Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection

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EXECUTIVE SUMMARY
This statement provides new recommendations for targeted tuberculin testing and treatment regimens for persons with latent 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 (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 addition, many changes to previous recommendations regarding testing for and treatment of LTBI are presented.

Targeted Tuberculin Testing
Targeted tuberculin testing for LTBI is a strategic component of tuberculosis (TB) control that identifies persons at high risk recent infection with Mycobacterium tuberculosis and those who have clinical conditions that are associated with an increase 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 if they are infected with M. tuberculosis, or who have abnormal chest radiographs consistent with prior TB), ≥5 mm of induration is considered positive. For other 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); 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 kg in 6 mo or more, and those who have clinical conditions that are associated with an increased risk for progression of LTBI to active TB.

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 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, ...
The isoniazid daily regimen for 9 mo is recommended because prospective, randomized trials in HIV-negative persons indic:

of isoniazid is likely achieved by 9 mo, and minimal additional benefit is gained by extending therapy to 12 mo. When comp:

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 sub:

mo rather than 9 mo may provide a more favorable outcome from a cost-effectiveness standpoint. Thus, based on local condi:

Both the 9-mo and 6-mo isoniazid regimens may be given intermittently (i.e., twice weekly). When isoniazid is given interm:

The 2-mo daily regimen of rifampin and pyrazinamide is recommended on the basis of a prospective randomized trial of trea:

weekly treatment with rifampin and pyrazinamide for 2 or 3 mo may be considered when alternative regimens cannot be giv:

pyrazinamide also be given by DOT, which can consist of five observed and two self-administered doses each week. In situ:

Rifampin given daily for 4 mo is recommended on the basis of the efficacy of a similar regimen in a) a prospective randomiz:

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:

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 ,
- For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 mo is recommended. For wom:
- 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 fo:
- For persons who are likely to be infected with isoniazid- and rifampin-resistant (multidrug) TB and who are at high:

Clinical and Laboratory Monitoring

Once patients have been identified and then tested for LTBI, they should receive an initial clinical evaluation. They should a:

pyrazinamide). This evaluation should include questioning about side effects and a brief physical assessment checking for si:

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 ':

oxaloacetic transaminase) (AST [SGOT]) or alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]) (i:

within 3 mo of delivery), persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cir:

However, such testing may be considered on an individual basis, particularly for patients who are taking other medications fi:

treatment of LTBI.

Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver function tests are abn:

during the course of treatment (e.g., liver function studies for patients with symptoms compatible with hepatotoxicity or a uri:

three times the upper limit of normal if associated with symptoms and five times the upper limit of normal if the patient is as:

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 d:

countries with a low incidence of TB, most new, active cases have occurred among persons who were once infected, contain:

benefit both infected persons and susceptible persons in their communities. Until recently, isoniazid was the only drug prove:

Shortly after isoniazid was found to be effective for the treatment of TB, clinical trials were begun to assess the ability of t:

the evaluation of the drug for treatment of infected contacts of TB patients and of other persons at high risk (e.g., those with radiog:

Society (ATS) (7). This initial statement recommended isoniazid for persons with evidence of previously untreated TB and f:

and PHS broadened the recommendations to include all persons who had had a purified protein derivative (PPD) tuberculin s:

not previously treated and their contacts, b) persons with tuberculin skin test conversions, c) persons with specified medical c:

drug that had "virtually no side effects," it was believed that "chemoprophylaxis [could] reduce future morbidity from TB in:

However, despite this belief, the goal of reducing TB morbidity by such a substantial percentage through the administration:

Hill in the District of Columbia, 19 persons developed clinical signs of liver disease and two persons died of hepatic failure f:

regarding pretreatment screening and monitoring to minimize the risk for severe complications (10). In 1974, following a stu:

persons aged older than 35 yr of age as candidates for treatment (12). Subsequent controversy over the appropriate age cut-off for th:

a decrease in the use of isoniazid for treating persons with LTBI---even persons at high risk for whom treatment was indicated:

and other persons at risk for hepatotoxicity (15). Recent studies have suggested that since the advent of routine monitoring, t:

Because widespread use and the potential impact of isoniazid treatment of LTBI became limited by actual and perceived tox:

introduction of rifampin, which appeared to be a better sterilizing agent than isoniazid, suggested the possibility that rifampi:

evaluate the efficacy of treatment for LTBI in persons coinfected with HIV and M. tuberculosis led to a series of studies of s:

