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 spring 2000, the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC) published revised guidelines for testing for and treating latent tuberculosis infection (see Reference 1). These guidelines are endorsed by the Infectious Diseases Society of America and the American College of Physicians. Sections that relate to infants and children are endorsed by the American Academy of Pediatrics.

The CDC/ATS revised guidelines refer to “treatment of latent tuberculosis infection (LTBI)” instead of “preventive therapy” and recommend:

1. That a tuberculin skin test (TST) be performed only if a plan has been developed for ensuring that those with a positive test complete treatment *(a decision to test is a commitment to treat!)*;
2. That the duration of treatment for latent TB infection be changed for both HIV-positive and HIV-negative adults;
3. That treatment regimens other than isoniazid alone be considered for adults;
4. That all TST-positive individuals at high risk for progression to TB disease be considered for treatment, regardless of age.

This issue summarizes and synthesizes the CDC/ATS recommendations for physicians and other health-care providers in New York City. It offers 10 “basics” and a pullout Guide on fundamental aspects of testing and treating latent TB infection, including when and how to administer therapy, how to interpret the TST in BCG-vaccinated individuals, and how to treat HIV-positive individuals who are taking antiretroviral agents.

**When recommendations of the New York City Department of Health differ from, or elaborate upon, the ATS/CDC guidelines, the text is italicized in black boldface.**

---

**Acknowledgments.** – Paula I. Fujiwara, M.D., M.P.H., Assistant Commissioner; Sonal S. Munsiff, M.D., Director of Epidemiology; and Dara Shapiro, M.P.H., Assistant Director of Public Health Education; Tuberculosis Control Program.
10 Basics

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

Target tuberculin skin testing (use the Mantoux method only) to identify (1) those who are at high risk of being recently infected with M. tuberculosis—and thus at high risk of developing active disease—and (2) those who, once infected, are at increased risk of developing TB disease because of medical conditions. The first group includes individuals:

- who are close contacts of people with infectious TB
- whose tuberculin skin tests have converted to positive within the past 2 years
- who have immigrated within the past 5 years from areas with high rates of TB (see Step 1 of the Guide)
- who live or work in institutional settings where they may be in contact with those with infectious TB disease

The second group comprises individuals who have underlying medical conditions that substantially increase their risk of developing active TB disease, if infected. This group includes persons with HIV infection, injection drug users, and persons with evidence of old, healed TB lesions in their chest X-rays.

Routine tuberculin skin testing of persons at low risk for TB infection or disease is not recommended. (See Step 1 of the Guide.)

2 Know when to test.

Guidelines for testing of specific high-risk groups are as follows:

- **Close contacts of persons with active TB disease** should receive a baseline TST 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 12 weeks after M. tuberculosis infection for the immune system to respond to the skin test, a TST given during the 12-week window period may be falsely negative. Close contacts tested during the window period who had a negative result on the initial TST should be retested 12 weeks from the contact’s most recent exposure to active TB.

- **All HIV-positive individuals** should receive a TST as soon as possible after HIV infection is diagnosed and at least every 12 months thereafter (see References 3 and 4 and Point 7).

- **Recent immigrants from countries with high rates of TB** (those who have been in the United States <5 years) should receive a skin test the first time they enter the medical care system in the U.S. and anytime they return to the U.S. after a prolonged (>1 month) stay abroad in areas with high TB rates (see Step 1 of the Guide).

- **Recommendations for how frequently to test individuals who live or work in institutional settings** (e.g., prisons, hospitals) vary according to risk of transmission (see References 8-10).

Tuberculin skin testing 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!

3 Determine if the tuberculin skin test is positive.

Based on the size of the induration, there are three cutoff points for defining a positive result: ≥5, ≥10, and ≥15 millimeters of induration (see Step 2 of the Guide). For individuals who are at highest risk of developing TB disease if infected with M. tuberculosis, a ≥2 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 latent TB infection; however, if these persons are tested, a higher cutoff of ≥15 mm is recommended.

