



Guidelines for Testing and Treatment of Latent Tuberculosis Infection

Sonal Munsiff, MD
Diana Nilsen, MD
Felicia Dworkin, MD

NYC Department of Health & Mental Hygiene, Bureau of Tuberculosis Control

October 2005

TB IS PREVENTABLE!

Table of Contents

	Page
Introduction.....	2
Ten Points for Testing and Treatment of Latent Tuberculosis Infection	3
1. Target all tuberculin skin testing to persons at high risk for TB	4
2. Test all people who are at high risk, regardless of BCG history.....	4
3. Decide which test to use for diagnosing latent TB infection	5
4. Determine if the test for TB infection is positive	6
5. Rule out active TB disease in persons with positive skin tests.....	6
6. Provide treatment for high-risk individuals diagnosed with latent TB infection, regardless of age.	6
7. Take special care when testing and treating HIV-positive individuals.....	8
8. Carefully consider treatment for pregnant women, children, contacts of persons with multidrug-resistant TB, and individuals with evidence of old, healed TB	9
9. Monitor all patients carefully during the treatment of LTBI	11
10. Ensure adherence during LTBI treatment.....	12
A Five-Step Guide to Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection	13
1. Know whom to test.....	13
2. Determine if the test is positive	16
3. Evaluate for TB disease	17
4. Give treatment for latent TB infection.....	18
5. Adjust treatment in HIV-positive patients taking antiretroviral agents.....	20
References.....	21
Resources for Patient Education.....	26

Introduction

Despite the dramatic decline in the number of reported cases of tuberculosis (TB) in New York City, many New Yorkers remain at high risk for developing active tuberculosis disease, once infected with *Mycobacterium tuberculosis*. Groups at especially high risk include contacts of persons with active tuberculosis, HIV-infected persons, individuals with certain predisposing medical conditions, and recent immigrants from countries with high rates of TB.

In April 2000, the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) revised their guidelines for the treatment of latent tuberculosis infection (LTBI). The Infectious Diseases Society of America and the American College of Physicians endorsed these guidelines. Sections that relate to infants and children were endorsed by the American Academy of Pediatrics. Since then, several new developments have occurred in this field.

1. In 2003, the CDC revised its guidelines on the use of rifampin & PZA for treatment of LTBI.
2. In October 2004, the Pediatrics Tuberculosis Collaborative Group published revised recommendations on targeted tuberculin skin testing and treatment of LTBI in children and adolescents.
3. The tuberculin skin test performed by the Mantoux method is the most commonly used method for identifying TB infection. Recently, blood-based testing has become available as an alternative to the TB skin test since 2001. A more specific version of that test was FDA approved in December 2004.

This document provides updated recommendations based on all of the above. It summarizes fundamental aspects of testing and treatment of LTBI (see “Ten Points for Testing and Treatment of LTBI”) and provides a Five-Step Guide. Topics covered include whom to test for TB, revised LTBI treatment regimens, updated recommendations on the treatment of HIV-positive individuals who are on antiretroviral agents and rifamycins, screening and treatment of children, and information on the use of blood-based TB tests. Terminology has been changed to reflect the availability of blood-based tests for TB infection. The term tuberculin skin test (TST) is not used throughout this document. A more general term, test for TB infection, is used except in specific instances that reference the TST. The Bureau of TB Control’s new recommendations on the treatment of LTBI in certain groups of patients are also discussed. References and resources for providers and patients are listed at the end.

Ten Points for Testing and Treatment of Latent Tuberculosis Infection

1. Target all testing for TB infection to persons at high risk for TB.

- Target testing to (1) those who are at high risk of being **recently infected with *M. tuberculosis***--and thus at increased risk of developing active disease--and (2) those who, once infected, are at high risk of **developing TB disease** because of medical conditions that substantially increase their risk of developing active TB disease (*see Step 1*).
- Testing for TB infection should only take place when a plan has been developed for persons to complete a course of treatment if found to have latent TB infection. **A decision to test is a commitment to treat!**
- Routine testing of persons at **low risk** for LTBI or TB disease is **not recommended**. However, in some instances, testing for such individuals may be necessary to meet local and state requirements.
- **Close contacts** of persons with active TB disease should receive a baseline test immediately after learning of exposure. Retesting is sometimes necessary, however, to determine whether or not infection resulted from the exposure. Because it can take up to 8 weeks after *M. tuberculosis* infection for the immune system to respond to the test, a test given during the 8-week window period may be falsely negative. Close contacts tested during the window period who had a negative result on the initial test should be retested 8 weeks after the most recent exposure to active TB. This is usually 8 weeks after the source case started effective treatment or was placed in isolation. Some close contacts may require a chest x-ray despite a negative test for TB infection, due to symptoms, age or underlying medical conditions (*see Point 6*). *Note: Some authorities consider the window period to be 12 weeks rather than 8 weeks.*
- **All HIV-positive individuals** should receive a test for TB infection as soon as possible after HIV infection is diagnosed and at least every 12 months thereafter (*see Point 7*).
- **Recent immigrants** (those who have been in the United States <5 years) from countries with high rates of TB should receive a test for TB infection the first time they enter the medical care system in the U.S. (*see Step 1 for list of high TB incidence countries*).
- **Individuals with prolonged stay** (>1 month) abroad in areas with high TB rates should be evaluated after return or at next medical evaluation (*see Step 1 for list of high TB incidence countries*).
- Recommendations for how frequently to test **individuals who live or work in institutional settings** (e.g., prisons, hospitals, nursing homes and shelters) vary according to risk of transmission based on CDC and local guidelines. Most guidelines

recommend testing annually. Such individuals who are going to undergo serial testing should have a two step TST as part of their baseline evaluation or a blood-based test for TB infection.