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 Elimination of Tuberculosis (19). Because testing persons for infection and provision of treatment are interrelated, these 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 tested. To focus on groups at the highest risk for TB, the term "targeted tuberculin testing" is used in these guidelines to encce Although the terms "preventive therapy" and "chemoprophylaxis" have been used for decades, they have also been confusing known or likely to be infected with *M. tuberculosis*, but it rarely results in true primary prevention (i.e., prevention of infecti- "treatment of LTBI" rather than "preventive therapy" or "chemoprophylaxis." This change in nomenclature will hopefully pr 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 detect tuberculosis or have clinical conditions that are associated with an increased risk of progression of LTBI to active TB (Table targeted testing.

Persons or groups with presumed recent *M. tuberculosis infection*. Persons infected with *M. tuberculosis* are at greatest risk contacts of persons with active TB and among patients in mental hospitals, the tuberculin skin tests of 1472 participants in th 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, these, 121 (4.7%) developed clinical TB within 15 yr of entry into the study: 54% developed disease during the first year aht In designing and planning targeted testing programs, several groups of persons can be identified as being at increased risk fo with infectious pulmonary TB (21); both of these characteristics are likely attributable to recent contact with infectious perso recently.

Persons who have immigrated from areas of the world with high rates of TB have incidence rates that approach those of thei in the native country before immigration and progression to disease soon after arrival in the United States. This hypothesis is transmission of TB among foreign-born case patients in the United States (23) and b) other data indicating that with time, the Children, especially those younger than 5 yr of age, who have a positive tuberculin skin test are likely to be in the early stage also increased in adolescents and young adults (25).

Recent U.S. studies (including RFLP studies) have helped characterize certain epidemiologically defined groups of persons v drug users) (23,26). In addition, persons who reside or work in institutional settings (e.g., hospitals, homeless shelters, correc acquiring TB infection. However, the risk for transmission varies greatly, and the likelihood that a specific institution is a site.

Clinical conditions associated with progression to active tuberculosis. HIV infection contributes most to an increased risk fo observation (Table 2) (28). In a prospective cohort study of persons with HIV infection in the United States, the annual risk of for progressing to active TB (10 cases per 1000 person-years) (30), and this risk is even greater for injection drug users coin 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 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 a risk of progression to disease that was twofold that of persons who were within 5% of the standard weight for their height an Studies indicate that several other clinical conditions increase the risk for active TB, although participants in these studies w Tuberculin-positive persons with silicosis have an approximately 30-fold greater risk for developing TB (36--38). Persons w with diabetes mellitus have a risk for developing active TB that is twofold to fourfold greater than persons without diabetes t been associated with active TB include gastrectomy with attendant weight loss and malabsorption (45--47), jejunoileal bypass and leukemia [54]).

Persons receiving prolonged therapy with corticosteroids and other immunosuppressive agents may be at risk for reactivati (55,56), and because lower doses or those given intermittently are not associated with TB, this dose is likely the lower limit prolonged periods of time, especially in populations at high risk for TB, but specific thresholds of dose and duration that cou other potential risk factors that commonly occur among such persons, alcohol use has been difficult to identify as a separate:

