

## Clinical Practice

*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.*

## LATENT TUBERCULOSIS INFECTION

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Patient 1, a 44-year-old man who recently immigrated from Peru, is found to have induration of 16 mm in diameter on a tuberculin skin test. He received bacille Calmette–Guérin (BCG) vaccine as an infant and is asymptomatic. Chest radiography shows fibronodular opacities in the upper lobe. Patient 2, a 27-year-old schoolteacher who was born in the United States, has induration of 17 mm on a tuberculin skin test, no symptoms, and a normal chest radiograph. Should these patients receive treatment for latent tuberculosis infection?

## THE CLINICAL PROBLEM

Despite intensified global efforts, the number of cases of tuberculosis worldwide is increasing. The World Health Organization (WHO) estimates that in 1999, there were 8.4 million new cases, up from 8.0 million in 1997.<sup>1</sup> The WHO also estimates that there are nearly 2 million deaths from tuberculosis annually; thus, the disease ranks second only to human immunodeficiency virus (HIV) infection as an infectious cause of death.<sup>2</sup> Approximately 1.7 billion people, nearly one third of the world's population, are thought to be infected with *Mycobacterium tuberculosis*.<sup>3</sup> The United States and other developed countries are not protected from the ongoing epidemic of tuberculosis occurring in the poor countries of the world: currently in the United States, about 50 percent of the new cases are occurring in persons born outside the country.<sup>4</sup>

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Although treatment of persons with active tuberculosis is the first priority for tuberculosis control, an important second priority in countries with a low incidence is identification and treatment of persons with latent tuberculosis infection. As the Institute of Medicine has argued,<sup>5</sup> “to make significant progress toward the elimination of tuberculosis in the United States, efforts to prevent cases from occurring must be amplified.”

In most persons, infection with *M. tuberculosis* is initially contained by host defenses, and the infection remains latent. However, latent tuberculosis infection has the potential to develop into tuberculosis at any time, and persons with active tuberculosis become sources of new infections. Treatment of latent infection greatly reduces the likelihood that active tuberculosis will develop. Thus, it has the potential both to preserve the health of an individual person and to protect the health of the public by reducing the number of potential sources of infection.<sup>6</sup>

## STRATEGIES AND EVIDENCE

## Identifying Latent Tuberculosis Infection

Until recently, the only test to identify latent tuberculosis infection was the tuberculin skin test.<sup>7</sup> However, a test measuring the release of interferon- $\gamma$  in whole blood in response to stimulation by purified protein derivative (PPD) has been approved by the Food and Drug Administration.<sup>8</sup> Both tests are discussed below. Regardless of the test used to diagnose latent tuberculosis infection, the basic principles for the application of the test and any actions that ensue from the result are the same.

*Who Should Be Tested?*

The goal of testing for latent tuberculosis infection is to identify persons who, because they are at increased risk for the development of tuberculosis, would benefit from treatment of the infection. Since only persons who would benefit from treatment should be tested, a decision to test presupposes a decision to treat if the test is positive.

There are two broad categories of candidates for testing for latent tuberculosis infection: persons who are likely to have been infected recently and persons who are at increased risk for tuberculosis because of certain clinical conditions (Table 1). Recent infection is identified when the induration from a tuberculin skin test increases by at least 10 mm within a two-year period (a condition termed “tuberculin conversion”). The risk of tuberculosis is highest soon after infection

**TABLE 1.** PERSONS AT INCREASED RISK WHO SHOULD BE TESTED FOR LATENT TUBERCULOSIS INFECTION.

RISK	EXAMPLES OF PERSONS WITH RISK
Increased risk of exposure to infectious cases	Persons with recent close contact with persons known to have active tuberculosis* Health care workers who work at facilities where patients with tuberculosis are treated
Increased risk of tuberculosis infection	Foreign-born persons from countries with a high prevalence of tuberculosis Homeless persons Persons living or working in facilities providing long-term care
Increased risk of active tuberculosis once infection has occurred	HIV-infected persons Persons with recent tuberculosis infection† Injection-drug users Patients with end-stage renal disease Patients with silicosis Patients with diabetes mellitus Patients receiving immunosuppressive therapy Patients with hematologic cancers Malnourished persons or those with a recent weight loss of more than 10% of their ideal body weight Persons who have undergone gastrectomy or jejunioileal bypass

\*We define close contact as at least 12 hours of contact with a person with infectious tuberculosis, but there are no well-established criteria for such contact.