- **Individuals with immunosuppressive conditions or on treatment with immunosuppressive agents** should be evaluated and treated for LTBI at the time that the condition is diagnosed or before starting treatment with immunosuppressive therapies, such as prolonged corticosteroids and TNF-alpha antagonists [infliximab (Remicade[®]), etanercept (Enbrel[®]), and adalimumab (Humira[®])]. Patients awaiting transplants should be evaluated for LTBI. A TST result of 5 mm or greater should be considered indicative of TB infection in all these individuals (*see step 2*). TST results in immunosuppressed individuals may be falsely negative due to the drug therapy or the underlying medical condition causing anergy; the individual may still be infected with *M. tuberculosis*. Two step testing in these individuals is recommended by some experts as this may increase the yield of positive TSTs. Blood-based tests have not been studied in these individuals.
- **Recommendations on the testing and treatment of children and adolescents** were published in October 2004 by the Pediatric Tuberculosis Collaborative Group. Targeted testing in children and adolescents should focus on pediatric populations at high risk for LTBI in addition to those patients at risk of progression to TB disease. Groups of children and adolescents that should have a test for TB infection include those at high risk of recent infection such as contacts and recent immigrants from high TB incidence countries, and those with high risk of progression because of underlying conditions (*see Step 1*). Children and adolescents should be screened for risk factors for TB disease and LTBI by using a risk-assessment questionnaire (*see Step 1 for a sample questionnaire*) and tested only if one or more (≥ 1) risk factor is present. Administrative or mandated tests for TB infection for entry to day care, school, summer camp or college are discouraged in the absence of risk factors. However, in NYC many children and adolescents will still need testing for LTBI because of requirements based on the NYC Health Code (*see “TB and the Law” document <http://www.nyc.gov/html/doh/pdf/tb/tb-law.pdf>*). Blood-based tests have not been adequately studied in children so at present most children should be tested with a TST.

2. **Test all people who are high risk, regardless of BCG history.**

Tests for TB infection are not contraindicated for persons who have been vaccinated with BCG. A history of BCG vaccination should not be considered when deciding whether to test and determining whether the test result is positive in high-risk individuals (*see Point 1 above and Step 2*).

Although BCG vaccination can cause a false positive cross-reaction to the TST (especially within the first 12 months after vaccination), sensitivity to tuberculin is highly variable and tends to decrease over time. There is no way to distinguish between a positive reaction due to BCG-induced sensitivity and a positive reaction due to true LTBI. Therefore, a positive reaction to the TST in BCG-vaccinated persons should be interpreted

as indicating infection with *M. tuberculosis* when the person tested is at increased risk of recent infection or has a medical condition that increases the risk of progression to active TB disease.

Since the QuantiFERON[®]-TB Gold test does not cross-react with BCG, this test will be particularly useful for testing individuals with history of BCG vaccination.

3. **Decide which test to use for diagnosing latent TB infection**

The QuantiFERON[®]-TB test (QFT) was approved by the U.S. Food and Drug Administration in 2001 as an aid for detecting latent TB infection. QFT is a blood test that measures interferon-gamma released from sensitized lymphocytes in whole blood incubated overnight with purified protein derivative (PPD) from *M. tuberculosis* and control antigens. The TST and QFT do not measure the same components of the immunologic response and are not interchangeable. Due to the many limitations of this test, it has not been used widely.

In 2001, the CDC recommended the QFT for LTBI screening as follows:

- a. Initial and annual screening of health care workers
- b. Recent immigrants
- c. Injection drug users
- d. Prison and jail inmates & employees
- e. Entrance requirements for schools, workplaces, and military personnel

It was not recommended for TB suspects and contacts, however.

In December 2004, the QuantiFERON[®]-TB Gold was approved by the FDA. This test uses antigens that are more specific for *M. tb* complex, but are not found in BCG strains and most non-tuberculous mycobacteria (NTM). This makes the test much more useful in clinical practice, as it can be used in any high-risk population. Exclusions have been removed for contacts and TB suspects. However, there is still little data in children and immunosuppressed individuals.

There are many potential advantages of this new test. It is a controlled laboratory test that provides results in a single patient visit every time with fast turn around. It is unaffected by BCG and NTM (estimated specificity >99%), has shown better detection of active TB (sensitivity up to 89%), and can be used in BCG vaccinated or prior TST-positive individuals. It has no 'booster' effect, thus eliminating 2-step testing. This new version will have a universal diagnostic cut-off (yes/no interpretation). CDC is currently reviewing its guidelines to reflect new clinical experience and recent FDA approval of this version. The BTBC is reviewing the new data to develop NYC Health Department guidelines for this test.

Another blood-based test, the Elispot[®] is approved for clinical use in Europe and is undergoing testing in the United States. Testing programs using the QuantiFERON[®] tests (or other blood based tests such as the Elispot[®] that are under evaluation) should only be implemented if quality laboratory services are ensured and if plans are in place for follow-up medical evaluation and treatment of persons who are diagnosed with LTBI.

4. Determine if the test for TB infection is positive.

TST results should always be recorded as millimeters (mm) of induration; if there is no induration, the result should be recorded as “0 mm”. Based on the size of the induration, there are three cutoff points for defining a positive TST result: ≥ 5 , ≥ 10 , and ≥ 15 mm of induration (*see Step 2*). For individuals who are at highest risk of developing TB disease if infected with *M. tuberculosis*, a ≥ 5 mm induration is considered positive. An induration of ≥ 10 mm should be considered positive for groups with an increased probability of developing TB disease. Routine tuberculin testing is not recommended for populations at low risk of LTBI; however, if these persons are tested, a cutoff of ≥ 15 mm is considered positive.

If a blood-based test is used, the determination of a positive result will be based on the manufacturer’s instructions.

Once an individual is tested and if the test for TB infection is negative, it is usually not necessary to retest again except in some instances noted above in point 1. If a new risk factor is identified, the person should be tested again at that time.

Documentation of the results of the test for TB infection should be provided to the individual, as repeat testing in the future is not necessary once a TST or blood based test is determined to be positive.

5. Rule out active TB disease in persons with positive test for TB infection.

Any individual with a newly identified positive test for TB infection should be evaluated for TB disease with a medical examination and a chest x-ray. If the initial chest x-ray is negative for active TB disease and the person has no symptoms consistent with active TB, the individual should be evaluated for treatment of LTBI (*see Point 6*). If a CXR was done within 3 months of start of LTBI treatment and was normal, a repeat CXR may not be necessary. If a decision is made to not treat the individual, further follow-up with periodic chest x-rays is generally not indicated.

An individual with TB symptoms or an abnormal chest x-ray should be appropriately evaluated with sputa and other tests as indicated. Active TB (pulmonary or extra-pulmonary) should be ruled out before treatment for LTBI is started (*see Step 3*).

6. Provide treatment for high-risk individuals diagnosed with latent TB infection, regardless of age. Forget the past age “limit” of 35 years.

