



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

LATENT TUBERCULOSIS INFECTION: A GUIDE FOR PRIMARY HEALTH CARE PROVIDERS

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and TB Prevention
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LIST OF ABBREVIATIONS

AFB	acid-fast bacilli
ART	antiretroviral therapy
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BCG	bacille Calmette-Guérin
CDC	Centers for Disease Control and Prevention
DOT	directly observed therapy
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assay
IFN- γ	interferon-gamma
INH	isoniazid
LTBI	latent TB infection
MDR TB	multidrug-resistant tuberculosis
MMWR	Morbidity and Mortality Weekly Report
PPD	purified protein derivative
QFT-GIT	QuantiFERON®-TB Gold In-tube
RIF	rifampin
RPT	rifapentine
TB	tuberculosis
TNF- α	tumor necrosis factor-alpha
TST	tuberculin skin test
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*. It is estimated that more than 11 million people in the United States have LTBI, which is about 4% of the total population. While not everyone with LTBI will develop TB disease, about 5 – 10% of infected people will develop TB disease if not treated. This equates to approximately 550,000 to 1,100,000 people who will develop TB at some point in their life, unless they receive adequate treatment for LTBI. 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*.

More 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*. In addition, recommendations for a new regimen for the treatment of LTBI were introduced. They can be found in the December 9, 2011 issue of *Morbidity and Mortality Weekly Report (MMWR)*, entitled *Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent Mycobacterium tuberculosis Infection*.

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 that is used to identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection (LTBI) or at high risk for developing TB disease once infected with *M. tuberculosis*. Identifying persons with LTBI is important to the goal of TB control and elimination because treatment of LTBI can prevent infected persons from developing TB disease and stop the further spread of TB. All testing activities should be accompanied by a plan for appropriate follow-up medical evaluation and treatment. Necessary medical evaluation and treatment resources need to be identified before testing activities begin. 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, unless medically contraindicated.

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. 27) contains a sample risk assessment tool.

Currently, there are 2 testing methods available for the detection of *M. tuberculosis* infection in the United States:

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

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

- 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 2 broad categories:

- Those who have an increased likelihood of exposure to persons with TB disease
- Those with clinical conditions or other factors associated with an increased 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. 28)
- 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 HIV infection/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 the following:

- 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- α antagonists
- Recent TST converters (that is, 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)
- Infants and children under the age of 5 who have a positive TB test result

Of note, the risk of progression is greatest in the first 1 or 2 years after infection.

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 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 Latent TB Infection and TB Disease

LTBI

- No symptoms or physical findings suggestive of TB disease.
- TST or IGRA result usually positive.
- Chest radiograph is typically normal.
- If done, respiratory specimens are smear and culture negative.
- Cannot spread TB bacteria to others.
- Should consider treatment for LTBI to prevent TB disease.

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.
- May spread TB bacteria to others.
- Needs treatment for TB disease.

TESTS FOR TB INFECTION

Tuberculin Skin Test (TST)

The TST is used to determine if a person is infected with *M. tuberculosis*. If a person is infected, a delayed-type hypersensitivity reaction is detectable 2 to 8 weeks after infection. The skin test is administered intradermally using the Mantoux technique by injecting 0.1ml of 5 TU purified protein derivative (PPD) solution. The reading and interpretation of TST reactions should be conducted within 48 to 72 hours of administration. For more information about tuberculin skin testing, visit the CDC website for additional resources (see Resources, p. 34) and refer to Appendix C on p. 29.

Key Points

- Training is essential for health care providers to gain proficiency in the administration and interpretation of the TST.
- 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 because a majority of BCG cross-reactivity wanes with time.
- A TST that was not measured and recorded in millimeters (mm) of induration must be repeated.

CLASSIFICATION OF TUBERCULIN SKIN TEST REACTIONS

Interpretation of TST results is based on the measurement of the reaction in millimeters, the person's risk of acquiring TB infection, or the risk of progression to disease if infected. See the risk stratification below.

