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Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

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Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

This Official Statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This Statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this Statement as it relates to infants and children were endorsed by the American Academy of Pediatrics (AAP), August 1999.

EXECUTIVE SUMMARY

This statement provides new recommendations for targeted tuberculin testing and treatment regimens for persons with latent tuberculosis infection (LTBI) and updates previously published guidelines (*1,2*). This statement is issued in recognition of the importance of these activities as an essential component of the TB Elimination Strategy promoted by the U.S. Public Health Service Advisory Council on the Elimination of Tuberculosis, and reports the deliberations of expert consultants convened by the American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC).

Isoniazid for 6–12 mo has been the mainstay of treatment for LTBI in the United States for more than 30 yr. However, the application of isoniazid for LTBI has been limited because of poor adherence, due to the relatively long duration of treatment required, and because of concerns about toxicity. Therefore, there has been interest in the development of shorter, rifampin-based regimens as alternatives to isoniazid for the treatment of LTBI. During the past decade, a series of studies of "short-course" treatment of LTBI in persons with human immunodeficiency virus (HIV) infection has been undertaken. The results of these trials have recently become available, and the in-depth analyses of these and prior studies of isoniazid form the scientific basis of the treatment guidelines presented in this report. In addition, many changes to previous recommendations regarding testing for and treatment of LTBI are presented (Table 1).

Targeted Tuberculin Testing

Targeted tuberculin testing for LTBI is a strategic component of tuberculosis (TB) control that identifies persons at high risk for developing TB who would benefit by treatment of LTBI, if detected. Persons with increased risk for developing TB include those who have had recent infection with *Mycobacterium tuberculosis* and those who have clinical conditions that are associated with an increased risk for progression of LTBI to active TB (*see* Tables 2 and 3). Following that principle, targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk. Infected persons who are considered to be at high risk for developing active TB should be offered treatment of LTBI irrespective of age.

Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction: ≥5 mm, ≥10 mm, and

≥15 mm of induration (*see* Table 7). For persons who are at highest risk for developing active TB if they are infected with *M. tuberculosis* (i.e., persons with HIV infection, who are receiving immunosuppressive therapy, who have had recent close contact with persons with infectious TB, or who have abnormal chest radiographs consistent with prior TB), ≥5 mm of induration is considered positive. For other persons with an increased probability of recent infection or with other clinical conditions that increase the risk for progression to active TB, ≥10 mm of induration is considered positive. These include recent immigrants (i.e., within the last 5 yr) from high prevalence countries; injection drug users; residents and employees of high-risk congregate settings (including health care workers with exposure to TB); mycobacteriology laboratory personnel; persons with clinical conditions such as silicosis, diabetes mellitus, chronic renal failure, leukemias and lymphomas, carcinoma of the head or neck and lung, weight loss of ≥10% ideal body weight, gastrectomy, and jejunoileal bypass; and children younger than 4 yr of age or infants, children, and adolescents exposed to adults in high-risk categories. For persons at low risk for TB, for whom tuberculin testing is not generally indicated, ≥15 mm of induration is considered positive.

Treatment of Latent Tuberculosis Infection

In this report, treatment recommendations use an adaptation of the rating system from recent U.S. Public Health Service documents (*3*) that grades the strength of the recommendation (A, B, or C) and the quality of evidence supporting the recommendation (I, II, or III). Four regimens are recommended for the treatment of adults with LTBI. (*See* Tables 8 and 10 for detailed recommendations, dosages, and contraindications.)

Drugs	Duration (mo)	Interval	Rating* (Evidence)† HIV⁻	Rating* (Evidence)† HIV⁺
Isoniazid	9	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampin–pyrazinamide	2	Daily	B (II)	A (I)
	2–3	Twice weekly	C (II)	C (I)
Rifampin	4	Daily	B (II)	B (III)

* A = preferred; B = acceptable alternative; C = offer when A and B cannot be given.

† I = randomized clinical trial data; II = data from clinical trials that are not randomized or were conducted in other populations; III = expert opinion.

The isoniazid daily regimen for 9 mo is recommended because prospective, randomized trials in HIV-negative persons indicate that 12 mo of treatment is more effective than 6 mo of treatment. However, in subgroup analyses of several trials the maximal beneficial effect of isoniazid is likely achieved by 9 mo, and minimal additional benefit is gained by extending therapy to 12 mo. When compared with placebo, both 6-mo and 12-mo regimens are effective in HIV-positive patients; however, these regimens have not been compared with each other in randomized trials.

Although a 9-mo regimen of isoniazid is the preferred regimen for the treatment of LTBI, a 6-mo regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations,

treatment for 6 mo rather than 9 mo may provide a more favorable outcome from a cost-effectiveness standpoint. Thus, based on local conditions, health departments or providers may conclude that a 6-mo rather than a 9-mo course of isoniazid is preferred.

Table 1. Changes from prior recommendations on tuberculin testing and treatment of latent tuberculosis infection (LTBI)

Tuberculin testing

- Emphasis on targeted tuberculin testing among persons at high risk for recent LTBI or with clinical conditions that increase the risk for tuberculosis (TB), regardless of age; testing is discouraged among persons at lower risk
- For patients with organ transplants and other immunosuppressed patients (e.g., persons receiving the equivalent of ≥15 mg/d prednisone for 1 mo or more), 5 mm of induration rather than 10 mm of induration rather than 10 mm of induration as a cut-off level for tuberculin positivity
- A tuberculin skin test conversion is defined as an increase of ≥10 mm of induration within a 2-yr period, regardless of age

Treatment of latent tuberculosis infection

- For human imunodeficiency virus (HIV)-negative persons, isoniazid given for 9 mo is preferred over 6-mo regimens
- For HIV-positive persons and those with fibrotic lesions on chest X-ray consistent with previous TB, isoniazid should be given for 9 mo instead of 12 mo
- For HIV-negative and HIV-positive persons, rifampin and pyrazinamide should be given for 2 mo
- For HIV-negative and HIV-positive persons, rifampin should be given for 4 mo

Clinical and laboratory monitoring

- Routine baseline and follow-up laboratory monitoring can be eliminated in most persons with LTBI, except for those with HIV infection, pregnant women (or those in the immediate postpartum period), and persons with chronic liver disease or those who use alcohol regularly
- Emphasis on clinical monitoring for signs and symptoms of possible adverse effects, with prompt evaluation and changes in treatment, as indicated

Both the 9-mo and 6-mo isoniazid regimens may be given intermittently (i.e., twice weekly). When isoniazid is given intermittently, it should be administered only as directly observed therapy (DOT).

The 2-mo daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV-infected persons that showed the 2-mo regimen to be similar in safety and efficacy to a 12-mo regimen of isoniazid. Twice-weekly treatment with rifampin and pyrazinamide for 2 or 3 mo may be considered when alternative regimens cannot be given. This intermittent regimen should always be administered as DOT. Some experts recommend that the 2-mo regimen of daily rifampin and pyrazinamide also be given by DOT, which can consist of five observed and two self-administered doses each week. In situations in which rifampin cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.

Rifampin given daily for 4 mo is recommended on the basis of the efficacy of a similar regimen in a) a prospective randomized trial of tuberculin-positive persons with silicosis and b) a nonrandomized trial in persons exposed to individuals with isoniazid-resistant TB. This option may be especially useful for patients who cannot tolerate isoniazid or pyrazinamide.

Before beginning treatment of LTBI, active TB should be ruled out by history, physical examination, chest radiography, and, when indicated, bacteriologic studies.

Special considerations for treatment of LTBI apply to the following populations:

- When isoniazid is chosen for treatment of LTBI in persons with HIV infection or those with radiographic evidence of prior TB, 9 mo rather that 6 mo is recommended.
- For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 mo is recommended. For women at risk for progression of LTBI to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk for active TB is lower, some experts recommend waiting until after delivery to start treatment.
- For children and adolescents, isoniazid given either daily or twice weekly for 9 mo is the recommended regimen.
- For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, rifampin and pyrazinamide given daily for 2 mo is recommended, and for patients with intolerance to pyrazinamide, rifampin given daily for 4 mo is recommended.
- For persons who are likely to be infected with isoniazid- and rifampin-resistant (multidrug) TB and who are at high risk for developing TB, pyrazinamide and ethambutol or pyrazinamide and a quinolone (i.e., levofloxacin or ofloxacin) for 6–12 mo are recommended. Immunocompetent contacts may be observed or treated for at least 6 mo, and immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 mo.

Clinical and Laboratory Monitoring

Once patients have been identified and then tested for LTBI, they should receive an initial clinical evaluation. They should also receive follow-up evaluations at least monthly (if receiving isoniazid alone or rifampin alone) and at 2, 4, and 8 wk (if receiving rifampin and pyrazinamide). This evaluation should include questioning about side effects and a brief physical assessment checking for signs of hepatitis. Patients should be educated about the side effects associated with treatment of LTBI and advised to stop treatment and promptly seek medical evaluation when they occur.

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (*see* Table 8). Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) or alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]) and bilirubin. Baseline testing is also indicated for patients with HIV infection, pregnant women, and women in the

immediate postpartum period (i.e., within 3 mo of delivery), persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), persons who use alcohol regularly, and persons at risk for chronic liver disease. Baseline testing is not routinely indicated in older persons. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI.

Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver function tests are abnormal and other persons at risk for hepatic disease. Laboratory testing may also be indicated for the evaluation of possible adverse effects that occur during the course of treatment (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate complaints of joint pain). Some experts recommend that isoniazid should be withheld if transaminase levels exceed three times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is asymptomatic.

INTRODUCTION

History of Treatment of Latent Tuberculosis Infection and Relevance to Tuberculosis Control

For more than three decades, treatment of persons with latent *Mycobacterium tuberculosis* infection (LTBI) to prevent the development of active disease has been an essential component of tuberculosis (TB) control in the United States (4). In the United States and other countries with a low incidence of TB, most new, active cases have occurred among persons who were once infected, contained this infection, and then later developed active TB (5). The identification and treatment of infected persons at highest risk for developing disease benefit both infected persons and susceptible persons in their communities. Until recently, isoniazid was the only drug proven effective and thus recommended for treatment of LTBI.

Shortly after isoniazid was found to be effective for the treatment of TB, clinical trials were begun to assess the ability of the drug to prevent progression of primary disease in children. When it was found that this intervention was highly effective, larger trials were begun to evaluate the drug for treatment of infected contacts of TB patients and of other persons at high risk (e.g., those with radiographic evidence of prior, untreated TB) (*6*). In 1965, isoniazid treatment of LTBI was first recommended for general use by the American Thoracic Society (ATS) (*7*). This initial statement recommended isoniazid for persons with evidence of previously untreated TB and persons with recent tuberculin skin test conversions, including all children younger than 3 yr of age with a positive tuberculin skin test. In 1967, ATS and PHS broadened the recommendations to include all persons who had had a purified protein derivative (PPD) tuberculin skin-test reaction of ≥10 mm. The recommendations stated that chemoprophylaxis is mandatory for a) persons with inactive cases of TB who were not previously treated and their contacts, b) persons with tuberculin skin test conversions, c) persons with specified medical conditions, and d) all persons younger than 20 yr of age who had had positive

tuberculin skin tests (*8*). With widespread use of such an inexpensive drug that had "virtually no side effects," it was believed that "chemoprophylaxis [could] reduce future morbidity from TB in high risk groups by some 50 to 75 percent" (*8*).

However, despite this belief, the goal of reducing TB morbidity by such a substantial percentage through the administration of isoniazid was never reached. In 1970, among several thousand persons who began isoniazid treatment as a result of an outbreak of TB on Capitol Hill in the District of Columbia, 19 persons developed clinical signs of liver disease and two persons died of hepatic failure attributed to isoniazid (*9*). The recognition that isoniazid was associated with potentially fatal hepatitis led to the development of guidelines regarding pretreatment screening and monitoring to minimize the risk for severe complications (*10*). In 1974, following a study to quantify the risk for isoniazid-related hepatitis (*11*), guidelines for treatment of LTBI were updated. The revised guidelines excluded low-risk persons aged older than 35 yr of age as candidates for treatment (*12*).

Subsequent controversy over the appropriate age cut-off for these low-risk, tuberculin-positive persons ensued, with one group concluding that the risks of treatment of LTBI outweighed the benefits for young adults (*13*). This controversy and resulting confusion led to a decrease in the use of isoniazid for treating persons with LTBI—even persons at high risk for whom treatment was indicated (*14*). In 1983, the guidelines were further revised to recommend routine clinical and laboratory monitoring for persons aged older than 35 yr of age and other persons at risk for hepatotoxicity (*15*). Recent studies have suggested that since the advent of routine monitoring, the risk for severe hepatotoxicity has been substantially reduced (*16*).

Because widespread use and the potential impact of isoniazid treatment of LTBI became limited by actual and perceived toxicity and patient nonadherence because of the relatively long period of treatment required, alternatives to isoniazid were suggested (*17*). The introduction of rifampin, which appeared to be a better sterilizing agent than isoniazid, suggested the possibility that rifampin-based regimens might be safer, more effective, and shorter. The occurrence of the human immunodeficiency virus (HIV) epidemic and the need to evaluate the efficacy of treatment for LTBI in persons coinfected with HIV and *M. tuberculosis* led to a series of studies of short-course treatment of LTBI in HIV-infected persons (*18*). The results of these studies have recently become available and have contributed substantially to guidelines on treatment of LTBI in persons with HIV infection (*3*).

Relationship of Tuberculin Testing to Treatment of Latent Tuberculosis Infection

As the rate of active TB in the United States has decreased, identification and treatment of persons with latent infection who are at high risk for active TB have become essential components of the TB elimination strategy promoted by the PHS Advisory Council on the Elimination of Tuberculosis (*19*). Because testing persons for infection and provision of treatment are interrelated, these recommendations include sections on program activities aimed at identifying high-risk infected persons and tuberculin skin testing, as well as recommendations on the use of new, short-course treatment regimens.

Change in Nomenclature

Identification of persons with LTBI has previously been accomplished by widespread tuberculin skin testing of individuals or groups at variable risk for TB. In many situations, this screening was done with limited consideration of the risk for TB in the population(s) being tested. To focus on groups at the highest risk for TB, the term "targeted tuberculin testing" is used in these guidelines to encourage directed program activities.

Although the terms "preventive therapy" and "chemoprophylaxis" have been used for decades, they have also been confusing. "Preventive therapy" has referred to the use of a simple regimen (usually isoniazid) to prevent the development of active TB disease in persons known or likely to be infected with *M. tuberculosis*, but it rarely results in true primary prevention (i.e., prevention of infection in persons exposed to persons with infectious TB). To describe the intended intervention more accurately, this report uses the terminology "treatment of LTBI" rather than "preventive therapy" or "chemoprophylaxis." This change in nomenclature will hopefully promote greater understanding of the concept for both patients and providers, resulting in more widespread implementation of this essential TB control strategy.

SCIENTIFIC RATIONALE

Targeted Tuberculin Testing

Groups at Risk and Risk Factors for Infection with M. tuberculosis

Targeted tuberculin testing for LTBI identifies persons at high risk for TB who would benefit by treatment of LTBI, if detected. Persons at high risk for TB (i.e., risk substantially greater than that of the general U.S. population) have either been infected recently with *M. tuberculosis* or have clinical conditions that are associated with an increased risk of progression of LTBI to active TB (Tables 2 and 3). Screening of low-risk persons and testing for administrative purposes (e.g., certification of school teachers) should be replaced by targeted testing.

Persons or groups with presumed recent M. tuberculosis *infection*. Persons infected with *M. tuberculosis* are at greatest risk for developing disease shortly after infection has occurred (Table 2). In two controlled trials examining the efficacy of treatment of LTBI among contacts of persons with active TB and among patients in mental hospitals, the tuberculin skin tests of 1472 participants in the placebo groups of the trials converted from negative to positive. Among persons whose tests converted, 19 developed disease in the first year of follow-up (12.9 cases per 1000 person-years) compared with 17 persons in the subsequent 7 yr of follow-up (1.6 cases per 1,000 person-years) (*6*). In a study of TB vaccines given to British schoolchildren, 2550 unvaccinated participants' tuberculin skin tests converted. Of these, 121 (4.7%) developed clinical TB within 15 yr of entry into the study: 54% developed disease during the first year after infection and 82% developed disease within 2 yr of infection (*20*).

In designing and planning targeted testing programs, several groups of persons can be identified as being at increased risk for being recently infected with *M. tuberculosis*. A high prevalence of either LTBI or active TB has been documented among close

contacts of persons with infectious pulmonary TB (*21*); both of these characteristics are likely attributable to recent contact with infectious persons. Likewise, persons whose tuberculin skin tests convert from negative to positive within a period of 2 yr are presumed to have been infected recently.

Table 2. Incidence of active tuberculosis (TB) in persons with a positive tuberculin test, by selected risk factors

Risk factor	TB cases/1,000 person-years
Recent TB infection	
Infection <1 yr past	12.9 (*6*)*
Infection 1–7 yr past	1.6
Human immunodeficiency virus (HIV) infection	35.0–162 (*28*)
Injection drug use	
HIV seropositive	76.0 (*31*)
HIV seronegative or unknown	10.0 (*31*)
Silicosis	68 (*36*)
Radiographic findings consistent with prior TB	2.0–13.6 (*32–34*)
Weight deviation from standard	
Underweight by ≥15%	2.6 (*35*)
Underweight by 10–14%	2.0
Underweight by 5–9%	2.2
Weight within 5% of standard	1.1
Overweight by ≥5%	0.7

* Numbers in parentheses are reference numbers.

Persons who have immigrated from areas of the world with high rates of TB have incidence rates that approach those of their countries of origin for the first several years after arrival in the United States (*22*). This high rate likely results from infection with *M. tuberculosis* in the native country before immigration and progression to disease soon after arrival in the United States. This hypothesis is supported by a) DNA fingerprinting studies with restriction fragment length polymorphism (RFLP) interpreted to correlate with low rates of recent transmission of TB among foreign-born case patients in the United States (*23*) and b) other data indicating that with time, the incidence of TB in foreign-born persons declines to approach that of the U.S. population (*24*).

Children, especially those younger than 5 yr of age, who have a positive tuberculin skin test are likely to be in the early stage of LTBI and are at high risk for progression to active disease, with the potential for disseminated TB (*25*). The risk for developing active TB is also increased in adolescents and young adults (*25*).

Recent U.S. studies (including RFLP studies) have helped characterize certain epidemiologically defined groups of persons with high rates of TB transmission and increased risk for being recently infected (e.g., homeless persons, those with HIV infection, and injection drug users) (*23,26*). In addition, persons who reside or work in institutional settings (e.g., hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for patients with AIDS [*27*]) with persons at risk for TB may have an ongoing risk for acquiring TB infection. However, the risk for transmission varies greatly, and the likelihood that a specific institution is a site of transmission of *M. tuberculosis* can be determined only by local epidemiological data.

Clinical conditions associated with progression to active tuberculosis. HIV infection contributes most to an increased risk for progression of LTBI to active TB. Rates of

progression to TB among HIV-infected persons have ranged from 35 to 162 per 1000 person-years of observation (Table 2) (*28*). In a prospective cohort study of persons with HIV infection in the United States, the annual risk of active-TB among persons with a positive tuberculin test was 45 cases per 1000 person-years (*29*). Injection drug users also have an increased risk for progressing to active TB (10 cases per 1000 person-years) (*30*), and this risk is even greater for injection drug users coinfected with HIV and TB (76 cases per 1000 person-years) (*31*). These higher rates may reflect increased transmission, more recent infection in this population, and the increased risk associated with injection drug use and HIV infection.