- **There are two recommended regimens for the treatment of latent TB infection** (*see Step 4 for details on the regimens*). A 9-month regimen of isoniazid (INH) is the preferred option for treatment of LTBI in all patients. The 4-month rifampin regimen (six months in children) is an acceptable alternative, especially if there are adverse reactions or resistance to INH, but not rifampin, or the individual is not going to be

available for more than 4 to 6 months and is thus unlikely to complete a 9-month INH regimen.

- **ATS/CDC no longer recommends the 2-month regimen containing rifampin and pyrazinamide as an option for LTBI treatment.** In 2003, the CDC reported high rates of hospitalization and death from liver injury associated with the use of a daily or twice-weekly 2-month regimen of rifampin plus pyrazinamide as treatment for LTBI. As a result, this regimen should generally not be offered to persons (either HIV negative or HIV-infected) with LTBI.
- **Close contacts** of persons with active infectious TB who are (1) HIV-infected, or (2) younger than 5 years old and tested during the 8-week window period (*see Point 1*) should be evaluated for TB disease with a chest x-ray and medical examination, regardless of the results of their test for TB infection. If active TB disease is ruled out, individuals in both these groups should start treatment for presumed latent TB infection. If the test results remain negative after the window period, treatment for LTBI should be discontinued in children but continued in HIV-infected contacts (*see Points 7 and 8*).
- **The risk of INH toxicity** has been shown to increase with age, in particular with age >55. Many such individuals will meet the current CDC/ATS/IDSA criteria for treatment. Those who are contacts or have clinical conditions associated with increased risk of progression to active TB should be treated regardless of age (*see Step 1*). However, based on the available literature and our clinical experience, the risk-benefit ratio from INH may not favor treatment of patients in this age group whose only risk factor is recent immigration. We recommend closer monitoring for INH toxicity in this group, if treated, and even the consideration that they be excluded from treatment.
- **Diabetes mellitus** has been shown to increase the risk of progressing from latent infection to active tuberculosis. However, the data is most convincing for insulin-dependent diabetics and those with poorly controlled disease. Such individuals who are found to have a positive test for TB infection should be treated for LTBI regardless of age. Those diabetics who are well controlled on oral agents or diet, and do not have additional clinical conditions associated with increased risk of progression to active TB or factors associated with recent infection should not be considered for treatment (*see Step 1*).
- **An individual not at high risk** for developing TB disease who has been inadvertently tested should, generally, not be considered for treatment, even if the test result is positive. However, treatment for LTBI is generally recommended for children with LTBI, regardless of risk factors (*see Point 8*).

7. **Take special care when testing and treating HIV-positive individuals.**

The management of persons co-infected with HIV and LTBI can be highly complex and

should be attempted in consultation with physicians who are expert in the treatment of both. In order to provide optimal treatment of HIV and LTBI, tuberculosis and HIV care providers should communicate closely with each other. The 9-month INH regimen may be administered concurrently with any antiretroviral regimen used to treat HIV infection (*see Step 4*).

HIV-positive persons who have had recent close contact with an infectious TB patient should receive treatment for LTBI regardless of age, result of tests for TB infection, or history of previous treatment for LTBI, as they may be newly infected and may not react to the TST due to anergy (*see Steps 4 and 5*). The reliability of blood-based tests has not been determined in this population. HIV-positive individuals with a history of prior untreated or inadequately treated TB disease should be re-evaluated for active disease and, if active TB is ruled out, receive treatment for old, healed TB or for latent TB infection, regardless of age or results of test for TB infection.

A regimen of rifampin or rifabutin may be used to treat LTBI in HIV-infected persons who have been exposed to INH-resistant, rifampin-susceptible tuberculosis or who have toxicity to INH. However, if a rifamycin-containing regimen is used for HIV-infected patients with LTBI, drug-drug interactions between the rifamycins and the protease inhibitor (PI) and the non-nucleoside reverse transcriptase inhibitor (NNRTI) classes of drugs must be considered; dose adjustments for antiretroviral drugs and rifamycins must be applied (*see Step 5*).

Previous recommendations specifically contraindicated the use of rifampin with any PI or NNRTI. However, new data indicate that rifampin can be used in patients with some antiretroviral regimens such as efavirenz and 2 or more nucleoside reverse transcriptase inhibitors. Please refer to references 1-3 in the HIV and Tuberculosis section for further information.

In many cases, rifabutin can be substituted for rifampin. Rifabutin may be used with regimens containing (1) the NNRTIs *efavirenz* and *nevirapine* or (2) a single PI (except *saquinovir* alone), with some dose adjustments. The currently approved PIs that can be used with rifabutin are *amprenavir*, *atazanavir*, *fos amprenavir*, *indinavir*, *nelfinavir*, and *lopinavir/ritonavir* (*Kaletra*). (*See Step 5 for the recommended dosages of rifabutin when it is co-administered with these agents.*) Data is lacking on the use of rifabutin in antiretroviral regimens containing combinations of NNRTIs and PIs or other multiple PI combinations.

Information on interactions between rifamycins and antiretroviral drugs is constantly evolving, and since recommendations are often based on anecdotal evidence, differences in opinion exist. As more data and new drugs emerge, it is essential that clinicians obtain the most current information regarding TB and HIV drug interactions.

- 8. Carefully consider treatment for pregnant women, children, contacts of persons with multidrug-resistant TB, and individuals with evidence of old, healed TB.**

Pregnancy

Pregnant women should receive a test for TB infection only if they are in a high-risk category (*see Step 1*). Although the need for treatment of active TB during pregnancy is unquestioned, the treatment of LTBI in pregnant women is more controversial because the possible risk of isoniazid hepatotoxicity must be weighed against the risk of developing active TB. In general, treatment of LTBI should be delayed until 2 to 3 months after delivery. However, for women who are HIV-positive or who have been infected recently (such as contacts to active TB cases, or known recent conversions), initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester.

The preferred regimen for treatment of LTBI in pregnant women is INH (*see Step 4*). Extensive use of INH during pregnancy has indicated that the drug is not teratogenic, even when given during the first trimester of pregnancy. Pregnant women taking INH should receive vitamin B₆.

Breastfeeding is not contraindicated when the mother is being treated for LTBI. Vitamin B₆ is not indicated in nursing infants unless the baby itself is also being given INH.

