Targeted Tuberculin Testing and Treatment of La

ATS/CDC Statement Committee on Latent Tuberculosis Infection Membership List, Ju

Co-Chairs

David L. Cohn, M.D.
Denver Public Health
Denver, CO
Richard J. O'Brien, M.D.
Centers for Disease Control and Prevention
Atlanta, GA

Writing Group

Lawrence J. Geiter, Ph.D.
Sequella Global Tuberculosis Foundation
Rockville, MD
Fred M. Gordin, M.D.
VA Medical Center
Washington, DC
Earl Hershfield, M.D.
University of Manitoba
Winnipeg, MB, Canada
C. Robert Horsburgh, Jr., M.D.
Emory University School of Medicine
Atlanta, GA
John A. Jereb, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Theresa J. Jordan, Ph.D.
New York University, New York, NY
New Jersey Medical School National Tuberculosis Center
Newark, NJ
Jonathan E. Kaplan, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Charles M. Nolan, M.D.
Seattle-King County Department of Health
Seattle, WA
Jeffrey R. Starke, M.D., Ph.D.
Texas Children's Hospital
Houston, TX

Zachary Taylor, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
M. Elsa Villarino, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA

Members

Nancy J. Binkin, M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA
Naomi N. Bock, M.D.
Emory University School of Medicine
Atlanta, GA
Kenneth G. Castro, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Richard E. Chaisson, M.D.
Johns Hopkins University
Baltimore, MD
George W. Comstock, M.D.
Johns Hopkins University
Hagerstown, MD
Mark S. Dworkin, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Wafaa El-Sadr, M.D., M.P.H.
Harlem Hospital Center
New York, NY
Paula I. Fujiwara, M.D., M.P.H.
Bureau of Tuberculosis Control
New York, NY
Jeffrey C. Glassroth, M.D.
University of Wisconsin Medical School
Madison, WI
Peter Godfrey-Faussett, M.D.
London School of Hygiene and Tropical Medicine
London, United Kingdom
Mark J. Goldberger, M.D., M.P.H.
Food and Drug Administration
Rockville, MD
James L. Hadler, M.D., M.P.H.
Department of Public Health
Hartford, CT
Philip C. Hopewell, M.D.
San Francisco General Hospital
San Francisco, CA
Michael D. Iseman, M.D.
National Jewish Medical and Research Center
Denver, CO
Richard F. Jacobs, M.D.
University of Arkansas
Little Rock, AR
Mack A. Land, M.D.
University of Tennessee
College of Medicine Memphis

Memphis, TN
Mark N. Lobato, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Richard I. Menzies, M.D.
Montreal Chest Hospital
Montreal, PQ, Canada
Giovanni B. Migliori, M.D.
Fondazione Salvadore Maugeri
Tradate, Italy
Bess I. Miller, M.D., M.Sc.
Centers for Disease Control and Prevention
Atlanta, GA
Alwyn Mwinga, M.D.
University Teaching Hospital
Lukasa, Zambia
Edward A. Nardell, M.D.
Cambridge Hospital
Cambridge, MA
James Neaton, Ph.D.
University of Minnesota
School of Public Health
Minneapolis, MN
Noreen L. Qualls, Dr.P.H.
Centers for Disease Control and Prevention
Atlanta, GA
Lee B. Reichman, M.D., M.P.H.
New Jersey Medical School
Newark, NJ
David N. Rose, M.D.
Long Island Jewish Hospital
New Hyde Park, NY
Shelley R. Salpeter, M.D.
Santa Clara Valley Medical Center
San Jose, CA
Holger Sawert, M.D., M.P.H.
Ministry of Public Health
Nonthaburi, Thailand
Patricia M. Simone, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Dixie E. Snider, Jr., M.D., M.P.H.
Centers for Disease Control and Prevention
Atlanta, GA
Joel Tsevat, M.D., M.P.H.
University of Cincinnati Medical Center
Cincinnati, OH
Andrew A. Vernon, M.D.
Centers for Disease Control and Prevention
Atlanta, GA
Christopher C. Whalen, M.D.
Case Western Reserve University
Cleveland, OH
Timothy C. Wilcosky, Ph.D.
Research Triangle Institute

Research Triangle Park, NC

NOTICE

This report is being published with the permission of the American Thoracic Society and as a courtesy to the *MMWR* readers

Targeted Tuberculin Testing and Treatment of Latent Tuberculo

This Official Statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Jo the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this Statement as it re

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 Co 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 a of concerns about toxicity. Therefore, there has been interest in the development of shorter, rifampin-based regimens as alter human immunodeficiency virus (HIV) infection has been undertaken. The results of these trials have recently become availal 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 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 f Based on the sensitivity and specificity of the purified protein derivative (PPD) tuberculin skin test and the prevalence of TB induration (*see* Table 7). For persons who are at highest risk for developing active TB if they are infected with *M. tuberculos* TB, or who have abnormal chest radiographs consistent with prior TB), ≥5 mm of induration is considered positive. For othe mm of induration is considered positive. These include recent immigrants (i.e., within the last 5 yr) from high prevalence cou mycobacteriology laboratory personnel; persons with clinical conditions such as silicosis, diabetes mellitus, chronic renal fai bypass; and children younger than 4 yr of age or infants, children, and adolescents exposed to adults in high-risk categories.

Treatment of Latent Tuberculosis Infection

In this report, treatment recommendations use an adaptation of the rating system from recent U.S. Public Health Service doc 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 subs
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 situa
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
  therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose ris
- 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
  recommended. Immunocompetent contacts may be observed or treated for at least 6 mo, and immunocompromised

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 sig
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.e., 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 fo
treatment of LTBI.
Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver function tests are abno
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 de
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 the
to evaluate 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 p
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
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 a
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 these low-risk, tuberculin-positive persons ensued, with one grou
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 toxi
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 reco 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 o tested. To focus on groups at the highest risk for TB, the term "targeted tuberculin testing" is used in these guidelines to enco 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 aft 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 sit

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 o for progressing to active TB (10 cases per 1000 person-years) (*30*), and this risk is even greater for injection drug users coinf 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 r 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 we 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 r been associated with active TB include gastrectomy with attendant weight loss and malabsorption (*45--47*), jejunoileal bypas and leukemia [*54*]).