4 Test all people who are high risk, even if they had BCG.

The tuberculin skin test is not contraindicated for persons who have been vaccinated with BCG, and a history of vaccination with BCG should not be considered when deciding whether to test and determining whether the TST result is positive in high-risk individuals (see Point 3 and Step 2 of the Guide).

Although BCG vaccination can cause a false-positive cross reaction to the TST (especially within the first 12 months after vaccination), sensitivity to tuberculosis is highly variable and tends to wane over time. There is no way to distinguish between a positive reaction due to BCG-induced sensitivity and a positive reaction due to true latent TB infection. 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.

5 Rule out active TB disease in persons with positive skin tests.

Any individual with a newly identified positive skin test should be evaluated for TB disease with a medical examination and a chest X-ray (see Step 3 of the Guide). If the chest X-ray is normal and the person has no symptoms consistent with active TB, he or she may be a candidate for treatment of LTBI. Regardless of their age, high-risk individuals with positive skin tests should receive treatment for LTBI (see Point 6). An individual with TB symptoms or abnormal chest X-ray should have a sputum examination or an appropriate evaluation for extra-pulmonary involvement in order to rule out active TB disease.

6 Forget the past age “limit” of 35 years. (It was never meant to discourage treatment of high-risk persons!) Provide treatment for all high-risk individuals diagnosed with latent TB infection, no matter what their age (see Point 1).

High-risk individuals fall into two categories: (1) people presumed to be recently infected, and (2) people whose underlying medical conditions substantially increase their risk of developing active TB disease (see Step 1 of the Guide). All high-risk individuals with a positive tuberculin skin test (see Step 2) for whom TB disease has been ruled out should be considered for treatment for latent TB infection, regardless of age.

There are four recommended regimens for the treatment of LTBI in adults (see Step 4 of the Guide). Close contacts of persons with active TB who are tested during the 12-week window period and (1) HIV-infected or (2) younger than 5 years old (see Point 2) should be evaluated for TB disease with a chest X-ray and medical exam, regardless of their TST results. If active TB disease is ruled out, individuals in both these groups should start treatment for presumed latent TB infection. If TST results remain negative after the window period, treatment for LTBI should be discontinued in children. (Also see Points 7 and 8.)

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 TST result is positive.

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

The management of persons co-infected with HIV and LTBI is highly complex and should be attempted only in consultation with physicians expert in the treatment of both. In order to provide optimal treatment for both infections, HIV- and tuberculosis-care providers should communicate closely with each other.

HIV-positive persons who have had recent close contact with an infectious TB patient should receive treatment for LTBI (see Steps 4 and 5 of the Guide) regardless of age, results of TSTs, or history of previous treatment for LTBI. HIV-positive individuals with a history of prior untreated or inadequately treated TB disease should be re-evaluated for active disease and, if negative for active TB, receive treatment for LTBI, regardless of age or results of TSTs.

If isoniazid (INH) is chosen as the LTBI regimen, 9 months of therapy is recommended. A 2-month regimen containing rifampin and pyrazinamide may also be used.

When prescribing rifampin, it should be noted that patients with HIV infection often are being treated with protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). PIs and NNRTIs are generally contraindicated with rifampin because of significant drug interactions. In some cases, rifabutin can be substituted for rifampin. Rifabutin may be used concurrently with protease inhibitors amprenavir (Agenerase®), indinavir (Crixivan®, and nelfinavir (Viracept®). Rifabutin also may be used with ritonavir (Norvir®) and saquinavir (Invirase®) if the protease
inhibitors are administered together. Rifabutin may be used with NNRTIs (e.g., efavirenz “Sustiva”®) and nevirapine (Viramune®). For the recommended dosages of rifabutin when it is coadministered with these agents, see Step 5 of the Guide. Interactions between rifamycins and antiretroviral regimens containing other PI combinations and PI/NNRTI combinations have not been studied. The effect of these combinations may be unpredictable. If patients need these combinations while receiving anti-TB treatment, it may be necessary to use alternatives to rifampin and rifabutin.