A TST reaction of **≥5 mm** of induration is considered positive in the following individuals:

- HIV-infected persons
- Recent contacts of a person with infectious TB disease
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients (including patients taking the 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 the following individuals:

- Recent arrivals to the United States (within last 5 years) from high-prevalence areas
- Injection drug users
- Residents or employees of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, hospitals and other health care facilities, residential facilities for patients with HIV infection/AIDS, and homeless shelters)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that increase the risk for progression to TB disease (see p. 7)
- Children younger than 5 years of age
- Infants, children, and adolescents exposed to adults in high risk categories (see p. 7)

A TST reaction of ≥ 15 mm of induration is considered positive in the following individuals:

- 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 a testing approach that is independent of a risk assessment.

Interferon–Gamma Release Assays (IGRAs)

IGRAs are used to determine if a person is infected with *M. tuberculosis* by measuring the immune response to TB proteins in whole blood. Specimens are mixed with peptides that simulate antigens derived from *M. tuberculosis* and controls. In 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.

As noted earlier, there are 2 U.S. Food and Drug Administration (FDA) approved IGRAs commercially available in the United States:

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

Key Points

- Advantages of IGRAs include the following:
 - Requires a single patient visit to conduct the test.
 - Does not cause booster phenomenon (see p. 13).
 - Laboratory test not affected by health care worker perception or bias.
 - Results can be available within 24 hours.
 - Unaffected by BCG and most environmental mycobacteria.
- Limitations of IGRAs include the following:
 - Blood sample must be processed within 8-30 hours after collection.
 - 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).

Interpretation of IGRA Results

The interpretation of IGRAs is based on the amount of INF- γ released, in QFT, or on the number of cells that release INF- γ , in T-SPOT®.TB. Laboratories should provide both the qualitative and quantitative results.

- Qualitative results are reported as positive, negative, indeterminate or borderline.
- Quantitative results are reported as numerical values that include a response to the TB antigen and 2 controls, nil and mitogen. Quantitative results may be useful for clinical decision making in individual cases, in combination with risk factors.

Selecting a Test to Detect TB Infection

- IGRAs are the preferred method of testing for -
 - Groups of people who have poor rates of return for TST reading and interpretation (e.g., homeless persons)
 - Persons who have received BCG vaccination
- 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; however, there are certain situations where results from both tests may be useful (see Appendix D, p. 31).

SPECIAL CONSIDERATIONS IN TESTING FOR TB INFECTION

BCG Vaccine

In many parts of the world where TB is common, BCG vaccine is used to protect infants and young children from serious, life-threatening disease, specifically miliary TB and TB meningitis. The World Health Organization (WHO) recommends that BCG vaccine be administered during infancy in TB endemic countries. BCG vaccination is not generally recommended in the United States. 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 person with a history of BCG vaccination can be tested and treated for LTBI if they react to the TST. TST reactions should be interpreted based on risk stratification regardless of BCG vaccination history.

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 who are not HIV-infected have a 10% risk over their lifetime. Thus the risk of progression to TB disease is 10 times greater for those who are HIV infected. This risk is reduced with antiretroviral therapy for HIV, but is still higher than that in HIV-negative persons with LTBI.

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*. The usefulness of energy testing in HIV-infected individuals or others has not been demonstrated; therefore, it is not recommended.