Persons receiving prolonged therapy with corticosteroids and other immunosuppressive agents may be at risk for reactivation (*55,56*), and because lower doses or those given intermittently are not associated with TB, this dose is likely the lower limit t 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 responsibil 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 importa 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 ha
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 Statem
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 tuberculin may also indicate infection with various nontuberculous mycobacteria or vaccination with Bacille Calmett
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 nontuberculou
predictive 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 b
can be improved by progressively increasing the reaction size that separates positive from negative reactors (at the expense o
Previous BCG vaccination. Intracutaneous inoculation with BCG is currently used in many parts of the world as a vaccine ag
skin test. Periodic skin testing may prolong reactivity to tuberculin in vaccinated persons (*74*). No reliable method has been d
reactions of $\geq$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 beca
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 sc
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
tubercle 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 ha
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 allotmen
subgroup, which constituted 78% of the entire study population, the resulting 5-yr incidence rates were 1.5% for persons rec
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 LT
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 fron 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 a with normal chest radiographs (*82*). However, the protection conferred by taking at least 9 mo of isoniazid is greater than tha

Clinical trials in HIV-positive persons. Seven randomized, controlled trials have evaluated different regimens for the treatme 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 (8 6 mo of isoniazid taken daily by tuberculin-positive persons, had differing results: the drug provided a significant level of pr weekly regimen of isoniazid in both tuberculin-positive and - negative persons in Zambia (*86*). The overall level of protectio 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 t Additional evaluations of isoniazid were conducted in tuberculin-negative persons who were not assessed for anergy (*83,85,* treatment should be targeted at tuberculin-positive persons. A recently published metaanalysis of these trials supports this co

Safety and tolerability. In 1965, when isoniazid was first recommended in the United States for treatment of LTBI, it was no suspected drug reactions was low and approximately equivalent for the placebo and isoniazid groups (*21*). The occurrence of hepatitis and indicated that asymptomatic increase in hepatic transaminases occurred among persons receiving the drug (*89*). understood (*9*).

The largest and most comprehensive study of isoniazid hepatitis was conducted by PHS during 1971--1972 (*11*). In this surv 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 female 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 inc drug to pregnant women in the third trimester and the immediate postpartum period (*92*) or by the concomitant administratio 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 carefu following the development of fulminant, isoniazid-related hepatitis continued to take the drug for a least 10 d after onset of s

Following the PHS surveillance study, guidelines on the use of isoniazid for the treatment of LTBI were revised to recomme a time, and that monthly questioning and education about signs and symptoms of hepatitis should be routine (*12*). The guidel of age or older (*15*).

More recently, a survey found that many public health TB clinics now use clinical, rather than biochemical, monitoring for h instructing them to stop treatment immediately if such symptoms occur and to report to the clinician for evaluation. After usi hospitalization) and no deaths among more than 11,000 persons with LTBI during isoniazid treatment over a 7-yr period (*99* 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 toler 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 litera literature emerged more than two decades ago, in a different environmental context with different risks and contingencies, its Although the likelihood that a patient treated with isoniazid would develop hepatitis was low, it presented a valid argument a drug, which appeared from the 1970s through the early 1980s, focused on persons at low risk for reacting to tuberculin, prim Because the debate over whether to prescribe or withhold isoniazid for persons older than 35 yr of age at low risk for reactin was used by most investigators (*103*). Despite many analyses, the decision to treat persons at low risk for reacting to tubercu 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) a evaluating rifampin were based on data from several studies in mouse models of chronic TB. One study compared isoniazid lung and spleen tissues within 4 mo, and the combination of rifampin and pyrazinamide sterilized tissues within 2 mo. The is 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 isonia came from a study using a Cornell mouse model (*106*) that compared 6-wk regimens of rifampin, rifampin--isoniazid, rifamp three regimens was similar, with trend toward a lower colony count in spleens of animals given more drugs, and lower colon 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 l isoniazid, 3 mo of rifampin, or 3 mo of isoniazid and rifampin were compared with a 6-mo placebo control. Analyzing only t