Operational Considerations

In A Strategic Plan for the Elimination of Tuberculosis in The United States, published by CDC in 1989 (61), the responsib tests, interpretation of test results, and intensive follow-up required to ensure adherence with and to prevent side effects of is However, in 1995, CDC published recommendations on targeted testing and treatment of LTBI that emphasized the importai their communities (2). This recommendation was based on the recognition that changes in the organization, delivery, and fin example, populations that previously received clinical services, including diagnosis of LTBI, at public health clinics are now
Because health departments might lack access to high-risk populations and the resources necessary to undertake targeted test TB in high-risk groups. Community sites where persons at high risk may be accessed and where targeted testing programs have 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 better diagnostic methods have yet been devised. Proper use of the tuberculin skin test requires knowledge of the antigen use epidemiologic and clinical experience with the test. Detailed information on these topics is provided in the ATS/CDC Statement Immunologic basis for the tuberculin reaction. Infection with *M. tuberculosis* produces a delayed-type hypersensitivity react 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 infectio to PPD tuberculosis may also indicate infection with various nontuberculous mycobacteria or vaccination with Bacille Calmette begin 56 h after injection, reach a maximum at 48–72 h, and subside over a period of a few days, although positive reactions Sensitivity and specificity of skin-test reactions. Knowledge of tuberculin-test sensitivity and specificity, as well as positive *p* approaches 100% (73). However, false-positive tuberculin tests occur in persons who have been infected with nontuberculous predictable value in persons who have a low probability of LTBI. The general U.S. population currently has an estimated *M. t* test has a specificity approaching 99%, testing of persons in such low-prevalence groups would result in most positive tests t can be improved by progressively increasing the reaction size that separates positive from negative reactors (at the expense of Previous BCG vaccination. Intracutaneous inoculation with BCG is currently used in many parts of the world as a vaccine aq skin test. Periodic skin testing may prolong reactivity to tuberculin in vaccinated persons (74). No reliable method has been *c* 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 bec 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. Pr with or without visible calcification, may be seen in the hilar area or upper lobes. Smaller nodules, with or without fibrotic *s* TB have well-demarcated, sharp margins and are often described as "hard." Bronchiectasis of the upper lobes is a nonspecifi or other infections. Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with substantial potential for f 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 sputu persons with normal chest radiographs, AFB are rarely seen on sputum smear examination, and tubercle bacilli are not found 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 efficac tuberculosis bacilli (78). Those animals receiving a daily dosage of at least 5 mg/kg were protected (i.e., survival was comparabl humans.

**Clinical trials in HIV-negative persons.** Many randomized, controlled clinical trials of isoniazid for the treatment of LTBI w than 100,000 participants at risk for TB, including children with primary TB, contacts of active case patients, persons who h isoniazid with placebo. The outcomes measured in these studies included progression of primary TB, tuberculin conversion i in TB among all persons participating in these trials, varied from 25 to 92%. However, when analysis was restricted to perso 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 du pulmonary lesions consistent with inactive TB. The 5-yr incidence rates of tuberculosis were 1.43% for placebo compared w regimen and 75% effectiveness for the 12- mo regimen; persons who received 6 mo of isoniazid had a 40% higher risk for TB The difference in the two regimens is magnified when study subjects who received "almost all" of the monthly drug allotment subgroup, which constituted 78% of the entire study population, the resulting 5-yr incidence rates were 1.5% for persons reco 69% efficacious and for 12 mo was 93% efficacious; participants on the 6-mo regimen had a fourfold higher risk for TB than regimens, such persons were less adherent to treatment. The 12-mo regimen provided a substantial reduction in risk compare Additional information on the efficacy and effectiveness of different lengths of therapy with isoniazid for the treatment of L1 assigned medication during the months they took isoniazid, those who took medication for at least 10 mo experienced a 68% The same data can be further examined to determine whether reduction in the rate of TB was affected more by duration of th medication during the 10-mo period (52–57% reduction compared to 68% reduction), suggesting that even an intermittent tr In a community-based study conducted in Bethel, Alaska (79), persons who took <25% of the prescribed annual dose had a t
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 the 6-mo regimen was determined to be half of the cost as either the 3-mo or 12-mo regimens. This cost-effectiveness with normal chest radiographs (82). However, the protection conferred by taking at least 9 mo of isoniazid is greater than that of rifampin regimens. This cost-effectiveness is demonstrated by the lower colony count in spleens of animals given more drugs, and lower colony counts in the lungs of mice given rifampin regimens. A comprehensive analysis of deaths from isoniazid-associated hepatitis in the United States found that women may be at increased risk of death (89). The occurrence of hepatitis was rare and was not assumed to be caused by isoniazid. However, studies conducted in the late 1960s suggested that isoniazid did cause an asymptomatic increase in hepatic transaminases among persons receiving the drug (89).

The largest and most comprehensive study of isoniazid hepatitis was conducted by PHS during 1971--1972 (11). In this survey 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%) higher among persons consuming alcohol daily than among those who did not drink alcohol. Rates among males and females: lower among participants in the IUAT trial, although the same positive association with age was observed (32). In the PHS's years after completion of the study, a review of death certificates showed a marked increase in deaths from cirrhosis during 1 study (90).

