



Complete Summary

GUIDELINE TITLE

- (1) Targeted tuberculin testing and treatment of latent tuberculosis infection.
- (2) Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States, 2001.
- (3) Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection--United States, 2003.

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep 2000 Jun; 49(RR-6): 1-54. [169 references]

Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection--United States, 2003. MMWR Morb Mortal Wkly Rep 2003 Aug 8; 52(31): 735-9. [16 references] [PubMed](#)

Update: fatal and severe liver injuries associated with Rifampin and Pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States 2001. MMWR Recomm Rep 2001 Aug 31; 50(34): 733-5.

COMPLETE SUMMARY CONTENT

- SCOPE
- METHODOLOGY - including Rating Scheme and Cost Analysis
- RECOMMENDATIONS
- EVIDENCE SUPPORTING THE RECOMMENDATIONS
- BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
- CONTRAINDICATIONS
- IMPLEMENTATION OF THE GUIDELINE
- INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
- IDENTIFYING INFORMATION AND AVAILABILITY

SCOPE

DISEASE/CONDITION(S)

Latent tuberculosis infection

GUIDELINE CATEGORY

Diagnosis
Evaluation
Prevention
Treatment

CLINICAL SPECIALTY

Family Practice
Infectious Diseases
Internal Medicine
Preventive Medicine

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide new recommendations for targeted tuberculin testing and treatment regimens for persons with latent tuberculosis infection (LTBI)
- To update previously published guidelines:

American Thoracic Society, Centers for Disease Control. 1994. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 149:1359-1374.

Centers for Disease Control and Prevention. 1995. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. *MMWR Morb Mortal Wkly Rep* 44(No. RR-11):19-34.

TARGET POPULATION

Persons at high risk for developing tuberculosis who would benefit by treatment of latent tuberculosis infection (LTBI), if detected:

- Persons who have had recent infection with mycobacterium tuberculosis
- Persons who have clinical conditions that are associated with an increased risk for progression of latent tuberculosis infection to active tuberculosis (i.e., human immunodeficiency virus [HIV] infection, weight loss of greater than 10 percent ideal body weight, silicosis, diabetes mellitus, chronic renal failure/hemodialysis, gastrectomy, jejunoileal bypass, solid organ

transplantation, carcinoma of head or neck, radiographic findings consistent with prior tuberculosis, injection drug use)

INTERVENTIONS AND PRACTICES CONSIDERED

1. Targeted tuberculin skin testing for latent tuberculosis infection (LTBI) with purified protein derivative (PPD)
2. Diagnostic exclusion of active tuberculosis by clinical history, physical examination, chest radiography, and, when indicated, bacteriologic studies
3. Treatment of latent tuberculosis infection
 - Isoniazid, daily for 9 months or twice weekly for 9 months
 - Isoniazid, daily for 6 months or twice weekly for 6 months
 - Rifampin, daily for 4 months
 - NOTE: rifampin plus pyrazinamide was considered but not recommended

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of the intradermal or Mantoux PPD (purified protein derivative) tuberculin skin test reactions
- Efficacy of drug treatment regimens in preventing tuberculosis:
 - 5-year tuberculosis incidence
 - tuberculosis morbidity rate
 - adverse events

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

2000 guideline: Not stated

2003 addendum: To estimate the incidence of rifampin with pyrazinamide (RZ)-associated severe liver injury and provide more precise data to guide treatment for latent tuberculosis infection (LTBI), the Centers for Disease Control and Prevention (CDC) collected data from cohorts of patients in the United States who received RZ for the treatment of LTBI during January 2000-June 2002 and for whom data were reported to CDC through June 6, 2003.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

2003 guideline addendum

Quality of Evidence Supporting the Recommendation

- I. Evidence from at least one properly randomized controlled trial.
- II. Evidence from at least one well-designed clinical trial without randomization from cohort or case-controlled analytic studies (preferably from more than one center), from multiple time-series studies, or from dramatic results from uncontrolled experiments.
- III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

2000 original guideline

Treatment recommendations use an adaptation of the rating system from recent United States Public Health Service documents that grades the quality of evidence supporting the recommendation:

- I. At least one randomized trial with clinical endpoints
- II. Data from clinical trials that were not randomized or were conducted in other populations
- III. Expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

2003 Guideline Addendum

Strength of the Recommendation:

- A. Both strong evidence of efficacy and substantial clinical benefit support recommendation for use. Should always be offered.
- B. Moderate evidence for efficacy or strong evidence for efficacy but only limited clinical benefit supports recommendation for use. Should generally be offered.