The risk for active TB is also increased in a) persons with pulmonary fibrotic lesions seen on chest radiographs (presumed to be from prior, untreated TB) and b) underweight persons. Persons with fibrotic lesions on chest radiographs consistent with prior, healed TB have a risk for progression to active TB of 2.0–13.6 per 1000 person-years of observation (*32–34*). A study of 23,541 U.S. Naval recruits with tuberculin reactions ≥10 mm demonstrated that recruits who were ≥15% underweight from the standard weight for their height had a risk of progression to disease that was twofold that of persons who were within 5% of the standard weight for their height and more than threefold that of persons who were overweight (*35*).

Studies indicate that several other clinical conditions increase the risk for active TB, although participants in these studies were not stratified by tuberculin-test status (Table 3).

Table 3. Relative risk* for developing active tuberculosis (TB), by selected clinical conditions

Clinical condition	Relative risk
Silicosis	30 (*37,38*)†
Diabetes mellitus	2.0–4.1 (*42–44*)
Chronic renal failure/hemodialysis	10.0–25.3 (*39–41*)
Gastrectomy	2–5 (*45–47*)
Jejunoileal bypass	27–63 (*48–49*)
Solid organ transplantation	
Renal	37 (*50*)
Cardiac	20–74 (*51,52*)
Carcinoma of head or neck	16 (*53*)

* Relative to control population; independent of tuberculin-test status.
† Numbers in parentheses are reference numbers.

Tuberculin-positive persons with silicosis have an approximately 30-fold greater risk for developing TB (*36–38*). Persons with chronic renal failure who are on hemodialysis also have an increased risk: 10–25 times greater than the general population (*39–41*). Persons with diabetes mellitus have a risk for developing active TB that is twofold to fourfold greater than persons without diabetes mellitus, and this risk is likely greater in persons with insulin-dependent or poorly controlled diabetes (*42–44*). Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption (*45–47*), jejunoileal bypass (*48,49*), renal (*50*) and cardiac (*51,52*) transplantation, carcinoma of the head or neck (*53*), and other neoplasms (e.g., lung cancer, lymphoma, and leukemia [*54*]).

Persons receiving prolonged therapy with corticosteroids and other immunosuppressive agents may be at risk for reactivation of TB, but the exact risk is unknown (*1*).

Because prednisone (or its equivalent) given >15 mg/d for 2–4 wk suppresses tuberculin reactivity (*55,56*), and because lower doses or those given intermittently are not associated with TB, this dose is likely the lower limit that could predispose persons to develop TB (*57*). Reactivation of TB is more likely to occur in persons receiving higher doses of corticosteroids for prolonged periods of time, especially in populations at high risk for TB, but specific thresholds of dose and duration that could increase the risk for TB are unknown (*58*). Persons who use alcohol may be at increased risk for acquiring or developing TB, but given the many other potential risk factors that commonly occur among such persons, alcohol use has been difficult to identify as a separate risk factor for TB (*2,42,59,60*).

Operational Considerations

In *A Strategic Plan for the Elimination of Tuberculosis in The United States*, published by CDC in 1989 (*61*), the responsibility for detection and treatment of LTBI in high-risk groups was assigned directly to public health agencies. At that time, the administration of skin tests, interpretation of test results, and intensive follow-up required to ensure adherence with and to prevent side effects of isoniazid treatment were believed to be beyond the scope of most private health care providers.

However, in 1995, CDC published recommendations on targeted testing and treatment of LTBI that emphasized the importance of health departments in assisting local providers in the development, implementation, and evaluation of TB screening programs appropriate for their communities (*2*). This recommendation was based on the recognition that changes in the organization, delivery, and financing of health care in the United States have led to most routine tuberculin testing being done outside of the public health system (*62*). For example, populations that previously received clinical services, including diagnosis of LTBI, at public health clinics are now increasingly being enrolled as members of managed care organizations.

Because health departments might lack access to high-risk populations and the resources necessary to undertake targeted testing programs, the participation of other health care providers is essential to ensure the successful implementation of community efforts to prevent TB in high-risk groups. Community sites where persons at high risk may be accessed and where targeted testing programs have been evaluated include neighborhood health centers (*63*), jails (*64*), homeless shelters (*65*), inner-city sites (*66*), methadone (*67*) and syringe/needle-exchange programs (*68*), and other community-based social service organizations (*69*).

Diagnosis of Latent Tuberculosis Infection

Tuberculin Skin Testing

The tuberculin skin test is the only proven method for identifying infection with *M. tuberculosis* in persons who do not have TB disease. Although the available tuberculin skin-test antigens are <100% sensitive and specific for detection of infection with *M. tuberculosis*, no better diagnostic methods have yet been devised. Proper use of the tuberculin skin test requires knowledge of the antigen used (tuberculin), the immunologic basis for the reaction to this antigen, the technique(s) of administering and reading the test, and the results of epidemiologic and clinical experience with the test. Detailed information on these topics is provided in the ATS/CDC Statement *Diagnostic Standards and Classification of Tuberculosis in Adults and Children* (*70*).

Immunologic basis for the tuberculin reaction. Infection with *M. tuberculosis* produces a delayed-type hypersensitivity reaction to certain antigenic components (tuberculins) that are contained in extract of culture filtrate of the organism. Purified protein derivative (PPD) tuberculin, which is used for most skin testing, is isolated from culture filtrate by protein precipitation.

The reaction to intracutaneously injected tuberculin is a delayed-type (cellular) hypersensitivity (DTH) reaction, and infection by *M. tuberculosis* usually results in a DTH response to PPD tuberculin that is detectable 2–12 wk after infection (71). However, a DTH reaction to PPD tuberculin may also indicate infection with various nontuberculous mycobacteria or vaccination with Bacille Calmette-Guérin (BCG), a live attenuated mycobacterial strain derived from *Mycobacterium bovis*. Delayed hypersensitivity reactions to tuberculin usually begin 5–6 h after injection, reach a maximum at 48–72 h, and subside over a period of a few days, although positive reactions often persist for up to 1 wk (*72*).

Sensitivity and specificity of skin-test reactions. Knowledge of tuberculin-test sensitivity and specificity, as well as positive predictive value, is required to interpret skin-test reactions properly. For persons with LTBI and normal immune responsiveness, test sensitivity approaches 100% (*73*). However, false-positive tuberculin tests occur in persons who have been infected with nontuberculous mycobacteria and in persons who have received BCG vaccine. These false-positive reactions result in a lower specificity and a low positive predictive value in persons who have a low probability of LTBI. The general U.S. population currently has an estimated *M. tuberculosis* infection rate of 5–10%, and children entering school in many areas of the country have a 0.1–1% prevalence of infection. Even if the test has a specificity approaching 99%, testing of persons in such low-prevalence groups would result in most positive tests being false-positive tests (*71*). However, the specificity of the test is also dependent on the criterion used to define a "positive" test. The specificity can be improved by progressively increasing the reaction size that separates positive from negative reactors (at the expense of decreasing test sensitivity) (*73*).

Previous BCG vaccination. Intracutaneous inoculation with BCG is currently used in many parts of the world as a vaccine against tuberculosis. Tuberculin reactivity caused by BCG vaccination generally wanes with the passage of time but can be boosted by the tuberculin skin test. Periodic skin testing may prolong reactivity to tuberculin in vaccinated persons (*74*). No reliable method has been developed to distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections, although reactions of ≥20 mm of induration are not likely caused by BCG (*75*).

HIV infection and anergy testing. HIV-infected persons may have a compromised ability to react to tuberculin skin tests because of cutaneous anergy associated with progressive HIV immunosuppression (*76*). However, the usefulness of anergy testing in selecting tuberculin-negative, HIV-infected persons who might benefit from treatment of LTBI has not been demonstrated (*77*).

Chest Radiographs

In persons with LTBI, the chest radiograph is usually normal, although it may show abnormalities suggestive of prior TB. Previous, healed TB can produce various radiographic findings that usually differ from those associated with active TB. Dense pulmonary nodules, with or without visible calcification, may be seen in the hilar area or

upper lobes. Smaller nodules, with or without fibrotic scars, are often seen in the upper lobes, and upper-lobe volume loss often accompanies these scars. Nodules and fibrotic lesions of previous, healed TB have well-demarcated, sharp margins and are often described as "hard." Bronchiectasis of the upper lobes is a nonspecific finding that sometimes occurs from previous pulmonary TB. Pleural scarring may be caused by prior TB but is more commonly caused by trauma or other infections. Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with substantial potential for future progression to active TB (*32*). Conversely, calcified nodular lesions (calcified granulomas) and apical or basal pleural thickening pose a lower risk for future progression to active TB.

Sputum Examinations

The presumptive diagnosis of active pulmonary TB is often made on the basis of microscopic examination of a stained sputum smear for acid-fast bacilli (AFB). Confirmation of the diagnosis usually requires identification of *M. tuberculosis* in culture. In asymptomatic persons with normal chest radiographs, AFB are rarely seen on sputum smear examination, and tubercle bacilli are not found in cultures of respiratory specimens. However, some HIV-infected persons with sputum culture-positive TB have been described as having normal chest radiographs.

Treatment of Latent Tuberculosis Infection

Isoniazid

Experimental studies. Before clinical trials of isoniazid for the treatment of LTBI were begun in the United States, its efficacy was demonstrated in guinea pigs. In a study conducted by PHS, guinea pigs receiving varying doses of isoniazid were challenged with virulent tubercle bacilli (*78*). Those animals receiving a daily dosage of at least 5 mg/kg were protected (i.e., survival was comparable to control animals who were not challenged with the bacillus). On the basis of these studies, the dose of 5 mg/kg was chosen for clinical studies in humans.

Clinical trials in HIV-negative persons. Many randomized, controlled clinical trials of isoniazid for the treatment of LTBI were conducted in the 1950s and 1960s (*6*). These trials were conducted in seven countries, both industrialized and developing, and involved more than 100,000 participants at risk for TB, including children with primary TB, contacts of active case patients, persons who had had tuberculin skin reactions, institutionalized patients with mental disease, and persons with inactive TB. Most studies compared 12 mo of isoniazid with placebo. The outcomes measured in these studies included progression of primary TB, tuberculin conversion in uninfected contacts, prevention of TB in infected persons, and recurrence of disease. The effectiveness of treatment, as measured by the decrease in TB among all persons participating in these trials, varied from 25 to 92%. However, when analysis was restricted to persons who were compliant with the medication, the protective efficacy was approximately 90%. Substantial protection was conferred even if pill taking was irregular but sustained, suggesting the possibility that intermittent treatment may be efficacious.

Only one trial, conducted by the International Union Against Tuberculosis (IUAT) (*32*), was designed to evaluate various durations of isoniazid. In this trial, a placebo

regimen was compared with isoniazid regimens lasting for 3, 6, and 12 mo among persons with fibrotic pulmonary lesions consistent with inactive TB. The 5-yr incidence rates of tuberculosis were 1.43% for placebo compared with 1.13, 0.50, and 0.36% for the 3-, 6-, and 12-mo regimens, respectively (Table 4). The rates indicated a 65% effectiveness for the 6-mo isoniazid regimen and 75% effectiveness for the 12-mo regimen; persons who received 6 mo of isoniazid had a 40% higher risk for TB compared with those who received 12 mo of therapy.

Table 4. Efficacy of various durations of isoniazid preventive therapy for persons with fibrotic lesions, by length of treatment—International Union Against Tuberculosis (IUAT) Trial, 1969–1977

Group	5-yr Tuberculosis incidence* (% reduction)			
	Placebo	12 wk	24 wk	52 wk
All participants (n = 27,830)†	14.3	11.3 (21)	5.0 (65)	3.6 (75)
Adherent participants‡ (n = 21,635)§	15	9.4 (31)	4.7 (69)	1.1 (93)
Fibrotic lesions <2 cm^2 (n = 18,663)†	11.6	9.2 (20)	4.0 (66)	4.2 (64)¶
Fibrotic lesions >2 cm^2 (n = 8,428)§	21.3	16.2 (24)	7.0 (67)	2.4 (89)

* Per 1000 person-years.

† Comparing placebo to 24 and 52 wk, p <0.05; differences between placebo and 12 wk and between 24 and 52 wk not significant.

‡ Collected pill calendars for "almost all" of the months assigned for their regimen and had taken at least 80% of the pills from the calendar by the time of the next monthly visit.

§ For all interregimen comparisons (p <0.05).

¶ Persons who developed tuberculosis on 52-wk regimen and had small fibrotic lesions were less likely to have collected pill calendars (47%) than all other groups (≥80%) (p <0.001).

Source: International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of vaious durations of isoniazid thereapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 1982;60:555-64.

The difference in the two regimens is magnified when study subjects who received "almost all" of the monthly drug allotments for their scheduled duration of therapy and who were believed to have taken ≥80% of the medication each month were compared. In this subgroup, which constituted 78% of the entire study population, the resulting 5-yr incidence rates were 1.5% for persons receiving placebo compared with 1.0, 0.5, and 0.1% for the 3-, 6-, and 12-mo regimens, respectively. In this analysis, isoniazid taken for 6 mo was 69% efficacious and for 12 mo was 93% efficacious; participants on the 6-mo regimen had a fourfold higher risk for TB than those on the 12-mo regimen. Although the incidence of TB was similar for persons with small lesions (<2 cm^2) assigned the 6-mo and 12-mo regimens, such persons were less adherent to treatment. The 12-mo regimen provided a substantial reduction in risk compared with the 6-mo regimen among compliant persons with small lesions (Table 4).

Additional information on the efficacy and effectiveness of different lengths of therapy with isoniazid for the treatment of LTBI has been derived from a randomized study of household contacts conducted by PHS (21). Among persons believed to have taken ≥80% of their assigned medication during the months they took isoniazid, those who took medication for at least 10 mo experienced a 68% reduction in TB (Table 5). In

Table 5. Tuberculosis morbidity rates per 1,000 household contacts, by percentage of pills taken and duration of therapy during participation in U.S. Public Health Service Trial

Percentage of pills taken	Duration of therapy (mo)	Placebo			Isoniazid			Percentage change
		Population*	Case-patients†	Rate‡	Population*	Case-patients†	Rate‡	
≥80%	10–12	5094	127	24.9	4802	38	7.9	–68.3
≥80%	1–9	752	14	18.6	767	12	15.6	–16.1
60–79%	≥10	953	25	26.2	804	9	11.2	–57.3
40–59%	≥10	368	7	19.0	438	4	9.1	–52.1

*Excludes contacts who were tuberculin negative both at admission and at 12 mo.

† Excludes case patients who stopped taking pills because they developed active disease (29 placebo, five isoniazid).

‡ Rate for 10 yr of observation.

Source: Adapted from Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis: a general review. Adv. Tuberc Res 1970;17:28–106.

contrast, among persons who took ≥80% of the medication for <10 mo, only a 16% reduction in the TB rate occurred. The same data can be further examined to determine whether reduction in the rate of TB was affected more by duration of therapy or the amount of medication. The effectiveness of isoniazid decreased slightly for less compliant patients who took 40–79% of the prescribed medication during the 10-mo period (52–57% reduction compared to 68% reduction), suggesting that even an intermittent treatment regimen would be effective if taken for at least 10 mo (Table 5).

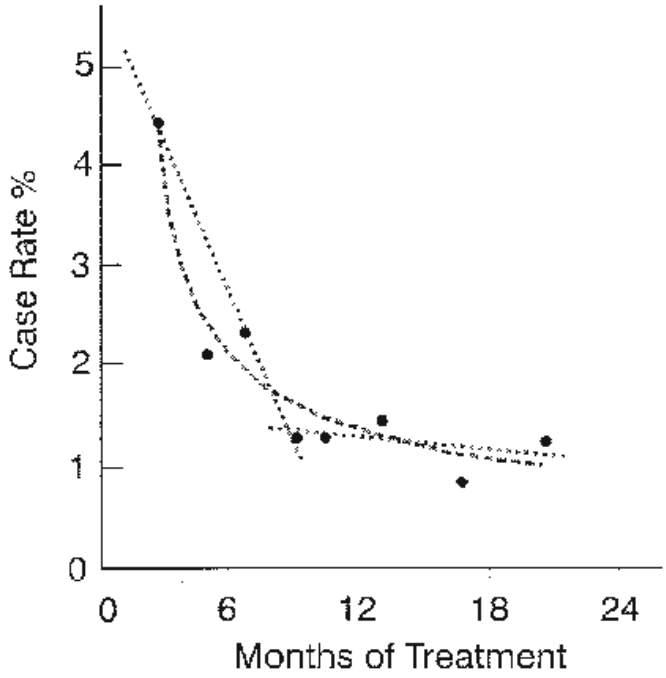
In a community-based study conducted in Bethel, Alaska (*79*), persons who took <25% of the prescribed annual dose had a threefold higher risk for TB than those who took ≥50% of the annual dose. However, a more recent analysis of study data indicated that the efficacy decreased significantly if <9 mo of isoniazid was taken (Figure 1) (*80*).

Effectiveness data from the IUAT study, published data on isoniazid-associated hepatitis, and cost information obtained from a survey of U.S. TB programs were used to assess the cost effectiveness of various durations of isoniazid (*81*). The cost per case of TB prevented with the 6-mo regimen was determined to be half of the cost as either the 3-mo or 12-mo regimens. This cost-effectiveness analysis was largely responsible for the widespread adoption of the 6-mo regimen of isoniazid for the treatment of LTBI in HIV-seronegative persons with normal chest radiographs (*82*). However, the protection conferred by taking at least 9 mo of isoniazid is greater than that conferred by taking 6 mo; it is not likely that further protection is conferred by extending the duration of treatment from 9 to 12 mo (*80*).

Clinical trials in HIV-positive persons. Seven randomized, controlled trials have evaluated different regimens for the treatment of LTBI infection in persons with HIV infection (Table 6). Five of these studies evaluated isoniazid regimens using comparison groups that either received a placebo or were not actively treated.

In the first study, conducted in Haiti during 1986–1992, 12 mo of daily isoniazid resulted in a substantial reduction in TB (83%) among tuberculin-positive persons (*83*). Protection was constant over the 4 yr of follow-up after treatment. Two other studies, which evaluated 6 mo of isoniazid taken daily by tuberculin-positive persons, had differing results: the drug provided a significant level of protection in Uganda (68%) (*84*) but did not provide a significant level of protection in Kenya (40%) (*85*). A fourth study evaluated a 6-mo, twice-weekly regimen of isoniazid in both tuberculin-positive

Figure 1*



*Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve (y=a+b/x); and dotted lines the calculated values based on the first four and the last five observations (y=a+bx). Source: Comstock, G.W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int. J. Tuberc. Lung Dis. 3:847–850. Reprinted by permission of the International Union Against Tuberculosis and Lung Disease.

and -negative persons in Zambia (*86*). The overall level of protection was minimal but significant (38%). Although the level of protection among tuberculin-positive persons was higher (70%), it was not significant because of the limited number of persons in this group.

The Uganda study also evaluated the 6-mo regimen of daily isoniazid in anergic persons, as did the fifth study conducted in the United States (*87*). In both studies, the level of protection against TB was low, and neither study demonstrated a significant level of protection.

Additional evaluations of isoniazid were conducted in tuberculin-negative persons who were not assessed for anergy (*83,85,86*). The level of protection provided by isoniazid among this population was not significant in any of the studies. Thus, for HIV-infected persons, treatment should be targeted at tuberculin-positive persons. A recently published metaanalysis of these trials supports this conclusion (*88*).