†Persons with recent infection include children less than four years of age and persons found to have tuberculin conversion, defined as an increase in induration of at least 10 mm on a tuberculin skin test within a two-year period.

has occurred; thus, persons who have had recent exposure to a patient with newly diagnosed tuberculosis represent a high priority for testing and, if they test positive, for treatment.

#### The Tuberculin Skin Test

The tuberculin skin test has been in use since the late 1800s, and its design is based on the observation by Robert Koch that infection with *M. tuberculosis* caused cutaneous reactivity to tuberculin, a concentrated filtrate from cultures of *M. tuberculosis* that had been heat-killed.<sup>7</sup> The standard tuberculin test consists of 0.1 ml (5 tuberculin units) of PPD administered intracutaneously, usually in the volar surface of the forearm. The reaction is read 48 to 72 hours after injection, although a reading obtained up to one week later is accurate.<sup>9</sup> The size of the reaction is determined by measurement of the induration (not erythema) across the forearm at the site of the injection. The criterion for interpreting the reaction as positive (indicating the presence of tuberculosis infection) varies depending on certain characteristics of the person being tested (Table 2). The general principle is that if a smaller reaction is defined as indicating infection, the sensitivity of the test is increased in those who are at greatest risk for the development of tuberculosis.

Sensitization to tuberculin can also be induced by infection with nontuberculous mycobacteria, including BCG, which is used in many parts of the world

as a vaccine against tuberculosis. Although it is not possible to distinguish between a tuberculin reaction that is caused by true infection and a reaction that is caused by BCG, one study showed that only 8 percent of persons who had received BCG vaccine at birth had a positive tuberculin test 15 years later.<sup>10</sup> Because most persons who receive BCG vaccine are from countries with a high incidence of tuberculosis, it is recommended that the history of BCG vaccination be ignored when tuberculin tests are interpreted.<sup>6</sup>

In addition, the tuberculin skin test is not 100 percent sensitive for infection with *M. tuberculosis*, and even among patients with proven tuberculosis and no apparent immunosuppression, 10 to 20 percent will have negative results on tuberculin skin tests.<sup>11,12</sup> Testing with control antigens such as mumps and candida was previously thought to help determine whether persons had true negative rather than false negative tuberculin tests. However, in several studies in HIV-infected persons, serial anergy testing has revealed that responses vary over time.<sup>13-15</sup> Such testing is therefore not recommended in HIV-infected persons. Because the role of anergy testing in the diagnosis of latent tuberculosis infection is not well defined for patients with normal immune systems or conditions causing immunocompromise other than HIV infection, most clinicians do not perform such tests.

Over time, delayed hypersensitivity resulting from mycobacterial infection may wane in some persons,

**TABLE 2.** CRITERIA FOR A POSITIVE TUBERCULIN SKIN TEST.

SIZE OF REACTION	PERSONS IN WHOM REACTION IS CONSIDERED POSITIVE
≥5 mm	HIV-infected persons Close contacts of persons with infectious tuberculosis Persons with an abnormal chest radiograph consistent with previous tuberculosis* Immunosuppressed patients receiving the equivalent of ≥15 mg of prednisone per day for ≥1 mo
≥10 mm	Foreign-born persons recently arrived (<5 yr earlier) from a country with high prevalence of tuberculosis Persons with a medical condition that increases the risk of tuberculosis† Injection-drug users Members of medically underserved, low-income populations (e.g., homeless persons) Residents and staff members of long-term care facilities (e.g., nursing homes, correctional institutions, homeless shelters) Health care workers Children <4 yr of age Persons with conversion on a tuberculin skin test (increase in induration of ≥10 mm within a 2-yr period)
≥15 mm	All others‡

\*An abnormal chest radiograph consistent with previous tuberculosis reveals fibrotic opacities occupying more than 2 cm<sup>2</sup> of the upper lobe; radiographs showing pleural thickening or isolated calcified granulomas are not considered to be suggestive of previous tuberculosis.

†Medical conditions that increase the risk of development of tuberculosis in the presence of latent tuberculosis infection include silicosis, end-stage renal disease, malnutrition, diabetes mellitus, carcinoma of the head and neck or lung, immunosuppressive therapy, lymphoma, leukemia, loss of more than 10 percent of ideal body weight, gastrectomy, and jejunioileal bypass.