There are some differences between the CDC recommendations and those of the New York City Department of Health (NYC DOH). The major ones are:

• CDC states that it is probably acceptable to use rifampin with efavirenz. In this setting, the CDC recommends increasing the dose of efavirenz to 800 mg, as the efavirenz exposure is decreased by about 25% when given with rifampin. The NYC DOH does not recommend administering efavirenz and rifampin together, as higher doses of efavirenz may be associated with higher toxicity.

• CDC states that is probably acceptable to use rifampin with ritonavir, whether it is given as the sole PI or along with saquinavir. The NYC DOH does not recommend this, as data on concurrent use of this combination are based on only two patients.

• CDC states that is probably acceptable to use Fortovase® (saquinavir soft gel capsules) with rifabutin without a dose change in either drug. However, the NYC DOH does not recommend the coadministration of these drugs. The use of rifabutin with saquinavir soft gel capsules has shown a 47% decrease in the exposure of saquinavir. The NYC DOH is concerned that this is a significant enough decrease in the exposure of saquinavir that the two drugs ought not to be used together.

Information on interactions between rifamycins and antiretroviral drugs is constantly evolving, and since recommendations are often based on anecdotal evidence, differences in opinion will continue to exist until better data become available. 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, and contacts of persons with multidrug-resistant TB.

Pregnant women should receive a tuberculin skin test only if they are in a high risk category (see Step 1 of the Guide). 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 after delivery. However, for women who are HIV-positive or who have been infected recently, 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 (daily or twice weekly). Extensive use of INH during pregnancy has indicated that the drug is not teratogenic, even when given during the first 4 months of pregnancy. Pregnant women taking INH should receive vitamin B6. In general, pyrazinamide should not be used for the treatment of LTBI in pregnant women.

Children younger than 5 years with LTBI have by definition been infected “recently” and are at high risk for progression to active TB disease. According to the American Academy of Pediatrics, the recommended regimen for children with (or without HIV infection) is 9 months of INH (10 mg/kg daily with a maximum of 300 mg, or 20-30 mg/kg twice weekly with a maximum of 900 mg). 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 HIV-infected children treated with INH. The NYC DOH recommends that children (with or without HIV infection) exposed to INH-resistant, rifampin-susceptible TB be treated with at least 6 months of rifampin (10-20 mg/kg daily or twice weekly with a maximum dose of 600 mg).

Contacts of persons with multidrug-resistant TB (MDRTB) 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. Immunocompetent contacts may be observed without treatment or treated for at least 6 months. HIV-infected persons should be treated for 12 months. All persons with suspected MDRTB infection should be followed for at least 2 years, irrespec-

9 Consider treatment for individuals with evidence of old, healed TB.

Individuals with no history of adequate treatment of TB who have (1) a TST reaction of ≥5 mm and (2) a chest X-ray that shows noncalcified fibrotic lesions suggestive of old, healed TB or silicosis are unlikely to have current TB disease. The NYC DOH recommends that these individuals be given one of the following regimens, depending on HIV status and TB treatment history:

• HIV-negative persons without a history of prior TB treatment should receive isoniazid, rifampin, pyrazinamide, and ethambutol for 2 months followed by isoniazid and rifampin for 2 months;

• HIV-positive persons and persons with a history of prior treatment with anti-TB medications should receive all 4 drugs for the entire 4 months.

The CDC recommends three possible regimens for individuals with evidence of old, healed TB and no history of treatment for TB:

• 9 months of isoniazid,

• 2 months of rifampin and pyrazinamide, or

• 4 months of rifampin (with or without isoniazid).

For patients who begin multidrug therapy for suspected pulmonary TB but are subsequently determined not to have active disease, the CDC recommends completion of treatment with at least 2 months of a regimen containing rifampin and pyrazinamide if the tuberculin skin test is positive and other causes of the radiographic abnormalities have been excluded.

10 Monitor all patients carefully during the treatment of LTBI.

All patients receiving treatment for latent TB infection should be monitored clinically. This involves education of patients about the symptoms and signs of adverse drug reactions and the need for prompt cessation of treatment and clinical evaluation should symptoms occur. Symptoms and signs could 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.