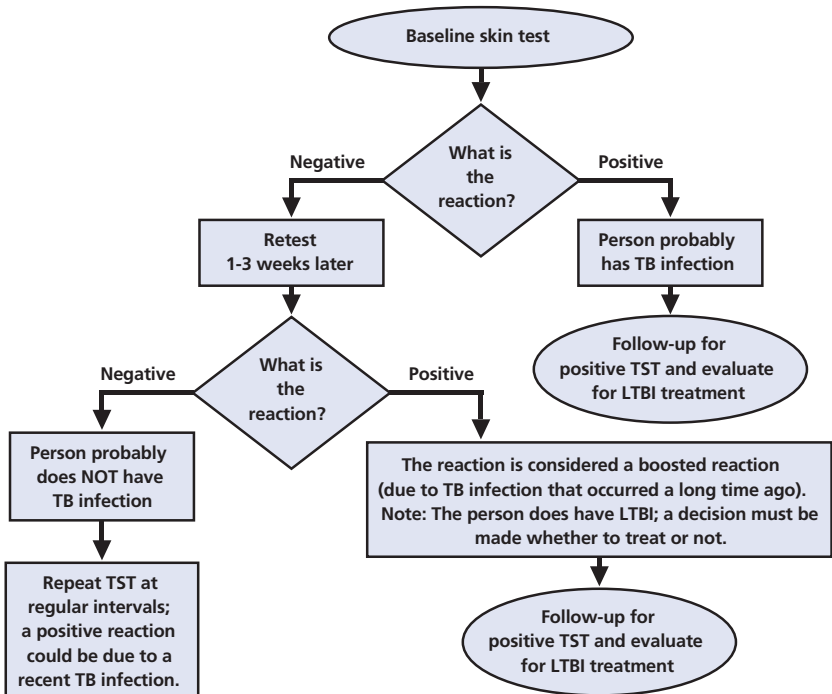
After the initiation of antiretroviral therapy (ART), repeat testing for LTBI is recommended for HIV-infected persons previously known to have negative TST or IGRA results. This is because the immune response may be restored by ART.

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 phenomenon” 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 the person infected and evaluate and treat the person accordingly. If the first test result is negative, the TST should be repeated in 1–3 weeks. If the second test result is positive, consider the person infected and evaluate and treat the person accordingly; if both 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 TST TESTING



Contacts

- For contacts of a person with infectious TB disease, retesting in 8–10 weeks after exposure has ended is indicated when the initial TST or IGRA result is negative. In contact investigations, retesting is not called two-step testing. The second test is needed to determine if infection occurred, but was too recent to be detected at the time of the first test.
- Children under the age of 5 years and immunosuppressed persons (e.g., HIV infected) who have negative TST or IGRA results should have a chest radiograph. If chest radiograph is normal, treatment should be started for LTBI and another TST or IGRA performed 8–10 weeks after contact has ended.
- If a repeat TST or IGRA result is positive, treatment should be continued. If it is negative, treatment can usually be discontinued.
- If testing is repeated, the same type of test (TST or IGRA) should be used.

Pregnancy

- TST is both safe and reliable throughout the course of pregnancy.
- Test only if specific risk factors are present for acquiring LTBI or for progression of LTBI to TB disease (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:

- A chest radiograph should be ordered 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 (e.g., “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 of LTBI after TB disease is excluded.
- Persons with fully calcified, discrete granulomas do not have an increased risk for progression to TB disease.

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 tests for TB infection, previous treatment for LTBI or TB disease, and a risk assessment for liver disease, are indicated for an individual with positive TB test results. Written documentation of a previously positive TST or IGRA result is required; a patient's verbal history is not sufficient. Appendix E (p. 32) provides an example of a documentation form.

TREATMENT OF LATENT TB INFECTION

OVERVIEW

There are several treatment regimens available for the treatment of latent TB infection (LTBI) (see Table 2, p. 18). Providers should choose the appropriate regimen based on the following:

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

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or are given an intermittent dosing regimen, directly observed therapy (DOT) for LTBI should be considered.

TREATMENT REGIMENS

Isoniazid (INH) Regimen

There are 2 options for treatment with INH:

- 9-month regimen
- 6-month regimen

The 9-month regimen is preferred because it is more efficacious. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, health care providers may prefer to implement the 6-month regimen rather than the 9-month regimen. Every effort should be made to ensure that patients adhere to LTBI treatment for at least 6 months. The preferred regimen for children aged 2 to 11 years is 9 months of daily INH.

12-Dose (Isoniazid and Rifapentine [RPT]) Regimen

The directly observed 12-dose once-weekly regimen of INH and RPT is recommended as an option equal to the standard INH 9-month daily regimen for treating LTBI in otherwise healthy people, 12 years of age and older, who were recently in contact with infectious TB, or who had tuberculin skin test or blood test for TB infection conversions, or those with radiologic findings consistent with healed pulmonary TB.