‡These persons should not be screened in the absence of an indication.

resulting in a nonreactive tuberculin skin test despite the presence of true infection. However, the stimulus of this negative tuberculin test may “boost” or increase the size of the reaction to a second test administered later, resulting in a positive tuberculin test and misleadingly suggesting tuberculin conversion (the “booster” phenomenon).<sup>9,16</sup> Persons who will undergo annual tuberculin skin testing (e.g., health care workers) should undergo two-step testing on initial evaluation, with a second tuberculin test administered one week after a negative initial test.

#### **Whole-Blood Interferon-Gamma Assay**

An in vitro assay of whole blood for cell-mediated immunity, based on the release of interferon- $\gamma$  from T lymphocytes in response to stimulation with *M. tuberculosis* PPD, shows promise for the identification of latent tuberculosis infection.<sup>17</sup> In a multicenter trial, there was excellent agreement between the tuberculin skin test and the assay.<sup>8</sup> Because the tuberculin test was used as the reference standard, the blood test could not be shown to be better than the tuberculin test. As studied, the assay seemed to be confounded by BCG to the same extent as the tuberculin test. However, another assay that uses the secreted antigen ESAT-6, which is not present in BCG, to detect the release of interferon- $\gamma$  from T cells specific to *M. tuberculosis* offers the possibility of distinguishing between true tuberculosis infection and a BCG-induced reaction.<sup>18</sup>

#### **Ruling out Active Tuberculosis**

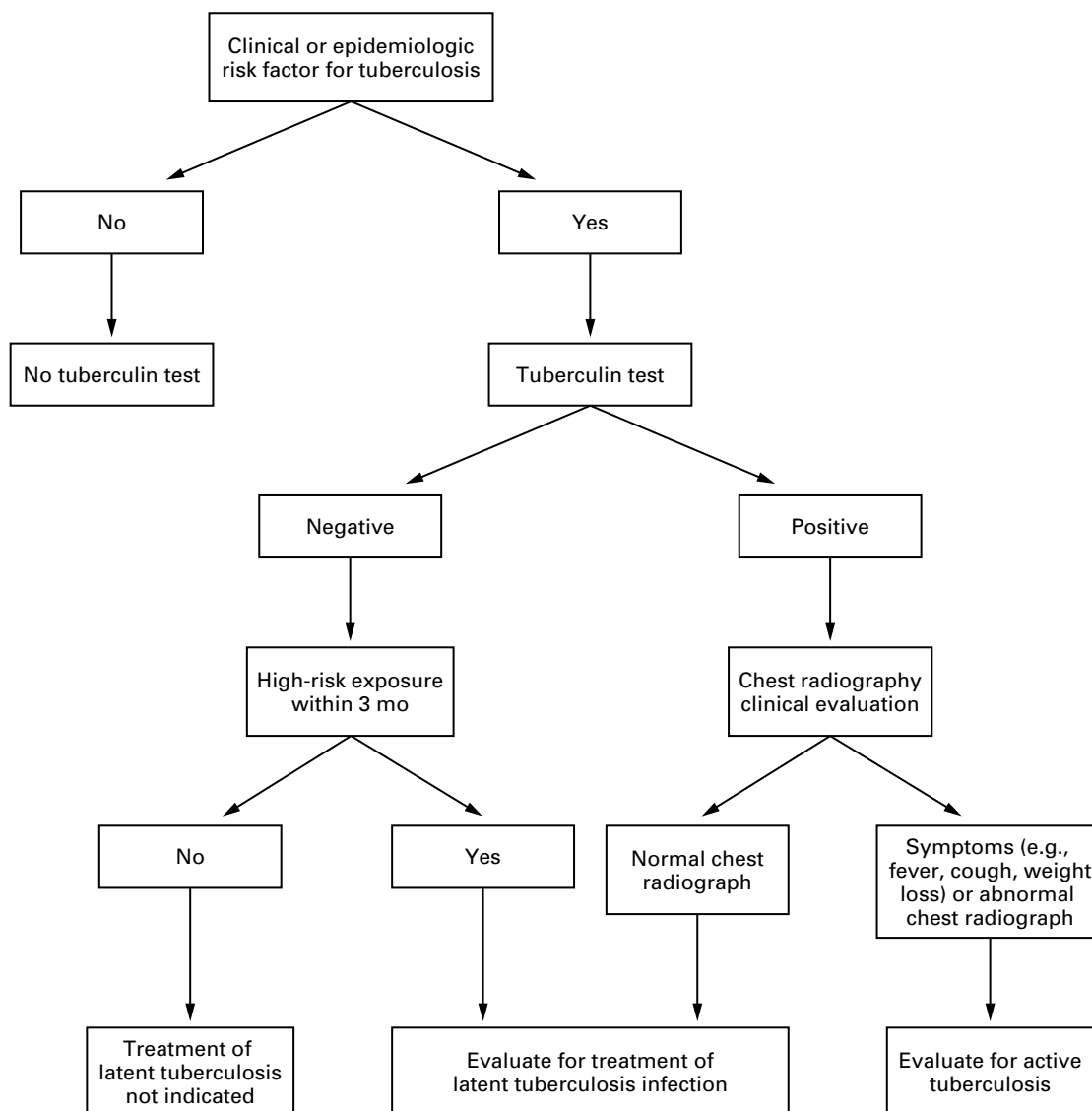
The diagnosis of latent tuberculosis infection requires not only a positive tuberculin skin test, but also that active tuberculosis be ruled out. This is usually accomplished by a careful history taking, appropriate evaluation of symptoms, and radiographic examination of the chest (Fig. 1). Combination chemotherapy for presumptive tuberculosis should be initiated pending culture if there is a high clinical suspicion of active tuberculosis. Treatment for latent infection should be administered only after negative results have been obtained on culture and active tuberculosis is no longer clinically suspected.