Safety and tolerability. In 1965, when isoniazid was first recommended in the United States for treatment of LTBI, it was not thought to cause severe toxicity. In the PHS studies conducted among TB contacts, the percentage of persons stopping treatment because of suspected drug reactions was low and approximately equivalent for the placebo and isoniazid groups (*21*). The occurrence of hepatitis was rare and was not assumed to be caused by isoniazid. However, studies conducted in the late 1960s

Table 6. Prospective, randomized clinical trials of preventive therapy of tuberculosis (TB) in persons infected with human immunodeficiency virus (HIV)

Study (reference no.)	Study subjects' purified protein derivative (PPD) status* (n)	Drug regimen (mo)	No. TB Cases (%)	TB rate/100 person-years	Relative risk of TB (95% confidence interval)
Pape (*83*)	PPD$^+$ (25)	Placebo, daily (12)	6 (24)	10.0	1
Haiti 1986–1992	PPD$^+$ (38)	Isoniazid 300 mg, daily (12)	2 (5)	1.7	0.17 (0.03–0.83)
	PPD$^-$ (35)	Placebo, daily (12)	5 (14)	5.7	1
	PPD$^-$ (20)	Isoniazid 300 mg, daily (12)	2 (10)	3.2	0.56 (0.11–2.5)
Whalen (*84*)	PPD$^+$ (464)	Placebo, daily (6)	21 (5)	3.41	1
Uganda 1993–1997	PPD$^+$ (536)	Isoniazid 300 mg, daily (6)	7 (1)	1.08	0.32 (0.14–0.76)
	PPD$^+$ (556)	Isoniazid 300 mg/Rifampin 600 mg, daily (3)	9 (2)	1.32	0.41 (0.19–0.89)
	PPD$^+$ (462)	Isoniazid 300 mg/Rifampin 600 mg/ Pyrazinamide 2000 mg, daily (3)	10 (2)	1.73	0.43 (0.20–0.92)
	Anergic (323)	Placebo, daily (6)	10 (3)	3.06	1
	Anergic (395)	Isoniazid 300 mg, daily (6)	9 (2)	2.53	0.75 (0.30–1.89)
Hawken (*85*)	PPD$^{+/-}$ (342)	Placebo, daily (6)	23 (7)	3.86	1
Kenya 1992–1996	PPD$^{+/-}$ (342)	Isoniazid 300 mg, daily (6)	25 (7)	4.29	0.92 (0.49–1.71)
	PPD$^+$ (67)	Placebo, daily (6)		8.03	1
	PPD$^+$ (69)	Isoniazid 300 mg, daily (6)		5.59	0.60 (0.23–1.60)
	PPD$^-$ (235)	Placebo, daily (6)		2.73	1
	PPD$^-$ (224)	Isoniazid 300 mg, daily (6)		3.28	1.23 (0.55–2.76)
Mwinga (*86*)	PPD$^{+/-}$ (350)†	Placebo (isoniazid), twice weekly (6)	44 (13)	8.06	1
Zambia 1992–1996	PPD$^{+/-}$ (352)†	Isoniazid 900 mg, twice weekly (6)	27 (8)	4.94	0.62 (0.38–0.99)
	PPD$^{+/-}$ (351)†	Rifampin 600 mg/pyrazinamide 3500 mg twice weekly (3)	25 (7)	4.65	0.58 (0.35–0.95)
Gordin (*87*)	Anergic (257)	Placebo, daily (6)	6 (2)	0.9	1
United States 1991–1996	Anergic (260)	Isoniazid 300 mg, daily (6)	3 (1)	0.4	0.48 (0.12–1.91)
Halsey (*110*)	PPD$^+$ (370)	Isoniazid, 600–800 mg, twice weekly (6)	14 (4)	1.7	1
Haiti 1990–1994	PPD$^+$ (380)	Rifampin 450–600 mg/pyrazinamide 1500–2500 mg, twice weekly (2)	19 (5)	1.8	1.1
Gordin (*111*)	PPD$^+$ (792)	Isoniazid 300 mg, daily (12)	26 (3)	1.1	1
United States, Mexico, Haiti, Brazil 1991–1997	PPD$^+$ (791)	Rifampin 600 mg/pyrazinamide 20 mg/kg, daily (2)	19 (2)	0.8	0.67 (0.36–1.24)

*PPD$^+$ = PPD ≥5 mm; PPD$^-$ = PPD <5 mm.

† Percentage tuberculin-positive; 27% in placebo, 23% in isoniazid, and 22% in rifampin/pyrazinamide.

SOURCE: Adapted from Cohn DL, El-Sadr WM. Treatment of latent tuberculosis infection. *In*: Reichman LB, Hershfield E, eds. Tuberculosis: a comprehensive international approach, 2nd ed. New York: Marcel Dekker, 2000;471–502.

suggested that isoniazid did cause hepatitis and indicated that asymptomatic increase in hepatic transaminases occurred among persons receiving the drug (*89*). It was not until the 1970s, when several persons receiving isoniazid for LTBI died from hepatitis, that the likelihood of isoniazid hepatitis was understood (*9*).

The largest and most comprehensive study of isoniazid hepatitis was conducted by PHS during 1971–1972 (*11*). In this survey, nearly 14,000 persons who received isoniazid were monitored for the development of hepatitis. The overall rate of probable isoniazid hepatitis was 1%, but it was age related, with no cases occurring among persons younger than 20 yr of age and the highest rate (2.3%) occurring among persons older than 50 yr of age. An association of hepatitis also was found with alcohol consumption, with rates being fourfold higher among persons consuming alcohol daily than among those who did not drink alcohol. Rates among males and females were

equivalent and were lower among black males and higher among Asian males compared with rates among white males. Hepatitis rates were lower among participants in the IUAT trial, although the same positive association with age was observed (*32*). In the PHS surveillance study, eight deaths from hepatitis occurred among the participants, seven of which were among persons living in Baltimore. Several years after completion of the study, a review of death certificates showed a marked increase in deaths from cirrhosis during 1972 in Baltimore and surrounding counties, suggesting that another cofactor may have been associated with the cluster of deaths observed in the study (*90*).

A comprehensive analysis of deaths from isoniazid-associated hepatitis in the United States found that women may be at increased risk of death (*91*). Other reports have suggested that the risk for isoniazid-associated hepatitis may be increased by the administration of the drug to pregnant women in the third trimester and the immediate postpartum period (*92*) or by the concomitant administration of acetaminophen (*93*). Although experimental evidence suggests that acetaminophen hepatotoxicity is potentiated by isoniazid (*94*), a more detailed study of deaths from isoniazid-associated hepatitis did not implicate acetaminophen as a factor (*95*).

Isoniazid-related deaths continue to be reported. However, the likelihood of this occurrence can be greatly reduced by careful monthly monitoring and stopping of medication if symptoms occur (*96*). In a recent study, seven of eight patients receiving a liver transplant following the development of fulminant, isoniazid-related hepatitis continued to take the drug for a least 10 d after onset of symptoms of hepatotoxicity (*97*).

Following the PHS surveillance study, guidelines on the use of isoniazid for the treatment of LTBI were revised to recommend that low-risk persons older than 35 year of age with reactive tuberculin skin tests not be treated, that no more than 1 mo drug supply be issued at a time, and that monthly questioning and education about signs and symptoms of hepatitis should be routine (*12*). The guidelines were further revised to recommend baseline and periodic liver-function tests for persons at risk for hepatotoxicity, including persons aged 35 yr of age or older (*15*).

More recently, a survey found that many public health TB clinics now use clinical, rather than biochemical, monitoring for hepatotoxicity during treatment of LTBI (*98*). Clinical monitoring is based on educating patients about the symptoms of hepatotoxicity and instructing them to stop treatment immediately if such symptoms occur and to report to the clinician for evaluation. After using clinical monitoring exclusively, one public health TB clinic reported only 11 cases of clinical hepatotoxicity (one of which required hospitalization) and no deaths among more than 11,000 persons with LTBI during isoniazid treatment over a 7-yr period (*99*). Based on this emerging experience with clinical monitoring, some authorities have called for the establishment of new recommendations for drug toxicity monitoring "that are congruent with established therapeutic/toxicity relationships" (*98*).

Recent studies of isoniazid treatment of LTBI in HIV-infected persons have demonstrated that the medication was well tolerated and not associated with substantial increases in hepatic side effects. In a recent meta-analysis of placebo-controlled trials, adverse drug reactions were slightly but not significantly more common among persons receiving isoniazid (*88*).

Despite the high efficacy and relative safety of isoniazid treatment for LTBI, its use has been frequently debated; much literature has been published regarding whether and when to prescribe isoniazid (*13,100–102*). However, because the arguments

embodied in that literature emerged more than two decades ago, in a different environmental context with different risks and contingencies, its appropriateness to current circumstances is uncertain.

Although the likelihood that a patient treated with isoniazid would develop hepatitis was low, it presented a valid argument against the use of isoniazid among persons who had no increased risk for developing active TB. Most of the arguments concerning the use of this drug, which appeared from the 1970s through the early 1980s, focused on persons at low risk for reacting to tuberculin, primarily those 35 yr of age or older who were likely at higher risk for isoniazid-associated hepatitis than younger patients.

Because the debate over whether to prescribe or withhold isoniazid for persons older than 35 yr of age at low risk for reacting to tuberculin involved a trade-off between risk for developing active TB versus risk for developing isoniazid-induced hepatitis, decision analysis was used by most investigators (*103*). Despite many analyses, the decision to treat persons at low risk for reacting to tuberculin at any age continued to be controversial. Although various analyses supported both sides of the debate, none of the calculated benefits of isoniazid was substantial.

Short-course Regimens

Experimental studies in animals. Because of high rates of nonadherence with the long duration of isoniazid (i.e., 6–12 mo) and the rare occurrence of fatal isoniazid hepatitis, short-course, rifampin-containing treatment regimens have recently been evaluated. The studies evaluating rifampin were based on data from several studies in mouse models of chronic TB. One study compared isoniazid with regimens of rifampin alone; rifampin and pyrazinamide; and isoniazid, rifampin, and pyrazinamide (*104*). The rifampin-only regimen sterilized lung and spleen tissues within 4 mo, and the combination of rifampin and pyrazinamide sterilized tissues within 2 mo. The isoniazid, rifampin, and pyrazinamide regimen was of intermediate efficacy, taking longer than the rifampin and pyrazinamide regimen to sterilize tissues. The isoniazid regimen had not sterilized tissues by the end of 6 mo.

The apparent superiority of the rifampin–pyrazinamide regimen over the regimen containing the same two drugs plus isoniazid might be explained by impaired absorption of rifampin when given simultaneously with other drugs in mice (*105*). Support for this hypothesis came from a study using a Cornell mouse model (*106*) that compared 6-wk regimens of rifampin, rifampin–isoniazid, rifampin–pyrazinamide, and rifampin–pyrazinamide–isoniazid, with delayed administration of rifampin when given with other drugs. The efficacy of all three regimens was similar, with trend toward a lower colony count in spleens of animals given more drugs, and lower colony counts in the lungs of mice given rifampin–isoniazid. Experimental studies have also suggested that rifabutin alone, taken daily, and rifabutin–isoniazid, taken twice weekly, may effectively treat LTBI in 3 mo (*107*).

Clinical trials in HIV-negative persons. The only randomized clinical trial to evaluate rifampin-containing regimens among HIV-seronegative persons was conducted in tuberculin-positive persons with silicosis in Hong Kong (*36*). In this study, daily regimens of 6 mo of isoniazid, 3 mo of rifampin, or 3 mo of isoniazid and rifampin were compared with a 6-mo placebo control. Analyzing only those patients who were assumed to be compliant yielded an estimate of efficacy in preventing TB of 63% for the 3-mo rifampin regimen, 48% for the 6-mo isoniazid regimen, and 41% for the 3-mo isoniazid–rifampin regimen. All of these differences were significantly different from the placebo regimen

but were not statistically different from each other. The annual incidence rate was about 7% per year in the placebo group and about 4% per year in the three active-treatment regimens combined.

The largest programmatic experience using rifampin-based treatment of LTBI comes from Blackburn, England, where children at increased risk of TB have been treated with daily rifampin–isoniazid since 1981 (*108*). During 1981–1996, the treatment duration was shortened from 9 to 3 mo, and the proportion of pediatric TB case patients as a percentage of all reported cases decreased from 25 to 4%. Although not a controlled clinical trial, these data suggest that this intervention has been highly effective in reducing the rate of childhood TB in this city. Thus, this regimen is currently recommended for the treatment of both adults and children with LTBI in the United Kingdom (*109*).

Clinical trials in HIV-positive persons. Most clinical trials of rifampin-based treatment of LTBI have been conducted among HIV-infected persons (Table 6); two were placebo controlled. The Uganda study also evaluated regimens of isoniazid–rifampin and isoniazid–rifampin–pyrazinamide taken daily for 3 mo in tuberculin-positive persons (*84*). The isoniazid–rifampin regimen provided 59% protection, and the three-drug regimen with pyrazinamide provided 57% protection—levels similar to those provided by 6 mo of isoniazid alone. The Zambia study also evaluated a self-administered regimen of rifampin and pyrazinamide taken twice weekly for 3 mo (*86*). The level of protection was 42%, similar to that conferred by the 6-mo, twice-weekly isoniazid regimen. Among tuberculin-positive persons, the level of protection conferred by rifampin and pyrazinamide was 70%, comparable with that conferred by 6 mo of isoniazid taken twice weekly, but not statistically significant.

In two trials, rifampin and pyrazinamide regimens have been compared with regimens of isoniazid alone in tuberculin-positive persons. A second study conducted in Haiti during 1990–1994 compared twice-weekly regimens of 6 mo of isoniazid and 2 mo of rifampin and pyrazinamide, with half of the doses directly observed (*110*). Protection at 12 mo was similar in the two groups, and, compared with the rate of TB observed among patients who received placebo in the earlier Haiti trial, the twice-weekly regimens were estimated to have reduced the risk for TB by approximately 80%. A multinational study comparing a 12-mo regimen of isoniazid taken daily with a 2-mo regimen of rifampin and pyrazinamide taken daily was conducted in the United States, Haiti, Brazil, and Mexico (*111*). A total of 1583 patients were enrolled and followed for an average of 3 yr. The annual risk of culture-confirmed TB was 0.8% for patients assigned the 2-mo regimen and 1.1% for patients assigned the 12-mo isoniazid regimen, a difference that was not significant.

In conclusion, as evidenced by the large multinational study, a 2-mo regimen of rifampin and pyrazinamide taken daily provides protection against TB equivalent to a 12-mo regimen of isoniazid taken daily. The data supporting the use of a twice-weekly rifampin and pyrazinamide treatment regimen are less conclusive. The only study that has evaluated a rifampin-alone regimen, the Hong Kong study in persons with silicosis, suggests that daily rifampin for 3 mo provides similar protection to that conferred from 6 mo of isoniazid (*36*). In the Uganda study, 3-mo regimens of a) isoniazid and rifampin and b) isoniazid, rifampin, and pyrazinamide provided protection equivalent to that of 6 mo of isoniazid (*84*).

All of the studies of treatment of LTBI in HIV-infected persons included death and/or progression of HIV disease as endpoints. In the earlier Haiti study, isoniazid likely conferred protection against progression of HIV disease among tuberculin-positive

subjects (*83*). In the multinational study, persons receiving the 2-mo regimen had lower mortality rates and less progression of HIV disease, although these differences were not statistically significant (*111*). In none of the other studies was active treatment protective against death or HIV progression.

Safety and tolerability. Before the conduct of the studies in HIV-infected persons, a pilot study to assess the safety and tolerability of short-course regimens was conducted in 402 HIV-seronegative adults in North America (*112,113*). Participants were randomized to receive either 2 mo of rifampin and pyrazinamide, 4 mo of rifampin only, or 6 mo of isoniazid. The rifampin–pyrazinamide regimen was associated with a higher number of AST elevations of >100 IU (17 compared with only one in the rifampin group and five in the isoniazid group) and more frequent adverse reactions resulting in drug discontinuation (15 compared with none in the rifampin group and two in the isoniazid group). The rates of adverse reactions and abnormal AST elevations were higher than those reported in studies involving HIV-positive populations and those described in a clinical trial of isoniazid, rifampin, and pyrazinamide for the treatment of active TB in HIV-seronegative persons (*114*).

Two smaller pilot studies of rifampin and pyrazinamide treatment of LTBI using identical protocols were conducted in adults in Poland (*115*) and children in Germany (*116*). The results of the study in Poland were similar to those in the study in North America; the children in Germany tolerated the regimens well and did not experience changes in hepatic function.

In the Hong Kong study of patients with silicosis, no significant differences were noted in the occurrence of severe adverse reactions in the three drug regimens studied (*36*). However, patients receiving isoniazid had a higher incidence of abnormal liver function tests during treatment.

In the clinical trials involving HIV-infected persons, a trend of increased adverse reactions occurred among persons taking a daily regimen that included pyrazinamide. The Uganda study reported that persons taking the three-drug, pyrazinamide-containing regimen had higher rates of paresthesias, arthralgias, and significant increases in serum AST (*84*). The multinational study reported minimal increases in the number of persons receiving the 2-mo rifampin and pyrazinamide regimen who had the drugs permanently discontinued, most commonly because of nausea and vomiting and narcotic withdrawal (*111*). However, abnormal liver function tests were more common among patients taking isoniazid.

In the Haiti study conducted during 1990–1994 and the Zambia study, regimens of twice-weekly rifampin and pyrazinamide were well tolerated. In the Haiti study, no severe adverse reactions were observed; rates of abnormal liver function were low (1–3%) and did not differ by regimen (*110*). In the Zambia study, 3% of persons given isoniazid stopped treatment because of an adverse reaction compared with 4% of those given rifampin and pyrazinamide (*86*). Biochemical hepatitis was more frequent in the isoniazid group, whereas rash was more common in persons receiving rifampin and pyrazinamide.

Adherence

Testing for and treating LTBI requires several steps, including administering the test, reading the test, medically evaluating infected persons, initiating treatment, and completing therapy. Because persons with LTBI are not clinically ill and may not be

motivated to undergo treatment, nonadherence occurs commonly in all steps of the treatment process.

The health care system can compromise patient adherence to testing and treatment of LTBI (*117*). A lengthy referral process may discourage patients from being evaluated for a positive tuberculin test or initiating treatment for LTBI. Long waiting times in the clinic may also discourage patients from attending follow-up visits. Other factors that may affect adherence with testing and treatment include the clinic's hours of operation, distance of the clinic from the patient's home, the cleanliness of the clinic, and the attitude of clinic staff.

Since the advent of effective chemotherapy for active TB, adherence to treatment regimens has been recognized as a substantial problem for TB control—especially for treatment of LTBI. Recent data reported to CDC indicate that only 60% of patients who start treatment for LTBI complete at least 6 mo of treatment (CDC, TB Program Management Reports); adherence is influenced by the length of therapy, complexity of the regimen, and side effects of the medications. Adherence to treatment decreases with time, whereas the efficacy of the regimen increases with the length of therapy (*32*). Patients may be more adherent to the 2-mo regimen of rifampin and pyrazinamide because of the shorter length of therapy; however, this regimen also involves taking multiple medications, and patients may not tolerate this regimen as well as isoniazid, thus potentially resulting in nonadherence.