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

• HIV-positive patients

• Patients with a history of heavy alcohol ingestion, liver disease, or chronic hepatitis

• Pregnant and postpartum women (up to 2-3 months after delivery)

• Patients with a history of drug injection

• Patients older than 55 years (if taking INH)

• Patients starting treatment with 2 or more anti-TB drugs

Monthly liver function tests should be conducted for all HIV-positive patients; patients with a history of heavy alcohol ingestion, liver disease, or chronic hepatitis; pregnant and postpartum women (up to 2-3 months after delivery); and patients currently injecting drugs.

In addition, laboratory testing should be used to evaluate specific adverse events that may occur during treatment.
A Guide to Tuberculin Skin Testing and the Treatment of Latent Tuberculosis Infection

ALSO INSIDE:

A Continuing Medical Education Activity for 2.0 Credits
Know Which Persons Are at High Risk for TB Infection or Disease and Should Be Tested for Latent TB Infection

<table>
<thead>
<tr>
<th>Drug</th>
<th>Duration</th>
<th>Adult dosage (maximum dosage)</th>
<th>Twice Weekly</th>
<th>Daily</th>
<th>Twice Weekly</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>9 months</td>
<td>5 mg/kg (300 mg)</td>
<td>15 mg/kg (900 mg)</td>
<td>270 doses within 12 months</td>
<td>76 doses within 12 months</td>
<td>Preferred over INH for 6 months for all individuals.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>6 months</td>
<td>5 mg/kg (200 mg/kg)</td>
<td>15 mg/kg (900 mg)</td>
<td>180 doses within 9 months</td>
<td>52 doses within 9 months</td>
<td>For HIV-negative adults, this 6-month regimen is an acceptable alternative to the 9-month INH regimen and may provide a more cost-effective outcome.</td>
</tr>
<tr>
<td>Rifampin (RIF) plus Pnynosamide (PZA)</td>
<td>2 months**</td>
<td>10 mg/kg (600 mg)</td>
<td>10 mg/kg (600 mg)</td>
<td>80 doses within 3 months</td>
<td>16 doses within 3 months</td>
<td>May be offered to contacts of patients with INH-resistant TB. In HIV+ persons, RIF generally should not be coadministered with all currently available PIs and NNRTIs.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>4 months</td>
<td>10 mg/kg (600 mg)</td>
<td>120 doses within 6 months</td>
<td></td>
<td></td>
<td>For persons who cannot tolerate PZA. Please see Point 8 for rifampin regimen for children.</td>
</tr>
</tbody>
</table>

**See Point 8 for children’s regimens for RIF.**

<table>
<thead>
<tr>
<th>Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors That Can Be Used Concomitantly With Rifaximin</th>
<th>Rifaximin Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir (Agenerase®), Indinavir® (Crixivan®), and Nelfinavir (Viracept®)</td>
<td>150 mg (daily) or 300 mg (intermittently)</td>
</tr>
<tr>
<td>Efavirenz (Sustiva®)</td>
<td>600 mg (daily or intermittently)</td>
</tr>
<tr>
<td>Nelfinavir (Viracept®)</td>
<td>300 mg (daily or intermittently)</td>
</tr>
<tr>
<td>Ritonavir (Norvir®) and Saquinavir (Fortovase®), if administered together, each at a dose of 400 mg BD</td>
<td>150 mg (intermittently)</td>
</tr>
</tbody>
</table>

**Increase dosage of indinavir to 1000 mg every 8 hours when concomitated with rifatin.**
ANSWER KEY

Please place an “X” in the box next to your answer for each of the corresponding questions.

1. ☐ A ☐ B ☐ C

2. ☐ A ☐ B ☐ C

3. ☐ A ☐ B ☐ C

4. ☐ A ☐ B ☐ C ☐ D ☐ E

5. ☐ A ☐ B ☐ C ☐ D ☐ E

6. ☐ A ☐ B ☐ C

Please indicate degree: ☐ M.D. ☐ D.O. ☐ P.A. ☐ N.P. ☐ R.N.