Children

All children who are classified as having latent TB infection after active disease is ruled out should be treated for LTBI. Children younger than 5 years with LTBI have by definition been infected recently and are at high risk for progression to active TB disease. Treatment is recommended for all children and adolescents diagnosed with LTBI because:

- a) The drugs used are safe in the pediatric population.
- b) Infection with *M. tuberculosis* is more likely to have been recent.
- c) Young children are at higher risk for progression to TB disease.
- d) The pediatric population has more years to potentially develop TB disease.

The recommended regimen for children (with or without HIV infection) is 9 months of INH. The risk for isoniazid-related hepatitis is minimal in infants and children, who generally tolerate the drug better than adults. Vitamin B₆ should be given to undernourished or HIV-infected children treated with INH. Children (with or without HIV infection) who have been exposed to a person with INH-resistant, rifampin-susceptible TB, or are intolerant to INH should be treated with at least 6 months of rifampin (*see Step 4*).

Contacts of persons with MDRTB

Contacts of persons with multidrug-resistant tuberculosis (MDRTB, i.e organisms are resistant to at least isoniazid and rifampin) are unlikely to benefit from treatment with isoniazid or rifampin. Therefore, a regimen containing other drugs active against *M. tuberculosis* should be considered. When possible, selection of drugs should be guided by in vitro susceptibility test results of an isolate obtained from the person to whom the patient was exposed. If thought to be newly infected, these contacts should be evaluated for an alternative regimen for LTBI according to their age and immune status:

- a) Contacts who are HIV positive, otherwise immunosuppressed, and/or younger than 5 years old should be given multidrug therapy (at least 2 medications), guided by

- the in vitro susceptibility results of the source case isolate, for at least 12 months.
- b) Contacts older than 5 years old who are immunocompetent, newly identified as having TB infection (e.g. TST conversion or no evidence of prior tests for TB infection and now have a positive reaction) can be managed either by a multidrug regimen for 6-12 months, or by monitoring the patient with medical exams and chest x-rays at 4 month intervals for 2 years.

All persons with suspected MDRTB infection should be followed for at least 2 years, irrespective of treatment. Expert consultation should be sought for the treatment of contacts exposed to MDRTB cases.

Individuals with evidence of old, healed TB

For asymptomatic individuals who have a TST reaction ≥ 5 mm or a positive blood test for TB infection, and a chest x-ray that shows noncalcified fibrotic lesions suggestive of old, healed TB, treatment decision is based on several factors. These include clinical suspicion, prior TB treatment history, sputum results and repeat x-ray. All such patients should be evaluated for active tuberculosis, with a physical exam, chest x-ray and sputa.

If sputa are smear negative and there is no evidence of adequate prior treatment for TB, treatment should be started with isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months. This regimen has several advantages: it can be used to treat patients who may have isoniazid-resistant organisms; it may promote better adherence than the 9-month treatment regimen for LTBI; and it allows patients to start treatment at the first medical visit, rather than waiting until sputum cultures are shown to be negative for *M. tb*.

If a culture comes back positive, then treat as active tuberculosis with an appropriate regimen. If all cultures are negative by two months, repeat a CXR:

- a) If the x-ray shows no change, the lesions presumably were inactive. Classify the patient as having old TB:
 - i. If the patient has no prior TB treatment history, continue with 2 additional months of isoniazid and rifampin only.
 - ii. If there is a history of same prior TB treatment, continue all four drugs for an additional 2 months.
 - iii. Other diagnoses should also be pursued as warranted.
- b) If the x-ray shows improvement, the lesions presumably were active. Classify the person as having culture negative active TB:
 - i. If the patient has no prior TB treatment history, continue with 2 additional months of isoniazid and rifampin only.
 - ii. If there is a history of same prior TB treatment, continue all four drugs for an additional 2 months.

At the end of 4 months of therapy, the patient should receive an end-of-treatment x-ray to serve as a baseline for future reference. Some patients classified as old TB may show improvement on the 4-month x-ray; they should be reclassified as having culture negative active TB.

Some individuals who have culture-negative TB may need 6 months of therapy (i.e., extensive fibrotic disease or HIV infection). Clinical judgment should be used to make this decision.

If there is low clinical suspicion of active tuberculosis, and smears are negative, there is an additional option not to treat until the cultures are finalized. If cultures are negative, and a 2-month x-ray shows no change, there are two possible regimens for LTBI therapy for individuals with evidence of old, healed TB and no history of treatment for TB:

- i. 9 months of isoniazid *or*
- ii. 4 months of rifampin (some authorities recommend using isoniazid as well)

9. Monitor all patients carefully during the treatment of LTBI.

All patients receiving treatment for latent TB infection should be monitored on a monthly basis. This involves a directed clinical exam, blood tests as needed, and education of patients about the signs and symptoms of adverse drug reactions and the need for prompt cessation of treatment and clinical evaluation, should symptoms occur. Signs and symptoms of adverse effects can include: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 days or more, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, and arthralgia. Appropriate educational materials in the patient's language should be provided (*see link to our website in the references section for such materials*)

At baseline, a complete blood cell count and liver function tests (LFTs) should be done for all of the following persons:

- a) HIV-positive patients
- b) Patients with a history of alcohol abuse, liver disease, and hepatitis
- c) Pregnant and postpartum women (up to 2-3 months after delivery)
- d) Patients with a history of drug injection
- e) Patients starting treatment with 2 or more anti-TB drugs
- f) Anyone over age 35 years
- g) Patients taking hepatotoxic medications for other medical conditions

Monthly liver function tests should be conducted for:

- All HIV-positive patients
- Patients with a history of alcohol abuse, liver disease, chronic hepatitis
- Pregnant and postpartum women (up to 2-3 months after delivery)
- Patients currently injecting drugs
- Patients on hepatotoxic agents
- Patients with baseline abnormal LFTs not due to these other conditions.

In addition, laboratory testing should be used to evaluate specific adverse events that may occur during treatment.