A comprehensive analysis of deaths from isoniazid-associated hepatitis in the United States found that women may be at increased risk for developing active TB versus risk for developing isoniazid hepatitis. The occurrence of hepatitis was rare and was not assumed to be caused by isoniazid. However, studies conducted in the late 1960s suggested that isoniazid did cause an asymptomatic increase in hepatic transaminases among persons receiving the drug (89). The occurrence of hepatitis was rare and was not assumed to be caused by isoniazid. However, studies conducted in the late 1960s suggested that isoniazid did cause an asymptomatic increase in hepatic transaminases among persons receiving the drug (89).

The Uganda study also evaluated the 6-mo regimen of daily isoniazid in anergic persons, as did the fifth study conducted in 1 Additional evaluations of isoniazid were conducted in tuberculin-negative persons who were not assessed for anergy (83,85,87), treatment should be targeted at tuberculin-positive persons. A recently published metaanalysis of these trials supports this conclusion (87).

Safety and tolerability. In 1965, when isoniazid was first recommended in the United States for treatment of LTBI, it was not suspected drug reactions was low and approximately equivalent for the placebo and isoniazid groups (21). The occurrence of hepatitis indicated that asymptomatic increase in hepatic transaminases among persons receiving the drug (89).

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the 6-mo isoniazid regimen, and 41% for the 3-mo isoniazid–rifampin regimen. All of these differences were significantly different from 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 childhood infection was reduced by 9 to 3 mo, and the proportion of pediatric TB case patients as a percentage of all reported cases decreased from 30 to 7% between childhood and adulthood. Thus, this regimen is currently recommended for the treatment of both adults and children with LTBI. Clinical trials in HIV-positive persons. Most clinical trials of rifampin-based treatment of LTBI have been conducted among HIV-seronegative persons (84). The isoniazid–rifampin regimen provided 59% protection for 6 mo on regimens containing rifampin and pyrazinamide, with half of the doses directly observed (110). Protection at 12 mo was similar in the two groups, and, compared to placebo, rifampin and pyrazinamide regimens were associated with a higher number of AST elevations of >100 IU (17 compared with only one in the rifampin group and five in the placebo group). The Zambian study also evaluated a self-administered regimen of rifampin and pyrazinamide taken twice weekly for 3 mo, the level of protection conferred by rifampin and pyrazinamide was 70%, comparable with that conferred by 6 mo of isoniazid-isoniazid group and more frequent adverse reactions occurring in drug discontinuation (15 compared with none in the rifampin group). The rifampin–pyrazinamide regimen isoniazid group and more frequent adverse reactions occurring in drug discontinuation (15 compared with none in the rifampin group).

In conclusion, as evidenced by the large multinational study, a 2-mo regimen of rifampin and pyrazinamide taken daily provided protection against TB equivalent to the 12-mo regimen of isoniazid taken daily with a 2-mo regimen of rifampin and 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 placebo group). The Zambian study also evaluated a self-administered regimen of rifampin and pyrazinamide taken twice weekly for 3 mo, the level of protection conferred by rifampin and pyrazinamide was 70%, comparable with that conferred by 6 mo of isoniazid-isoniazid group and more frequent adverse reactions occurring in drug discontinuation (15 compared with none in the rifampin group). The rifampin–pyrazinamide regimen isoniazid group and more frequent adverse reactions occurring in drug discontinuation (15 compared with none in the rifampin group).

In the Haiti study conducted during 1990–1994 and the Zambia study, regimens of twice-weekly rifampin and pyrazinamide differed by regimen (110). In the Zambia study, 3% of persons given isoniazid stopped treatment because of an adverse reaction was more common in persons receiving rifampin and pyrazinamide. Adherence to rifampin and pyrazinamide regimen. The results of the study in Poland were similar to those in the study in North America; the 6-mo regimen provided 59% protection, and the three-drug regimen provided protection equivalent to that conferred by 6 mo of isoniazid.

Sensitivity and tolerability. Before the conduct of the studies in HIV-infected persons, a pilot study to assess the safety and tolerability of rifampin and pyrazinamide was conducted among HIV-infected persons (83). Protection at 12 mo was similar in the two groups, and, compared to placebo, rifampin and pyrazinamide regimens were associated with a higher number of AST elevations of >100 IU (17 compared with only one in the rifampin group and five in the placebo group). The Zambian study also evaluated a self-administered regimen of rifampin and pyrazinamide taken twice weekly for 3 mo, the level of protection conferred by rifampin and pyrazinamide was 70%, comparable with that conferred by 6 mo of isoniazid-isoniazid group and more frequent adverse reactions occurring in drug discontinuation (15 compared with none in the rifampin group). The rifampin–pyrazinamide regimen isoniazid group and more frequent adverse reactions occurring in drug discontinuation (15 compared with none in the rifampin group).