The 12-dose regimen can be considered for other groups on a case by case basis when it offers practical advantages, such as completion within a limited timeframe. The regimen may be used in otherwise healthy HIV-infected persons, 12 years of age and older, who are not on antiretroviral medications. It may also be considered for children aged 2-11 years if completion of 9 months of INH is unlikely and hazard of TB disease is great.

The 12-dose regimen is NOT recommended for the following individuals:

- Children younger than 2 years of age
- People with HIV/AIDS who are taking antiretroviral therapy (ART)
- People presumed to be infected with INH or rifampin-resistant *M.tuberculosis*
- Pregnant women, or women expecting to become pregnant while taking this regimen

Rifampin (RIF) Regimen

A 4-month regimen of RIF can be considered for persons who cannot tolerate INH or who have been exposed to INH-resistant TB. It should not be used to treat HIV-infected persons taking some combinations of ART.

The choice between the 12-dose regimen and other recommended LTBI treatment regimens depends on several factors, including:

- Feasibility of DOT
- Resources for drug procurement and patient monitoring
- Considerations of medical and social circumstances that could affect patient adherence
- Preferences of the patient and prescribing health care provider

**TABLE 2:
Choosing the Most Effective LTBI Treatment Regimen**

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)	9 months	Adult: 5 mg/kg Children: 10-20 mg/kg** Maximum dose: 300 mg	Daily	270
		Adult: 15 mg/kg Children: 20-40 mg/kg** Maximum dose: 900 mg	Twice weekly†	76
	6 months	Adult: 5 mg/kg Children: Not recommended Maximum dose: 300 mg	Daily	180
		Adult: 15 mg/kg Children: Not recommended Maximum dose: 900 mg	Twice weekly†	52
Isoniazid (INH) and Rifapentine (RPT)	3 months	Adults and Children 12 years of age and older: INH* : 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT* : 10.0–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum	Once weekly†	12
Rifampin (RIF)	4 months	Adult: 10 mg/kg*** Maximum dose: 600 mg	Daily	120

† Intermittent regimens must be provided via DOT, i.e., health care worker observes the ingestion of medication.

* Isoniazid (INH) is formulated as 100 mg and 300 mg tablets. Rifapentine (RPT) is formulated as 150 mg tablets in blister packs that should be kept sealed until usage.

** 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.

*** In the United States, the recommended regimen for treatment of LTBI in children is a 9-month course of INH. For the treatment of LTBI in infants, children, and adolescents when INH could not be tolerated or the child has had contact with a patient infected with an isoniazid-resistant but rifamycin-susceptible organism the American Academy of Pediatrics recommends 6 months of daily rifampin (RIF) (180 doses) at a dosage of 10-20 mg/kg.

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 guidance below should be followed. Those who have negative results should be retested in 8–10 weeks after exposure has ended. However, if the chest radiograph is normal, LTBI treatment should be initiated in TST-negative children \leq 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 high-risk contacts, 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) or INH and RPT for those over 12 years of age
- If person is exposed to known isoniazid-resistant TB -
 - Positive TST or IGRA result → Treat with rifampin (RIF) for 4 months
- If person is exposed to known multidrug-resistant (MDR) TB -
 - Positive TST or IGRA result → Consult an expert in the treatment of MDR 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 receiving ART 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 anti-retroviral medications).

- HIV-infected individuals who are otherwise healthy and are not taking ART can be considered for the 12-dose regimen.
- If the test for TB infection is negative, consider treatment 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.
- The 12-dose regimen is not recommended for pregnant women or women expecting to become pregnant during the treatment period.
- 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).
- The preferred regimen for children aged 2 to 11 years is 9 months of daily INH.
- The 12-dose regimen is not recommended for children younger than 2 years of age.
- DOT should be considered for children of all ages, and is strongly recommended when the 12-dose regimen is used.

Additional Notes of Importance

- Old fibrotic lesions can represent previous TB disease. Persons with old fibrotic lesions with TST result of ≥ 5 mm of induration or a positive IGRA result and negative culture should be treated for LTBI.
- Calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping represent healed primary *M. tuberculosis* infection and do not increase the risk of TB disease. The decision to treat for LTBI would be the same as for a person with a normal chest radiograph.
- The 12-dose regimen is not recommended for people presumed to be infected with INH or RIF-resistant *M. tuberculosis*.
- All doses of the 12-dose regimen should be given by DOT.