10. **Ensure adherence during LTBI treatment.**

Many people with LTBI do not complete treatment. Most people with LTBI are not sick and may not feel the urgency to complete the prolonged treatment. Patients receiving treatment for latent TB infection need to be encouraged to return monthly for follow-up. Providers need to educate patients about the importance of adherence to treatment and potential side effects of treatment. Barriers to adherence should be addressed and overcome. (*See resources for patients at end of the document*)

Providers should use various measures to assess and promote adherence:

- a) Use directly observed therapy (DOT) for LTBI when available, especially for children, contacts, and HIV-infected persons. DOT can be performed at many locations such as clinics, schools, homes, work sites, and day care programs.
- b) Provide assistance with transportation.
- c) Provide incentives and other enablers.
- d) Minimize wait time at clinics.
- e) Question the patient at monthly visits about the number of pills missed in the past week.
- f) Remind the patient to bring in the medication bottle(s) and do pill counting (but not in their presence).
- g) Send reminder letters or make phone calls prior to the appointment.
- h) Follow up promptly on missed appointments to prevent delinquency.

If interruptions in treatment occur, patients can be given 2-3 additional months to complete the regimen. Decision regarding completion of treatment should be based on the total number of medication doses administered as well as the duration of therapy (*see Step 4*). For those on INH, if there is a gap of greater than 3 months, treatment may need to be restarted unless more than 6 months of treatment has already been taken; in that case treatment should be considered completed.

A Five-Step Guide to Testing and Treatment of Latent Tuberculosis Infection

STEP 1: Know Whom to Test

Individuals Who May Have Been Recently Infected	Individuals With Clinical Conditions Associated with Progression from LTBI to Active TB
<ul style="list-style-type: none"> • Close contacts of persons with active TB • Persons whose TB skin tests (TSTs) have converted to positive (≥ 10 mm increase) within the past 2 years • Persons who have immigrated within the past 5 years from areas with high TB rates* • Persons with prolonged stay (> 1 month) in areas with high TB rates* • Persons who live or work in clinical or institutional settings where TB exposure may be likely (e.g., hospitals, prisons, homeless shelters, nursing homes, mycobacteriology labs) • Children < 5 years of age exposed to adults in high-risk categories 	<ul style="list-style-type: none"> • Persons with HIV infection • Injection drug users • Persons with evidence of old, healed TB lesions on chest x-ray • Underweight persons ($\geq 10\%$ under ideal body weight) • Persons with certain medical conditions (e.g., silicosis, chronic renal failure, diabetes mellitus, some cancers, gastrectomy/jejunoileal bypass) • Persons receiving immunosuppressive therapy (e.g. prolonged corticosteroid therapy [the equivalent of > 15 mg/d of prednisone for one month or more], TNF-α blockers)

*See table on page 15.

Sample Risk Assessment Questionnaire for Children

1. Was your child born outside the United States?
If yes, this question would be followed by: Where was your child born? If the child was born in Africa, Asia, Latin America, or Eastern Europe, a TST should be placed.
2. Has your child traveled outside the United States?
If yes, this question would be followed by: Where did the child travel, with whom did the child stay, and how long did the child travel? If the child stayed with friends or family members in Africa, Asia, Latin America, or Eastern Europe for > 1 month cumulatively, a TST should be placed.
3. Has your child been exposed to anyone with TB disease?
If yes, this question should be followed by questions to determine if the person had TB disease or LTBI, when the exposure occurred, and what the nature of the contact was. If confirmed that the child has been exposed to someone with suspected or known TB disease, a TST should be placed.

If it is determined that a child had contact with a person with TB disease, notify the health department.
4. Does your child have close contact with a person who has a positive TB skin test?
If yes, see question 3 (above) for follow-up questions.

Risk-assessment questionnaires can include the following questions based on local epidemiology and priorities.

1. Does your child spend time with anyone who has been in jail (or prison) or a shelter, uses illegal drugs, or has HIV?
2. Has your child drunk raw milk or eaten dairy products such as fresh cheese products obtained from abroad?
3. Does your child have a household member or caregiver who was born outside the United States?
4. Does your child have a household member or caregiver who has traveled outside the United States?

1

Countries/Areas with an Estimated or Reported High Incidence of TB, 2002

<p>Africa All countries except Seychelles</p> <p>Eastern Mediterranean Afghanistan Bahrain Djibouti Iraq Morocco Pakistan Qatar Somalia Sudan Syrian Arab Republic Yemen</p> <p>Europe Armenia Azerbaij�n Belarus Bosnia & Herzegovina Bulgaria Croatia Estonia Georgia Kazakhstan Kyrgyzstan Latvia Lithuania Portugal Republic of Moldova Romania Russian Federation Tajikistan Turkmenistan Ukraine Uzbekistan</p>	<p>North, Central and South America Argentina Bahamas Belize Bolivia Brazil Colombia Dominican Republic Ecuador El Salvador Guatemala Guyana Haiti Honduras Mexico² Nicaragua Panama Paraguay Peru Suriname</p> <p>Southeast Asia Bangladesh Bhutan India Indonesia Korea, DPR (North) Maldives Myanmar (formally Burma) Nepal Sri Lanka Thailand Timor-Leste</p>	<p>Western Pacific Brunei Darussalam Cambodia China (including Hong Kong) Guam Kiribati Korea, South Lao PDR (Laos) Macao (China) Malaysia Marshall Islands Micronesia Mongolia New Caledonia Northern Mariana Islands Palau Papua New Guinea Philippines Solomon Islands Vanuatu Viet Nam</p>
--	---	---

Notes

1. Source: World Health Organization. *Global Tuberculosis Control: Surveillance, Planning, Financing: WHO Report 2004*. Geneva, Switzerland. http://www.who.int/tb/publications/global_report/en/. "High-incidence areas" are defined by the New York City Tuberculosis Control Program as areas with reported or estimated ≥ 20 smear-positive cases per 100,000 persons.

2. Has an estimated incidence of < 20 smear-positive cases per 100,000 persons; however, the Mexican community in NYC has a high burden of disease.