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Targeted tuberculin testing programs should be designed for one purpose: to identify persons at high risk for TB who would infection with *M. tuberculosis* and those who, regardless of duration of infection, are at increased risk for progression to acti employment in a setting where TB transmission may occur), screening of low-risk persons is discouraged because it diverts 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 LT 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 encourag epidemiology of TB. Thus designing and conducting skin-test-screening surveys to determine whether population groups are community health centers and schools serving foreign-born persons, and selected community-based organizations. Mandate 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 in assessing the community's TB problem, identifying high-risk groups based on the local epidemiology of TB, and ascertaining; based approach, recruiting health professionals, educating such professionals about TB, and motivating them to institute targ institutions that conduct testing and treatment programs. The health department should assist in identifying potential funding treatment, written protocols for activities including patient tracking and skin testing, and patient and provider educational ma antituberculosis drugs. Finally, the health department should be responsible for providing or facilitating the ongoing evaluati tests administered that are read, proportion of tests read that are positive, and initiation and completion rates of treatment). TI 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 suc is unfamiliar to most persons, and education of the patient is essential (120). Other known barriers include culturally derived afford the costs of medical evaluation and treatment, and lack of access to medical care (118). Patients should not be expecte treatment, the more likely patients will adhere to therapy especially as targeted testing and treatment of LTBI are extended be

**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 * intradermal, or Mantoux, method. It is administered by injecting 0.1 ml of 5 tuberculin units (TU) PPD intradermally into th recorded in millimeters. Multiple puncture tests (i.e., Tine and Heaf) and PPD strengths of 1 TU and 250 TU are not suffici

Interpreting skin-test reactions. Based on the sensitivity and specificity of the tuberculin skin test and the prevalence of TB i induration (Table 7). For persons who are at highest risk for developing TB disease if they become infected with *M. tubercul systemic corticosteroids* have a high likelihood of developing TB disease if they are infected with *M. tuberculosis*. Likewise are at high risk for TB. Thus, to ensure that persons at highest risk are evaluated and appropriately treated, the sensitivity pro A reaction of ≥10 mm of induration should be considered positive for those persons with an increased probability of recent i users) (Table 7). In addition to those groups listed, high-prevalence populations identified by analysis of local epidemiologic Routine tuberculin testing is not recommended for populations at low risk for LTBI. However, if these persons are tested (e.g. ≥15 mm is recommended.

Skin-test conversion. For persons with negative tuberculin skin-test reactions who undergo repeat skin testing (e.g., health ca with *M. tuberculosis*.

Previous vaccination with BCG. Tuberculin skin testing is not contraindicated for persons who have been vaccinated with Bt method can reliably distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobac 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

**Chest Radiographs**

A chest radiograph is indicated for all persons being considered for treatment of LTBI to exclude active pulmonary TB. Chi radiographs; additional radiographs should be performed at the physician's discretion. Because of the risk for progressive an persons with infectious TB disease should have chest radiographs (with appropriate shielding) as soon as feasible, even dur If chest radiographs are normal and no symptoms consistent with active TB are present, tuberculin-positive persons may be c medical evaluation, bacteriologic examinations, and a comparison of the current and old chest radiographs) should be done t

**Sputum Examinations**

Sputum examination is not indicated for most persons being considered for treatment of LTBI. However, persons with chest submitted for AFB smear and culture. Most persons with radiographs that show only calcified pulmonary nodules do not req sputum specimens submitted for mycobacterial examination, even if the chest radiograph is normal. If the results of sputum: bacteriologic results are negative but the activity or etiology of a radiographic abnormality is questionable, further evaluation excluded. In such situations, multidrug therapy can be started and continued pending results of sputum cultures. A repeat che
Treatment of Latent Tuberculosis Infection