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 medications. 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 rifamycins, 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; and 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 occurs in about 0.1% 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 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. Younger patients with underlying risk factors for liver disease 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. It 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 only in such conditions or to prevent neuropathy in pregnant or breastfeeding women.

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

- 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. They are generally self-limited and may not be a true hypersensitivity; continued treatment may be possible.
- Rarely, rifamycins can be associated with hypersensitivity reactions, including hypotension, nephritis or thrombocytopenia, and manifested by symptoms such as fever, headache, dizziness/ lightheadedness, musculoskeletal pain, petechiae, and pruritis.
- 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 and dentures may be permanently stained.
- RIF and RPT interact with a number of drugs, causing drug-drug interactions. They are known to reduce concentrations of methadone, warfarin, hormonal contraceptives, and phenytoin. Women using hormonal contraceptives should be advised to consider an alternative method of contraception (e.g., a barrier method).
- RIF is contraindicated, or should be used with caution, in HIV-infected individuals being treated with certain antiretroviral medications. Substitution of rifabutin for RIF in the 4-month regimen may be considered for such patients. RPT should not be used in HIV-infected persons taking antiretroviral therapy.

PATIENT MONITORING AND EDUCATION DURING TREATMENT

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

Clinical Monitoring

- Patients should visit the health care provider who is managing their treatment on a monthly basis to be assessed for the following:
 - Signs of hepatitis
 - Adherence to medication regimen
 - Symptoms of possible adverse drug reactions or interactions
- Patients being treated for LTBI 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 the absence of symptoms or radiographic abnormalities.
- Review the importance of completing treatment for LTBI.
- Discuss possible side effects of LTBI medications that may include:
 - 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) is 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 wait until the next clinic visit to stop treatment.
- It is generally recommended that medication be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms or 5 times the upper limit of normal if the patient is asymptomatic.

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 Barriers

- 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 Barriers

- Misinformation or confusion about certain issues such as -
 - The meaning of TST results, 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” as they relate to test results
 - Modes of TB transmission and prevention
 - Exposure vs. becoming infected
 - 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 (e.g., fasting from food)

Treatment Barriers

- Complexity and duration of treatment
- Medication side effects
- Obtaining refills
- Frequency of office visits
- Cost, including insurance co-payment

TECHNIQUES TO IMPROVE ADHERENCE

- Collaborate with local health department to provide treatment.
 - DOT, if patient is high risk (e.g., HIV infected, young child, or TB contact)
 - DOT should be provided with the 12-dose regimen or other intermittent regimens
 - Case management to coordinate care and services
 - Free or low-cost medication
 - Rewards for adherence (incentives) such as grocery store or restaurant vouchers, nutritional supplements, cell phone minutes, or movie tickets
 - Enablers to overcome barriers such as free van transportation or bus tickets
- Provide patient education and instructions in patient’s primary language at every visit.
- Ensure confidentiality.
- Suggest or provide patient reminders such as pill box, calendar, or timer.

POST-TREATMENT FOLLOW-UP

- Patient should receive documentation that includes TST or IGRA results, chest radiograph results, names and dosages of medication and duration of treatment. The patient should be instructed to present this document any time future TB 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 disease		

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 2011, approximately 62% 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 7 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 TUBERCULIN SKIN TEST (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 TST administration.
- 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 2 points.

Recording and Documentation

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

Storage and Handling

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

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

APPENDIX D

CERTAIN SITUATIONS WHERE RESULTS FROM BOTH TST AND IGRA MAY BE USEFUL

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

- When the initial test is **negative** and -
 - The risk for infection, progression to disease, and/or a poor outcome is high (e.g., HIV-infected persons or children under 5 years of age who are exposed to a person with infectious TB).
 - There is clinical suspicion for TB disease (e.g., signs, symptoms, and/or radiographic evidence suggestive of TB disease) and confirmation of *M. tuberculosis* infection is desired.
 - Taking a positive result from a second test as evidence of infection increases detection sensitivity.
- When the initial test is **positive** and -
 - Additional evidence of infection is required to encourage acceptance and adherence to treatment (e.g., foreign-born health care workers who believe their positive TST is due to BCG).
 - 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 increases the likelihood that the test reflects infection. An alternative is to assume, without additional testing, that the initial result is a false positive or that the risk for disease does not warrant additional evaluation or treatment, regardless of test results.