the 6-mo isoniazid regimen, and 41% for the 3-mo isoniazid--rifampin regimen. All of these differences were significantly d
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 childr
shortened from 9 to 3 mo, and the proportion of pediatric TB case patients as a percentage of all reported cases decreased fro
childhood TB in this city. Thus, this regimen is currently recommended for the treatment of both adults and children with LT
Clinical trials in HIV-positive persons. Most clinical trials of rifampin-based treatment of LTBI have been conducted among
rifampin--pyrazinamide taken daily for 3 mo in tuberculin-positive persons (*84*). The isoniazid--rifampin regimen provided 5
alone. The Zambia study also evaluated a self-administered regimen of rifampin and pyrazinamide taken twice weekly for 3
persons, the level of protection conferred by rifampin and pyrazinamide was 70%, comparable with that conferred by 6 mo o
In two trials, rifampin and pyrazinamide regimens have been compared with regimens of isoniazid alone in tuberculin-positi
pyrazinamide, with half of the doses directly observed (*110*). Protection at 12 mo was similar in the two groups, and, compar
reduced the risk for TB by approximately 80%. A multinational study comparing a 12-mo regimen of isoniazid taken daily w
patients were enrolled and followed for an average of 3 yr. The annual risk of culture-confirmed TB was 0.8% for patients as
In conclusion, as evidenced by the large multinational study, a 2-mo regimen of rifampin and pyrazinamide taken daily provi
pyrazinamide treatment regimen are less conclusive. The only study that has evaluated a rifampin-alone regimen, the Hong K
In the Uganda study, 3-mo regimens of a) isoniazid and rifampin and b) isoniazid, rifampin, and pyrazinamide provided prot
All of the studies of treatment of LTBI in HIV-infected persons included death and/or progression of HIV disease as endpoir
the multinational study, persons receiving the 2-mo regimen had lower mortality rates and less progression of HIV disease, a
progression.
Safety and tolerability. Before the conduct of the studies in HIV-infected persons, a pilot study to assess the safety and tolera
receive either 2 mo of rifampin and pyrazinamide, 4 mo of rifampin only, or 6 mo of isoniazid. The rifampin--pyrazinamide
isoniazid group) and more frequent adverse reactions resulting in drug discontinuation (15 compared with none in the rifamp
involving HIV-positive populations and those described in a clinical trial of isoniazid, rifampin, and pyrazinamide for the tre
Two smaller pilot studies of rifampin and pyrazinamide treatment of LTBI using identical protocols were conducted in adult
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 r
during treatment.
In the clinical trials involving HIV-infected persons, a trend of increased adverse reactions occurred among persons taking a
higher rates of paresthesias, arthralgias, and significant increases in serum AST (*84*). The multinational study reported minin
commonly because of nausea and vomiting and narcotic withdrawal (*111*). However, abnormal liver function tests were mor
In the Haiti study conducted during 1990--1994 and the Zambia study, regimens of twice-weekly rifampin and pyrazinamide
differ by regimen (*110*). In the Zambia study, 3% of persons given isoniazid stopped treatment because of an adverse reactio
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 i
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
also discourage patients from attending follow-up visits. Other factors that may affect adherence with testing and treatment i
Since the advent of effective chemotherapy for active TB, adherence to treatment regimens has been recognized as a substan
for LTBI complete at least 6 mo of treatment (CDC, TB Program Management Reports); adherence is influenced by the leng
the regimen increases with the length of therapy (*32*). Patients may be more adherent to the 2-mo regimen of rifampin and py
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
have taken $\geq$80% of the prescribed medication compared with 55% of persons taking isoniazid for 6 mo (*110*). Nonadherenc
2-mo rifampin and pyrazinamide regimen compared with 69% for the 12-mo isoniazid regimen (*111*). In the pilot study of H
nonadherent, compared with about 20% of those assigned to the 6-mo isoniazid regimen (*113*). However, overall completion
Determinants of adherence to treatment of TB and LTBI are not well understood (*118*). For example, demographic factors ar
adversely affect adherence (*119*). The main strategies that have been employed to promote adherence with treatment of LTB
(*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 o
needs and the use of incentives and enablers (*123--125*). Although randomized trials have yet to be reported, available inform
(*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 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 r 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 LTB 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. Mandated 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). Th 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 succe 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 therapyespecially 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 v intradermal, or Mantoux, method. It is administered by injecting 0.1 ml of 5 tuberculin units (TU) PPD intradermally into the recorded in millimeters. Multiple puncture tests (i.e., Tine and Heaf) and PPD strengths of 1 TU and 250 TU are not sufficien

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 in 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 BC 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. Chil radiographs; additional radiographs should be performed at the physician's discretion. Because of the risk for progressive and persons with infectious TB disease should have chest radiographs (with appropriate shielding) as soon as feasible, even durin 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 s 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 occurrin
those found in serum. Hepatitis is the most severe toxic effect of isoniazid, and alcohol consumption may increase toxicity (7
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 ir
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 inhib
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 v
increased rifampin levels and decreased protease-inhibitor levels, resulting in increased risk for rifampin toxicity and decreas
nucleoside reverse transcriptase inhibitors (NNRTIs). Intermittent administration of doses of rifampin >10 mg/kg may be ass
the recommended dose of 10 mg/kg/d. Rifampin is excreted in urine, tears, sweat, and other body fluids and colors them oran
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 res
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 23 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. D
myalgias, 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, ß-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 g
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 r
The ratings system is similar to that used in previous PHS documents (*3*) and includes a letter and a Roman numeral: the lett
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 previou
uninfected 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
for 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-m
persons (*32,84*). From a societal perspective, treatment for 6 mo rather than 9 mo may provide a more cost-effective outcom
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 v
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 therapy. The 6-mo regimen of isoniazid should consist of at least 180 doses administered within 9 mo. Twice-weekly ison
The daily regimen of rifampin (or rifabutin) and pyrazinamide should consist of at least 60 doses to be administered within 3
Ideally, patients should receive medication on a regular dosing schedule until completion of the indicated course. However, i
clinicians might need to continue the regimen originally prescribed (as long as needed to complete the recommended duratio
recommended. In either situation, when therapy is restored after an interruption of more than 2 mo, a medical examination to
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 that 6 mo. In addition, rifampin is generally contraindicate
infected persons who are candidates for treatment of LTBI and need PI or NNRTI therapy, rifabutin can be substituted for rif
saquinavir, or delavirdine. Caution is advised if rifabutin is administered with soft-gel saquinavir, because data regarding use
No specific data have been generated for treatment of LTBI with rifabutin-containing regimens, but such a recommendation
studies in mice (*107,130*). Rifabutin can be administered at one half the usual daily dose (i.e., reduced from 300 mg to 150 m
daily rifabutin dose is 450 mg or 600 mg when used with efavirenz; pharmacokinetic studies suggest that rifabutin might be
likely more complex; in such situations, the use of rifabutin is not recommended until additional data are available. The subs
with HIV (*131*). Furthermore, the drug interactions between rifapentine and HIV protease inhibitors have not been studied in
together (*132*).
In tuberculin-negative, HIV-infected persons, treatment of LTBI has not been effective (*3*). However, most tuberculin-negati
ended is not indicative of LTBI. Furthermore, some experts recommend treatment of possible LTBI for HIV-infected resider
Persons with fibrotic lesions/suspected disease. For patients 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 rif
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 beer
Persons with evidence suggestive of healed, primary TB (i.e., calcified solitary pulmonary nodules, calcified hilar lymph noc
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 progressin
have not demonstrated an effect of pregnancy on cutaneous delayed hypersensitivity to tuberculin (*136, 137*). The current cla
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 progres
is more controversial. Some experts prefer to delay treatment until after delivery because pregnancy itself does not increase t
hepatotoxicity (*91, 92*). However, because conditions that promote hematogenous spread of organisms to the placenta (e.g., r
pregnant women with these conditions and LTBI should be treated during pregnancy and have careful clinical and laboratory
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 no
utero to rifampin had abnormalities (i.e., limb reductions, central nervous system abnormalities, and hypoprothrombinemia)
the use of rifampin in the mother (*141*). However, extensive experience with the use of rifampin to treat TB in pregnant wom
concerning the effects of the drug on the fetus. Thus, although pyrazinamide may be considered after the first trimester in wo
The preferred regimen for treatment of LTBI in pregnant women is isoniazid, administered either daily or twice weekly. Alth
are infected with HIV or who have been infected recently, initiation of therapy should not be delayed on the basis of pregnan
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 breastfeed
antituberculosis drugs (*143*). Breastfeeding is not contraindicated when the mother is being treated for LTBI. However, infan
inadequate for treatment of the infant.
Children and adolescents. Several fundamental aspects of the natural history and treatment of LTBI in children must be co
infected recently, and are at high risk for progression to disease. Data suggest that untreated infants with LTBI have up to a 4
than older children and adults to develop life-threatening forms of TB, especially meningeal and disseminated disease. Child
with several large clinical trials demonstrating risk reduction of 7090% (*145,146*). The risk for isoniazid-related hepatitis is r
use in children. Because of differences in pathogenesis of TB infection and disease in children compared with adults, inform
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-adm
considered in children at risk for hepatic disease. When children taking antituberculosis therapy develop hepatitis, a search fo
recommended for children taking isoniazid, but should be given to (*1*) breastfeeding infants, (*2*) children and adolescents wit
Isoniazid given twice weekly has been used extensively to treat LTBI in children, especially schoolchildren and close contac

