# Guide for Primary Health Care Providers:

# Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

CDC
TB Elimination™
SAFER • HEALTHIER • PEOPLE™

New Jersey Medical School
National Tuberculosis Center
*A Founding Component of the International Center for Public Health*

# Guide for Primary Health Care Providers

## Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

Department of Health and Human Services
Centers for Disease Control and Prevention
National Center for HIV, STD, and TB Prevention
Division of Tuberculosis Elimination
Atlanta, Georgia
2005

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| | |
|---|---|
| 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 |
| DHP | delayed-type hypersensitivity |
| DOT | directly observed therapy |
| EMB | ethambutol |
| FDA | Food and Drug Administration |
| HAART | highly active antiretroviral therapies |
| HIV | human immunodeficiency virus |
| IFN-γ | interferon-gamma |
| INH | isoniazid |
| LTBI | latent TB infection |
| MDR TB | multidrug-resistant tuberculosis |
| MDR LTBI | multidrug-resistant latent TB infection |
| MMWR | *Morbidity and Mortality Weekly Report* |
| NNRTIs | nonnucleoside reverse transcriptase inhibitors |
| PI | protease inhibitors |
| PPD | purified protein derivative |
| PZA | pyrazinamide |
| QFT | QuantiFERON®-TB test and QuantiFERON®-TB Gold test |
| RIF | rifampin |
| TB | tuberculosis |
| TNF-α | tumor necrosis factor-alpha |
| TST | tuberculin skin test |
| USPHS | U.S. Public Health Service |
| WHO | World Health Organization |

# INTRODUCTION

Latent tuberculosis infection (LTBI) is infection with *Mycobacterium tuberculosis* organisms (tubercle bacilli) without signs and symptoms nor radiographic or bacteriologic evidence of tuberculosis (TB) disease. When small droplet nuclei containing the tubercle bacilli reach the alveoli, they are engulfed by macrophages and usually destroyed. However, when a number survive and multiply, they can cause LTBI.

Approximately one-third of the world's population is infected with *M. tuberculosis*. In the United States, it is estimated that 9–14 million people have LTBI. Without treatment, approximately 5–10% will progress to TB disease at some point in their lifetime. Identifying and treating those at highest risk for TB disease will help us 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.

The Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) published guidelines in the June 9, 2000 issue of *Morbidity and Mortality Weekly Report (MMWR), entitled Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection*. In addition, updates to the 2000 guidelines have been published. Major changes from prior recommendations fall into three categories: testing for LTBI, treatment of LTBI, and clinical monitoring (see Table 1).

Terminology used in the guidelines also reflects a change. The commonly used terms "preventive therapy" and "chemoprophylaxis" have been replaced with "treatment of latent TB infection (LTBI)." This more accurately describes the use of a treatment regimen to prevent the development of TB disease in persons with LTBI (see Table 2).

**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.**

**TABLE 1:**
**Changes Found in the 2000 Guidelines and Subsequent Updates**

*Testing for LTBI*

- Tuberculin skin testing discouraged for those at low risk for developing TB disease
- Testing recommended for high-risk individuals, regardless of age
- Lower cut-off point established for organ transplant recipients and other immunosupressed persons (on daily prednisone for one or more months); 5 mm induration considered positive
- TST conversion considered an increase in induration of at least 10 mm within a 2-year period, regardless of age
- The QuantiFERON®-TB test and QuantiFERON®-TB Gold test (QFT) are blood tests that measures a person's immune reactivity to *M. tuberculosis*
- Prolonged use of immunosuppressive agents such as TNF-α antagonists increases risk of progression from LTBI to TB disease

*Treatment of LTBI*

- INH for 9 months preferred over 6-month regimen for HIV-negative individuals
- INH for 9 months for HIV-infected persons or those with old TB (fibrotic lesions on chest radiograph)
- RIF for 4 months for HIV-uninfected and HIV-infected individuals
- RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events

*Clinical and laboratory monitoring*

- Baseline and laboratory monitoring needed for HIV-infected persons, pregnant or postpartum women, and persons who have chronic liver disease or who regularly use alcohol
- Follow-up only indicated if baseline tests are abnormal
- Tests include serum AST, ALT, and bilirubin
- Emphasis on clinical monitoring for signs of possible adverse drug reactions

*Key: INH – Isoniazid RIF – Rifampin PZA – Pyrazinamide*

**TABLE 2:**
**Changes in Terminology**

***Latent TB infection (LTBI)*** is a condition in which TB bacteria are present, but contained. Individuals with LTBI have no symptoms and cannot spread the disease to others. They may develop TB disease later in life if they do not receive treatment.