STEP 2: Determine if the Test is Positive

The reaction to tuberculin skin test (TST) is classified as positive based on the individual's risk factor(s) and the following measurements of induration:

<p>≥5 mm for</p>	<ul style="list-style-type: none"> • Persons with HIV-infection • Recent contacts of persons with active TB • Persons with evidence of old, healed TB lesions on chest x-rays • Patients with organ transplants and other immunosuppressed persons
<p>≥10 mm for</p>	<ul style="list-style-type: none"> • Persons who have immigrated within the past 5 years from areas with high TB rates (<i>see Step 1</i>) • Injection drug users • Persons who live or work in institutional settings where exposure to TB may be likely (e.g., hospitals, prisons, homeless shelters, SROs, nursing homes) • Mycobacteriology laboratory personnel • Persons with clinical conditions associated with increased risk of progression to active TB, including: <ul style="list-style-type: none"> ▪ Silicosis, ▪ Chronic renal failure ▪ Diabetes mellitus ▪ Weight loss of ≥10% of ideal body weight ▪ Gastrectomy/jejunoileal bypass ▪ Certain cancers such as carcinoma of the head or neck or lung, leukemias and lymphomas ▪ Immunosuppressive agents such as corticosteroids and TNF-α blockers • Children <5 years of age or children/adolescents exposed to adults in high-risk categories • Persons with prolonged stay in areas with high TB rates
<p>≥15 mm for</p>	<ul style="list-style-type: none"> • Persons at low risk for TB disease for whom testing is not generally indicated

If a blood-based test is used, the criteria vary for determination of a positive reaction. Refer to the package instructions for each test, as well as other published guidelines.

STEP 3: Evaluate for TB Disease

Any person with a newly positive result for a test for TB infection should be evaluated for TB disease with a medical examination and a chest x-ray. An individual with TB symptoms or an abnormal chest x-ray should be appropriately evaluated with sputa and other tests as indicated. Active TB should be ruled out before treatment for LTBI is started.

Suspected and confirmed TB cases should be reported as required by law **within 24 hours**. A report may be made by telephone to the TB Hotline, (212) 788-4162. However, a completed Universal Reporting Form (URF) must follow within 48 hours. The URF can be faxed to the Bureau of Tuberculosis Control at (212) 788-4179 or mailed to DOHMH at 125 Worth Street, Room 315, CN-6, New York, NY 10013.

Providers should report

1. Individuals who have:

- A smear (from any anatomic site) positive for acid-fast bacilli (AFB).
- A nucleic acid amplification test (e.g., Roche's AMPLICOR[®], Genprobe's MTD[™]) result positive for *Mycobacterium tuberculosis*.
- A culture positive for *Mycobacterium tuberculosis*.
- Biopsy, pathology, or autopsy findings consistent with active tuberculous disease, including but not limited to, caseating granulomas in biopsies of lungs, lymph nodes or other specimens.
- Been started on two or more anti-TB medications for treatment of suspected or confirmed active TB.
- Clinically suspected pulmonary or extrapulmonary tuberculosis, such that the physician or other health care provider has initiated or intends to initiate isolation or treatment for tuberculosis.

2. A child younger than five years old (up to the day of the fifth birthday) with a positive TST result.

When an individual has an AFB-positive smear or has started treatment for TB, reporting should never be delayed pending identification of *M. tuberculosis* with rapid diagnostic tests (e.g., nucleic acid amplification tests) or culture. Whenever TB is suspected, the case should be reported, even if bacteriologic evidence of disease is lacking or treatment has not yet started.

Laboratories should report:

- AFB-positive smears (regardless of anatomic site)
- Cultures positive for *M. tuberculosis*
- Any culture result associated with an AFB-positive smear (even if negative for *M. tuberculosis*)
- A nucleic acid amplification test (e.g., Roche's AMPLICOR[®], Genprobe's MTD[™]) result positive for *Mycobacterium tuberculosis*.
- Results of susceptibility tests performed on *M. tuberculosis* cultures
- Pathology findings consistent with TB, including the presence of AFB and granulomas

STEP 4: Give Treatment for Latent TB Infection

Drug and Duration	Dosage		Major Adverse Reactions	Comments
	Daily	Twice Weekly	Recommended Monthly Monitoring*	
Isoniazid (INH) C: 9 months A: 9 months	C: 10-15 mg/kg (maximum 300 mg) A: 5 mg/kg (maximum 300 mg) Completion Criteria 270 doses within 12 months	C: 20-30 mg/kg (maximum 900 mg) A: 15 mg/kg (maximum 900 mg) Completion Criteria 76 doses within 12 months	Hepatic enzyme elevation; hepatitis; peripheral neuropathy; CNS effects; increased phenytoin levels; possible interaction with disulfiram (Antabuse®) Clinical evaluation Hepatic enzymes (if baseline is abnormal or patient has risk factors for toxicity) <i>See point 9</i>	Preferred regimen for all individuals. - Vitamin B6 (25 mg/day) may decrease peripheral and CNS effects and should be used in patients who are abusing alcohol, pregnant, breastfeeding infants on INH, malnourished, or have HIV infection, cancer, chronic renal or liver disease, diabetes, or pre-existing peripheral neuropathy. - Aluminum-containing antacids reduce absorption.
Rifampin (RIF) C: 6 months A: 4 months	C: 10-20 mg/kg (maximum 600 mg) Completion Criteria 182 doses within 9 months A: 600 mg [range 8-12 mg/kg] (maximum 600 mg) Completion Criteria 120 doses within 6 months	C: Not recommended A: 600 mg** [range 8-12 mg/kg] (maximum 600 mg) Completion Criteria 34 doses within 6 months	Hepatitis, fever, thrombocytopenia, flu-like syndrome. Reduces levels of many drugs, including methadone, warfarin, birth control pills, oral hypoglycemic agents, theophylline, dapsone, ketoconazole, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors. Clinical evaluation Hepatic enzymes (if baseline is abnormal or patient has risk factors for toxicity) <i>See point 9</i> Complete blood cell count, including platelets as needed	May be used to treat persons who have been exposed to INH-resistant, rifampin-susceptible TB or who have severe toxicity to INH, or are unlikely to be available for more than 4-6 months. - Orange discoloration of secretions, urine, tears, and contact lenses - Patients receiving methadone will need their methadone dosage increased by an average of 50%, to avoid opioid withdrawal. - Interactions with many drugs can lead to decreased levels of either or both. - May make glucose control more difficult in diabetics. - Contraindicated for patients taking most PIs and NNRTIs.*** - Patients should be advised to use barrier contraceptives while on RIF.