definitively. DOT should be considered when it is unlikely that the child and family will be adherent to daily self-administrat
In the United States, rifampin alone has been used for the treatment of LTBI in infants, children, and adolescents when isoni
(*149)*. However, no controlled clinical trials have been conducted. A 3-mo regimen of rifampin and isoniazid has been used i
rifampin and pyrazinamide therapy in children with LTBI, although a randomized study involving a limited number of childr
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 T
(Table 10). In addition, some tuberculin-negative contacts should be considered for treatment. Because of susceptib
contact has ended. If the repeat skin test is positive, treatment should continue for the recommended period of time;
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 v
to recommend either rifampin alone or in combination with isoniazid or ethambutol when the risk of isoniazid-resis
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 th
who received rifampin or isoniazid and rifampin (*153*). Similarly, of 157 high school students who took rifampin after being
rifampin prophylaxis failure was reported among contacts of a case patient with isoniazid-resistant TB in a community outbr
For contacts of patients with isoniazid-resistant, rifampin-susceptible TB, a 2-mo regimen of rifampin and pyrazinamide is re
cannot be used, rifabutin can be substituted.

- Contacts of patients with multidrug-resistant tuberculosis. The occurrence of outbreaks of multidrug-resistant TB (M
focused attention on options for treatment of persons exposed to and presumed to be infected by such organisms (*15*
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 conta
selection of drugs for such a regimen should be guided by *in vitro* susceptibility test results from the isolate to which the pati
For persons who are likely to be infected with MDR TB and at high risk of developing TB, pyrazinamide and ethambutol or
are known to be susceptible to these agents (*157*). Immunocompetent contacts may be observed without treatment or treated
fluoroquinolones include gastrointestinal symptoms and hepatic transaminase elevations (158). All persons with suspected M
exposed to patients with MDR TB.

No studies have been published regarding treatment of LTBI in children following exposure to multidrug-resistant TB. Ethar
susceptible to both drugs. Long-term use of fluoroquinolones in children should be avoided. Deleterious effects on growing c
of children with cystic fibrosis treated with ciprofloxacin or ofloxacin (*161*). When pyrazinamide and ethambutol cannot be u

Low-risk tuberculin test reactors. When treatment of LTBI is being considered for persons who are at low risk for develop
vulnerable contacts (e.g., infants and HIV-infected persons) if treatment were not given and the patient were to develop activ
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 reg

Directly observed therapy and measures to increase adherence. Any regimen that is given intermittently (i.e., twice week
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 pers
used for the treatment of household contacts of patients receiving DOT for active TB and for treatment observed by staff me

If it is not possible to provide DOT to enhance adherence with treatment of LTBI, the prescribed regimen should be incorpor
explain in simple, clear language what LTBI is, the health threat it presents, and how it is eradicated. Patients should be enco
necessary. Each visit between patient and medical provider during therapy is an opportunity to reinforce the patient's underst
In addition to education about potential drug toxicity, patients should be told about common side effects and counseled on dr
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 wa
expenses. Even the least intensive approaches to improve adherence increase program costs. The costs of these approaches to
recent infection or those persons at high risk for progression to active TB, if infected. In addition, programs should invest in
patients to accept and to complete treatment is necessary to achieve the full potential of this intervention to protect persons fr