#### **Treatment Regimens for Latent Tuberculosis Infection**

##### **Isoniazid**

Isoniazid has been evaluated in randomized, controlled trials conducted by the U.S. Public Health Service that included more than 70,000 participants from a variety of populations.<sup>19</sup> When all these studies are considered together, the effectiveness of the drug, as compared with placebo, in reducing the incidence of active tuberculosis averages about 60 percent, with a range of 25 to 92 percent, the higher values being associated with better adherence to the treatment regimen.<sup>19</sup> In most studies, 300 mg of isoniazid was given daily for one year.

In the only study that assessed different durations



**Figure 1.** Tuberculosis Screening Flowchart.

Clinical and epidemiologic risk factors are listed in Table 1. Criteria for positive results on tuberculin skin tests are shown in Table 2. A chest radiograph is considered abnormal if it reveals parenchymal abnormalities; radiographs showing pleural thickening or isolated calcified granulomas are not considered to be suggestive of previous tuberculosis. Patients with abnormal chest radiographs, especially those with opacities occupying more than 2 cm<sup>2</sup> of the upper lobe, should be evaluated for active tuberculosis by sputum examination before beginning treatment for latent tuberculosis infection. Treatment for latent tuberculosis infection should not be started until active tuberculosis has been ruled out. Although there are no well-defined criteria for high-risk exposure, we define it as recent close contact, for at least 12 hours, with a person with infectious tuberculosis. Because the tuberculin skin test may not become positive until three months after exposure, treatment for latent tuberculosis infection should be considered in persons with such exposure even if the initial tuberculin test is negative, especially if the contact is a young child or is immunocompromised. Further treatment should be definitively guided by a repeated tuberculin test three months after the contact has ended. If the test is positive, treatment should be continued; if the test is negative, treatment should be discontinued.

of isoniazid therapy, 6 months of treatment was 65 percent effective and 12 months of treatment was 75 percent effective (but not statistically different from 6 months) in preventing tuberculosis among patients with radiographic abnormalities suggestive of inactive tuberculosis.<sup>20</sup> Through the interpolation of data from randomized trials, the optimal duration of isoniazid treatment for latent tuberculosis infection has been determined to be nine months.<sup>6,21</sup>

The most important side effect of isoniazid is hepatitis. Although liver-enzyme abnormalities are relatively common, occurring in 10 to 20 percent of persons taking the drug, symptomatic hepatitis is uncommon.<sup>22,23</sup> The frequency of isoniazid-related hepatitis (defined as both symptoms of hepatitis and liver-enzyme levels more than five times the upper limit of normal) increases with increasing age and was 2.3 percent among persons older than 50 years of age in a U.S. Public Health Service study.<sup>24</sup> Because of the increased risk of hepatitis associated with advanced age, an age of more than 35 years was previously considered a contraindication to treatment with isoniazid. However, in a more recent report, the incidence of isoniazid-related hepatitis was determined to be only 1 case per 1000 persons, although the incidence was not analyzed according to age.<sup>25</sup> Alcohol consumption is an important cofactor for isoniazid-related hepatitis; thus, patients should be advised to abstain from alcohol while taking isoniazid. Another adverse effect of isoniazid, peripheral neuropathy, occurs in up to 2 percent of patients taking the drug in the doses that are usually prescribed.<sup>26</sup> It is caused by interference with the metabolism of pyridoxine and can be effectively prevented by pyridoxine supplementation.<sup>27</sup>