Rifabutin (RBT) C: 6 months A: 4 months	C: 5 mg/kg (maximum 300 mg) (Little data) Completion Criteria 182 doses within 9 months	C: Not recommended	Rash; hepatitis; fever; neutropenia; thrombocytopenia. Reduced levels of many drugs including protease inhibitors, non-nucleoside reverse transcriptase inhibitors, dapsone, ketoconazole, and birth control pills.	May be used to treat LTBI in HIV-infected persons who fit the criteria for RIF treatment but for whom RIF is contraindicated or others who need a rifamycin but are intolerant to RIF. - Orange discoloration of secretions, urine, tears, and contact lenses - Interaction occurs with many drugs. - For HIV-infected persons, adjust the daily or intermittent dose of RBT and monitor for decreased antiretroviral activity and for RBT toxicity, if taken concurrently with PIs and NNRTIs. *** - Methadone dosage generally does not need to be increased. - Patients should be advised to use barrier contraceptives.
	A: 5 mg/kg (maximum 300 mg) Completion Criteria 120 doses within 6 months	A: 5 mg/kg (maximum 300 mg) Completion Criteria 34 doses within 6 months	Clinical evaluation Hepatic enzymes (if baseline is abnormal or patient has risk factors for toxicity) <i>See point 9</i> Complete blood cell count, including platelets as needed	

C: Children
A: Adults

*Baseline hepatic enzymes should be done for all over the age of 35, and regardless of age, all HIV-infected persons, pregnant and postpartum women (up to 2-3 months postpartum), those with history of hepatitis or liver disease or alcohol abuse, injection drug users, and those on treatment with other potential hepatotoxic agents. A baseline CBC with platelets should be done on anyone prescribed a rifamycin-containing regimen.

** There is very little data or clinical experience on the use of intermittent treatment of latent TB infection with rifampin or rifabutin. These regimens should be used with caution.

*** Please see the NYC Bureau of TB Control's *Clinical Policies and Protocols* manual and our HIV/TB treatment guidelines (www.nyc.gov/health/tb).

STEP 5: Adjust Treatment in HIV-Positive Patients Taking Antiretroviral Agents

Generic Name	Brand Name	OK with rifampin?	OK with rifabutin?*
Protease Inhibitors (PIs)			
amprenavir (AMP)	Agenerase®	no	yes
atazanavir (TAZ)	Reyataz®	no	yes
fos-amprenavir (fos-AMP)	Lexiva®	no	yes
indinavir (IDV)	Crixivan®	no	yes
lopinavir/ritonavir (LPV/r)	Kaletra®	no	yes
nelfinavir (NFV)	Viracept®	no	yes
ritonavir (RTV)	Norvir®	no	yes
saquinavir (SQV)	Invirase® Fortovase®	no	no
Tipranavir/ritonavir (TPV/r)	Aptivus® and Norvir®	no	yes
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
delavirdine (DLV)	Rescriptor®	no	no
efavirenz (EFV)**	Sustiva®	yes	yes
nevirapine (NVP)	Viramune®	***	yes
Other Antiretroviral Drugs			
abacavir (ABC)	Ziagen®	yes	yes
didanosine (ddI)	Videx®	yes	yes
emtricitabine (FTC)	Emtriva®	yes	yes
enfuvirtide (T-20)	Fuzeon®	yes	yes
lamivudine (3TC)	Epivir®	yes	yes
stavudine (d4T)	Zerit®	yes	yes
tenofovir (TDF)	Viread®	yes	yes
zalcitabine (ddC)	Hivid®	yes	yes
zidovudine (AZT)	Retrovir®	yes	yes
AZT+3TC	Combivir®	yes	yes
ABC+AZT+3TC	Trizivir®	yes	yes
FTC +TDF	Truvada®	yes	yes
<p>*When antiretrovirals are used with rifabutin, the dosage of the PI, NNRTI, and/or rifabutin may need to be adjusted. Please refer to the latest edition of our “Antiretroviral Drugs and Treatment of Tuberculosis Guidelines” at www.nyc.gov/html/doh/pdf/tb/tbanti.pdf</p> <p>RBT dosage and frequency vary depending on the PI or NNRTI being used. <i>With EFV: RBT 450-600 mg daily or 600mg 2 or 3 times per week. (EFV dose is unchanged with RBT).</i> <i>With NVP: RBT 300 mg (either daily or 2 or 3 times per week).</i> <i>With IDV, NFV, AMP, TAZ, or fos-AMP; RBT 150 mg daily or 300 mg 2 or 3 times per week.</i> <i>With LPV/r and TPV/r: RBT 150 mg 3 times per week. (In patients being treated for active TB, the other anti-TB drugs should be given daily in the intensive phase for patients with a CD4 count < 100 cells).</i></p> <p>With rifabutin: increase NFV to 1000 mg 3 times/day or use standard BID dose increase IDV to 1000 mg 3 times/day</p> <p>**With rifampin: increase EFV dose to 800 mg daily (EFV dose is unchanged with rifabutin) *** Limited circumstances; refer to above website.</p> <p>Useful websites: www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm or www.AIDSinfo.nih.gov</p>			

References and Resources

General Latent Tuberculosis Infection

1. American Thoracic Society and Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2000; 161(4) S221-S247.
2. Centers for Disease Control and Prevention. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection – United States, 2003. *MMWR* 2003;52(31): 735-739.
3. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities. *MMWR* 1994;43(RR-13). (Updated recommendations are expected in March 2005)
4. Centers for Disease Control and Prevention. Prevention and control of tuberculosis in correctional facilities. Recommendations of the Advisory Council for the Elimination of Tuberculosis. *MMWR* 1996;45(RR-8).
5. Centers for Disease Control and Prevention. Prevention and control of tuberculosis in facilities providing long-term care to the elderly. Recommendations of the Advisory Council for Elimination of Tuberculosis. *MMWR* 1990;39(RR-10).
6. Centers for Disease Control and Prevention. Management of persons exposed to multidrug-resistant tuberculosis. *MMWR* 1992;41(RR-11):61-71.
7. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis* 1999;3:847-850.
8. Horsburgh, RC Jr. Priorities for the treatment of latent tuberculosis infection in the United States. *N Engl J Med* 2004;350:2060-7
9. Menzies RI. Tuberculin skin test. In: Reichman LB and Hershfield ES, eds. Tuberculosis: A Comprehensive International Approach. New York: Marcel Dekker, 2000: 279-322.
10. New York City Department of Health, Tuberculosis Control Program. *Clinical Policies and Protocols*, 3rd edition. June 1999.
11. Reichman LB, Lardizabal A, Hayden CH. Considering the role of four months of rifampin in the treatment of latent tuberculosis infection. *Am J Respir Crit Care Med* 2004 Oct 15;170(8):832-5.