Individual Drugs

Isoniazid. Isoniazid is the most widely used of the antituberculosis agents---it is bactericidal, relatively nontoxic, easily admi
µg/ml). Absorption from the gastrointestinal tract is nearly complete, with peak serum concentrations of 2–5 µg/ml occurring
those found in serum. Hepatitis is the most severe toxic effect of isoniazid, and alcohol consumption may increase toxicity (1
at a dose of 5 mg/kg. In persons with conditions in which neuropathy is common (e.g., diabetes, uremia, alcoholism, malnutr
pyridoxine and isoniazid. Mild central nervous system effects are common with isoniazid and may necessitate adjustments if
both drugs. When these drugs are given concomitantly, the serum level of phenytoin should be monitored. No known interac
Rifampin. Rifampin is a rifamycin derivative that is bactericidal for M. tuberculosis. Most strains of M. tuberculosis are inh
occurring 1.5–3.0 h after ingestion. Although approximately 75% of the drug is protein bound, it penetrates well into tissues
are inflamed. The most common adverse reaction to rifampin is gastrointestinal upset. Other reactions include skin eruptions
enzymes, it may accelerate clearance of drugs metabolized by the liver (e.g., methadone, coumadin derivatives, glucocorticoi
metabolism of estrogen, rifampin may interfere with the effectiveness of oral contraceptives. In persons with HIV infection \( \uparrow \)
increased rifampin levels and decreased protease-inhibitor levels, resulting in increased risk for rifampin toxicity and decreas
nucleoside reverse transcriptase inhibitors (NRTIs). Intermittent administration of doses of rifampin \( >10 \) mg/kg may be as
the recommended dose of 10 mg/kg/d. Rifampin is excreted in urine, tears, sweat, and other body fluids and colors them orar
Pyrazinamide. Pyrazinamide is bactericidal for M. tuberculosis in an acid environment. The drug is active against organisms
for M. tuberculosis is 20 µg/ml. Absorption from the gastrointestinal tract is nearly complete, with peak serum concentration
gastrointestinal upset (Table 8). The most severe adverse reaction is liver injury. No substantial increase in hepatotoxicity re:
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
of 0.1 µg/ml. A dose of 300 mg results in peak serum concentrations of 5 µg/ml after 2 h. The major advantage of rifabutin
metabolized in the liver (and to a lesser extent in the intestinal wall); only 8% of a dose is excreted unchanged in the urine. E
myalgia, and dysguesia. Hepatotoxicity is rare, but rifabutin can cause drug-induced hepatitis. Rates of side effects increase
uveitis (128) and abnormal skin pigmentation (129). Similar to rifampin, rifabutin can also decrease concentrations and clini
dapsone, ketoconazole, and cyclosporin, as well as itraconazole, β-blockers, and theophylline. Doses of these medications m:
infection, may lead to increased levels of rifabutin and decreased levels of the protease inhibitor; however, these effects are \( \uparrow \) 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 inclu
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 n
The ratings system is similar to that used in previous PHS documents (3) and includes a letter and a Roman numeral: the letti
clinicians can use the ratings to differentiate between recommendations based on data from clinical trials and those based on
available).

Recommended regimens. Four regimens are recommended for the treatment of adults with LTBI (Table 10). The antitubercu
weekly treatment should receive DOT, because nonadherence to intermittent dosing results in a larger proportion of the total
institutional settings, community outreach programs, and for some persons living in households with patients who are receiv
Isoniazid for 9 mo. The isoniazid daily regimen for 9 mo receives an A recommendation. Prospective, randomized trials of
benefit is gained by extending treatment to 12 mo. Thus, this updated recommendation represents a shortening of the previo
infected persons (1). Both 12-mo and 6-mo regimens of isoniazid have substantially reduced rates of TB in HIV-infected p:
the recommendation for 9 mo of isoniazid in HIV-infected persons is based on extrapolation of available data. Intermittent d:
active TB (where twice-weekly dosing is equivalent to daily dosing), twice-weekly dosing of isoniazid is also acceptable
Isoniazid for 6 mo. Although a 9-mo regimen of isoniazid is the preferred treatment of LTBI for an individual patient, a 6-n
persons (32,84). From a societal perspective, treatment for 6 mo rather than 9 mo may provide a more cost-effective outcome
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 t
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
efficacy to a 12-mo regimen of isoniazid (111). Although this regimen has not been evaluated in HIV-uninfected persons wit
at the A level for HIV-infected persons and at the B level for HIV-uninfected persons until further data are available. Two ra
persons (86, 110); in neither case was the sample size adequate to conclude with certainty that efficacy was equivalent to dai
rifampin and pyrazinamide given twice weekly for 2–3 mo may be considered when alternative regimens cannot be given. T
Rifampin for 4 mo. Rifampin given daily for 3 mo has resulted in better protection than placebo in treatment of LTBI in HI
active TB (4%), experts have concluded that a 4-mo regimen would be more prudent when using rifampin alone. This 4-mo
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 that 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 in the regimen. The 6-mo regimen of  isoniazid should consist of at least 180 doses administered within 6 mo. Twice-weekly isoniazid regimens should consist of at least 60 doses to be administered within 3 mo. Ideally, patients should receive medication on a regular dosing schedule until completion of the regimen. However, clinicians might need to continue the regimen originally prescribed (as long as needed to complete the recommended duration) recommended. In either situation, when therapy is restored after an interruption of more than 2 mo, a medical examination to determine whether the regimen is complete is indicated.