Pretreatment Evaluation and Monitoring of Treatment

Pretreatment evaluation. The pretreatment evaluation of persons who are targeted for treatment of LTBI provides an opportu
treatment and 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 f

contraceptives are at increased risk for becoming pregnant and should be advised to consider an additional form of contracep
each patient.
Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for LTBI (Table 8). Patients who
Baseline testing is also indicated for patients infected with HIV, pregnant women and those in the immediate postpartum per
alcohol regularly, and others who are at risk for chronic liver disease. Baseline testing is no longer routinely indicated in pers
medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the u
Monitoring of treatment. Clinical monitoring is indicated for all patients; this involves education of patients about the sympt
evaluation should symptoms occur. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine,
(especially right upper quadrant discomfort), easy bruising or bleeding, and arthralgia (Table 8). Clinical monitoring begins a
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
8). These evaluations represent opportunities to review the indications for treatment, adherence with therapy since the last vi
questionnaire may facilitate those interviews.
Routine laboratory monitoring during treatment of LTBI is indicated for patients whose baseline liver function tests are abno
symptoms compatible with hepatotoxicity or a uric acid measurement to evaluate patients who develop acute arthritis) shoul
patient's transaminase level exceeds 3 times the upper limit of normal if associated with symptoms and five times the upper l
Reporting of serious adverse events. Practitioners and other health professionals should report serious adverse events associa
with hospitalization, permanent disability, or death. Reporting may be by mail, telephone (1-800-FDA-1088), fax (1-800-FD

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
low, the test's positive predictive value is poor. In addition, the requirement that the person tested return for the test to be rea
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 p

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 H
effective (*86,110*). Before additional trials of intermittent rifampin regimens are undertaken, animal model data are needed t

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 i
regimen. Data from these programs should be examined, especially as they relate to acceptability and completion of treatmer

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 pre
hepatotoxicity of isoniazid in pregnant and postpartum women. Studies are needed to establish the safety and effectiveness o
studies would be HIV-infected children in places in which TB is prevalent and household contacts of TB case patients. In ad
effectiveness of alternative therapies for MDR LTBI in children are needed. Finally, epidemiologic research to determine the

Reporting and Monitoring in New Settings

These recommendations call for the establishment of LTBI treatment programs in new community settings (e.g., managed ca
settings other than health departments. These studies should assess the knowledge base of treating clinicians and identify the

Combination Rifampin and Pyrazinamide Preparations

If field and programmatic data establish the effectiveness and acceptability of the rifampin and pyrazinamide regimen for the
of combination products in preventing the emergence of drug resistance in patients with active TB is not as compelling for p
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 derivati
experimental studies involving mice, the combination of rifapentine and isoniazid given once weekly for 3 mo was as active
could be dosed less frequently without compromising efficacy (*166*). The class of nitroimidazole compounds is also of intere
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 resp
of certain cytokines (e.g., interferon gamma) may protect against the development of active TB. If further studies support thi
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 "t high risk and specific subgroups characterized by varied risks and benefits of treatment. Using this conceptual framework wi

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-tolerate models until investigations better establish these risks. By investigating the effect of a range of toxicities and adherence on th 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), additio Policies designed to target and treat populations at high risk for TB are motivated by the need to benefit the individual patien 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.

Acknowledgment

The Writing Group wishes to express their appreciation to Elisha Freifeld of the ATS for administrative assistance and to Ra

References

1. American Thoracic Society, Centers for Disease Control. 1994. Treatment of tuberculosis and tuberculosis infection
2. Centers for Disease Control and Prevention. 1995. Screening for tuberculosis and tuberculosis infection in high-risk
3. Centers for Disease Control and Prevention. 1998. Prevention and treatment of tuberculosis among patients infected
4. Centers for Disease Control and Prevention. 1995. Essential components of a tuberculosis prevention and control pr
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-
7. American Thoracic Society. 1965. Preventive treatment in tuberculosis: a statement by the Committee on Therapy.
8. American Thoracic Society. 1967. Chemoprophylaxis for the prevention of tuberculosis: a statement by an Ad Hoc
9. Garibaldi, R. A., R. E. Drusin, S. H. Ferebee, and M. B. Gregg. 1972. Isoniazid-associated hepatitis: report of an ou
10. American Thoracic Society, National Tuberculosis and Respiratory Disease Association, Center for Disease Contro
11. Kopanoff, D. E., D. E. Snider, Jr., and G. J. Caras. 1979. Isoniazid-related hepatitis: a U.S. Public Health Service co
12. American Thoracic Society, American Lung Association, Center for Disease Control. 1974. Preventive therapy of t
13. Taylor, W. C., M. D. Aronson, and T. L. Delbanco. 1981. Should young adults with a positive tuberculin test take is
14. Mehta, J. B., A. K. Dutt, L. Harvill, and W. Henry. 1988. Isoniazid preventive therapy for tuberculosis: are we losin
15. American Thoracic Society, Centers for Disease Control. 1983. Treatment of tuberculosis and other mycobacterial d
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 imp
18. O'Brien, R. J., and J. H. Perriæns. 1995. Preventive therapy for tuberculosis in HIV infection: the promise and the re
19. Advisory Council on the Elimination of Tuberculosis. 1999. Tuberculosis elimination revisited: obstacles, opportun
20. Sutherland, I. 1968. The ten-year incidence of clinical tuberculosis following "conversion" in 2550 individuals aged
21. Ferebee, S. H., and F. W. Mount. 1962. Tuberculosis morbidity in a controlled trial of the prophylactic use of isonia
22. McKenna, M. T., E. McCray, and I. Onorato. 1995. The epidemiology of tuberculosis among foreign-born persons
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.
    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
25. Comstock, G. W., V. T. Livesay, and S. F. Woolpert. 1974. The prognosis of a positive tuberculin reaction in childh
26. Schluger, N. W., R. Huberman, N. Wolinsky, R. Dooley, W. N. Rom, and R. S. Holzman. 1997. Tuberculosis infec
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. Hershfi
29. Markowitz, N., N. I. Hansen, P. C. Hopewell, J. Glassroth, P. A. Kvale, B. T. Mangura, T. C. Wilcosky, J. M. Walla
    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 act
31. Selwyn, P. A., D. Hartel, V. A. Lewis, E. E. Schoenbaum, S. H. Vermund, R. S. Klein, A. T. Walker, and G. H. Frie
    J. Med. 320:545--550.
32. International Union Against Tuberculosis Committee on Prophylaxis. 1982. Efficacy of various durations of isoniaz
33. Falk, A., and G. F. Fuchs. 1978. Isoniazid (INH) prophylaxis with isoniazid in inactive tuberculosis: a Veterans Adr