#### **Rifampin**

In the only study that evaluated the efficacy of rifampin alone as treatment for latent tuberculosis infection, rifampin given daily for three months to persons with latent tuberculosis infection and silicosis had an efficacy that was significantly better than that of placebo and equivalent to that of isoniazid given daily for six months.<sup>28</sup> Adverse reactions to rifampin are uncommon. There are several important drug interactions, most notably with the protease-inhibitor class of antiretroviral drugs, that limit the use of rifampin in patients with HIV infection.

#### **Rifampin and Pyrazinamide**

In clinical trials, a regimen of rifampin and pyrazinamide was shown to be as effective and as safe as isoniazid in HIV-infected persons with latent tuberculosis infection.<sup>29-31</sup> However, there has been relatively little experience with this regimen in persons without HIV infection, and case reports of severe hepatitis, including eight hepatitis-related deaths, have aroused

concern about the safety of the regimen.<sup>32</sup> A recent multicenter clinical trial involving adults without HIV infection confirmed that rifampin and pyrazinamide are associated with a greater risk of hepatotoxicity than is isoniazid.<sup>33</sup> In that study, 8 percent of the patients who received rifampin and pyrazinamide had liver-enzyme levels more than five times the upper limit of normal, as compared with 1 percent of those who received isoniazid.

### **AREAS OF UNCERTAINTY**

Although studies suggest that isoniazid given for nine months provides the optimal protection against active tuberculosis, this duration has not itself been studied directly, and the optimal duration of therapy is a particularly important question for HIV-infected persons. An analysis from a trial conducted in Uganda showed that isoniazid alone initially protected against the development of tuberculosis in tuberculin-positive HIV-infected persons but that its benefit was lost one year after treatment began.<sup>34,35</sup> However, patients treated with either isoniazid plus rifampin or isoniazid, rifampin, and pyrazinamide for three months had sustained benefit. Also uncertain is the future role of the whole-blood interferon- $\gamma$  assay for the diagnosis of latent tuberculosis infection.

Finally, a decision analysis in this issue of the *Journal*<sup>36</sup> suggests that because of the high prevalence of isoniazid-resistant tuberculosis infection in Vietnam, Haiti, and the Philippines, persons from those countries in the United States should be treated with a rifampin-based regimen to obtain maximal health and economic benefits.<sup>37</sup> These observations will need to be confirmed in prospective studies.

### **GUIDELINES**

#### **Determining Whom to Treat**

The current joint recommendations of the American Thoracic Society and the Centers for Disease Control and Prevention<sup>38</sup> are designed to target tuberculin testing to persons at high risk for the development of tuberculosis who, if they test positive, will be candidates for treatment of latent tuberculosis infection (Table 1).<sup>6</sup> Because persons should be targeted for treatment on the basis of their increased risk of development of tuberculosis, age does not play a part in the decision to treat. In persons with the highest risk of tuberculosis (Table 2), induration of 5 mm or more in diameter on a tuberculin skin test is used to diagnose latent tuberculosis infection. This group includes persons with HIV infection, close contacts of persons with active tuberculosis, persons with an abnormal chest radiograph showing upper-lobe fibrosis consistent with previous tuberculosis, and immunosuppressed patients who have been receiving the equiva-

lent of at least 15 mg of prednisone per day for at least one month. In persons with an intermediate risk of tuberculosis, an induration of 10 mm or more should be used to define latent infection.

For the first several years after their arrival in the United States, foreign-born persons from countries with a high prevalence of tuberculosis have rates of tuberculosis that are similar to those in their countries of origin.<sup>37</sup> For this reason, it is recommended that persons who have arrived within the past five years be treated if latent tuberculosis infection is identified. Persons with none of the risk factors in Table 1 should not be tested. Before treatment of latent tuberculosis infection is begun, it is essential that active tuberculosis be ruled out (Fig. 1).