In addition, repeating an IGRA or performing a TST might be useful when the initial IGRA result is indeterminate, borderline, or invalid and a reason for testing persists.

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

APPENDIX E

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: _____

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>

State TB Control Offices
<http://www.cdc.gov/tb/links/tboffices.htm>

Find TB Resources
<http://www.findtbresources.org>

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

Regional Training and Medical Consultation Centers –
TB Training and Education Products
<https://sntc.medicine.ufl.edu/rtmccproducts.aspx>

TB REGIONAL TRAINING AND MEDICAL CONSULTATION CENTERS (RTMCCS)

The CDC's Division of Tuberculosis Elimination funds regionally assigned TB Regional Training and Medical Consultation Centers (RTMCCs) to cover all 50 states and the U.S. territories. The primary purpose of each RTMCC is to provide the following:

- Training and technical assistance to increase human resource development in TB programs
- Medical consultation to TB programs and medical providers
- TB educational materials

For the most current information about the TB RTMCCs, visit the CDC website at www.cdc.gov/tb.

EDUCATIONAL MATERIALS FOR HEALTH CARE PROVIDERS

- Mantoux Tuberculin Skin Test Training Resources (Centers for Disease Control and Prevention)
- Management of LTBI in Children and Adolescents (NJMS Global Tuberculosis Institute, 2009)
- Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) Pocket Drug Card (NJMS Global Tuberculosis Institute, 2009)
- Fact Sheets
 - Targeted TB Testing and Interpreting Tuberculin Skin Test Results
 - Treatment of Latent Tuberculosis Infection: Maximizing Adherence
 - Tuberculin Skin Testing
 - Interferon-Gamma Release Assays (IGRAs) – Blood Tests for TB Infection
 - Treatment Options for Latent Tuberculosis Infection (Centers for Disease Control and Prevention)
- Slide Set
 - Targeted TB Testing and Treatment of Latent Tuberculosis Infection (Centers for Disease Control and Prevention)

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

EDUCATIONAL MATERIALS FOR PATIENTS

- Brochures
 - 12-Dose Regimen for Latent TB Infection
 - Questions and Answers About Tuberculosis
 - Patient Education Series (English, Spanish, Tagalog)
- Fact Sheets
 - What You Need to Know About Your Medicine for Latent Tuberculosis (TB) Infection – Fact Sheet Series
 - You Can Prevent TB

CDC patient education materials may be viewed, downloaded, and ordered online at http://www.cdc.gov/tb/education/patient_edmaterials.htm

REFERENCES

American Academy of Pediatrics. Tuberculosis. Red Book: 2012 Report of the Committee on Infectious Diseases. L.K. Pickering (Ed.), 29th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2012: 736-759.

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. 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. 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/mmwr/preview/mmwrhtml/mm5302a6.htm>

CDC. Guidelines for the prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009; 58 (No. RR4): 1-198. <http://www.cdc.gov/mmwr/pdf/rr/rr58e324.pdf>

CDC. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the American Academy of Pediatrics. *MMWR* 2009; 58 (No. RR 11): 1-166. <http://www.cdc.gov/mmwr/pdf/rr/rr58e0826.pdf>

CDC. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection – United States - 2010. *MMWR* 2010;59(RR05). <http://www.cdc.gov/mmwr/PDF/RR/RR5202.pdf>

CDC. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. *MMWR* 2011;60(48); 1650-1653. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w

Reichman, LB, Bhavaraju, R, eds. *Guidelines for the Diagnosis of Latent Tuberculosis Infection in the 21st Century, 2nd Edition*. Newark: New Jersey Medical School Global Tuberculosis Institute; 2008. <http://www.umdnj.edu/globaltb/products/diagnosisoftbi.htm>