34. Steinbruck, P., D. Dankova, L. B. Edwards, B. Doster, and V. T. Livesay. 1972. The risk of tuberculosis in patients
35. Palmer, C. E., S. Jablon, and P. Q. Edwards. 1957. Tuberculosis morbidity of young men in relation to tuberculin se
36. Hong Kong Chest Service, Tuberculosis Research Centre, Madras, and British Medical Research Council. 1992. A
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 tuberculo
39. Lundin, A. P., A. J. Adler, G. M. Berlyne, and E. A. Friedman. 1979. Tuberculosis in patients undergoing maintena
40. Chia, S., M. Karim, R. K. Elwood, and J. M. FitzGerald. 1998. Risk of tuberculosis in dialysis patients: a populatio
41. Andrew, O. T., P. Y. Schoenfeld, P. C. Hopewell, and M. H. Humphreys. 1980. Tuberculosis in patients with end-st
42. Pablos-MÄndez, A., J. Blustein, and C. A. Knirsch. 1997. The role of diabetes mellitus in the higher prevalence of t
43. Boucot, K. R., E. S. Dillon, D. A. Cooper, and P. Meier. 1952. Tuberculosis among diabetics: the Philadelphia Surv
44. Oscarsson, P. N., and H. Silwer. 1958. Incidence of pulmonary tuberculosis among diabetics: search among diabetic
45. Thorn, P. A., V. S. Brookes, and J. A. H. Waterhouse. 1956. Peptic ulcer, partial gastrectomy, and pulmonary tuber
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 ga
48. Pickleman, J. R., L. S. Evans, J. M. Kane, and R. J. Freeark. 1975. Tuberculosis after jejunoileal bypass for obesity.
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 fiv
51. Muñoz, P., J. Palomo, M. Muñoz, M. Rodirguez-Creixéms, T. Pelaez, and E. Bouza. 1995. Tuberculosis in heart tra
52. Korner, M. M., N. Hirata, G. Tenderich, K. Minami, H. Mannebach, K. Kleesiek, and R. KÜrfer. 1997. Tuberculosi
53. Feld, R., G. P. Bodey, and D. Groschel. 1976. Mycobacteriosis in patients with malignant disease. *Arch. Intern. Me*
54. Kaplan,, M. H., D. Armstrong, and P. Rosen. 1974. Tuberculosis complicating neoplastic disease: a review of 201 c
55. Schatz, M., R. Patterson, R. Kloner, and J. Falk. 1976. The prevalence of tuberculosis and positive tuberculin skin t
56. Bovornkitti, S., P. Kangsadai, P. Sathirapat, and P. Oonsombatti. 1960. Reversion and reconversion rate of tubercul
57. Bateman, E. D. 1993. Is tuberculosis chemoprophylaxis necessary for patients receiving corticosteroids for respirato
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. 19
59. Friedman, L. N., M. T. Williams, P. S. Tejinder, and T. R. Frieden. 1996. Tuberculosis, AIDS, and death among sul
60. Buskin, S. E., J. L. Gale, N. S. Weiss, and C. M. Nolan. 1994. Tuberculosis risk factors in adults in King County, W
61. Centers for Disease Control. 1989. A strategic plan for the elimination of tuberculosis in the United States. *M.M.W.*
62. Goldberg, B. W. 1998. Managed care and public health departments: who is responsible for the health of the popula
63. Nelson, K. R., H. Bui, and J. H. Samet. 1997. Screening in special populations: a "case study" of recent Vietnamese
64. Nolan, C. M., L. Roll, S. V. Goldberg, and A. M. Elarth. 1997. Directly observed isoniazid preventive therapy for re
65. Nazar-Stewart, V., and C. M. Nolan. 1992. Results of a directlyobserved intermittent isoniazid preventive therapy p
66. Bock, N. N., B. S. Metzger, M. Tapia, and H. M. Blumberg. 1999. A tuberculin screening and isoniazid preventive
67. Gourevitch, M. N., P. Alcabes, W. C. Wasserman, and P. S. Arno. 1998. Cost-effectiveness of directly observed che
68. Perlman, D. C., M. P. Perkins, N. Solomon, L. Kochems, D. C. Des Jarlais, and D. Paone. 1997. Tuberculosis scree
69. Schluger, N. W., R. Huberman, I. Holzman, W. N. Rom, and D. I. Cohen. 1999. Screening for infection and disease
70. American Thoracic Society, Centers for Disease Control and Prevention. 2000. Diagnostic standards and classificat
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.*
73. Rose, D. N., C. B. Schecter, and J. J. Adler. 1995. Interpretation of the tuberculin skin test. *J. Gen. Intern. Med.* 10:
74. Sepulveda, R. L., X. Ferrer, C. Latrach, and R. U. Sorensen. 1990. The influence of Calmette-Guérin Bacillus immu
75. McKay, A., A. Kraut, C. Murdzak, and A. Yassi. 1999. Determinants of tuberculin reactivity among health care wo
76. Graham, N. M. H., K. E. Nelson, L. Solomon, M. Bonds, R. T. Rizzo, J. Scavotto, J. Astemborski, and D. Vlahov. 1
77. Centers for Disease Control and Prevention. 1997. Anergy skin testing and tuberculosis preventive therapy for HV-
78. Ferebee, S. H., and C. E. Palmer. 1956. Prevention of experimental tuberculosis with isoniazid. *Am. Rev Tuberc. Pu*
79. Comstock, G. W., and S. H. Ferebee. 1970. How much isoniazid is needed for prophylaxis? *Am. Rev. Respir. Dis.* 1
80. Comstock, G. W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adu
81. Snider, D.E., Jr., G. J. Caras, and J. P. Koplan. 1986. Preventive therapy with isoniazid: cost-effectiveness of differe
82. American Thoracic Society, Centers for Disease Control. 1986. Treatment of tuberculosis and tuberculosis infection
83. Pape, J. W., S. S. Jean, J. L. Ho, A. Hafher, and W. D. Johnson, Jr. 1993. Effect of isoniazid prophylaxis on inciden
84. Whalen, C. C., J. L. Johnson, A. Okwera, D. L. Hom, R. Huebner, P. Mugyenyi, R. D. Mugerwa, and J. J. Ellner. 19
-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
Isoniazid preventive therapy for tuberculosis in HIV-I-infected adults: results of a randomized controlled trial. *AIDS*