***Treatment of LTBI*** is treatment with medication that prevents the development of TB disease.

> ***Old terminology*** – Preventive therapy or chemoprophylaxsis

***Targeted tuberculin testing*** focuses on testing groups of people who are at high risk for TB infection and identifying those who would benefit from treatment.

> ***Old terminology*** – TB screening

# TARGETED TUBERCULIN TESTING

Targeted tuberculin testing is an essential TB prevention and control strategy. Finding and treating those with LTBI reduces the number of potential TB cases; however, unfocused testing is not cost-effective or useful. Targeted testing programs should be designed to find persons at high risk for developing TB disease and who would benefit from treatment. Once TB disease has been ruled out, treatment of LTBI should be offered to patients regardless of their age. Tuberculin testing programs should be conducted only among high-risk groups, with the intent to treat if LTBI is detected.

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 college students). A few simple questions will help health care providers assess a patient's risk for LTBI. Appendix A (p. 27) contains a sample risk assessment tool.

The two available methods of testing for *M. tuberculosis* infection are the tuberculin skin test (TST) and an approved blood test: QuantiFERON®-TB test and QuantiFERON®-TB Gold test (QFT).

## IDENTIFYING PERSONS AT RISK FOR DEVELOPING TB DISEASE

Generally, persons at high risk for developing TB disease fall into two broad categories: those who have been **recently infected** and those with **clinical conditions** that increase the risk of progression from LTBI to TB disease.

The risk of progression is greatest in the first 1 or 2 years after exposure. Persons likely to have been recently infected with *M. tuberculosis* include the following:

- Close contacts of a person with infectious TB
- 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)
- Persons who have immigrated from TB-endemic regions of the world (see Appendix B, p. 28)
- Children ≤5 years of age who have a positive TST result
- Persons who work or reside in facilities or institutions with people who are at high risk for TB, such as hospitals, homeless shelters, correctional facilities, nursing homes, or residential facilities for patients with AIDS

Also at risk are those with certain conditions associated with progression from LTBI to TB disease. These conditions 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, jejunoileal bypass, solid organ transplant, head and neck cancer, and other conditions that require prolonged use of prednisone or other immunosuppressive agents such as TNF-α antagonists.

# DIAGNOSIS OF LATENT TB INFECTION

The diagnosis of LTBI is based on information gathered from TST or QFT results, chest radiographs, physical examination, and, in certain circumstances, sputum examinations. The presence of TB disease must be ruled out before treatment for LTBI is initiated (i.e., waiting for culture results if specimens are obtained) because failure to rule out TB may result in inadequate treatment and development of drug resistance (see Table 3).

**TABLE 3:**
**Differentiating Between LTBI and TB Disease**

| LTBI | TB disease |
|---|---|
| • No symptoms or physical findings suggestive of disease<br>• Positive TST or QFT<br>• Chest radiograph negative for active disease | • Symptoms *may* include one or more of the following: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite<br>• Chest radiograph may be abnormal<br>• Respiratory specimens may be smear or culture positive<br>• TST or QFT usually positive |

## TESTING FOR LATENT TB INFECTION

### *Tuberculin Skin Test (TST)*

The tuberculin skin test (TST) detects individuals infected with *M. tuberculosis*. The skin test is administered intradermally using the Mantoux technique by injecting 0.1 ml of 5 TU purified protein derivitive (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 trained health care professionals. For more information about tuberculin skin testing, consult the CDC Mantoux Tuberculin Skin Test video and wall chart (see Resources, p. 32 and refer to Appendix C on p. 29).

Key Points

- The TST should not be performed on a person who has a documented history of either a positive TST result or treatment for TB disease.
- TST results should only be read and interpreted by a trained health care professional. Patients or family members should not be relied upon to measure TST results.
- TB disease must be ruled out before initiating treatment for LTBI to prevent inadequate treatment of TB disease.

### *QuantiFERON®-TB Test and QuantiFERON®-TB Gold Test (QFT)*

The QuantiFERON®-TB test and QuantiFERON®-TB Gold test (QFT) are blood tests that measure a person's immune reactivity to *M. tuberculosis*. Blood specimens are mixed with antigens and incubated for 16–24 hours. In a person with LTBI, the blood cells recognize the tuberculin antigen and release interferon-gamma (IFN-γ); results are based on the proportion of IFN-γ released. The first generation QFT (QuantiFERON®-TB test) was approved by the U.S. Food and Drug Administration (FDA) in 2001. The second generation test (QuantiFERON®-TB Gold test) was approved by the FDA in 2005.