The Haiti study of rifampin and pyrazinamide taken twice weekly and the multinational study both reported better adherence with the shorter, 2-mo regimens. In the Haiti study, 74% of persons assigned to the 2-mo rifampin and pyrazinamide regimen were believed to have taken ≥80% of the prescribed medication compared with 55% of persons taking isoniazid for 6 mo (*110*). Nonadherence was similar during the first 2 mo of therapy for both groups. The multinational study reported an 80% completion rate for persons assigned to the 2-mo rifampin and pyrazinamide regimen compared with 69% for the 12-mo isoniazid regimen (*111*). In the pilot study of HIV-seronegative persons, during the first 2 mo of therapy about 60% of those assigned to the rifampin and pyrazinamide regimen were judged to be nonadherent, compared with about 20% of those assigned to the 6-mo isoniazid regimen (*113*). However, overall completion rates were lower for the isoniazid regimen because of continued nonadherence during the last 4 mo of therapy.

Determinants of adherence to treatment of TB and LTBI are not well understood (*118*). For example, demographic factors are not reliable predictors of adherence. However, culturally influenced beliefs and attitudes may result in misinformation about TB and may adversely affect adherence (*119*). The main strategies that have been employed to promote adherence with treatment of LTBI are patient education (*120*), the use of lay health workers from the patient's social and/or cultural group (*118,121*), incentives (e.g., cash payments) (*122*), and directly observed therapy (DOT) (*64*).

The intervention most likely to improve adherence for treatment of LTBI has been DOT, which requires direct observation of the patient ingesting each dose of medication and usually includes the provision of comprehensive services that attempt to meet the patient's basic needs and the use of incentives and enablers (*123–125*). Although randomized trials have yet to be reported, available information suggests that DOT leads to higher rates of completion than self-supervised therapy, and, under certain circumstances, is more cost effective (*67*).

RECOMMENDATIONS

Implementation of Targeted Tuberculin Testing

Decision to Tuberculin Test Is Decision to Treat

Targeted tuberculin testing programs should be designed for one purpose: to identify persons at high risk for TB who would benefit by treatment of LTBI. Following that principle, targeted tuberculin testing programs should be conducted among groups at risk for recent infection with *M. tuberculosis* and those who, regardless of duration of infection, are at increased risk for progression to active TB (Table 7). With the exception of initial testing of persons at low risk whose future activity will place them at increased risk of exposure (e.g., employment in a setting where TB transmission may occur), screening of low-risk persons is discouraged because it diverts resources from activities of higher priority. In addition, a substantial proportion of tuberculin-test-positive persons from low-risk populations may have false-positive skin tests (*73*).

Testing is also discouraged unless a plan has been developed to complete a course of treatment in persons found to have LTBI. Such planning should include arrangements for medical evaluation (e.g., chest radiographs) of persons with positive skin tests and for the medical supervision of the course of treatment.

Identification and Access to High-risk Groups

A flexible approach to identifying high-risk groups is recommended, and state and local public health agencies are encouraged to analyze their TB case reports and data obtained from tuberculin skin testing to identify high-risk groups based on local trends in the epidemiology of TB. Thus designing and conducting skin-test-screening surveys to determine whether population groups are at high risk for TB may be desirable. Populations at risk can be accessed at HIV treatment facilities, drug treatment centers, homeless shelters, community health centers and schools serving foreign-born persons, and selected community-based organizations. Mandated skin-testing programs (e.g., those that formerly were conducted among teachers and foodhandlers) should be discouraged unless the targeted groups contain substantial proportions of persons at high risk (*126*).

Role of the Health Department

In this community-based approach to targeted testing and treatment of LTBI, the health department TB program should be instrumental in planning and coordination, setting performance standards, and overseeing quality of service. The health department is responsible for assessing the community's TB problem, identifying high-risk groups based on the local epidemiology of TB, and ascertaining the sites of most convenient access to those groups. In addition, the health department should assume responsibility for organizing the community-based approach, recruiting health professionals, educating such professionals about TB, and motivating them to institute targeted testing and treatment programs. The health department should also serve as advisor, consultant, and facilitator to community providers and institutions that conduct testing and treatment programs. The health department should assist in identifying potential funding sources and ensure linkages with essential clinical and

consultation sources. It should provide in-service training on tuberculin skin testing and treatment, written protocols for activities including patient tracking and skin testing, and patient and provider educational material translated into appropriate languages. The health department may also need to provide chest radiography and subsidize the supply of antituberculosis drugs. Finally, the health department should be responsible for providing or facilitating the ongoing evaluation of community-based targeted testing and treatment programs, including development and monitoring of program indicators (e.g., rates of skin tests administered that are read, proportion of tests read that are positive, and initiation and completion rates of treatment). The health department should also routinely collect and review these data to determine yield and relative effectiveness of targeted testing and treatment of LTBI in the community.

To achieve a high rate of acceptance of testing and completion of treatment in a community-based program, barriers to success should be anticipated, identified, and managed. The concept of taking drugs to treat a latent infection that is not causing current health problems is unfamiliar to most persons, and education of the patient is essential (*120*). Other known barriers include culturally derived health beliefs that differ from those of Western medicine, inability to communicate with medical providers in one's primary language, inability to afford the costs of medical evaluation and treatment, and lack of access to medical care (*118*). Patients should not be expected to pay directly for public health interventions (e.g., testing, evaluation, and treatment of LTBI). The more convenient this process of testing and treatment, the more likely patients will adhere to therapy—especially as targeted testing and treatment of LTBI are extended beyond the province of public health TB clinics to sites where primary health care is delivered.

Diagnosis of Latent Tuberculosis Infection

Tuberculin Skin Testing

Administering and reading tests. The tuberculin test, like all medical tests, is subject to variability, but many of the inherent variations in administering and reading tests can be avoided by careful attention to details. The preferred skin test for *M. tuberculosis* infection is the intradermal, or Mantoux, method. It is administered by injecting 0.1 ml of 5 tuberculin units (TU) PPD intradermally into the dorsal or volar surface of the forearm. Tests should be read 48–72 h after test administration, and the transverse diameter of induration should be recorded in millimeters. Multiple puncture tests (i.e., Tine and Heaf) and PPD strengths of 1 TU and 250 TU are not sufficiently accurate and should not be used.

Interpreting skin-test reactions. Based on the sensitivity and specificity of the tuberculin skin test and the prevalence of TB in different groups, three cut-off levels have been recommended for defining a positive tuberculin reaction: ≥5 mm, ≥10 mm, and ≥15 mm of induration (Table 7). For persons who are at highest risk for developing TB disease if they become infected with *M. tuberculosis*, a cut-off level of ≥5 mm is recommended. Persons who are immunosuppressed because of disease (e.g., HIV infection) or drugs (e.g., systemic corticosteroids) have a high likelihood of developing TB disease if they are infected with *M. tuberculosis*. Likewise, persons who have had recent close contact with an infectious TB case patient and those with abnormal chest

Table 7. Criteria for tuberculin positivity, by risk group

Reaction ≥5 mm of induration	Reaction ≥10 mm of induration	Reaction ≥15 mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees† of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19–34.

radiographs consistent with prior TB are at high risk for TB. Thus, to ensure that persons at highest risk are evaluated and appropriately treated, the sensitivity provided by a ≥5 mm cut-off for a positive test is appropriate.

A reaction of ≥10 mm of induration should be considered positive for those persons with an increased probability of recent infection or with other clinical conditions that increase the risk for TB (e.g., recent immigrants from high-prevalence countries and injection drug users) (Table 7). In addition to those groups listed, high-prevalence populations identified by analysis of local epidemiologic data should be targeted for testing.

Routine tuberculin testing is not recommended for populations at low risk for LTBI. However, if these persons are tested (e.g., at entry into a work site where risk for exposure to TB is anticipated and a longitudinal tuberculin testing program is in place), a higher cut-off of ≥15 mm is recommended.

Skin-test conversion. For persons with negative tuberculin skin-test reactions who undergo repeat skin testing (e.g., health care workers), an increase in reaction size of ≥10 mm within a period of 2 yr should be considered a skin-test conversion indicative of recent infection with *M. tuberculosis*.

Previous vaccination with BCG. Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, and the skin-test results of such persons can be used as described to support or exclude the diagnosis of *M. tuberculosis* infection. However, no method can reliably distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections. Therefore, a positive reaction to tuberculin in BCG-vaccinated persons indicates infection with *M. tuberculosis* when the person tested is at increased risk for recent infection or has medical conditions that increase the risk for disease (Table 7).

Anergy testing in persons infected with HIV. Anergy testing is not recommended for routine use in persons who are infected with HIV or otherwise immunocompromised (*77*). However, it may assist in guiding individual treatment decisions in selected situations.

Chest Radiographs

A chest radiograph is indicated for all persons being considered for treatment of LTBI to exclude active pulmonary TB. Children younger than 5 yr of age should have both posterior–anterior and lateral radiographs. All other persons should receive posterior–anterior radiographs; additional radiographs should be performed at the physician's discretion. Because of the risk for progressive and/or congenital TB, pregnant women who have a positive tuberculin skin test or who have negative skin-test results but who are recent contacts of persons with infectious TB disease should have chest radiographs (with appropriate shielding) as soon as feasible, even during the first trimester of pregnancy.

If chest radiographs are normal and no symptoms consistent with active TB are present, tuberculin-positive persons may be candidates for treatment of LTBI. If radiographic or clinical findings are consistent with pulmonary or extrapulmonary TB, further studies (e.g., medical evaluation, bacteriologic examinations, and a comparison of the current and old chest radiographs) should be done to determine if treatment for active TB is indicated.

Sputum Examinations

Sputum examination is not indicated for most persons being considered for treatment of LTBI. However, persons with chest radiographic findings suggestive of prior, healed TB infections should have three consecutive sputum samples, obtained on different days, submitted for AFB smear and culture. Most persons with radiographs that show only calcified pulmonary nodules do not require bacteriologic examination. HIV-infected persons with respiratory symptoms who are being considered for treatment of LTBI should also have sputum specimens submitted for mycobacterial examination, even if the chest radiograph is normal. If the results of sputum smears and cultures are negative and respiratory symptoms can be explained by another etiology, the person is a candidate for treatment of LTBI. If bacteriologic results are negative but the activity or etiology of a radiographic abnormality is questionable, further evaluation with bronchoscopy or needle aspiration biopsy should be undertaken. Single drug treatment of LTBI should not be started until active TB has been excluded. In such situations, multidrug therapy can be started and continued pending results of sputum cultures. A repeat chest film should be obtained to exclude active TB, as indicated by improvement in the abnormality even in the presence of negative cultures.

Treatment of Latent Tuberculosis Infection

Individual Drugs

Isoniazid. Isoniazid is the most widely used of the antituberculosis agents—it is bactericidal, relatively nontoxic, easily administered, and inexpensive. Isoniazid is highly active against *M. tuberculosis* (most strains being inhibited *in vitro* by concentrations of 0.05–0.20 µg/ml). Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations of 2–5 µg/ml occurring 0.5–2.0 h after administration of a 300-mg dose. The drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum. Hepatitis is the most severe toxic effect of isoniazid, and alcohol consumption may increase toxicity (Table 8). Peripheral neuropathy, caused by interference with metabolism of pyridoxine, is associated with isoniazid administration but is uncommon at a dose of 5 mg/kg. In persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutrition, and HIV infection), pyridoxine should be given with isoniazid. Pregnant women and persons with seizure disorders should also take both pyridoxine and isoniazid. Mild central nervous system effects are common with isoniazid and may necessitate adjustments in the timing of administration of the drug to enhance compliance. The interaction of isoniazid and phenytoin increases the serum concentration of both drugs. When these drugs are given concomitantly, the serum level of phenytoin should be monitored. No known interactions exist between isoniazid and the antiretroviral medications used for the treatment of HIV infection.

Rifampin. Rifampin is a rifamycin derivative that is bactericidal for *M. tuberculosis*. Most strains of *M. tuberculosis* are inhibited in vitro by concentrations of 0.5 µg/ml. It is quickly absorbed from the gastrointestinal tract, with peak serum concentrations of 7–14 µg/ml occurring 1.5–3.0 h after ingestion. Although approximately 75% of the drug is protein bound, it penetrates well into tissues and cells. Penetration through noninflamed meninges is poor, but therapeutic concentrations are achieved in cerebrospinal fluid when the meninges are inflamed. The most common adverse reaction to rifampin is gastrointestinal upset. Other reactions include skin eruptions, hepatitis, and, rarely, thrombocytopenia (Table 8). The frequency of these reactions is low. Because rifampin induces hepatic microsomal enzymes, it may accelerate clearance of drugs metabolized by the liver (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin). By accelerating the metabolism of estrogen, rifampin may interfere with the effectiveness of oral contraceptives. In persons with HIV infection who are taking HIV protease inhibitors, rifampin is usually contraindicated because drug interactions between rifampin and these agents can lead to increased rifampin levels and decreased protease-inhibitor levels, resulting in increased risk for rifampin toxicity and decreased protease-inhibitor efficacy. Rifampin is also contraindicated or should be used with caution in HIV-infected patients who are taking non-nucleoside reverse transcriptase inhibitors (NNRTIs). Intermittent administration of doses of rifampin >10 mg/kg may be associated with thrombocytopenia, an influenza-like syndrome, hemolytic anemia, and acute renal failure. However, these reactions are uncommon at the recommended dose of 10 mg/kg/d. Rifampin is excreted in urine, tears, sweat, and other body fluids and colors them orange. Patients should be advised of discoloration of body fluids and of possible permanent discoloration of soft contact lenses.

Pyrazinamide. Pyrazinamide is bactericidal for *M. tuberculosis* in an acid environment. The drug is active against organisms in macrophages, presumably because of the acid environment within the cell. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 µg/ml. Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations of 30–50 µg/ml occurring approximately 2 h after ingestion with doses of 20–25 mg/kg. The most common side effect of pyrazinamide is gastrointestinal upset (Table 8). The most severe adverse reaction is liver injury. No substantial increase in hepatotoxicity results from adding 15–30 mg/kg of pyrazinamide to a regimen of rifampin during 2 mo of therapy for active TB (*114*). Hyperuricemia also occurs, but acute gout is uncommon (*127*). No known interactions exist between pyrazinamide and antiretroviral medications.

Rifabutin. Rifabutin is another rifamycin that is highly active against *M. tuberculosis*. Its mechanism of action is the same as that of rifampin, so that most rifampin-resistant strains are also resistant to rifabutin. Most strains of *M. tuberculosis* are inhibited by concentrations of 0.1 µg/ml. A dose of 300 mg results in peak serum concentrations of 5 µg/ml after 2–3 h. The major advantage of rifabutin is the longer serum half-life and reduced hepatic induction of microsomal metabolism compared with that of rifampin. Rifabutin is extensively metabolized in the liver (and to a lesser extent in the intestinal wall); only 8% of a dose is excreted unchanged in the urine. Doses of up to 300 mg daily are usually well tolerated. Side effects attributed to rifabutin include rash, gastrointestinal intolerance, neutropenia, myalgias, and dysguesia. Hepatotoxicity is rare, but rifabutin can cause drug-induced hepatitis. Rates of side effects increase when rifabutin is administered with a CYP-3A4 inhibitor (e.g., clarithromycin); side effects that have been noted under these circumstances include uveitis (*128*) and abnormal skin pigmentation (*129*). Similar to rifampin, rifabutin can also decrease concentrations and clinical efficacy of methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin, as well as itraconazole, ß-blockers, and theophylline. Doses of these medications may have to be increased when administered with rifabutin. When administered with rifabutin, protease inhibitors, used for the treatment of HIV infection, may lead to increased levels of rifabutin and decreased levels of the protease inhibitor; however, these effects are generally less than those that occur with rifampin and can be accommodated by dose adjustments (Table 8). NNRTIs, used for the treatment of HIV infection, may also necessitate rifabutin dose adjustment.

Treatment Regimens

Treatment of LTBI is an essential part of the strategy to eliminate TB in the United States. Persons with LTBI who are included among those at increased risk for TB should be offered treatment. The choice of the specific treatment regimen is based on many considerations as detailed in the following sections.

U.S. Public Health Service Rating System. To help clinicians make informed treatment decisions based on the most current research results, evidence-based ratings are assigned to the drug treatment recommendations (general recommendations have no rating) (Table 9). The ratings system is similar to that used in previous PHS documents (*3*) and includes a letter and a Roman numeral: the letter indicates the strength of the recommendation, and the Roman numeral indicates the quality of the evidence supporting the recommendation. Thus, clinicians can use the ratings to differentiate

Table 8. Medications to treat latent tuberculosis infection: doses, toxicities, and monitoring requirements

Drug	Oral dose (mg/kg) (maximum dose)				Adverse reactions	Monitoring	Comments
	Daily		Twice weekly*				
	Adults	Children	Adults	Children			
Isoniazid	5 (300 mg)	10–20 (300 mg)	15 (900 mg)	20–40 (900 mg)	Rash Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild central nervous system effects Drug interactions resulting in increased phenytoin (Dilantin) or Disulfiram (Antabuse) levels	Clinical monitoring monthly Liver function tests† at baseline in selected cases‡ and repeat measurements if: Baseline results are abnormal Patient is pregnant, in the immediate postpartum period, or at high risk for adverse reactions Patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption Pyridoxine (vitamin B_6, 10–25 mg/d) might prevent peripheral neurophathy and central nervous system effects
Rifampin	10 (600 mg)	10–20 (600 mg)	10 (600 mg)	—	Rash Hepatitis Fever Thrombocytopenia Flu-like symptoms Orange-colored body fluids (secretions, urine, tears)	Clinical monitoring at weeks 2, 4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests† at baseline in selected cases‡ and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions	Rifampin is contraindicated or should be used with caution in human immunodeficiency virus (HIV)-infected patients taking protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) Decreases levels of many drugs (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, estrogens, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin) Might permanently discolor soft contact lenses

Table 8. ***(Continued)*** **Medications to treat latent tuberculosis infection: doses, toxicities, and monitoring requirements**

Drug	Oral dose (mg/kg) (maximum dose)				Adverse reactions	Monitoring	Comments
	Daily		Twice weekly*				
	Adults	Children	Adults	Children			
Rifabutin	5 (300 mg)§	—	5 (300 mg)§	—	Rash Hepatitis Fever Thrombocytopenia Orange-colored body fluids (secretions, urine, tears) With increased levels of rifabutin Severe arthralgias Uveitis Leukopenia	Clinical monitoring at Weeks 2, 4, and 8 when pyrazinamide given Complete blood count, platelets, and liver function tests† at baseline in selected cases‡ and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions Use adjusted daily dose of rifabutin and monitor for decreased antiretroviral activity and for rifabutin toxicity if rifabutin taken concurrently with PIs or NNRTIs§	Rifabutin is contraindicated for HIV-infected patients taking hard-gel saquinavir or delavirdine; caution is also advised if rifabutin is adminis tered with soft-gel saquinavir Reduces levels of many drugs (e.g., PIs, NNTRIs, methadone, dapsone, ketoconazole, coumadin derivatives, hormonal contraceptive, digitalis, sulfonylureas, diazepam, ß-blockers, anticonvulsants, and theophylline) Might permanently discolor contact lenses
Pyrazinamide	15–20 (2.0 g)		50 (4.0 g)	—	Gastrointestinal upset Hepatitis Rash Arthralgias Gout (rare)	Clinical monitoring at Weeks 2, 4, and 8 Liver function tests† at baseline in selected cases‡ and repeat measurements if Baseline results are abnormal Patient has symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms Might make glucose control more difficult in persons with diabetes Should be avoided in pregnancy but can be given after first trimester

* All intermittent dosing should be administered by directly observed therapy.

† AST or ALT and serum bilirubin.

‡ HIV infection, history of liver disease, alcoholism, and pregnancy.

