Episodes of nonadherence should be recognized and addressed as soon as possible. Some examples of barriers to adherence are noted in the section that follows.

Office-Related Variables

- Long waiting time for appointment and referrals
- Long waiting time in provider's office
- Inconvenient office hours
- Complicated telephone system (not "user-friendly")

Patient-Related Variables

- Misinformation about topics such as
 - The TST; for example, a positive TST result is thought to be normal or common in all foreign-born persons
 - Differences between injections, vaccines, and TST
 - The words "positive" and "negative"
 - Transmission and prevention
 - Safety of family and friends around someone with LTBI
- Residential instability
- Lack of financial resources
- Poor access to health care
- Stigma associated with tuberculosis
- Co-existing medical conditions
- Culture and language
- Religious practices i.e., fasting from food

Treatment Variables

- Complexity and duration of treatment
- Medication side effects
- Obtaining refills
- Frequency of office visits

TECHNIQUES TO IMPROVE ADHERENCE

- Collaborate with local health department to provide
 - DOT, especially if intermittent therapy is desirable or if patient is high risk (e.g., HIV infected, young child, or TB contact)
 - Case management to coordinate care and services
 - Free or low-cost medication
 - Incentives (rewards for adherence)
 - Grocery store or restaurant vouchers
 - Nutritional supplements
 - Cell phone minutes
 - Movie tickets
 - Enablers (to overcome barriers)
 - Free van transportation or bus tickets
 - Effective patient education
- Provide patient education and instructions in patient's primary language
- Reinforce patient education at each visit
- Ensure confidentiality
- Suggest or provide patient reminders such as pill box, calendar, timer

POST-TREATMENT FOLLOW-UP

- Patient should receive documentation of TST or IGRA results and treatment completion that includes name, dates, chest radiograph result, and dosage and duration of medication. The patient should be instructed that he or she should present this document any time future testing is required.
- Providers should re-educate patient about the signs and symptoms of TB disease and advise them to contact the medical provider if he or she develops any of these signs or symptoms.
- Regardless of whether the patient completes treatment for LTBI, serial or repeat chest radiographs are not indicated unless the patient develops signs or symptoms suggestive of TB disease.

APPENDIX A

SAMPLE TB RISK ASSESSMENT TOOL

Persons with any of the following risk factors should be tested for TB infection unless there is written documentation of a previous positive TST or IGRA result.

Risk Factor	Yes	No
Recent close or prolonged contact with someone with infectious TB disease	_____	_____
Foreign-born person from or recent traveler to high-prevalence area	_____	_____
Chest radiographs with fibrotic changes suggesting inactive or past TB	_____	_____
HIV infection	_____	_____
Organ transplant recipient	_____	_____
Immunosuppression secondary to use of prednisone (equivalent of ≥ 15 mg/day for ≥ 1 month) or other immunosuppressive medication such as TNF- α antagonists	_____	_____
Injection drug user	_____	_____
Resident or employee of high-risk congregate setting (e.g., prison, long term care facility, hospital, homeless shelter)	_____	_____
Medical conditions associated with risk of progressing to TB disease if infected (e.g., diabetes mellitus, silicosis, cancer of head or neck, Hodgkin's disease, leukemia, and end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndrome, low body weight [10% or more below ideal for given population])	_____	_____
Signs and symptoms of TB	_____	_____

Adapted from a form developed by Minnesota Department of Health TB Prevention and Control Program

APPENDIX B

IDENTIFYING PERSONS FROM HIGH-RISK 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 2009, approximately 60% of TB cases in the United States occurred in foreign-born individuals.
- The majority of U.S. cases among foreign-born individuals are in people from seven countries (Mexico, Philippines, Vietnam, India, China, Haiti, and Guatemala).
- For a list of high burden countries and profiles of these countries, see the Stop TB Partnership website: <http://www.stoptb.org/countries/tbdata.asp> – *Note that the ranking of countries changes yearly.*

APPENDIX C

ADMINISTRATION AND MEASUREMENT OF THE TST*

Administration

The Mantoux test is the recommended TST. It is administered by injecting 0.1 ml of 5 TU 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 TST. 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 the TST.
- Instruct patient not to scratch the site, but to use cool compress to relieve any itching or swelling.
- Inform patient of the importance of returning for a reading of the TST within 48–72 hours (2–3 days).
- Give written appointment card for TST reading.
- Provide written information about TST (pamphlet or brochure).

Measurement

- Measure the induration (hard bump) rather than erythema.
- 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 tuberculin skin testing ruler or ruler with millimeters to measure the distance between the two 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 patient and ordering health care provider with written documentation.