QFT advantages:

- Requires a single patient visit
- Does not cause booster phenomenon (see p. 13)
- Less subject to reader bias than TST

QFT disadvantages:

- Blood sample must be processed in 12 hours

QFT is recommended for:

- Initial and serial testing for those at increased risk for LTBI

CDC discourages use of diagnostic tests for LTBI among populations at low risk for infection with *M. tuberculosis*. However, initial testing is occasionally performed among certain population groups for surveillance purposes or where cases of infectious TB disease might result in extensive transmission to highly susceptible populations, including the following:

- Initial and serial testing of persons who are at low risk for LTBI, but whose future activity places them at increased risk of exposure.
- Testing of those who are not considered to have an increased possibility of infection, such as persons meeting entrance requirements for certain schools and workplaces.

QFT is not currently recommended for

- Screening of pregnant women, children under the age of 17, or persons with clinical conditions that increase the risk of progression to disease
- Confirmation of TST results
- Diagnosis of *M. avium*-complex disease

Refer to the CDC website for the most current information on the use of QFT: http://www.cdc.gov/tb.

## SPECIAL CONSIDERATIONS IN TESTING FOR LATENT 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 BCG vaccination once in infancy in TB endemic countries. 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. However, there is no reliable skin test method for distinguishing between vaccine-related reactions and reactions caused by mycobacterial infections. QuantiFERON®-TB Gold test, which uses *M. tuberculosis* specific antigens, is designed to not cross react with BCG and may cause less false positive reactions. 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 15–16).

### *HIV Infection*

The risk of progression from LTBI to TB disease is 7% to 10% each year for those with both LTBI and HIV infection. Those with LTBI and who are HIV negative only have a 10% risk over their lifetime.

HIV-infected persons may have a compromised ability to react to the TST, but should be tested for LTBI as soon as their HIV status becomes known. A negative TST reaction does not rule out LTBI. Annual repeat testing should be considered for HIV-infected persons who are TST-negative on initial evaluation and who belong to populations in which a substantial risk for exposure to *M. tuberculosis* exists. Because the usefulness of anergy testing in HIV-infected individuals has not been demonstrated, it is not recommended.

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

### *Booster Phenomenon*

Some people with LTBI 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 will be tested periodically (e.g., health care workers). If the first test result in the two-step baseline testing is positive, consider that the person has LTBI and evaluate and treat the person accordingly. If the first test result is negative, the second step of the two-step baseline testing should be repeated in 1–3 weeks. If the second test result is positive, consider that the person has LTBI and evaluate and treat the person accordingly; if both steps are negative, consider the person uninfected and classify the TST as a negative baseline (see Figure 1).

**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 |

Note: A single step approach would be used for serial testing at baseline with QFT because boosting does not occur with QFT.

*Contacts*

- For contacts of an infectious TB case, retesting in 8–10 weeks is indicated when the initial TST result is negative.
- Children under the age of 5 years and immunosuppressed persons (e.g., HIV-infected) who have a negative TST result should be treated and another TST performed 8–10 weeks after contact has ended.
- If a repeat TST result is positive, treatment should be continued. If a repeat TST result is negative, treatment can be discontinued.
- Retesting is not called two-step testing. The second test is needed in case infection occurred but was too early in onset at the time of the first test.

*Pregnancy*

- Pregnancy and the post partum period may affect the pathogenesis of TB and may increase the risk of progression from infection to TB disease.
- The TST has no adverse effects on the pregnant mother or fetus.
- Test only if specific risk factors are present, such as HIV infection or recent contact with a person who has infectious TB (see p. 9 for additional risk factors).
- There is potential increased risk of hepatotoxicity during pregnancy and the post-partum period.
- Consider delay of treatment 2–3 months post partum unless at higher risk (e.g., HIV infected, recent contact).
- If a TST reaction is positive, obtain a chest radiograph using proper shielding.

## CLASSIFICATION OF TUBERCULIN SKIN TEST REACTIONS

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

- HIV-infected persons
- Recent contact of infectious TB cases
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Organ transplant recipients
- Those who are immunosupressed for other reasons (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 healthcare facilities, residential facilities for patients with AIDS, and homeless shelters)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions previously mentioned (see p. 9)
- Children younger than 4 years of age
- Infants, children, or adolescents exposed to adults at high risk for TB disease (see p. 9)

A tuberculin skin test reaction of **≥15 mm of induration** is considered positive in

- Persons with no risk factors for TB

Although skin testing programs should be conducted only among high-risk groups, certain individuals may require testing for employment or school attendance. An approach independent of risk assessment is not recommended by CDC or ATS.