§ If nelfinavir, indinavir, amprenavir, or ritonavir is administered with rifabutin, blood concentrations of these protease inhibitors decrease. Thus, the dose of rifabutin is reduced from 300 mg to 150 mg/d when used with nelfinavir, indinavir, or amprenavir; and to 150 mg (two or three times a week) when used with ritonavir. If efavirenz is administered with rifabutin, blood concentrations of rifabutin decrease. Thus, when rifabutin is used concurrently with efavirenz, the daily dose of rifabutin should be increased from 300 mg to 450 mg or 600 mg. Pharmacokinetic studies suggest that rifabutin might be given at usual doses with nevirapine. It is not currently known whether dose adjustment of rifabutin is required when used concurrently with soft-gel saquinavir. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available.

Table 9. Adapted Public Health Service rating system for the strength of treatment recommendations and quality of evidence

Strength of the recommendation
A. Preferred; should generally be offered
B. Alternative; acceptable to offer
C. Offer when preferred or alternative regimens cannot be given
D. Should generally not be offered
E. Should never be offered
Quality of evidence supporting the recommendation
I. At least one randomized trial with clinical endpoints
II. Clinical trials that either are not randomized or were conducted in other populations
III. Expert opinion

between recommendations based on data from clinical trials and those based on the opinions of experts familiar with the relevant clinical practice and scientific rationale for such practice (when clinical trial data are not available).

Recommended regimens. Four regimens are recommended for the treatment of adults with LTBI (Table 10). The antituberculosis medications used in these regimens have varying doses, toxicities, and monitoring requirements (Table 8). All patients being given twice-weekly treatment should receive DOT, because nonadherence to intermittent dosing results in a larger proportion of the total doses missed than does daily dosing. DOT should be used whenever feasible, especially with 2-mo regimens and in certain settings (e.g., some institutional settings, community outreach programs, and for some persons living in households with patients who are receiving home-based DOT for active TB).

Isoniazid for 9 mo. The isoniazid daily regimen for 9 mo receives an A recommendation. Prospective, randomized trials of up to 12 mo of therapy in HIV-uninfected persons suggest that the maximal beneficial effect of isoniazid is achieved by 9 mo; minimal additional benefit is gained by extending treatment to 12 mo. Thus, this updated recommendation represents a shortening of the previous recommendation of isoniazid daily for 12 mo for HIV-infected persons and a lengthening of the previously recommended 6 mo for HIV-uninfected persons (*1*). Both 12-mo and 6-mo regimens of isoniazid have substantially reduced rates of TB in HIV-infected persons compared with placebo (*88*), but the 6-mo regimen has not been directly compared with the 12-mo regimen in HIV-infected persons. Thus, the recommendation for 9 mo of isoniazid in HIV-infected persons is based on extrapolation of available data. Intermittent dosing of 9 mo of isoniazid for treatment of LTBI has not been studied comparatively. However, analogous with the continuation phase of treatment for active TB (where twice-weekly dosing is equivalent to daily dosing), twice-weekly dosing of isoniazid is also acceptable for treatment of LTBI, but is recommended at the B level as an acceptable alternative regimen.

Isoniazid for 6 mo. Although a 9-mo regimen of isoniazid is the preferred treatment of LTBI for an individual patient, a 6-mo regimen also provides substantial protection and has been demonstrated to be superior to placebo in both HIV-infected and HIV-uninfected persons (*32,84*). From a societal perspective, treatment for 6 mo rather than 9 mo may provide a more cost-effective outcome (*81*). Thus, based on individual situations, health departments or other providers may prefer to concentrate efforts in

Table 10. Recommended drug regimens for treatment of latent tuberculosis (TB) infection in adults

Drug	Interval and duration	Comments	Rating* (Evidence)† HIV⁻	HIV⁺
Isoniazid	Daily for 9 mo‡,§	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
	Twice weekly for 9 mo‡,§	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 mo§	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 mo§	DOT must be used with twice-weekly dosing	B (II)	C (I)
Rifampin plus pyrazinamide	Daily for 2 mo	May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible TB	B (II)	A (I)
		In HIV-infected patients, protease inhibitors or NNRTIs should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenivir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir¶		
	Twice weekly for 2–3 mo	DOT must be used with twice-weekly dosing	C (II)	C (I)
Rifampin	Daily for 4 mo	For persons who cannot tolerate pyrazinamide	B (II)	B (III)
		For persons who are contacts of patients with isoniazid-resistant, rifampin-susceptible TB who cannot tolerate pyrazinamide		

* Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given.

† Quality of evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion.

‡ Recommended regimen for children younger than 18 yr of age.

§ Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 mo as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

¶ Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitors or NNRTIs, dose adjustment of rifabutin may be required (see Table 8).

ensuring the implementation of a 6-mo rather than a 9-mo course of isoniazid. Isoniazid for 6 mo, taken either daily or twice weekly, is recommended at the B level for HIV-negative persons and at the C level for HIV-positive persons. The shorter regimen is not recommended for children or persons with radiographic evidence of prior tuberculosis.

Rifampin and pyrazinamide for 2 mo. The 2-mo daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of treatment of LTBI in HIV-infected persons that demonstrated the 2-mo regimen to be similar in safety and efficacy to a 12-mo regimen of isoniazid (*111*). Although this regimen has not been evaluated in HIV-uninfected persons with LTBI, the efficacy is not expected to differ significantly. However, the toxicities may be increased (*113*); therefore, the recommendation is made at the A level for HIV-infected persons and at the B level for HIV-uninfected persons until further data are available. Two randomized, prospective trials of intermittent dosing of rifampin and pyrazinamide for 2 and 3 mo, respectively, have been reported in HIV-infected persons (*86, 110*); in neither case was the sample size adequate to conclude with certainty that efficacy was equivalent to daily dosing. Moreover, both studies compared the twice-weekly rifampin and pyrazinamide regimen to the 6-mo isoniazid regimen. Therefore, rifampin and pyrazinamide given twice weekly for 2–3 mo may be considered when alternative regimens cannot be given. This recommendation is made at the C level.

Rifampin for 4 mo. Rifampin given daily for 3 mo has resulted in better protection than placebo in treatment of LTBI in HIV-uninfected persons with silicosis in a randomized prospective trial (*36*). However, because the patients receiving rifampin had a high rate of active TB (4%), experts have concluded that a 4–mo regimen would be more prudent when using rifampin alone. This 4-mo rifampin regimen is recommended at the B level for both HIV-infected and HIV-uninfected persons. This option may be useful for patients who cannot tolerate isoniazid or pyrazinamide.

Choice of regimen. Because more than one regimen can be used to treat LTBI, health care providers should discuss options with the patient, and, when possible, help patients make the decision, unless medical indications dictate a specific regimen. Discussion should include the length and complexity of the regimens, possible adverse effects, and potential drug interactions.

Completion of treatment. Completion of therapy is based on total number of doses administered—not on duration of therapy alone. The 9-mo regimen of daily isoniazid should consist of 270 doses, at minimum, administered within 12 mo, allowing for minor interruptions in therapy. The 6-mo regimen of isoniazid should consist of at least 180 doses administered within 9 mo. Twice-weekly isoniazid regimens should consist of at least 76 doses administered within 12 mo for the 9-mo regimen and 52 doses within 9 mo for the 6-mo regimen. The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses to be administered within 3 mo. The regimen of daily rifampin alone should consist of at least 120 doses administered within 6 mo.

Ideally, patients should receive medication on a regular dosing schedule until completion of the indicated course. However, in practice some doses may be missed, requiring the course to be lengthened. When reinstituting therapy for patients who have interrupted treatment, clinicians might need to continue the regimen originally prescribed (as long as needed to complete the recommended duration of the particular

regimen) or renew the entire regimen if interruptions were frequent or prolonged enough to preclude completion of treatment as recommended. In either situation, when therapy is restored after an interruption of more than 2 mo, a medical examination to rule out active TB disease is indicated.

Special considerations.

Treatment of HIV-infected persons. Recommendations for HIV-infected adults largely parallel those for HIV-uninfected adults, although the quality of evidence and strengths of the recommendations vary (Table 10). However, when isoniazid is chosen for treatment of LTBI in persons with HIV infection, 9 mo is recommended rather that 6 mo. In addition, rifampin is generally contraindicated or should be used with caution in persons who are taking protease inhibitors (PIs) or NNRTIs (*169*). Experts have recommended that for HIV-infected persons who are candidates for treatment of LTBI and need PI or NNRTI therapy, rifabutin can be substituted for rifampin in some circumstances; rifabutin can safely be used with indinavir, nelfinavir, amprenavir, ritonavir, and efavirenz, but not with hard-gel saquinavir, or delavirdine. Caution is advised if rifabutin is administered with soft-gel saquinavir, because data regarding use of rifabutin with soft-gel saquinavir or nevirapine are limited.

No specific data have been generated for treatment of LTBI with rifabutin-containing regimens, but such a recommendation is supported by analogy with treatment for active TB (where rifabutin can be substituted for rifampin with no loss of efficacy) and by experimental studies in mice (*107,130*). Rifabutin can be administered at one half the usual daily dose (i.e., reduced from 300 mg to 150 mg/d) with indinavir, nelfinavir, or amprenavir or at one-fourth the usual dose (i.e., 150 mg every other day or three times a week) with ritonavir. The daily rifabutin dose is 450 mg or 600 mg when used with efavirenz; pharmacokinetic studies suggest that rifabutin might be given at usual doses with nevirapine. For patients receiving multiple PIs or a PI in combination with an NNRTI, drug interactions with rifabutin are likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available. The substitution of rifapentine for rifampin is not recommended because rifapentine's safety and effectiveness have not been established for patients infected with HIV (*131*). Furthermore, the drug interactions between rifapentine and HIV protease inhibitors have not been studied in detail, although one study has indicated that rifapentine causes substantial reduction in the serum level of indinavir when the drugs are given together (*132*).

In tuberculin-negative, HIV-infected persons, treatment of LTBI has not been effective (*3*). However, most tuberculin-negative HIV-infected contacts of patients with active TB should receive treatment for presumptive LTBI—even when repeat testing after contact has ended is not indicative of LTBI. Furthermore, some experts recommend treatment of possible LTBI for HIV-infected residents of institutions that pose an ongoing high risk for exposure to *M. tuberculosis* (e.g., prisons, jails, and homeless shelters).

Persons with fibrotic lesions/suspected disease. For patients who have a chest radiograph demonstrating old fibrotic lesions thought to represent previous infection with TB and a positive tuberculin skin test (≥5 mm) without evidence of active disease and no history of treatment for TB, three acceptable regimens can be used for treatment. These regimens include 9 mo of isoniazid, 2 mo of rifampin plus pyrazinamide, or 4 mo of rifampin (with or without isoniazid), providing that infection with drug-resistant organisms is judged to be unlikely. Patients who begin multidrug therapy for

suspected pulmonary TB but are subsequently determined not to have active disease (i.e., AFB cultures are negative and chest radiographs are stable) should complete treatment with at least 2 mo of a regimen containing rifampin and pyrazinamide if the tuberculin skin test is positive and other causes of the radiographic abnormalities have been excluded.

Persons with evidence suggestive of healed, primary TB (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are not at increased risk for TB. Their risk for TB and need for treatment of LTBI should be determined by consideration of other risk factors and the size of the tuberculin reaction (Table 7).

Pregnancy and lactation. Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease (*133, 134*). Although one study demonstrated a decrease in lymphocyte reactivity to tuberculin during pregnancy (*135*), other studies have not demonstrated an effect of pregnancy on cutaneous delayed hypersensitivity to tuberculin (*136, 137*). The current classification scheme for interpreting the Mantoux tuberculin skin test is likely valid in pregnancy, although it has not been verified in this group of women. There is no evidence that the tuberculin skin test has adverse effects on the pregnant mother or fetus (*138*).

Pregnant women should be targeted for tuberculin skin testing only if they have a specific risk factor for LTBI or for progression of LTBI to disease. Although the need for treatment of active TB during pregnancy is unquestioned, the treatment of LTBI in pregnant women is more controversial. Some experts prefer to delay treatment until after delivery because pregnancy itself does not increase the risk of progression to disease, and two studies suggest that women in pregnancy and the early postpartum period may be vulnerable to isoniazid hepatotoxicity (*91, 92*). However, because conditions that promote hematogenous spread of organisms to the placenta (e.g., recent infection and HIV infection) or progression of LTBI to disease can endanger both the mother and baby (*139*), many experts agree that pregnant women with these conditions and LTBI should be treated during pregnancy and have careful clinical and laboratory monitoring for hepatitis. The possible risk for isoniazid hepatotoxicity must be weighed against the risk for developing active TB and the consequences to both the mother and her child should active disease develop.

Extensive use of isoniazid during pregnancy has indicated that although it readily crosses the placental barrier, the drug is not teratogenic even when given during the first 4 mo of gestation (*140*). Regarding rifampin, one study revealed that 3% of 446 fetuses exposed *in utero* to rifampin had abnormalities (i.e., limb reductions, central nervous system abnormalities, and hypoprothrombinemia) compared with 2% for ethambutol and 1% for both isoniazid and controls (*138*). Hemorrhagic disease of the newborn has been described following the use of rifampin in the mother (*141*). However, extensive experience with the use of rifampin to treat TB in pregnant women suggests it is safe in most circumstances. Although pyrazinamide has been used to treat TB in pregnant women, no published data exist concerning the effects of the drug on the fetus. Thus, although pyrazinamide may be considered after the first trimester in women with HIV infection (*142*), it should otherwise be avoided.

The preferred regimen for treatment of LTBI in pregnant women is isoniazid, administered either daily or twice weekly. Although rifampin is probably safe, no efficacy data support its use. For women at high risk for progression of LTBI to disease, especially

those who are infected with HIV or who have been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For these women, careful clinical and/or laboratory monitoring for hepatitis should be undertaken. Pregnant women taking isoniazid should receive pyridoxine supplementation.

Toxic effects of antituberculosis drugs delivered in breast milk have not been reported. One study concluded that a breastfeeding infant would develop serum levels of no more than 20% of the usual therapeutic levels of isoniazid for infants and <11% of other antituberculosis drugs (*143*). Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infants whose breastfeeding mothers are taking isoniazid should receive supplemental pyridoxine. The amount of isoniazid provided by breast milk is inadequate for treatment of the infant.

Children and adolescents. Several fundamental aspects of the natural history and treatment of LTBI in children must be considered when making recommendations about therapy. Infants and young children (i.e., those younger than 5 yr of age) with LTBI have been infected recently, and are at high risk for progression to disease. Data suggest that untreated infants with LTBI have up to a 40% likelihood of developing TB (*144*). The risk for progression decreases gradually through childhood. Infants and young children are more likely than older children and adults to develop life-threatening forms of TB, especially meningeal and disseminated disease. Children with LTBI have more years at risk to develop TB than adults. Isoniazid therapy for LTBI appears to be more effective for children than adults, with several large clinical trials demonstrating risk reduction of 70–90% (*145,146*). The risk for isoniazid-related hepatitis is minimal in infants, children, and adolescents, who generally tolerate the drug better than adults (*147,148*). Isoniazid therapy is widely accepted for use in children. Because of differences in pathogenesis of TB infection and disease in children compared with adults, information from clinical trials involving adults cannot be applied directly to children without confirmatory pediatric trials. The only published efficacy trials of treatment of LTBI in children have studied isoniazid alone.

The only recommended regimen for treatment of LTBI in HIV-uninfected children is a 9-mo course of isoniazid as self-administered daily therapy or by DOT twice weekly. Routine monitoring of serum liver enzyme concentrations is not necessary but should be considered in children at risk for hepatic disease. When children taking antituberculosis therapy develop hepatitis, a search for causes other than isoniazid or other drugs should be undertaken and the therapy discontinued. Routine administration of pyridoxine is not recommended for children taking isoniazid, but should be given to (*1*) breastfeeding infants, (*2*) children and adolescents with diets likely to be deficient in pyridoxine, and (*3*) children who experience paresthesias while taking isoniazid.

Isoniazid given twice weekly has been used extensively to treat LTBI in children, especially schoolchildren and close contacts of case patients (*125*). On the basis of clinical experience, this method of administration is safe, but its effectiveness has not been established definitively. DOT should be considered when it is unlikely that the child and family will be adherent to daily self-administration.

In the United States, rifampin alone has been used for the treatment of LTBI in infants, children, and adolescents when isoniazid could not be tolerated or the child has had contact with a case patient infected with an isoniazid-resistant but rifamycin-susceptible organism (*149*). However, no controlled clinical trials have been conducted.

A 3-mo regimen of rifampin and isoniazid has been used in England, with programmatic data suggesting that the regimen is effective (*108*). No reports have been published concerning the efficacy of rifampin and pyrazinamide therapy in children with LTBI, although a randomized study involving a limited number of children indicated that this regimen was well tolerated (*116*).

No studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. The American Academy of Pediatrics currently recommends a 9-mo course of isoniazid (*150*). Most experts recommend that routine monitoring of serum liver enzyme concentrations be performed and pyridoxine given when HIV-infected children are treated with isoniazid. The optimal length of rifampin therapy in children with LTBI is not known; however, the American Academy of Pediatrics recommends 6 mo of treatment (*150*).

Contacts of patients with tuberculosis.

- Contacts of patients with drug-susceptible tuberculosis. Persons who are contacts of patients with drug-susceptible TB and who have positive tuberculin skin-test reactions (≥5 mm) should be treated with one of the recommended regimens—regardless of age (Table 10). In addition, some tuberculin-negative contacts should be considered for treatment. Because of susceptibility to severe disease, children younger than 5 yr of age with negative skin tests should be treated and another skin test performed 8–12 wk after contact has ended. If the repeat skin test is positive, treatment should continue for the recommended period of time; if the repeat skin test is negative, the treatment should be stopped. Immunosuppressed persons, including those with HIV infection, who are contacts of persons with active TB should also receive treatment, even if repeat skin testing does not indicate LTBI.
- Contacts of patients with isoniazid-resistant tuberculosis. No definitive data exist concerning treatment of contacts who have been exposed to patients with probable or confirmed isoniazid-resistant TB. A decision analysis and Delphi methodology have been used to recommend either rifampin alone or in combination with isoniazid or ethambutol when the risk of isoniazid-resistant infection is >50% (*151*). An expert panel has recommended use of rifampin for vulnerable contacts (e.g., those with HIV infection) of patients with isoniazid-resistant TB (*152*).

In an outbreak of isoniazid- and streptomycin-resistant TB among homeless persons, six (9%) of 71 persons with skin tests that converted who received no preventive therapy developed TB, compared with three (8%) of 38 who received isoniazid, and zero of 98 persons who received rifampin or isoniazid and rifampin (*153*). Similarly, of 157 high school students who took rifampin after being exposed to a patient with isoniazid-resistant, active TB, none developed TB during the second year of the study (*149*). However, one episode of rifampin prophylaxis failure was reported among contacts of a case patient with isoniazid-resistant TB in a community outbreak (*154*).

For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, a 2-mo regimen of rifampin and pyrazinamide is recommended. For patients with intolerance to pyrazinamide, a 4-mo regimen of rifampin alone is recommended. In situations in which rifampin cannot be used, rifabutin can be substituted.

- Contacts of patients with multidrug-resistant tuberculosis. The occurrence of outbreaks of multidrug-resistant TB (MDR TB) (i.e., TB caused by strains of *M. tuberculosis* resistant to at least isoniazid and rifampin) and the rise in resistance rates worldwide have focused attention on options for treatment of persons exposed to and presumed

to be infected by such organisms (*155*). As with exposure to isoniazid-resistant TB, this problem has not been evaluated in prospective studies. A Delphi technique among 31 experts failed to achieve consensus on the management of such persons (*156*).