Special considerations.

Treatment of HIV-infected persons. Recommendations for HIV-infected adults largely parallel those for HIV-uninfected a LTBI in persons with HIV infection, 9 mo is recommended rather than 6 mo. In addition, rifampin is generally contraindicated in persons who are candidates for treatment of LTBI and need PI or NNRTI therapy, rifabutin can be substituted for rifampin in pregnant women with these conditions and LTBI should be treated during pregnancy and have careful clinical and laboratory monitoring for 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 (142). Furthermore, the drug interactions between rifapentine and HIV protease inhibitors have not been studied in HIV-infected persons (131).

In tuberculin-negative, HIV-infected persons, treatment of LTBI has not been effective (3). However, most tuberculin-negativ ended is not indicative of LTBI. Furthermore, some experts recommend treatment of possible LTBI for HIV-infected persons with HIV fibrotic lesions/suspected disease. For women who have a chest radiograph demonstrating old fibrotic lesion treatment for TB, three acceptable regimens can be used for treatment. These regimens include 9 mo of isoniazid, 2 mo of rifampin unlikely. Patients who begin multidrug therapy for suspected pulmonary TB but are subsequently determined not to have act rifampin and pyrazinamide if the tuberculin skin test is positive and other causes of the radiographic abnormalities have been considered.

Pregnant women with evidence suggestive of healed, primary TB (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes not on duration of therapy alone. The 9 mo regimen of daily isoniazid 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 and 27 doses within 6 mo for the 3 mo regimen. When reinstituting therapy for patients who have interrupted treatment, the daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses administered within 3 mo. The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses administered within 3 mo. The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses administered within 3 mo. The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses administered within 3 mo.
definitely. 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 (INH) resistant. However, no controlled clinical trials have been conducted. A 3-mo regimen of rifampin and isoniazid has been used to treat drug-susceptible tuberculosis. No studies have been published regarding the efficacy of any form of treatment for LTBI in HIV-infected children. The Ame liver enzyme concentrations be performed and pyridoxine given when HIV-infected children are treated with isoniazid. The treatment (150).

**Contacts of patients with tuberculosis.**

- Contacts of patients with drug-susceptible tuberculosis. Persons who are contacts of patients with drug-susceptible TB (Table 10). In addition, some tuberculin-negative contacts should be considered for treatment. Because of susceptibility to rifampin prophylaxis, many experts recommend using a combination of two other drugs to which the infecting organism is resistant. The regimen is rifampin and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or ofloxacin) for 6 mo. Fort contacts of patients with isoniazid-resistant TB, rifampin-resistant TB, rifampin-susceptible TB, a 2-mo regimen of rifampin and pyrazinamide is recommended. Rifabutin can be substituted.

- Contacts of patients with multidrug-resistant tuberculosis. The occurrence of outbreaks of multidrug-resistant TB is relatively rare, but the treatment options are limited. 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 isoniazid and rifampin is recommended.

- Contacts of patients with drug-susceptible tuberculosis. Persons who are contacts of patients with drug-susceptible TB (Table 10). In addition, some tuberculin-negative contacts should be considered for treatment. Because of susceptibility to rifampin prophylaxis failure was reported among contacts of a case patient with isoniazid-resistant TB in a community outbreak. For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, a 2-mo regimen of rifampin and pyrazinamide is recommended. Rifabutin can be substituted.