86. Mwinga, A., M. Hosp, P. Godfrey-Faussett, M. Quigley, P. Mwaba, B. N. Mugala, O. Nyirenda, N. Luo, J. Pobee, A
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. Pere
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 prophyla
89. Mitchell, J. R., H. J. Zimmerman, K. G. Ishak, U. P. Thorgeirsson, J. A. Timbrell, W. R. Snodgrass, and S. D. Nelso
90. Comstock, G. W. 1986. Prevention of tuberculosis among tuberculin reactors: maximizing benefits, minimizing risk
91. Snider, D.E., Jr., and G. J. Caras. 1992. Isoniazid-associated hepatitis deaths: a review of available information. *Am*
92. Franks, A. L., N. J. Binkin, D. E. Snider, Jr., W. M. Rokaw, and S. Becker. 1989. Isoniazid hepatitis among pregnar
93. Murphy, R., R. Swartz, and P. B. Watkins. 1990. Severe acetaminophen toxicity in a patient receiving isoniazid. *An*
94. Burk, R. F., K. E. Hill, R. W. Hunt, and A. E. Martin. 1990. Isoniazid potentiation of acetaminophen hepatotoxicity
95. Millard, P. S., T. C. Wilcosky, S. J. Reade-Christopher, and D. J. Weber. 1996. Isoniazid-related fatal hepatitis. *Wes*
96. Moulding, T. S., A. G. Redeker, and G. C. Kanel. 1989. Twenty isoniazid-associated deaths in one state. *Am. Rev. F*
97. Centers for Disease Control and Prevention. 1993. Severe isoniazidassociated hepatitisNew York, 19911993. *M.M.*
98. Leff, D. R., and A. R. Leff. 1997. Tuberculosis control policies in major metropolitan health departments in the Uni
99. Nolan, C. M., S. V. Goldberg, and S. E. Buskin. 1999. Hepatotoxicity associated with isoniazid preventive therapy:
100. Tsevat, J., W. C. Taylor, J. B. Wong, and S. G. Pauker. 1988. Isoniazid for the tuberculin reactor: take it or leave it.
101. Rose, D. N., C. B. Schechter, and A. L. Silver. 1986. The age threshold for isoniazid chemoprophylaxis: a decision
102. Salpeter, S. R., G. D. Sanders, E. E. Salpeter, and D. K. Owens. 1997. Monitored isoniazid prophylaxis for low-risk
103. Colice, G. L. 1990. Decision analysis, public health policy, and isoniazid chemoprophylaxis for young adult tubercu
104. Lecoeur, H. F., C. Truffot-Pernot, and J. H. Grosset. 1989. Experimental short-course preventive therapy of tubercu
105. Grosset, J., C. Truffot-Pernot, C. Lacroix, and B. Ji. 1992. Antagonism between isoniazid and the combination pyra
106. Dhillon, J., J. M. Dickinson, K. Sole, and D. A. Mitchison. 1996. Preventive chemotherapy of tuberculosis in Corne
107. Jabes, D., C. Della Bruna, R. Rossi, and P. Olliaro. 1994. Effectiveness of rifabutin alone or in combination with isc
108. Ormerod, L. P. 1998. Rifampicin and isoniazid prophylactic chemotherapy for tuberculosis. *Arch. Dis. Child* 78:169
109. Joint Tuberculosis Committee of the British Thoracic Society. 1998. Chemotherapy and management of tuberculosi
110. Halsey, N. A., J. S. Coberly, and J. Desormeaux, P. Losikoff, J. Atkinson, L. H. Moulton, M. Contave, M. Johnson,
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
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). *A*
113. Geiter, L. J. 1997. Results of a randomized, controlled trial to assess the toxicity and patient adherence with two sho
only, in comparison with a control regimen of six months-isoniazid [thesis]. Johns Hopkins University, School of H
114. Combs, D. L., R. J. O'Brien, and L. J. Geiter. 1990. USPHS tuberculosis short-course chemotherapy trial 21: effecti
115. Grazcyk, J., R. J. O'Brien, E. Bek, H. Nimerowsak, and L. J. Geiter. 1991. Assessment of rifampin containing regim
116. Magdorf, K., A. F. Arizzi-Ruche, L. J. Geiter, R. J. O'Brien, and U. Wahn. 1994. Compliance and tolerance of new
117. Snider, D. E., and M. D. Hutton. 1989. Improving patient compliance in tuberculosis treatment programs. Departme
118. Sumartojo, E. 1993. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Am. Rev. R*
119. Carey, J. W., M. J. Oxtoby, L. P. Nguyen, V. Huynh, M. Morgan, and M. Jeffery. 1997. Tuberculosis beliefs among
120. Morisky, D. E., C. K. Malotte, P. Choi, P. Davidson, S. Rigler, B. Sugland, and M. Langer. 1990. A patient educatio
121. Harborview Medical Center, University of Washington. Ethnic Medicine Guide. , http://www.hslib.washington.edu
122. White, M. C., J. P. Tulsky, P. Reilly, H. W. McIntosh, T. M. Hoynes, and J. Goldenson. 1998. A clinical trial of a fi
123. Heal, G., R. K. Elwood, and J. M. FitzGerald. 1998. Acceptance and safety of directly observed versus self-adminis
124. Wobeser, W., T. To, and V. H. Hoeppner. 1989. The outcome of chemoprophylaxis on tuberculosis prevention in th
125. Kohn, M. R., M. R. Arden, J. Vasilakis, and I. R. Shenker. 1996. Directly observed preventive therapy: turning the t
126. Judson, F. N., J. A. Sbarbaro, J. M. Tapy, and D. L. Cohn. 1983. Tuberculosis screening: evaluation of a food handl
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 pu
128. Shafran, S. D., J. Singer, D. P. Zarowny, J. Deschênes, P. Phillips, F. Turgeon, F. Y. Aoki, E. Toma, M. Miller, R. I
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. Cor
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
131. Vernon, A., W. Burman, D. Benator, A. Khan, and L. Bozeman. 1999. Acquired riifamycin monoresistance in patie
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 associat