Persons infected with isoniazid- and rifampin-resistant organisms are unlikely to benefit from treatment with regimens containing these agents. Therefore, use of a regimen containing other agents active against *M. tuberculosis* should be considered. When possible, selection of drugs for such a regimen should be guided by *in vitro* susceptibility test results from the isolate to which the patient was exposed and is presumed infected.

For persons who are likely to be infected with MDR TB and at high risk of developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or ofloxacin) for 6–12 mo are recommended, if the organisms from the index case-patient are known to be susceptible to these agents (*157*). Immunocompetent contacts may be observed without treatment or treated for at least 6 mo; immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 mo. Side effects of pyrazinamide and fluoroquinolones include gastrointestinal symptoms and hepatic transaminase elevations (158). All persons with suspected MDR TB infection should be followed for at least 2 yr, irrespective of treatment. Expert consultation should be sought for the treatment of persons exposed to patients with MDR TB.

No studies have been published regarding treatment of LTBI in children following exposure to multidrug-resistant TB. Ethambutol at 15 mg/kg is safe in children (*159*). The combination of pyrazinamide and ethambutol for 9–12 mo is recommended if the isolate is susceptible to both drugs. Long-term use of fluoroquinolones in children should be avoided. Deleterious effects on growing cartilage have been observed in animals treated with fluoroquinolones (*160*), although no defects in bone growth occurred among a limited number of children with cystic fibrosis treated with ciprofloxacin or ofloxacin (*161*). When pyrazinamide and ethambutol cannot be used, many experts recommend using a combination of two other drugs to which the infecting organism is likely susceptible (*162, 163*).

Low-risk tuberculin test reactors. When treatment of LTBI is being considered for persons who are at low risk for developing TB, the decision should be based on factors such as likelihood of drug toxicity if treatment is given and likelihood of TB transmission to vulnerable contacts (e.g., infants and HIV-infected persons) if treatment were not given and the patient were to develop active TB. Included in this decision are the patient's preferences and values. When the assessed risk of drug toxicity exceeds the anticipated benefits of therapy, treatment for LTBI is not usually appropriate.

BCG-vaccinated persons. A history of BCG vaccination, with or without a BCG scar, should not influence the decision regarding whether to treat LTBI. The criteria previously described should be applied without modification (164).

Directly observed therapy and measures to increase adherence. Any regimen that is given intermittently (i.e., twice weekly) should be given only under direct observation. Some experts recommend that the 2-mo regimen of daily rifampin and pyrazinamide also be given by DOT, which, for ease of administration, may consist of five observed and two self-administered doses each week.

Patients with the highest priority for DOT are those at the highest risk of progression from latent to active TB, including persons with HIV infection and young children who are contacts of infectious patients with pulmonary TB. DOT may be conveniently and

effectively used for the treatment of household contacts of patients receiving DOT for active TB and for treatment observed by staff members in certain facilities (e.g., schools and homeless shelters).

If it is not possible to provide DOT to enhance adherence with treatment of LTBI, the prescribed regimen should be incorporated into patients' daily routines. Medical providers can encourage adherence to treatment by establishing rapport with patients. Providers should explain in simple, clear language what LTBI is, the health threat it presents, and how it is eradicated. Patients should be encouraged to ask questions. Patient education should ideally be conducted in the patient's primary language, or through a medical interpreter, if necessary. Each visit between patient and medical provider during therapy is an opportunity to reinforce the patient's understanding of LTBI and its treatment.

In addition to education about potential drug toxicity, patients should be told about common side effects and counseled on drug management. (For example, medications should be taken with food when gastrointestinal symptoms have occurred after medication was taken on an empty stomach, and salicylic acid can be used for symptomatic treatment of arthralgia caused by pyrazinamide.)

Most interventions to improve adherence require substantial financial resources. Providing flexible clinic hours, reducing waiting times for patients, spending time with patients to counsel and educate, and directly observing patients ingesting medications increase operating expenses. Even the least intensive approaches to improve adherence increase program costs. The costs of these approaches to improving patient adherence underscore the need to target tuberculin testing and treatment of LTBI to those groups with an increased risk for recent infection or those persons at high risk for progression to active TB, if infected. In addition, programs should invest in approaches to increase adherence, especially for those persons who are at greatest risk for progressing to disease. Better success in motivating patients to accept and to complete treatment is necessary to achieve the full potential of this intervention to protect persons from TB and to reduce the incidence of the disease in the community.

Pretreatment Evaluation and Monitoring of Treatment

Pretreatment evaluation. The pretreatment evaluation of persons who are targeted for treatment of LTBI provides an opportunity for health care providers to a) establish rapport with patients, b) discuss the details of the patients' risk for TB, c) emphasize the benefits of treatment and the importance of adherence to the drug regimen, d) review possible adverse effects of the regimen, including interactions with other drugs, and e) establish an optimal follow-up plan. The evaluation should include an interview conducted in the patients' primary language with assistance of qualified medical interpreters, if necessary.

The patient history should document risk factors for TB, prior treatment for TB or LTBI, and preexisting medical conditions that constitute a contraindication to treatment or are associated with an increased risk for adverse effects of treatment. A detailed history of current and previous drug therapy should be obtained, with particular attention to previous adverse reactions to drugs contemplated for treatment of LTBI, and to current use of drugs which may interact with the drugs used for treatment. Women receiving rifampin and oral contraceptives are at increased risk for becoming pregnant and should be advised to consider an additional form of contraception. Practitioners should consider using a standardized history form to ensure that all elements

of the pretest evaluation are thoroughly covered for each patient.

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (Table 8). Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin. Baseline testing is also indicated for patients infected with HIV, pregnant women and those in the immediate postpartum period (i.e., within 3 mo of delivery), persons with a history of liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who use alcohol regularly, and others who are at risk for chronic liver disease. Baseline testing is no longer routinely indicated in persons older than 35 yr of age. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of LTBI.

Monitoring of treatment. Clinical monitoring is indicated for all patients; this involves education of patients about the symptoms and signs that can result as adverse effects of the drug(s) being prescribed and the need for prompt cessation of treatment and clinical evaluation should symptoms occur. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever lasting 3 or more days, abdominal tenderness (especially right upper quadrant discomfort), easy bruising or bleeding, and arthralgia (Table 8). Clinical monitoring begins at the first visit and should be repeated at each monthly visit. At monthly visits, patients should be instructed to interrupt therapy and contact their providers immediately upon the onset of such symptoms or any unexplained illness occurring during treatment.

Patients being treated for LTBI should receive a clinical evaluation, including a brief physical assessment checking for signs of hepatitis, at least monthly if receiving isoniazid alone or rifampin alone and at 2, 4, and 8 wk if receiving both rifampin and pyrazinamide (Table 8). These evaluations represent opportunities to review the indications for treatment, adherence with therapy since the last visit, symptoms of adverse drug effects and drug interactions, and plans to continue treatment. As with the baseline evaluation, a standardized questionnaire may facilitate those interviews.

Routine laboratory monitoring during treatment of LTBI is indicated for patients whose baseline liver function tests are abnormal and for other persons at risk for hepatic disease (Table 8). In addition, laboratory testing (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate patients who develop acute arthritis) should be used to evaluate possible adverse effects that occur during the course of treatment. Some experts recommend that isoniazid be withheld if a patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is asymptomatic.

Reporting of serious adverse events. Practitioners and other health professionals should report serious adverse events associated with the treatment of LTBI to the U.S. Food and Drug Administration's MedWatch program. Serious adverse events include those associated with hospitalization, permanent disability, or death. Reporting may be by mail, telephone (1-800-FDA-1088), fax (1-800-FDA-0178), or the Internet site (www.fda.gov/medwatch).

PRIORITIES FOR FUTURE RESEARCH

Diagnosis

The only widely available method to detect LTBI is the tuberculin skin test. However, the specificity of the test is decreased by cross reactions from BCG vaccination and sensitization by nontuberculous mycobacteria. When used in populations in which the risk for TB is low, the test's positive predictive value is poor. In addition, the requirement that the person tested return for the test to be read 48–72 h after test administration creates operational problems. Thus, more specific and sensitive tests are needed to diagnose LTBI and to identify persons at greatest risk for progressing to active disease. Especially useful would be tests that distinguish skin-test reactions caused by TB infection from those caused by BCG vaccination or infection with nontuberculous mycobacteria, tests that correlate with the presence of living organisms, and tests that accurately identify LTBI in immunodeficient persons.

Operational Research

Acceptability, Tolerability, and Effectiveness of Daily Rifampin and Pyrazinamide

More data are needed regarding the acceptability, tolerability, and effectiveness of the 2-mo regimen of daily rifampin and pyrazinamide in HIV-negative persons. Data are especially needed from older adults and children.

Intermittent Rifampin-containing Regimens

No studies of rifampin alone taken twice weekly for the treatment of LTBI have been conducted. Data from two studies in HIV-infected persons that included intermittent (i.e., twice weekly) rifampin and pyrazinamide administration suggested that these regimens were effective (*86,110*). Before additional trials of intermittent rifampin regimens are undertaken, animal model data are needed to compare these regimens with regimens using other longer-acting rifamycin derivatives (*see* Efficacy Studies of New Drugs).

Isoniazid Taken Twice Weekly

It is unlikely that a formal efficacy study of intermittent isoniazid for the treatment of LTBI will be undertaken, unless it is included as a control arm for studies of newer regimens. However, several TB-control programs have had considerable experience using this regimen. Data from these programs should be examined, especially as they relate to acceptability and completion of treatment. The analysis of aggregate data available in TB programs may also be useful in estimating the effectiveness of this regimen.

Studies in Children and Pregnant Women

Studies are needed to provide information regarding the use of newer regimens for the treatment of LTBI in children and pregnant women. The safety of pyrazinamide for pregnant women and their fetuses should be determined. More information is needed

regarding hepatotoxicity of isoniazid in pregnant and postpartum women. Studies are needed to establish the safety and effectiveness of rifampin alone and rifampin plus pyrazinamide for treatment of LTBI in infants, children, and adolescents. The best target populations for these studies would be HIV-infected children in places in which TB is prevalent and household contacts of TB case patients. In addition, the effectiveness of twice-weekly regimens for treatment of LTBI in children should be confirmed. Data concerning the safety and effectiveness of alternative therapies for MDR LTBI in children are needed. Finally, epidemiologic research to determine the best tools to identify children at high risk for LTBI should be undertaken.

Reporting and Monitoring in New Settings

These recommendations call for the establishment of LTBI treatment programs in new community settings (e.g., managed care organizations and neighborhood clinics). Consequently, operational research will be needed to evaluate the implementation of these programs in settings other than health departments. These studies should assess the knowledge base of treating clinicians and identify the obstacles to be overcome for the successful implementation of community-based LTBI treatment programs.

Combination Rifampin and Pyrazinamide Preparations

If field and programmatic data establish the effectiveness and acceptability of the rifampin and pyrazinamide regimen for the treatment of LTBI, the availability of a combination product would facilitate its administration. However, the argument concerning the usefulness of combination products in preventing the emergence of drug resistance in patients with active TB is not as compelling for persons being treated for LTBI. Nonetheless, methods to facilitate provision of this treatment and increase adherence (e.g., blister packs containing medication for 2 wk of treatment for several different body weights) would be useful.

Efficacy Studies of New Drugs

No novel compounds currently can be considered candidates for the treatment of LTBI. However, several rifamycin derivatives with half-lives substantially greater than rifampin are of interest because of the possibility of widely spaced, intermittent administration. In experimental studies involving mice, the combination of rifapentine and isoniazid given once weekly for 3 mo was as active as rifampin and pyrazinamide given daily for 2 mo (*165*). Rifalazil, which has an even longer half-life, is more active than rifapentine and perhaps could be dosed less frequently without compromising efficacy (*166*). The class of nitroimidazole compounds is also of interest because of their potential activity against dormant tubercle bacilli (*167*). Unfortunately, no animal models of LTBI exist that optimize the preclinical evaluation of new drugs.

Studies of Immunomodulators and Vaccines

Recent studies have indicated that immunotherapy with specific cytokines and immunomodulators may be beneficial to response to TB treatment. However, their application in the treatment of LTBI is uncertain. Some epidemiologic studies have suggested that high levels of certain cytokines (e.g., interferon gamma) may protect against the development of active TB. If further studies support this finding,

interventions that stimulate production of protective cytokines may have a role in the treatment of LTBI. The development of a postinfection vaccine to be administered to persons with LTBI has been given high priority (*168*).

Decision/Cost-Effectiveness Analyses

Focus on Testing for and Treatment of Latent TB Infection in High-risk and Diverse Populations

Future decision and cost-effectiveness analyses should be expanded to include targeted testing. Instead of beginning at the "treat-don't-treat" point, new models might be most useful if they begin with the decision of whether to test. These studies should focus on groups at high risk and specific subgroups characterized by varied risks and benefits of treatment. Using this conceptual framework will help place decision modeling more clearly into a "real world" context, incorporating the linked contingencies that exist.

Comparison of Strategies Using Both Shorter and Longer Treatment Regimens

Future decision and cost-effectiveness analyses should compare the shorter course regimens to the longer, 9-mo regimen of daily isoniazid. These analyses will benefit from investigations of the toxicities and efficacies of shorter regimens. In addition, although adherence presumably will be better with shorter treatment regimens, the rifampin and pyrazinamide regimen may be less well-tolerated in some groups of patients, thus resulting in low adherence. Decision and cost-effectiveness analyses should explore a range of toxicities in the models until investigations better establish these risks. By investigating the effect of a range of toxicities and adherence on the decision outcome, studies can help identify priority areas for research. Updated analyses on the use of alternate regimens for the treatment of drug-resistant LTBI are also needed.

Use of Multiple Analytic Perspectives

When two different perspectives are relevant for a decision, both perspectives should be modeled and analyzed. For example, when the benefits to an individual person with LTBI are different from the benefits to the public, both perspectives must be made explicit in decision models. When decision analysis is inadequate to deal with public health issues (e.g., reduction in contagion), additional models are needed to augment views of the benefits and costs of following each viable course of action.

Policies designed to target and treat populations at high risk for TB are motivated by the need to benefit the individual patient as well as the health of the public by averting active disease in persons most likely to develop it. As policies are instituted that identify high-risk groups for testing and treatment, the social and ethical ramifications of these policies must be considered. The individual persons who comprise many of the high-risk groups targeted for testing and treatment often represent disenfranchised segments of urban populations (e.g., persons who are homeless, incarcerated, and medically underserved, and residents in long-term care facilities). Ideally, the outcomes and utilities that are used in these decision models will incorporate the values and preferences of these patients and the outcomes important to the general public.

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References

1. American Thoracic Society, Centers for Disease Control. 1994. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am. J. Respir. Crit. Care Med.* 149:1359–1374.
2. Centers for Disease Control and Prevention. 1995. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. *M.M.W.R.* 44(No. RR-11):19–34.
3. Centers for Disease Control and Prevention. 1998. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations. *M.M.W.R.* 47(No. RR-20):36–42.
4. Centers for Disease Control and Prevention. 1995. Essential components of a tuberculosis prevention and control program: recommendations of the Advisory Council for the Elimination of Tuberculosis. *M.M.W.R.* 44(No. RR-11):1–16.
5. Styblo, K. 1980. Recent advances in epidemiological research in tuberculosis. *Adv. Tuberc. Res.* 20:1–63.
6. Ferebee, S. H. 1970. Controlled chemoprophylaxis trials in tuberculosis: a general review. *Adv. Tuberc. Res.* 17:28–106.
7. American Thoracic Society. 1965. Preventive treatment in tuberculosis: a statement by the Committee on Therapy. *Am. Rev. Respir. Dis.* 91: 297–298.
8. American Thoracic Society. 1967. Chemoprophylaxis for the prevention of tuberculosis: a statement by an Ad Hoc Committee. *Am. Rev. Respir. Dis.* 96:558–562.
9. Garibaldi, R. A., R. E. Drusin, S. H. Ferebee, and M. B. Gregg. 1972. Isoniazid-associated hepatitis: report of an outbreak. *Am. Rev. Respir. Dis.* 106:357–365.
10. American Thoracic Society, National Tuberculosis and Respiratory Disease Association, Center for Disease Control. 1971. Preventive treatment of tuberculosis. *Am. Rev. Respir. Dis.* 104:460–463.
11. Kopanoff, D. E., D. E. Snider, Jr., and G. J. Caras. 1979. Isoniazid-related hepatitis: a U.S. Public Health Service cooperative surveillance study. *Am. Rev. Respir. Dis.* 117:991–1001.
12. American Thoracic Society, American Lung Association, Center for Disease Control. 1974. Preventive therapy of tuberculosis infection. *Am. Rev. Respir. Dis.* 110:371–373.
13. Taylor, W. C., M. D. Aronson, and T. L. Delbanco. 1981. Should young adults with a positive tuberculin test take isoniazid? *Ann. Intern. Med.* 94:808–813.
14. Mehta, J. B., A. K. Dutt, L. Harvill, and W. Henry. 1988. Isoniazid preventive therapy for tuberculosis: are we losing our enthusiasm? *Chest* 94:138–141.
15. American Thoracic Society, Centers for Disease Control. 1983. Treatment of tuberculosis and other mycobacterial diseases. *Am. Rev. Respir. Dis.* 127:790–796.
16. Salpeter, S. R. 1993. Fatal isoniazid-induced hepatitis: its risk during chemoprophylaxis. *West J. Med.* 159:560–564.
17. Snider, D. E., Jr., and L. S. Farer. 1984. Preventive therapy for tuberculosis infection: an intervention in need of improvement. *Am. Rev. Respir. Dis.* 130:355–356.
18. O'Brien, R. J., and J. H. Perriæns. 1995. Preventive therapy for tuberculosis in HIV infection: the promise and the reality. *AIDS* 9:665–673.
19. Advisory Council on the Elimination of Tuberculosis. 1999. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. *M.M.W.R.* 48(No. RR-9):1–13.
20. Sutherland, I. 1968. The ten-year incidence of clinical tuberculosis following "conversion" in 2550 individuals aged 14 to 19 years. TSRU Progress Report (KNCV, The Hague, Netherlands).
21. Ferebee, S. H., and F. W. Mount. 1962. Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. *Am. Rev. Respir. Dis.* 85:490–521.
22. McKenna, M. T., E. McCray, and I. Onorato. 1995. The epidemiology of tuberculosis among foreign-born persons in the United States, 1986 to 1993. *N. Engl. J. Med.* 332:1071–1076.