## OTHER DIAGNOSTIC CONSIDERATIONS

### *Chest Radiograph*

Chest radiographs help differentiate between LTBI and pulmonary TB disease in individuals with positive TST or QFT results. The following guidelines are recommended:

- Order chest radiograph as part of a medical evaluation for a person who has a positive TST or QFT
- A chest radiograph is also indicated in the absence of a positive TST result 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 physician's judgment
- Persons with nodular or fibrotic lesions consistent with old TB are high-priority candidates for treatment
- Persons with calcified granulomas only are low 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 a positive TST or QFT result 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, including previous positive reactions and risk assessment for liver disease, are indicated for positive skin test reactors. Written documentation of a previously positive TST or QFT result is required; a patient's verbal history is not sufficient. Appendix D (p. 31) 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 4).

**TABLE 4: Treatment Regimens**

| Drug/Dose | Frequency/Duration | Rating* (Evidence)† HIV negative | Rating* (Evidence)† HIV positive |
|---|---|---|---|
| **Preferred Regimen** | | | |
| **Isoniazid**<br>Adult: 5 mg/kg<br>Children: 10-20 mg/kg<br>Maximum dose 300 mg | Daily x 9 months | A (II) | A (II) |
| **Alternate Regimens** | | | |
| **Isoniazid**<br>Adult: 15 mg/kg<br>Children: 20-40 mg/kg<br>Maximum dose 900 mg | Twice weekly x 9 months§ | B (II) | B (II) |
| **Isoniazid**<br>Adults: 5 mg/kg<br>Maximum dose 300 mg | Daily x 6 months | B (I) | C (I) |
| **Isoniazid**<br>Adults: 15 mg/kg<br>Maximum dose 900 mg | Twice weekly x 6 months§ | B (II) | C (I) |
| **Rifampin**<br>Adults: 10 mg/kg<br>Children: 10-20 mg/kg<br>Maximum dose 600 mg | Daily x 4 months | B (II) | B (II) |

**Note:** A regimen of rifampin and pyrazinamide for the treatment of LTBI should generally not be offered due to risk of severe adverse events.

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*

*§ 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, prolonged exposure to a person with known or suspected infectious TB (i.e., pulmonary or laryngeal TB with positive sputum smear). They should be evaluated immediately for TB disease and LTBI. If the TST is positive, the guidelines below should be followed. Those who have negative TST reactions should be retested in 8–10 weeks. **However, 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; this should be continued until the results of the second test and other medical evaluation are known.** This treatment is known as "window prophylaxis" and accounts for the time period immediately after exposure when a TST may remain negative.

- If person is exposed to known *drug-susceptible* TB or drug susceptibility is unknown:
  - Positive TST result → treat regardless of age with isoniazid (INH) for 9 months preferred
  - Negative TST result → retest in 8–10 weeks

- If person is exposed to known *isoniazid-resistant* TB:
  - Positive TST result → treat for 4 months with rifampin (RIF)
  - Negative TST result → retest in 8–10 weeks

- If person is exposed to known *multidrug-resistant* TB (MDR TB):
  - Positive TST result → An expert in the treatment of multidrug-resistant TB should be consulted.
  - Negative TST result → retest in 8–10 weeks

- In general, TST-positive contacts with a documented history of prior adequate treatment for LTBI do not need to be re-treated. Re-treatment may be indicated for persons at high risk of becoming re-infected and progressing to TB disease (e.g., immunocompromised 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 TST result is negative, treat if person has recent, prolonged exposure to infectious TB or if there is ongoing risk for exposure.

*Pregnancy*

- Consider immediate treatment for LTBI if the woman is HIV-infected or 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 preferred regimen
- Supplementation with 50 mg of pyridoxine (vitamin B6) is recommended

*Breastfeeding*

- Breastfeeding is not contraindicated in women taking INH
- Supplementation with 50 mg of pyridoxine (vitamin B6) is recommended for nursing women and for breastfed infants
- Amount of INH in breast milk is inadequate for treatment of infants exposed to TB

*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
- Risk of INH-related hepatitis in infants, children, and adolescents is minimal
- Routine monitoring of serum liver enzymes is not necessary
- DOT should be considered

*Additional Notes of Importance*

- Old fibrotic lesions can represent previous TB disease. Persons with TST result of ≥5mm of induration 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. Persons should not receive treatment unless other risk factors are present.