134.Carter, E. J., and S. Mates. 1994. Tuberculosis during pregnancy: the Rhode Island experience, 1987 to 1991. *Chest*
135.Smith, J. K., E. A. Caspery, and E. J. Field. 1972. Lymphocyte reactivity to antigen in pregnancy. *Am. J. Obstet. Gy*
136.Montgomery, W. P., R. C. Young, Jr., and M. P. Allen. 1968. The tuberculin test in pregnancy. *Am. J. Obstet. Gyne*
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.
139.Cantwell, M. F., Z. M. Shehab, A. M. Costello, L. Sands, W. F. Green, E. P. Ewing, S. E. Valway, and I. M. Onorat
140.Scheinhorn, D. J., and V. A. Angelillo. 1977. Antituberculous therapy in pregnancy: risks to the fetus. *West. J. Med*
141.Eggermont, E., N. Logghe, W. Van De Casseye, M. Casteels-Van Daele, J. Jaeken, J. Cosemans, M. Verstraete, and
142.Centers for Disease Control and Prevention. 1999. 1999 USPHS/IDSA guidelines for the prevention of opportunisti
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. M*
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 comparis
146.Mount, F. W., and S. H. Ferrebee. 1961. Preventive effects of isoniazid in the treatment of primary tuberculosis in c
147.O'Brien, R. J., M. W. Long, F. S. Cross, M. A. Lyle, and D. E. Snider, Jr. 1983. Hepatotoxicity from isoniazid and r
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, an
155:1735--1738.
150.American Academy of Pediatrics. 2000. Tuberculosis. In Red Book: Report of the Committee on Infectious Disease
151.Koplan, J. P., and L. S. Farer. 1980. Choice of preventive treatment for isoniazid-resistant tuberculosis infection: us
152.Bailey, W. C., R. B. Byrd, J. C. Glassroth, P. C. Hopewell, and L. B. Reichman. 1985. Preventive treatment of tube
153.Polesky, A., H. W. Farbe, D. J. Gottlieb, H. Park, S. Levinson, J. J. O'Connell, B. McInnis, R. L. Nieves, and J. Ber
154.Livengood, J. R., T. G. Sigler, L. R. Foster, J. G. Bobst, and D. E. Snider. 1985. Isoniazid--resistant tuberculosis: a
155.Pablos-Mendez, A., M. C. Raviglione, A. Laszlo, N. B. Binkin, H. L. Rieder, F. Bustreo, D. L. Cohn, C. S. B. Lamb
Med. 338:1641--1649.
156.Passannante, M. R., C. T. Gallagher, and L. B. Reichman. 1994. Preventive therapy for contacts of multidrug-resista
157.Centers for Disease Control and Prevention. 1992. Management of persons exposed to multidrug-resistant tuberculo
158.Ridzon, R., J. Meador, R. Maxwell, K. Higgins, P. Weismuller, and I. M. Onorato. 1997. Asymptomatic hepatitis in
159.TrÄbucq, A. 1997. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review
160.Gough, A. W., O. B. Kasali, R. E. Sigler, and V. Baragi. 1992. Quinolone arthropathy---acute toxicity to immature
161.Danisovicova, A., M. Brezina, S. Belan, H. Kayserova, E. Kaiserova, I. Hruskovic, K. Orosovç, S. Dluholucky, K.
quinolone-induced arthropathy---a multicenter survey. *Chemotherapy* 40:209214.
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--5
164.Centers for Disease Control and Prevention. 1996. The role of BCG vaccine in the prevention and control of tuberc
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 o
166.Reddy, M. V., J. Luna-Herrera, D. Daneluzzi, and P. R. Gangadharam. 1996. Chemotherapeutic activity of benzoxa
167.Stover, C. K., Y. Yuan, P. G. Warrener, D. R. VanDevanter, D. R. Sherman, M. H. Langhorne, K. Tanaka, C. E. Ba
159(Suppl.):AI6.
168.Centers for Disease Control and Prevention. 1998. Development of new vaccines for tuberculosis: recommendation
169.Centers for Disease Control and Prevention. 2000. Notice to Readers: Updated guidelines for the use of rifabutin or
inhibitors. *M.M.W.R.* 49:185--189.

Table 1

Return to top.
Figure 1

Morbidity and Mortality Weekly Report
Centers for Disease Control and Prevention
1600 Clifton Rd, MailStop E-90, Atlanta, GA 30333, U.S.A

This