### Treatment Regimens

The first choice for treatment of latent tuberculosis infection is isoniazid (Table 3). Current guidelines recommend a duration of at least six and preferably nine months in adults and nine months in children. For persons with poor adherence to treatment, directly observed treatment may be the optimal approach, with direct observation either daily or twice weekly. In persons who are predisposed to neuropathy (e.g., those with diabetes, uremia, malnutrition, or HIV infection), pregnant women, and persons with seizure disorders, pyridoxine (25 mg per day) should be given

with isoniazid. Rifampin alone for four months is the second choice and should be used for patients who are intolerant of isoniazid or who are presumed to have infection with isoniazid-resistant strains of *M. tuberculosis*.

A third choice for treatment is rifampin and pyrazinamide for two months. Because of the possibility of severe hepatotoxicity, this regimen is generally reserved for persons who are not likely to complete a longer treatment regimen and who can be monitored closely. It is not recommended for pregnant women or children. Before any of these treatments is initiated, it is essential that patients be educated about potential adverse effects of the treatment regimen being used (Table 3).

### CONCLUSIONS AND RECOMMENDATIONS

The goal of testing for latent tuberculosis infection is to identify infected patients who will benefit from treatment. The patients who will benefit are those who either are at increased risk for having recently acquired infection or have a medical condition that increases their risk of progression to active tuberculosis. Patient 1 described in the vignette should be presumed to have tuberculosis infection; his history of BCG should be ignored. However, because of the abnormality on his chest radiograph, treatment for latent tuberculosis infection should not be started until sputum cultures

TABLE 3. RECOMMENDED REGIMENS FOR LATENT TUBERCULOSIS INFECTION.\*

TREATMENT REGIMEN	DOSE		TOXIC EFFECTS	MONITORING SCHEDULE	COMMENTS
	ADULTS	CHILDREN			
Isoniazid for 6–9 mo	5 mg/kg of body weight (maximum, 300 mg) daily or 900 mg twice weekly	10–20 mg/kg (maximum, 300 mg)	Hepatitis; rash; peripheral neuropathy	Clinical monitoring monthly; base-line measurement of liver enzymes only in persons with risk factors for hepatitis	Directly observed therapy must be used with twice-weekly administration; risk of hepatitis increases with age and alcohol use.
Rifampin for 4 mo	10 mg/kg (maximum, 600 mg)	10–20 mg/kg (maximum, 600 mg)	Hepatitis; rash; thrombocytopenia; fever; orange-colored body fluids	Clinical monitoring monthly; base-line measurement of liver enzymes only in persons with risk factors for hepatitis	Drug interactions can result in decreased levels of many drugs (e.g., warfarin, contraceptive pills, and methadone).
Rifampin and pyrazinamide for 2 mo†	5 mg of rifampin/kg (maximum, 300 mg); 15–20 mg of pyrazinamide/kg (maximum, 2000 mg)	Not recommended	Hepatitis; rash; thrombocytopenia; orange-colored body fluids; arthralgia	Measurement of liver enzymes in all patients at base line and after 2, 4, and 6 wk; clinical monitoring at wk 2, 4, 6, and 8	Do not dispense more than a 2-wk supply of medication; permanently stop treatment if serum aminotransferase levels are >5 times upper limit of normal in an asymptomatic person or above the normal range with symptoms or if serum bilirubin level is above normal range.

\*For those receiving isoniazid or rifampin alone, liver-enzyme tests should be conducted at base line in persons with HIV infection, a history of liver disease, alcoholism, or pregnancy. Repeated measurements of liver enzymes should be obtained if base-line results are abnormal, if the patient has just given birth, or if symptoms of adverse effects occur. Rifampin should be used with caution in HIV-infected persons taking protease inhibitors or nonnucleoside reverse-transcriptase inhibitors; a switch to rifabutin should be considered.

†This regimen is not recommended for pregnant women.

are negative for *M. tuberculosis*. After cultures are negative, the preferred regimen would be isoniazid given for nine months. Patient 2 is at low risk for the development of tuberculosis and should not have been tested. Nonetheless, she has latent tuberculosis infection, as evidenced by her tuberculin reaction of more than 15 mm. However, she should not be treated, because she has no conditions that increase her risk of progression to tuberculosis and it is unknown when she became infected. One cannot conclude that she has had recent tuberculin conversion, because she has not had a negative tuberculin test within the past two years.

Supported by grants from the National Institutes of Health (AI 01549 and AI 34238).

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