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 and 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.*

APPENDIX D

SAMPLE DOCUMENTATION FORMS

Record of TB Skin Test

To Whom It May Concern:

The following is a record of Mantoux tuberculin skin testing:

Name: _____ Date of birth: _____

Date and time test administered: _____

Administered by: _____

Manufacturer of PPD: _____

Expiration date: _____ Lot Number: _____

Date and time test read: _____ Read by: _____

Date: _____

Results (in millimeters) _____

Record of Interferon-Gamma Release Assay for TB

To Whom It May Concern: _____

The following is a record of IGRA results:

Name: _____

Date of birth: _____

Type of test: _____ Date: _____

Laboratory: _____

Qualitative result: _____ Nil (IU IFN- γ): _____

Mitogen (IU IFN- γ): _____ *M. tb* antigens (IU IFN- γ): _____

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: _____

TST: Date: _____ Results (in millimeters of induration): _____

IGRA: Date: _____ Type of test: _____ Result: _____

Chest radiograph: Date: _____ Results: _____

Date medication started: _____ Date completed: _____

Medication(s): _____

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

Signature of Provider _____

Date _____

RESOURCES

WEBSITES

Centers for Disease Control and Prevention (CDC)
Division of Tuberculosis Elimination
<http://www.cdc.gov/tb>

TB Education and Training Resources
<http://www.findtbresources.org>

World Health Organization
<http://www.who.org>

REGIONAL TRAINING AND MEDICAL CONSULTATION CENTERS (RTMCCS)

- Francis J. Curry National Tuberculosis Center
Website: <http://www.nationaltbcenter.edu>
Phone: 415-502-4600
Serving Alaska, California (Los Angeles, San Diego, and San Francisco), Colorado, Hawaii, Idaho, Montana, Nevada, Oregon, Utah, Washington, Wyoming, and the U.S. Affiliated Pacific Islands (USAPI).
- Heartland National Tuberculosis Center
Website: <http://www.heartlandntbc.org>
Phone: 1-800-839-5864
Serving Arizona, Illinois (Chicago), Iowa, Kansas, Minnesota, Missouri, New Mexico, Nebraska, North Dakota, Oklahoma, South Dakota, Texas (Houston), and Wisconsin.
- New Jersey Medical School – Global Tuberculosis Institute
Website: <http://www.umdnj.edu/globaltb>
Phone: 973-972-3270
Serving Connecticut, District of Columbia, Delaware, Indiana, Massachusetts, Maryland (Baltimore City), Maine, Michigan (Detroit), New Hampshire, New Jersey, New York (New York City), Ohio, Pennsylvania (Philadelphia), Rhode Island, Vermont, and West Virginia.
- Southeastern National Tuberculosis Center
Website: <http://sntc.medicine.ufl.edu>
Phone: 352-265-7682
Serving Alabama, Arkansas, Florida, Georgia, Kentucky, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee, Virginia, Puerto Rico, and the U.S. Virgin Islands.

EDUCATIONAL MATERIALS FOR HEALTH CARE PROVIDERS*

- Mantoux Tuberculin Skin Testing Products
(Centers for Disease Control and Prevention)
- Management of LTBI in Children and Adolescents
(NJMS Global Tuberculosis Institute, 2009)
- Fact Sheets
 - Targeted Tuberculin Testing and Interpreting Tuberculin Skin Test Results
 - Treatment of Latent Tuberculosis Infection: Maximizing Adherence
 - Treatment Options for Latent Tuberculosis Infection
 - Interferon-Gamma Release Assay (IGRAs)
(Centers for Disease Control and Prevention)
- Slide Set
 - Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection: Applying CDC/ATS Guidelines in Your Clinical Practice
(Centers for Disease Control and Prevention)

* CDC education and training materials may be viewed, downloaded, and ordered online at <http://www.cdc.gov/tb>.

STATE HEALTH DEPARTMENT TB PROGRAM

Phone: _____

Fax: _____

LOCAL HEALTH DEPARTMENT TB PROGRAM

Phone: _____

Fax: _____

REFERENCES

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CDC. Update: adverse event data and revised American Thoracic Society/ CDC recommendations against the use of rifampin and pyrazinamide for the treatment of latent tuberculosis infection—United States, 2003. *MMWR* 2003;52(31):735-9.

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<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5302a6.htm>

CDC. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection – United States - 2010. *MMWR* 2010;59(RR05).

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<http://www.cdc.gov/mmwr/pdf/rr/rr58e324.pdf>

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