Name ____________________________________________________

Address __________________________________________________

City ____________________ State _____ ZIP Code __________

Telephone (___________) ____________________________________

Expiration—May 1, 2001

For eligibility to receive continuing medical education credit, the response card or a photocopy of the card must be completed and returned by fax or by mail, postmarked no later than May 1, 2001. This issue of CITY HEALTH INFORMATION, including this continuing medical education activity, is also available on the Internet for downloading (but not for electronic response) at www.nyc.gov/health.

Instructions

1. Read this issue of CITY HEALTH INFORMATION, which contains the correct answers to the questions on this page.

2. Complete all information on the response card, including your name, mailing address, and phone number.

3. Select your answers to the questions, and check the corresponding boxes on the response card. To receive continuing medical education credit, you must answer all questions, and 4 of the first 5 questions must be answered correctly. You will receive a CME or CNE certificate for 2.0 hours and a list of answers to the questions.

4. Return the response card or a photocopy of the card postmarked no later than May 1, 2001. Fax to (212) 442-3535 or mail to: CME Administrator, New York City Department of Health, 125 Worth Street, CN #12, New York, N.Y. 10213-0288.
A Directory of Tuberculosis-Care Resources

The New York City Department of Health

Reporting

TB Hotline for Physicians ... (212) 788-4162
To report a suspected or confirmed case of tuberculosis and to obtain information on the treatment and drug susceptibility of your TB patient.
Fax (212) 788-4179

Directly-Observed Therapy

Information ..................... (212) 442-9777
Assistance in arranging a program for your patient.

Laboratory Services

Mycobacteriology Reference Laboratory .................... (212) 447-6745
To submit specimens and cultures to obtain test results of previous submissions.

Education

Information ..................... (212) 442-9968
For questions about tuberculosis, for copies of Department of Health publications, and to obtain training information and educational materials in English and other languages.

Chest Centers

Free, confidential, state-of-the-art care for patients with tuberculosis, their contacts, and other persons at risk for TB infection. Some centers are open on Saturdays and on some late nights. Call center for hours. Phone numbers may change; call (212) 442-9968 for updated numbers.

Bronx/ Staten Island Network
Morrissania ...................... (718) 901-6536, 6538
1309 Fulton Avenue, Bronx, NY 10456
Fax (718) 590-6736

Richmond .......................... (718) 983-4530
51 Stuyvesant Place, Staten Island, NY 10301
Fax (718) 983-4529

Brooklyn Network
Bedford .................................. (718) 574-2462, 2463
485 Throop Avenue, Brooklyn, NY 11221
Fax (718) 455-1895

Brownsville .......................... (718) 495-7256, 7258
259 Bristol Street, Brooklyn, NY 11212
Fax (718) 346-8255

Fort Greene ....................... (718) 643-8357, 6551
295 Flatbush Avenue Extension, Brooklyn, NY 11201
Fax (718) 643-6367

Manhattan Network
Chelsea ......................... (212) 239-1749, 1757
303 Ninth Avenue, New York, NY 10001
Fax (212) 290-2324

Washington Heights ................ (212) 304-5435
600 W. 168th Street, New York, NY 10032
Fax (212) 740-9162

Queens Network
Corona ................................ (718) 476-7635, 7636
34-33 Junction Boulevard, Jackson Heights, NY 11372
Fax (718) 476-7818

Far Rockaway .............. (718) 474-2100, 2101
67-10 Rockaway Beach Boulevard, Far Rockaway, NY 11692
Fax (718) 945-2596

Division of TB Elimination ....... (404) 639-1820
http://www.cdc.gov/nchstp/tb
For CDC publications and other information.

National Jewish Medical and Research Center

Information ..................... (800) 423-8891

Clinical Consultation ............... Ext. 1279

Mycobacteriology .................. Ext. 1339

Pharmacokinetics .................. Ext. 1925

References and Additional Reading


Published by the New York City Department of Health, City Health Information features descriptive data, analysis, and reports from the Health Department about public health issues of interest to the medical community.

Copyright © 2000

125 Worth Street, Rm. 315, CN 6, New York, N.Y. 10013 (212) 788-5394 Fax (212) 788-9810 www.nyc.gov/health