Blood based tests for Latent Tuberculosis Infection

1. Mazurek, GH, Villarino, ME. Guidelines for using the QuantiFERON-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. Centers for Disease Control and Prevention. *MMWR* 2002;51: Dispatch 1-5.
2. Pai M, Riley LW, Colford JM. Interferon- γ assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis* 2004;4:761-776
3. Cellestis. QuantiFERON[®]-TB Gold, The Whole Blood IFN-gamma Test Measuring Responses to ESAT-6 & CFP-10 Peptide Antigens. Catalogue Number: 0594 0201. Package Insert.
4. Cellestis. QuantiFERON[®]-TB Gold: Clinical Studies. January 2005.
5. Cellestis. Clinicians Guide to QuantiFERON[®]-TB Gold. *Clinicians Guide 05981000A (13.01.05)*
6. Oxford Immunotech. The T SPOT-TB test: For the identification of tuberculosis infection. http://www.pneumologiamo.it/materiale/pdf/granger_06_07_2004.pdf

HIV and Tuberculosis

1. Munsiff SS, Burzynski JB, Nilsen D. Antiretroviral drugs and the treatment of tuberculosis. New York City Department of Health and Mental Hygiene Bureau of Tuberculosis Control. March 2005 www.nyc.gov/html/doh/pdf/tb/tbanti.pdf
2. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. January 20, 2004. www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm
3. The Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 29, 2004 (www.AIDSinfo.nih.gov).
4. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: Principles of therapy and revised recommendations. *MMWR* 1998;47(RR-20).

Immunosuppression

1. Munoz P, Rodriguez C, Bouza E. *Mycobacterium tuberculosis* infection in recipients of solid organ transplants. *JID* 2005; 40:581-7.
2. Centers for Disease Control and Prevention. Tuberculosis associated with blocking agents against tumor necrosis factor-alpha – California, 2002-2003. *MMWR*

2004;53:683-5.

3. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor- α neutralizing agent. *N Engl J Med* 2001;345:1098–104.
4. Gardam MA, Keystone EC, Menzies R, et al. Anti-tumour necrosis factor agents and tuberculosis risk: mechanisms of action and clinical management. *Lancet Infect Dis* 2003;3:148–55.

Pediatrics

1. American Academy of Pediatrics. Tuberculosis in 2003 Red Book: Report of the Committee on Infectious Diseases. 26th edition. Elk Grove Village, IL: American Academy of Pediatrics; 2003. pp 642-60
2. Pediatric TB Collaborative Group. Targeted tuberculin skin testing and treatment of latent TB infection in children and adolescents. *Pediatrics* 2004;114:1175-1201.
3. Shingadia D and Novelli V. Diagnosis and treatment of tuberculosis in children. *Lancet Infect Dis* 2003;3:624-32.
4. Tuberculin Skin Test: Pediatric and Adolescent Risk Assessment Questionnaire (Poster). Accessible at <http://www.harlemtbcenter.org/prods.htm>
5. Tuberculin Skin Test: Pediatric and Adolescent Risk Assessment Questionnaire (Card). Accessible at <http://www.harlemtbcenter.org/prods.htm>
6. Improving Completion Rates for Treatment of LTBI in Children and Adolescents. Provider. (Booklet to assist providers with maintaining adherence). <http://www.harlemtbcenter.org/prods.htm>

Treatment of Active TB

1. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med* 2003;167:603-662.
2. World Health Organization. Treatment of tuberculosis: guidelines for national programme, 2nd ed. Geneva: World Health Organization (WHO/TB/97.220:1-66); 1997.
3. Enarson DA, Rieder HL, Arnadottir T, Trebucq A. Management of tuberculosis: a guide for low-income countries. 5th ed. Paris: International Union Against Tuberculosis and Lung Disease; 2000. p. 1-89.
4. Bureau of Tuberculosis Control. Clinical Policies and Protocols, 3rd ed. New York City Department of Health; 1999. Accessible at <http://www.nyc.gov/html/doh/pdf/tb/manu.pdf>

Drug Toxicity

1. Kopanoff DE, Snider DE Jr., Caras GJ. Isoniazid-Related Hepatitis: A U.S. Public Health Service Cooperative Surveillance Study. *Am Rev of Respiratory Dis* 1978;117:991-1001.
2. Salpeter SR, Sanders GD, Salpeter AB, Owens DK. Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 years of age: A risk-benefit and cost-effectiveness analysis. *Ann Intern Med* 1997;127:1051-61.
3. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: A 7-year survey from a public health tuberculosis clinic. *JAMA* 1999; 1281:1014-18.
4. van Hest RV, Baars H, Kik S, et. al. Hepatotoxicity of rifampin-pyrazinamide and INH preventive therapy and tuberculosis treatment. *Clinic Infect Dis* 2004;39:488-96.

Diabetes and TB

1. Kim SJ, Hong YP, Lew WJ, Yang SC, Lee EG. Incidence of pulmonary TB among diabetics. *Tuber Lung Dis* 1995;76:529-33.
2. Pablos-Mendez A, Blustein J, Knirsch C. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *Am J Pub Health* 1997;87:574-9.
3. Perez-Guzman C, Torres-Cruz A, Villarreal-Velard H, Vargas M. Progressive age-related changes in pulmonary tuberculosis images and the effect of diabetes. *Am J Respir Crit Care Med* 2000;62:1738-40.
4. Feleke Y, Abdulkadir J, Aderaye G. Prevalence and clinical features of tuberculosis in Ethiopian diabetic patients. *East Afr Med J* July 1999;76:361-4.
5. Silwer H, Oscarsson PN. Incidence and coincidence of diabetes mellitus and pulmonary tuberculosis in a Swedish county. *Acta Med Scand* 1958;161:5-48.

Resources for Patient Education

New York City Bureau of TB Control

<http://www.nyc.gov/html/doh/html/tb/tb1.html>

- Stop TB (General information about LTBI in English, Spanish, Bengali, Chinese, French, Haitian Creole, Hindi, Russian, Urdu)
- Facts about INH (In English and Spanish)
- Let me introduce you to DOT for LTBI (in English and Spanish)
- Student TB Patrol Presents Students Fight Against Tuberculosis (in English and Spanish)

Charles P. Felton National TB Center at Harlem

<http://www.harlemtbcenter.org/prods.htm>

- Pediatric Calendar for LTBI Completion (Booklet to assist with adherence)