23. Chin, D. P., K. DeRiemer, P. M. Small, A. Ponce de Leon, R. Steinhart, G. F. Schecter, C. L. Daley, A. R. Moss, E. A. Paz, R. M. Jasmer, C. B. Agasino, and P. H. Hopewell. 1998. Differences in contributing factors to tuberculosis incidence in U.S.-born and foreign-born persons. *Am. J. Respir. Crit. Care Med.* 158:1797–1803.
24. Zuber, P. L. F., M. T. McKenna, N. J. Binkin, I. M. Onorato, and K. G. Castro. 1997. Long-term risk of tuberculosis among foreign-born persons in the United States. *J.A.M.A.* 278:304–307.
25. Comstock, G. W., V. T. Livesay, and S. F. Woolpert. 1974. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am. J. Epidemiol.* 99:131–138.
26. Schluger, N. W., R. Huberman, N. Wolinsky, R. Dooley, W. N. Rom, and R. S. Holzman. 1997. Tuberculosis infection and disease among persons seeking social services in New York City. *Int. J. Tuberc. Lung Dis.* 1:31–37.
27. Sepkowitz, K. A. 1995. AIDS, tuberculosis, and the health care worker. *Clin. Infect. Dis.* 20:232–242.
28. Cohn, D. L., and W. M. El-Sadr. 2000. Treatment of latent tuberculosis infection. In L. B. Reichman and E. Hershfield, editors. Tuberculosis: A Comprehensive International Approach, 2nd ed. Marcel Dekker, New York. 471–502.
29. Markowitz, N., N. I. Hansen, P. C. Hopewell, J. Glassroth, P. A. Kvale, B. T. Mangura, T. C. Wilcosky, J. M. Wallace, M. J. Rosen, and L. B. Reichman. 1997. Incidence of tuberculosis in the United States among HIV-infected persons. *Ann. Intern. Med.* 126:123–132.
30. Selwyn, P. A., B. M. Sckell, P. Alcabes, G. H. Friedland, R. S. Klein, and E. E. Schoenbaum. 1992. High risk of active tuberculosis in HIVinfected drug users with cutaneous anergy. *J.A.M.A.* 268:504–509.
31. Selwyn, P. A., D. Hartel, V. A. Lewis, E. E. Schoenbaum, S. H. Vermund, R. S. Klein, A. T. Walker, and G. H. Friedland. 1989. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N. Engl. J. Med.* 320:545–550.
32. International Union Against Tuberculosis Committee on Prophylaxis. 1982. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 60:555–564.
33. Falk, A., and G. F. Fuchs. 1978. Isoniazid (INH) prophylaxis with isoniazid in inactive tuberculosis: a Veterans Administration cooperative study. XII. *Chest* 73:44–48.
34. Steinbruck, P., D. Dankova, L. B. Edwards, B. Doster, and V. T. Livesay. 1972. The risk of tuberculosis in patients with fibrous lesions radiographically diagnosed. *Bull. Int. Union Tuberc.* 47:144–171.
35. Palmer, C. E., S. Jablon, and P. Q. Edwards. 1957. Tuberculosis morbidity of young men in relation to tuberculin sensitivity and body build. *Am. Rev. Tuberc.* 76:517–539.
36. Hong Kong Chest Service, Tuberculosis Research Centre, Madras, and British Medical Research Council. 1992. A double-blind placebocontrolled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am. Rev. Respir. Dis.* 145:36–41.
37. Paul, R. 1961. Silicosis in northern Rhodesia copper miners. *Arch. Environ. Health* 2:96–109.
38. Westerholm, P., A. Ahlmark, R. Maasing, and I. Segelberg. 1986. Silicosis and risk of lung cancer or lung tuberculosis: a cohort study. *Environ. Res.* 41:339–350.
39. Lundin, A. P., A. J. Adler, G. M. Berlyne, and E. A. Friedman. 1979. Tuberculosis in patients undergoing maintenance hemodialysis. *Am. J. Med.* 67:597–602.
40. Chia, S., M. Karim, R. K. Elwood, and J. M. FitzGerald. 1998. Risk of tuberculosis in dialysis patients: a population-based study. *Int. J. Tuberc. Lung Dis.* 2:989–991.
41. Andrew, O. T., P. Y. Schoenfeld, P. C. Hopewell, and M. H. Humphreys. 1980. Tuberculosis in patients with end-stage renal disease. *Am. J. Med.* 68:59–65.
42. Pablos-MÄndez, A., J. Blustein, and C. A. Knirsch. 1997. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *Am. J. Public Health* 87:574–579.
43. Boucot, K. R., E. S. Dillon, D. A. Cooper, and P. Meier. 1952. Tuberculosis among diabetics: the Philadelphia Survey. *Am. Rev Tuberc.* 65(Suppl.):1–50.

44. Oscarsson, P. N., and H. Silwer. 1958. Incidence of pulmonary tuberculosis among diabetics: search among diabetics in the county of Kristianstad. *Acta Med. Scand.* 161(Suppl. 335):23–48.
45. Thorn, P. A., V. S. Brookes, and J. A. H. Waterhouse. 1956. Peptic ulcer, partial gastrectomy, and pulmonary tuberculosis. *Br. Med. J.* 1:603–608.
46. Snider, D. E., Jr. 1985. Tuberculosis and gastrectomy. *Chest* 87:414–415.
47. Steiger, Z., W. O. Nickel, G. J. Shannon, E. G. Nedwicki, and R. F. Higgins. 1976. Pulmonary tuberculosis after gastric resection. *Am. J. Surg.* 131:668–671.
48. Pickleman, J. R., L. S. Evans, J. M. Kane, and R. J. Freeark. 1975. Tuberculosis after jejunoileal bypass for obesity. *J.A.M.A.* 234:744.
49. Bruce, R. M., and L. Wise. 1977. Tuberculosis after jejunoileal bypass for obesity. *Ann. Intern. Med.* 87:574–576.
50. Lichtenstein, I. H., and R. R. MacGregor. 1983. Mycobacterial infections in renal transplant recipients: report of five cases and review of the literature. *Rev. Infect. Dis*. 5:216–226.
51. Muñoz, P., J. Palomo, M. Muñoz, M. Rodirguez-Creixéms, T. Pelaez, and E. Bouza. 1995. Tuberculosis in heart transplant recipients. *Clin. Infect. Dis.* 21:398–402.
52. Korner, M. M., N. Hirata, G. Tenderich, K. Minami, H. Mannebach, K. Kleesiek, and R. KÜrfer. 1997. Tuberculosis in heart transplant recipients. *Chest* 111:365–369.
53. Feld, R., G. P. Bodey, and D. Groschel. 1976. Mycobacteriosis in patients with malignant disease. *Arch. Intern. Med.* 136:67–70.
54. Kaplan,, M. H., D. Armstrong, and P. Rosen. 1974. Tuberculosis complicating neoplastic disease: a review of 201 cases. *Cancer* 33:850–858.
55. Schatz, M., R. Patterson, R. Kloner, and J. Falk. 1976. The prevalence of tuberculosis and positive tuberculin skin tests in a steroid-treated asthmatic population. *Ann. Intern. Med.* 84:261–265.
56. Bovornkitti, S., P. Kangsadai, P. Sathirapat, and P. Oonsombatti. 1960. Reversion and reconversion rate of tuberculin skin test reactions in correlation with use of prednisone. *Dis. Chest* 38:51–55.
57. Bateman, E. D. 1993. Is tuberculosis chemoprophylaxis necessary for patients receiving corticosteroids for respiratory disease? *Respir. Med.* 87:485–487.
58. Kim, H. A., C. D. Yoo, H. J. Baek, E. B. Lee, C. Ahn, J. S. Han, S. Kim, J. S. Lee, K. W. Choe, and Y. W. Song. 1998. Mycobacterium tuberculosis infection in a corticosteroid-treated rheumatic disease patient population. *Clin. Exp. Rheumatol.* 16:9–13.
59. Friedman, L. N., M. T. Williams, P. S. Tejinder, and T. R. Frieden. 1996. Tuberculosis, AIDS, and death among substance abusers on welfare in New York City. *N. Engl. J. Med.* 334:828–833.
60. Buskin, S. E., J. L. Gale, N. S. Weiss, and C. M. Nolan. 1994. Tuberculosis risk factors in adults in King County, Washington, 1988 through 1990. *Am. J. Public Health* 84:1750–1756.
61. Centers for Disease Control. 1989. A strategic plan for the elimination of tuberculosis in the United States. *M.M.W.R.* 38(Suppl. S-3):1–25.
62. Goldberg, B. W. 1998. Managed care and public health departments: who is responsible for the health of the population? *Ann. Rev. Public Health* 19:527–537.
63. Nelson, K. R., H. Bui, and J. H. Samet. 1997. Screening in special populations: a "case study" of recent Vietnamese immigrants. *Am. J. Med*. 102:435–440.
64. Nolan, C. M., L. Roll, S. V. Goldberg, and A. M. Elarth. 1997. Directly observed isoniazid preventive therapy for released jail inmates. *Am. J. Respir. Crit. Care Med.* 155:583–586.
65. Nazar-Stewart, V., and C. M. Nolan. 1992. Results of a directlyobserved intermittent isoniazid preventive therapy program in a shelter for homeless men. *Am. Rev. Respir. Dis.* 146:57–60.
66. Bock, N. N., B. S. Metzger, M. Tapia, and H. M. Blumberg. 1999. A tuberculin screening and isoniazid preventive therapy program in an inner-city population. *Am. J. Respir. Crit. Care Med.* 159:295–300.

67. Gourevitch, M. N., P. Alcabes, W. C. Wasserman, and P. S. Arno. 1998. Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis. *Int. J. Tuberc. Lung Dis.* 2:531–540.
68. Perlman, D. C., M. P. Perkins, N. Solomon, L. Kochems, D. C. Des Jarlais, and D. Paone. 1997. Tuberculosis screening at a syringe exchange program. *Am. J. Public Health* 87:862–863.
69. Schluger, N. W., R. Huberman, I. Holzman, W. N. Rom, and D. I. Cohen. 1999. Screening for infection and disease as a tuberculosis control measure among indigents in New York City, 1994–1997. *Int. J. Tuberc. Lung Dis*. 3:281–286.
70. American Thoracic Society, Centers for Disease Control and Prevention. 2000. Diagnostic standards and classification of tuberculosis in adults and children. *Am. J. Respir. Crit. Care Med.* 161:1376–1395.
71. Huebner, R. E., W. Schein, and J. B. Bass, Jr. 1993. The tuberculin skin test. *Clin. Infect. Dis.* 17:968–975.
72. Cauthen, G. W., and S. E. Valway. 1994. Tuberculin reactions read at 2 and 7 days. *Am. J. Respir. Crit. Care Med.* 149(Pt. 2):A101.
73. Rose, D. N., C. B. Schecter, and J. J. Adler. 1995. Interpretation of the tuberculin skin test. *J. Gen. Intern. Med.* 10:635–642.
74. Sepulveda, R. L., X. Ferrer, C. Latrach, and R. U. Sorensen. 1990. The influence of Calmette-Guérin Bacillus immunization on the booster effect of tuberculin testing in healthy young adults. *Am. Rev. Respir. Dis*. 142:24–28.
75. McKay, A., A. Kraut, C. Murdzak, and A. Yassi. 1999. Determinants of tuberculin reactivity among health care workers: interpretation of positivity following BCG vaccination. *Can. J. Infect. Dis.* 10:134–139.
76. Graham, N. M. H., K. E. Nelson, L. Solomon, M. Bonds, R. T. Rizzo, J. Scavotto, J. Astemborski, and D. Vlahov. 1992. Prevalence of tuberculin positivity and skin test anergy in HIV-I seropositive and seronegative intravenous drug users. *J.A.M.A.* 267:369–373.
77. Centers for Disease Control and Prevention. 1997. Anergy skin testing and tuberculosis preventive therapy for HV-1 infected persons: revised recommendations. *M.M.W.R.* 46(No. RR-15):1–10.
78. Ferebee, S. H., and C. E. Palmer. 1956. Prevention of experimental tuberculosis with isoniazid. *Am. Rev Tuberc. Pulmon. Dis.* 73:1–18.
79. Comstock, G. W., and S. H. Ferebee. 1970. How much isoniazid is needed for prophylaxis? *Am. Rev. Respir. Dis.* 101:780–782.
80. Comstock, G. W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int. J. Tuberc. Lung Dis.* 3:847–850.
81. Snider, D.E., Jr., G. J. Caras, and J. P. Koplan. 1986. Preventive therapy with isoniazid: cost-effectiveness of different durations of therapy. *J.A.M.A.* 255:1579–1583.
82. American Thoracic Society, Centers for Disease Control. 1986. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am. Rev. Respir. Dis.* 134:355–363.
83. Pape, J. W., S. S. Jean, J. L. Ho, A. Hafher, and W. D. Johnson, Jr. 1993. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet* 342:268–272.
84. Whalen, C. C., J. L. Johnson, A. Okwera, D. L. Hom, R. Huebner, P. Mugyenyi, R. D. Mugerwa, and J. J. Ellner. 1997. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N. Engl. J. Med.* 337:801–808.
85. Hawken, M. P., H. K. Meme, L. C. Elliot, J. M. Chakaya, J. S. Morris, W. A. Githui, E. S. Juma, J. A. Odhiambo, L. N. Thiong'o, J. N. Kimari, E. N. Ngugi, J. J. Bwayo, C. F. Gilks, F. A. Plummer, J. D. H. Porter, P. P. Nunn, and K. P. W. J. McAdam. 1997. Isoniazid preventive therapy for tuberculosis in HIV-I-infected adults: results of a randomized controlled trial. *AIDS* 11:875–882.
86. Mwinga, A., M. Hosp, P. Godfrey-Faussett, M. Quigley, P. Mwaba, B. N. Mugala, O. Nyirenda, N. Luo, J. Pobee, A. M. Elliott, K. P. W. J. McAdam, and J. D. H. Porter. 1998. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 12:2447–2457.

87. Gordin, F. M., J. P. Matts, C. Miller, L. S. Brown, R. Hafner, S. L. John, M. Klein, A. Vaughn, C. L. Besch, G. Perez, S. Szabo, and W. El-Sadr. 1997. A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. *N. Engl. J. Med.* 337:315–320.
88. Bucher, H. C., L. E. Griffith, G. H. Guyatt, P. Sudre, M. Naef, P. Sendi, and M. Battegay. 1999. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *AIDS* 13:501–507.
89. Mitchell, J. R., H. J. Zimmerman, K. G. Ishak, U. P. Thorgeirsson, J. A. Timbrell, W. R. Snodgrass, and S. D. Nelson. 1976. Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. *Ann. Intern. Med.* 84:181–192.
90. Comstock, G. W. 1986. Prevention of tuberculosis among tuberculin reactors: maximizing benefits, minimizing risks. *J.A.M.A.* 256:2729–2730.
91. Snider, D.E., Jr., and G. J. Caras. 1992. Isoniazid-associated hepatitis deaths: a review of available information. *Am. Rev. Respir. Dis.* 145: 494–497.
92. Franks, A. L., N. J. Binkin, D. E. Snider, Jr., W. M. Rokaw, and S. Becker. 1989. Isoniazid hepatitis among pregnant and postpartum Hispanic patients. *Pub. Health Rep.* 104:151–155.
93. Murphy, R., R. Swartz, and P. B. Watkins. 1990. Severe acetaminophen toxicity in a patient receiving isoniazid. *Ann. Intern. Med.* 113:799–800.
94. Burk, R. F., K. E. Hill, R. W. Hunt, and A. E. Martin. 1990. Isoniazid potentiation of acetaminophen hepatotoxicity in the rat and 4-methylpyrazole inhibition of it. *Res. Commun. Chem. Path. Pharmacol.* 69:115–158.
95. Millard, P. S., T. C. Wilcosky, S. J. Reade-Christopher, and D. J. Weber. 1996. Isoniazid-related fatal hepatitis. *West J. Med.* 164:486–491.
96. Moulding, T. S., A. G. Redeker, and G. C. Kanel. 1989. Twenty isoniazid-associated deaths in one state. *Am. Rev. Respir. Dis.* 140:700–705.
97. Centers for Disease Control and Prevention. 1993. Severe isoniazidassociated hepatitis—New York, 1991–1993. *M.M.W.R.* 42:545–547.
98. Leff, D. R., and A. R. Leff. 1997. Tuberculosis control policies in major metropolitan health departments in the United States. *Am. J. Respir. Crit. Care Med.* 156:1487–1494.
99. Nolan, C. M., S. V. Goldberg, and S. E. Buskin. 1999. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *J.A.M.A.* 281:1014–1018.
100. Tsevat, J., W. C. Taylor, J. B. Wong, and S. G. Pauker. 1988. Isoniazid for the tuberculin reactor: take it or leave it. *Am. Rev. Respir. Dis.* 137:215–220.
101. Rose, D. N., C. B. Schechter, and A. L. Silver. 1986. The age threshold for isoniazid chemoprophylaxis: a decision analysis for low-risk tuberculin reactors. *J.A.M.A.* 256:2709–2713.
102. Salpeter, S. R., G. D. Sanders, E. E. Salpeter, and D. K. Owens. 1997. Monitored isoniazid prophylaxis for low-risk tuberculin reactors older than 35 yr of age: a risk-benifit and cost effectiveness analysis. *Ann. Intern. Med.* 127:1051–1061.
103. Colice, G. L. 1990. Decision analysis, public health policy, and isoniazid chemoprophylaxis for young adult tuberculin skin reactors. *Arch. Intern. Med.* 150:2517–2522.
104. Lecoeur, H. F., C. Truffot-Pernot, and J. H. Grosset. 1989. Experimental short-course preventive therapy of tuberculosis with rifampin and pyrazinamide. *Am. Rev. Respir. Dis.* 140:1189–1193.
105. Grosset, J., C. Truffot-Pernot, C. Lacroix, and B. Ji. 1992. Antagonism between isoniazid and the combination pyrazinamide-rifampin against tuberculosis infection in mice. *Antimicrob. Agents Chemother.* 36:548–551.
106. Dhillon, J., J. M. Dickinson, K. Sole, and D. A. Mitchison. 1996. Preventive chemotherapy of tuberculosis in Cornell model mice with combinations of rifampin, isoniazid, and pyrazinamide. *Antimicrob. Agents Chemother.* 40:552–555.

107. Jabes, D., C. Della Bruna, R. Rossi, and P. Olliaro. 1994. Effectiveness of rifabutin alone or in combination with isoniazid in preventive therapy of mouse tuberculosis. *Antimicrob. Agents Chemother.* 38:2346–2350.
108. Ormerod, L. P. 1998. Rifampicin and isoniazid prophylactic chemotherapy for tuberculosis. *Arch. Dis. Child* 78:169–171.
109. Joint Tuberculosis Committee of the British Thoracic Society. 1998. Chemotherapy and management of tuberculosis in the United Kingdom. *Thorax* 53:536–548.
110. Halsey, N. A., J. S. Coberly, and J. Desormeaux, P. Losikoff, J. Atkinson, L. H. Moulton, M. Contave, M. Johnson, H. Davis, L. Geiter, E. Johnson, R. Huebner, R. Boutos, and R. E. Chaisson. 1998. Rifampin and pyrazinamide vs. isoniazid for prevention of tuberculosis in HIV-1 infected persons: an international randomized trial. *Lancet* 351:786–792.
111. Gordin, F. M., R. E. Chaisson, J. P. Matts, C. Miller, M. de Lourdes Garcia, R. Hafner, J. L. Valdespino, J. Coberly, M. Schechter, A. J. Klukowicz, M. A. Barry, and R. J. O'Brien. 2000. An international, randomized trial of rifampin and pyrazinamide versus isoniazid for prevention of tuberculosis in HIV-infected persons. *J.A.M.A.* 283: 1445–1450.
112. Geiter, L. J., R. J. O'Brien, and D. E. Kopanoff. 1990. Short-course preventive therapy for tuberculosis (abstract). *Am. Rev. Respir. Dis.* 141(Pt. 2):A437.
113. Geiter, L. J. 1997. Results of a randomized, controlled trial to assess the toxicity and patient adherence with two short-course regimens for the prevention of tuberculosis, a two-momth regimen of rifampin and pyrazinamide or a four-month regimen of rifampin only, in comparison with a control regimen of six months-isoniazid [thesis]. Johns Hopkins University, School of Hygiene and Public Health, Baltimore, MD.
114. Combs, D. L., R. J. O'Brien, and L. J. Geiter. 1990. USPHS tuberculosis short-course chemotherapy trial 21: effectiveness, toxicity, and acceptability. *Ann. Intern. Med.* 112:397–406.
115. Grazcyk, J., R. J. O'Brien, E. Bek, H. Nimerowsak, and L. J. Geiter. 1991. Assessment of rifampin containing regimens for tuberculosis preventive therapy: preliminary results from a pilot study in Poland (abstract). *Am. Rev. Respir. Dis.* 143:A119.
116. Magdorf, K., A. F. Arizzi-Ruche, L. J. Geiter, R. J. O'Brien, and U. Wahn. 1994. Compliance and tolerance of new antituberculotic short- term chemoprevention regimes in childhood: a pilot study. *Pneumologie* 48:761–764.
117. Snider, D. E., and M. D. Hutton. 1989. Improving patient compliance in tuberculosis treatment programs. Department of Health and Human Services, CDC, Atlanta, GA.
118. Sumartojo, E. 1993. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am. Rev. Respir. Dis.* 147:1311–1320.
119. Carey, J. W., M. J. Oxtoby, L. P. Nguyen, V. Huynh, M. Morgan, and M. Jeffery. 1997. Tuberculosis beliefs among recent Vietnamese refugees in New York State. *Public Health Rep.* 112:66–72.
120. Morisky, D. E., C. K. Malotte, P. Choi, P. Davidson, S. Rigler, B. Sugland, and M. Langer. 1990. A patient education program to improve adherence rates with antituberculosis drug regimens. *Health Educ. Q.* 17:253–267.
121. Harborview Medical Center, University of Washington. Ethnic Medicine Guide. , http:// www.hslib.washington.edu/cli nical/ethnomed/.
122. White, M. C., J. P. Tulsky, P. Reilly, H. W. McIntosh, T. M. Hoynes, and J. Goldenson. 1998. A clinical trial of a financial incentive to go to the tuberculosis clinic for isoniazid after release from jail. *Int. J. Tuberc. Lung Dis.* 2:506–512.
123. Heal, G., R. K. Elwood, and J. M. FitzGerald. 1998. Acceptance and safety of directly observed versus self-administered isoniazid preventive therapy in aboriginal peoples in British Columbia. *Int. J. Tuberc. Lung Dis.* 2:979–983.
124. Wobeser, W., T. To, and V. H. Hoeppner. 1989. The outcome of chemoprophylaxis on tuberculosis prevention in the Canadian Plains Indian. *Clin. Invest Med.* 12:149–153.
125. Kohn, M. R., M. R. Arden, J. Vasilakis, and I. R. Shenker. 1996. Directly observed preventive therapy: turning the tide against tuberculosis. *Arch. Pediatr. Adolesc. Med.* 150:727–779.