## ADVERSE EFFECTS OF DRUGS USED TO TREAT LTBI

Many 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 physician must weigh the risks and benefits for each individual. Obtaining a detailed and accurate medical history and updating information at frequent intervals will detect persons who require close monitoring and aid the physician 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 isoniazid and rifampin, 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 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 0.1% to 0.15% 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. 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.
- 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 provider should periodically assess the patient's progress. This evaluation involves the following:

### *Laboratory Testing*

- Baseline laboratory testing (measurements of serum AST, ALT, and bilirubin) 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 signs of 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.

*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 physician 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 physician

## ASSESSING ADHERENCE

Many variables affect a patient's adherence to the medication regimen for treatment of LTBI. Episodes of nonadherence should be detected 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

*Treatment Variables*

- Visits for administering, reading, and counseling between TST and QFT
- 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 or TB contact)
  - — Case management to coordinate care and service
  - — Free or low-cost medication
  - — Incentives (rewards for adherence)
    - ■ Grocery store or restaurant vouchers
    - ■ Nutritional supplements
    - ■ 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 QFT results and treatment completion that includes name, dates, chest radiograph, 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.
- Patient should be re-educated about the signs and symptoms of TB disease and told to contact his or her 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 are candidates for tuberculin testing, unless there is written documentation of a previous positive TST or QFT.

| 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, LTC 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 2003, 53% of TB cases in the U.S. occurred in foreign-born individuals.

- More than 60% of U.S. cases among foreign-born individuals reported in 2003 were in people from seven countries (Mexico, Philippines, Vietnam, India, China, Haiti, and South Korea).

# 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; obtain documentation
- 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, 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 physician 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.

*Contact the local health department TB program for training on the Mantoux tuberculin skin test.

# APPENDIX D

## SAMPLE TST AND TREATMENT DOCUMENTATION FORMS

### Tuberculin Skin Test Record

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 of induration): _____

### Treatment Completion Letter

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): _____

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

**U.S. Regional Training and Medical Consultation Centers (RTMCCs)**

- Francis J. Curry National Tuberculosis Center
  Phone: 415-502-4600
  Serving AK, CA, CO, HI, ID, MT, NV, OR, UT, WA, WY, Federated States of Micronesia, Northern Mariana Islands, Republic of Marshall Islands, American Samoa, Guam, Republic of Palau
- Heartland National Tuberculosis Center
  Phone: 1-800-839-5864
  Serving AZ, IA, IL, KS, MN, MO, NM, NE, ND, OK, SD, TX, WI
- Northeastern National Tuberculosis Center
  Phone: 973-972-3270
  Serving CT, DC, DE, IN, MA, MD, ME, MI, NH, NJ, NY, OH, PA, RI, VT, WV
- Southeastern National Tuberculosis Center
  Phone: 352-265-7682
  Serving AL, AR, FL, GA, KY, LA, MS, NC, SC, TN, VA, Puerto Rico, U.S. Virgin Islands

**Educational Materials for Health Care Providers***

- Mantoux Tuberculin Skin Test video and wall chart (Centers for Disease Control and Prevention, 2002)
- Management of LTBI in Children and Adolescents (NJMS National Tuberculosis Center, 2003)

- Fact Sheets
  (Centers for Disease Control and Prevention, 2005)
  — Targeted Tuberculin Testing and Interpreting Tuberculin Skin Test Results
  — Treatment of Latent Tuberculosis Infection: Maximizing Adherence
  — Treatment Options for Latent Tuberculosis Infection
- Slide Set
  (Centers for Disease Control and Prevention, 2005)
  — Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection: Applying CDC/ATS Guidelines in Your Clinical Practice

*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


ATS/CDC/IDSA. Treatment of tuberculosis. *MMWR* 2003;52 (No. RR-11).
http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

CDC. Targeted tuberculin testing and treatment of latent TB infection. *MMWR* 2000;49 (No. RR-6).
http://www.cdc.gov/mmwr/PDF/rr/rr4906.pdf

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.
http://www.cdc.gov/mmwr/PDF/wk/mm5231.pdf

CDC. Guidelines for using the QuantiFERON®-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. *MMWR* 2003;52(RR02):15-18.
http://www.cdc.gov/mmwr/PDF/RR/RR5202.pdf

CDC. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR* 2004;53(2):37.
http://www.cdc.gov/nchstp/tb/pubs/mmwr/mm5302.pdf

CDC. Tuberculosis associated with blocking agents against tumor necrosis factor - Alpha - California, 2002–2003. *MMWR* 2004; 53 (No. 30).
http://www.cdc.gov/mmwr/PDF/wk/mm5330.pdf

CDC. Guidelines for preventing opportunistic infections among HIV-infected persons—2002: Recommendations of the U.S. Public Health Service and the Infectious Diseases Society of America. *MMWR* 2002;51(RR-8).
http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf

# NOTES