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 isoniazid and rifampin is recommended. Rifabutin can be substituted.

**BCG-vaccinated persons.** A history of BCG vaccination, with or without a BCG scar, should not influence the decision reg.

**Directly observed therapy and measures to increase adherence.** Any regimen that is given intermittently (i.e., twice weekly or daily) 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 who received rifampin or isoniazid and rifampin (153). Similarly, of 157 high school students who took rifampin after being exposed to an outbreak of isoniazid-resistant tuberculosis. No definitive data exist concerning treatment of contacts to recommend either rifampin alone or in combination with isoniazid or ethambutol when the risk of isoniazid-resistance is low. DOT should be considered when it is unlikely that the child and family will be adherent to daily self-administration.

In an outbreak of isoniazid- and streptomycin-resistant TB among homeless persons, six (9%) of 71 persons with skin tests received rifampin or isoniazid and rifampin (153). Similarly, of 157 high school students who took rifampin after being exposed to an outbreak of isoniazid-resistant tuberculosis. No definitive data exist concerning treatment of contacts to recommend either rifampin alone or in combination with isoniazid or ethambutol when the risk of isoniazid-resistance is low. DOT should be considered when it is unlikely that the child and family will be adherent to daily self-administration.

**Pretreatment Evaluation and Monitoring of Treatment**

**Pretreatment evaluation.** The pretreatment evaluation of persons who are targeted for treatment of LTBI provides an opportunity to treat the importance of adherence to the drug regimen, d) review possible adverse effects of the regimen, including 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 and previous drug therapy should be obtained, with particular attention to previous adverse reactions to drugs contemplated for treatment.
contraceptives are at increased risk for becoming pregnant and should be advised to consider an additional form of contraception each patient.

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (Table 8). Patients who are at risk for chronic liver disease. Baseline testing is no longer routinely indicated in persons infected with HIV, pregnant women and those in the immediate postpartum period. Active hepatitis and end-stage liver disease are relative contraindications to the use of rifampin and pyrazinamide for the treatment of LTBI. Clinical monitoring begins with immediate 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 and symptoms 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. Data from these programs should be examined, especially as they relate to acceptability and completion of treatment for LTBI in children and pregnant women. The safety of pyrazinamide for pregnant women and their fetuses should be determined. More information is needed regarding the use of rifampin and pyrazinamide given daily for 2 mo on or infection with nontuberculous mycobacteria, tests that correlate with the presence of dormant tubercle bacilli.

**Efficacy Studies of New Drugs**

No novel compounds currently can be considered candidates for the treatment of LTBI. However, several rifamycin derivatives—such as rifampicin and isoniazid—given once weekly for 3 mo were as active 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.

**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 a specific cytokine correlate with a better outcome in TB patients.

**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 as the test's positive predictive value is poor. In addition, the requirement that the person tested return for the test to be read persons at greatest risk for progressing to active disease. Especially useful would be tests that distinguish skin-test reactions 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. Before additional trials of intermittent rifampin regimens are undertaken, animal model data are needed to establish the effectiveness of alternative therapies for MDR LTBI in children are needed. Finally, epidemiologic research to determine the effectiveness of the rifamycin derivatives is also needed.

**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 prehepatoxicity of isoniazid in pregnant and postpartum women. Studies are needed to establish the safety and effectiveness of the 2-mo regimen of daily rifampin and pyrazinamide. Studies should assess the knowledge base of treating clinicians and identify the need for new clinical research.

**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 in children, the combination products in preventing the emergence of drug resistance in patients with active TB is not as compelling for preclinical evaluation of new drugs.

**Efficacy Studies of New Drugs**

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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 "t high risk and specific subgroups characterized by varied risks and benefits of treatment. Using this conceptual framework w

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 c presumably will be better with shorter treatment regimens, the rifampin and pyrazinamide regimen may be less well-tolerates models until investigations better establish these risks. By investigating the effect of a range of toxicities and adherence on t l 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 decision models. When decision analysis is inadequate to deal with public health issues (e.g., reduction in contagion), addit Policies designed to target and treat populations at high risk for TB are motivated by the need to benefit the individual pati groups for testing and treatment, the social and ethical ramifications of these policies must be considered. The individual per (e.g., persons who are homeless, incarcerated, and medically underserved, and residents in long-term care facilities). Ideally, important to the general public.

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Table 1