126. Judson, F. N., J. A. Sbarbaro, J. M. Tapy, and D. L. Cohn. 1983. Tuberculosis screening: evaluation of a food handler's program. *Chest* 83: 879-82.
127. Cohn, D. L., B. J. Catlin, K. L. Peterson, F. N. Judson, and J. A. Sbarbaro. 1990. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis: a twice-weekly, directly observed, and cost-effective regimen. *Ann. Intern. Med.* 112:407–415.
128. Shafran, S. D., J. Singer, D. P. Zarowny, J. Deschênes, P. Phillips, F. Turgeon, F. Y. Aoki, E. Toma, M. Miller, R. Duperval, C. Lemieux, and W. F. Schlech, III. 1998. Determinants of rifabutin-associated uveitis in patients treated with rifabutin, clarithromycin, and ethambutol for Mycobacterium avium complex bacteremia: a multivariate analysis. *J. Infect. Dis.* 77:252–255.
129. Sun, E., M. Heath-Chiozzi, D. W. Cameron, A. Hsu, R. G. Granneman, C. J. Maurath, and J. M. Leinard. 1996. Concurrent ritonavir and rifabutin increases risk of rifabutin-associated adverse events [Abstract no. MoB171]. In Programs and abstracts of the XI International Conference on AIDS. Vancouver, BC, Canada. 18.
130. McGregor, M. M., P. Olliaro, L. Wolmarans, B. Mabuza, M. Bredell, M. Felten, and B. Fourie. 1996. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am. J. Respir. Crit. Care Med.* 154:1462–1467.
131. Vernon, A., W. Burman, D. Benator, A. Khan, and L. Bozeman. 1999. Acquired riifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 353:1843–1847.
132. Jarvis, B., and H. M. Lamb. 1998. Rifapentine. Drugs 56:607–616.
133. Good, J. T., Jr., M. D. Isemen, P. T. Davidson, S. Lakshnminarayan, and S. A. Sahn. 1981. Tuberculosis in association with pregnancy. *Am. J. Obstet. Gynecol.* 140:492–498.
134. Carter, E. J., and S. Mates. 1994. Tuberculosis during pregnancy: the Rhode Island experience, 1987 to 1991. *Chest* 106:1466–1470.
135. Smith, J. K., E. A. Caspery, and E. J. Field. 1972. Lymphocyte reactivity to antigen in pregnancy. *Am. J. Obstet. Gynecol.* 113:602–606.
136. Montgomery, W. P., R. C. Young, Jr., and M. P. Allen. 1968. The tuberculin test in pregnancy. *Am. J. Obstet. Gynecol.* 100:829–831.
137. Present, P. A., and G. W. Comstock. 1975. Tuberculin sensitivity in pregnancy. *Am. Rev. Respir. Dis.* 112:413–415.
138. Snider, D. E., Jr., P. M. Layde, M. W. Johnson, and M. A. Lyle. 1980. Treatment of tuberculosis during pregnancy. *Am. Rev. Respir. Dis.* 122:65–69.
139. Cantwell, M. F., Z. M. Shehab, A. M. Costello, L. Sands, W. F. Green, E. P. Ewing, S. E. Valway, and I. M. Onorato. 1994. Brief report: congenital tuberculosis. *N. Engl. J. Med.* 330:1051–1054.
140. Scheinhorn, D. J., and V. A. Angelillo. 1977. Antituberculous therapy in pregnancy: risks to the fetus. *West. J. Med.* 127:195–198.
141. Eggermont, E., N. Logghe, W. Van De Casseye, M. Casteels-Van Daele, J. Jaeken, J. Cosemans, M. Verstraete, and M. Renaer. 1976. Hemorrhagic disease of the newborn in the offspring of rifampin and isoniazid treated mothers. *Acta. Paediatr. Belg.* 29:87–89.
142. Centers for Disease Control and Prevention. 1999. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus: U.S. Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). *M.M.W.R.* 48(No. RR-10):13–14.
143. Snider, D. E., Jr., and K. E. Powell. 1984. Should women taking antituberculosis drugs breast-feed? *Arch. Intern. Med.* 144:589–590.
144. Miller, F. J. W., R. M. E. Seale, and N. M. Taylor. 1963. Tuberculosis in children. Little Brown, Boston, MA. 77.
145. Comstock, G. W., L. M. Hammes, and A. Pio. 1969. Isoniazid prophylaxis in Alaskan boarding schools: a comparison of two doses. *Am. Rev. Respir. Dis.* 100:773–779.
146. Mount, F. W., and S. H. Ferrebee. 1961. Preventive effects of isoniazid in the treatment of primary tuberculosis in children. *N. Engl. J. Med.* 265:713–721.

147. O'Brien, R. J., M. W. Long, F. S. Cross, M. A. Lyle, and D. E. Snider, Jr. 1983. Hepatotoxicity from isoniazid and rifampin among children treated for tuberculosis. *Pediatrics* 72:491–499.
148. Stein, M. T., and D. Liang. 1979. Clinical hepatotoxicity of isoniazid in children. *Pediatrics* 64:499–505.
149. Villarino, M. E., R. Ridzon, P. C. Weismuller, M. Elcock, R. M. Maxwell, J. Meador, P. J. Smith, M. L. Carson, and L. J. Geiter. 1997. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. *Am. J. Respir. Crit. Care Med.* 155:1735–1738.
150. American Academy of Pediatrics. 2000. Tuberculosis. In Red Book: Report of the Committee on Infectious Diseases, 25th ed. American Academy of Pediatrics, Elk Grove Village, IL. (In press)
151. Koplan, J. P., and L. S. Farer. 1980. Choice of preventive treatment for isoniazid-resistant tuberculosis infection: use of decision analysis and the Delphi technique. *J.A.M.A.* 244:2736–2740.
152. Bailey, W. C., R. B. Byrd, J. C. Glassroth, P. C. Hopewell, and L. B. Reichman. 1985. Preventive treatment of tuberculosis. *Chest* 87:1285–1325.
153. Polesky, A., H. W. Farbe, D. J. Gottlieb, H. Park, S. Levinson, J. J. O'Connell, B. McInnis, R. L. Nieves, and J. Bernardo. 1996. Rifampin preventive therapy for tuberculosis in Boston's homeless. *Am. J. Respir. Crit. Care Med.* 154:1473–1477.
154. Livengood, J. R., T. G. Sigler, L. R. Foster, J. G. Bobst, and D. E. Snider. 1985. Isoniazid–resistant tuberculosis: a community outbreak and report of a rifampin prophylaxis failure. *J.A.M.A.* 253:2847–2849.
155. Pablos-Mendez, A., M. C. Raviglione, A. Laszlo, N. B. Binkin, H. L. Rieder, F. Bustreo, D. L. Cohn, C. S. B. Lambregts-Van Weezenbeek, S. J. Kim, P. Chaulet, and P. Nunn. 1998. Global surveillance for antituberculosis–drug resistance, 1994–1997. *N. Engl. J. Med.* 338:1641–1649.
156. Passannante, M. R., C. T. Gallagher, and L. B. Reichman. 1994. Preventive therapy for contacts of multidrug-resistant tuberculosis: a Delphi survey. *Chest* 106:431–434.
157. Centers for Disease Control and Prevention. 1992. Management of persons exposed to multidrug-resistant tuberculosis. *M.M.W.R.* 41(No. RR-11):61–71.
158. Ridzon, R., J. Meador, R. Maxwell, K. Higgins, P. Weismuller, and I. M. Onorato. 1997. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. *Clin. Infect. Dis.* 24:1264–1265.
159. TrÄbucq, A. 1997. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int. J. Tuberc. Lung Dis.* 1:12–15.
160. Gough, A. W., O. B. Kasali, R. E. Sigler, and V. Baragi. 1992. Quinolone arthropathy—acute toxicity to immature articular cartilage. *Toxicol. Pathol.* 20:436–449.
161. Danisovicova, A., M. Brezina, S. Belan, H. Kayserova, E. Kaiserova, I. Hruskovic, K. Orosovç, S. Dluholucky, K. Gaova E. MathÄova, I. Marinovç, and V. Kr mÄry, Jr. 1994. Magnetic resonance imaging in children receiving quinolones: no evidence of quinolone-induced arthropathy—a multicenter survey. *Chemotherapy* 40:209–214.
162. Steiner, P., and M. Rao. 1993. Drug-resistant tuberculosis in children. *Semin. Pediatr. Infect. Dis.* 4:275–282.
163. Swanson, D. S., and J. R. Starke. 1995. Drug-resistant tuberculosis in pediatrics. *Pediatr. Clin. North Am.* 42:553–581.
164. Centers for Disease Control and Prevention. 1996. The role of BCG vaccine in the prevention and control of tuberculosis in the United States: a joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. *M.M.W.R.* 45(No. RR-4):8–9.
165. Chapuis, L., B. Ji, C. Truffot-Pernot, R. J. O'Brien, M. C. Raviglione, and J. H. Grosset. 1994. Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice. *Am. J. Respir. Crit. Care Med.* 150:1355–1362.

166. Reddy, M. V., J. Luna-Herrera, D. Daneluzzi, and P. R. Gangadhararn. 1996. Chemotherapeutic activity of benzoxazinorifamycin, KRM1648, against Mycobacterium tuberculosis in C57BL/6 mice. *Tuberc. Lung Dis.* 77:154–159.
167. Stover, C. K., Y. Yuan, P. G. Warrener, D. R. VanDevanter, D. R. Sherman, M. H. Langhorne, K. Tanaka, C. E. Barry, and W. R. Baker. 1999. A novel compound series and development candidate for the treatment of tuberculosis. *Am. J. Respir. Crit. Care Med.* 159(Suppl.):AI6.
168. Centers for Disease Control and Prevention. 1998. Development of new vaccines for tuberculosis: recommendations of the Advisory Council for the Elimination of Tuberculosis (ACET). *M.M.W.R.* 47(No. RR-13):1–6.
169. Centers for Disease Control and Prevention. 2000. Notice to Readers: Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis in HIV-infected persons taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *M.M.W.R.* 49:185–189.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

MMWR
MORBIDITY AND MORTALITY
WEEKLY REPORT

June 9, 2000 / Vol. 49 / No. RR-6

Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Targeted Tuberculosis Testing and Treatment of Latent Tuberculosis Infection

EXPIRATION — JUNE 9, 2001

You must complete and return the response form electronically or by mail by **June 9, 2001**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 3.0 hours Continuing Medical Education (CME) credit, 0.3 hour Continuing Education Units (CEUs), or 3.5 hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

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1. Read this *MMWR* (Vol. 49, RR-6), which contains the correct answers to the questions beginning on the next page.
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7. Immediately print your Certificate of Completion for your records.

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ACCREDITATION

Continuing Medical Education (CME). This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) by the Centers for Disease Control and prevention (CDC) and American Thoracic Society (ATS). The CDC and ATS are accredited by the ACCME to provide continuing medical education for physicians. The CDC designates this educational activity for a maximum of 3.0 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

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Continuing Nursing Education (CNE). This activity for 3.5 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

GOALS and OBJECTIVES

This *MMWR* provides recommendations regarding targeted tuberculin testing and treatment of latent tuberculosis infection (LTBI) that were developed by the American Thoracic Society and the Division of Tuberculosis Elimination, CDC. The goal of this report is to guide clinical practice and policy development associated with targeted testing and the treatment of latent tuberculosis infection. Upon completion of this educational activity, the reader should be able to 1) describe the purpose of targeted tuberculin testing; 2) describe the classification of the tuberculin reaction; 3) describe the regimens for treatment of latent TB infection for HIV-positive and HIV-negative persons; and 4) describe how patients should be monitored during treatment of LTBI.

To receive continuing education credit, please answer all of the following questions.

1. Which of the following statements is TRUE?

A. All pregnant women should be targeted for tuberculin skin testing.

B. Tuberculin skin testing is not recommended for recent close contacts to an infectious TB case-patient.

C. Routine tuberculin skin testing is not recommended for populations at low risk for LTBI.

D. Tuberculin skin testing is contraindicated for persons who have been vaccinated with BCG.

2. Which of the following statements is FALSE?

A. Baseline laboratory testing is indicated for all patients at the start of treatment for LTBI.

B. Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements.

C. Baseline laboratory testing is indicated for patients with HIV infection, pregnant women, and those in the immediate postpartum period.

D. Baseline testing is no longer routinely indicated in persons aged >35.

3. In which groups is an induration size of 5 millimeters NOT considered a positive reaction?

A Recent contacts of a TB case-patient.

B. HIV-positive persons.

C. Patients with organ transplants and other immunosuppressed patients.

D. Children < 4 years, or children and adolescents exposed to adults in high-risk categories.

E. All of the above.

4. Which of the following groups should be given high priority for the treatment of LTBI?

A. Patients with end-stage renal disease/hemodialysis.

B. HIV-positive persons.

C. Recent contacts of a TB case-patient.

D. Persons with fibrotic changes on chest radiograph consistent with prior TB.

E. All of the above.

5. Which of the following regimens is an alternative to isoniazid for treatment of LTBI in HIV-positive persons?

A. Streptomycin and ethambutol.

B. Rifampin and pyrazinamide.

C. Ethambutol and pyrazinamide.

D. Rifampin and ethambutol.

6. Which of the following treatment regimens for LTBI is an alternative to isoniazid for HIV-positive persons who are receiving protease inhibitors or nonnucleoside reverse transcriptase inhibitors?

A. Streptomycin and ethambutol.

B. Rifampin and pyrazinamide.

C. Ethambutol and pyrazinamide.

D. Rifabutin and pyrazinamide.

7. How often should patients be evaluated for adverse reactions to TB medications during treatment of LTBI?

A. At least monthly if receiving isoniazid alone.

B. At least monthly if receiving rifampin alone.

C. At 2, 4, and 8 weeks if receiving both rifampin and pyrazinamide.

D. All of the above.

8. Which of the following statements is TRUE?

A. A 9-month regimen of isoniazid is the preferred treatment of LTBI in HIV-negative persons.

B. A 3-month regimen of daily rifampin may be useful for patients who cannot tolerate isoniazid or pyrazinamide.

C. A 2-month regimen of rifampin and pyrazinamide is the preferred treatment of LTBI for HIV-positive persons.

D. All of the above.

9. Which of the following is the preferred regimen for the treatment of LTBI in pregnant women?

A. Isoniazid administered daily or twice weekly.

B. Rifampin administered daily or twice weekly.

C. Rifampin and pyrazinamide administered daily.

D. Ethambutol administered daily.

10. A tuberculin skin test reaction of 10 millimeters of induration is considered positive in which group?

A. Persons with no risk factors for TB.

B. Recent contacts of TB case-patients.

C. HIV-positive persons.

D. Recent immigrants from high prevalence countries.

E. All of the above.

11. Indicate your work setting.

A. State/local health department.
B. Other public health setting.
C. Hospital clinic/private practice.
D. Managed care organization.
E. Academic institution.
F. Other.

12. Which best describes your professional activities?

A. Physician.
B. Nurse.
C. Health educator.
D. TB control staff.
E. Other.

13. I plan to use these recommendations as the basis for . . . (Indicate all that apply.)

A. health education materials.
B. insurance reimbursement policies.
C. local practice guidelines.
D. public policy.
E. other.

14. Each month, approximately how many TB patients do you treat?

A. None
B. 1-5.
C. 6-20.
D. 21-50.
E. 50-100.
F. >100.

15. How much time did you spend reading this report and completing the exam?

A. More than 2 ½ hours but fewer than 3 hours.
B. 3 to 3 ½ hours.
C. More than 3 ½ hours but fewer than 4 hours.
D. 4 hours or more.

16. After reading this report, I am confident I can describe the purpose of targeted tuberculin testing.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the classification of the tuberculin reaction.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe the regimens for treatment of latent TB infection for HIV-positive and HIV-negative persons.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can describe how patients should be monitored during treatment of LTBI.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

20. The objectives are relevant to the goal(s) of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. The tables and figures are useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. How did you learn abut this continuing education activity?

A. Internet/World Wide Web.
B. Advertisement (e.g., flyer, publication cover, newsletter, and journal).
C. Co-worker/supervisor.
D. Conference presentation.
E. MMWR subscriber.
F. Other.

Correct answers for questions 1–10.

1. C; 2. A; 3. D; 4. E; 5. B; 6. D; 7. D; 8. D; 9. A; 10. D.

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Targeted Tuberculosis Testing and Treatment of Latent Tuberculosis Infection

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5. [ ] A [ ] B [ ] C [ ] D
6. [ ] A [ ] B [ ] C [ ] D
7. [ ] A [ ] B [ ] C [ ] D
8. [ ] A [ ] B [ ] C [ ] D
9. [ ] A [ ] B [ ] C [ ] D
10. [ ] A [ ] B [ ] C [ ] D [ ] E
11. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
12. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
13. [ ] A [ ] B [ ] C [ ] D [ ] E
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16. [ ] A [ ] B [ ] C [ ] D [ ] E
17. [ ] A [ ] B [ ] C [ ] D [ ] E
18. [ ] A [ ] B [ ] C [ ] D [ ] E
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22. [ ] A [ ] B [ ] C [ ] D [ ] E
23. [ ] A [ ] B [ ] C [ ] D [ ] E
24. [ ] A [ ] B [ ] C [ ] D [ ] E

Signature ***Date I Completed Exam***

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