- C. Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (e.g., drug toxicity, drug interactions) or cost of the treatment of alternative approaches. Optional.
- D. Moderate evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should generally not be offered.
- E. Good evidence for lack of efficacy or for adverse outcome support a recommendation against use. Should never be offered.

2000 Original Guideline

Strength of the Recommendation:

- A. Preferred; should generally be offered
- B. Alternative; acceptable to offer
- C. Offer when preferred (A) or alternative (B) regimens cannot be given
- D. Should generally not be offered
- E. Should never be offered

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grades of evidence supporting the treatment recommendation (I–III) and the strength of the recommendations (A–E) are defined at the end of the Major Recommendations.

Note from the National Guideline Clearinghouse (NGC):

To reduce the risk for liver injury associated with rifampin-pyrazinamide therapy for latent tuberculosis infection, the American Thoracic Society and the Centers for Disease Control (CDC), with the endorsement of the Infectious Diseases Society of America, prepared recommendations on August 31, 2001 that supercede previous guidelines. These follow:

Revised recommendations on selecting appropriate latent tuberculosis infection therapy for patients and monitoring the use of rifampin-pyrazinamide to treat latent tuberculosis infection

1. The 2-month rifampin-pyrazinamide treatment regimen for latent tuberculosis infection should be used with caution, especially in patients concurrently taking other medications associated with liver injury, and those with alcoholism, even if alcohol use is discontinued during treatment. Rifampin-pyrazinamide is not recommended for persons with underlying liver disease or for those who have had isoniazid-associated liver injury. Persons being considered for treatment with rifampin-pyrazinamide should be informed of potential hepatotoxicity and asked whether they have had liver disease or adverse effects from isoniazid.
2. For persons not infected with HIV, 9 months of daily isoniazid remains the preferred treatment for latent tuberculosis infection; 4 months of daily rifampin is an acceptable alternative. Two months of daily rifampin-pyrazinamide may be useful when completion of longer treatment courses is unlikely and when the patient can be monitored closely.
3. Available data do not suggest excessive risk for severe hepatitis associated rifampin-pyrazinamide treatment among HIV-infected persons. In a large multinational trial, HIV-infected patients treated with rifampin-pyrazinamide had lower rates of serum aminotransferase elevations than those given isoniazid alone. The rifampin-pyrazinamide regimen also was well tolerated when given twice weekly to HIV-infected persons in Zambia and Haiti. However, experience from trials may not translate to all clinical practice settings, and it may be prudent to use 9 months of daily isoniazid for treatment of HIV-infected persons with latent tuberculosis infection when completion of treatment can be assured.
4. No more than a 2-weeks supply of rifampin-pyrazinamide (with a pyrazinamide dose ≤ 20 mg/kg/d and a maximum of 2 gm/d) should be dispensed at a time to facilitate periodic clinical assessments. Patients should be reassessed in person by a health-care provider at 2, 4, and 6 weeks of treatment for adherence, tolerance, and adverse effects, and at 8 weeks to document treatment completion. At each visit, health-care providers conversant in the patients' language should instruct patients to stop taking rifampin-pyrazinamide immediately and seek medical consultation if abdominal pain, emesis, jaundice, or other hepatitis symptoms develop. Provider continuity is recommended for monitoring.
5. A serum aminotransferase and bilirubin should be measured at baseline and at 2, 4, and 6 weeks of treatment in patients taking rifampin-pyrazinamide. Because some side effects may occur in the second month of treatment, patients should be monitored throughout the entire course of treatment. Asymptomatic serum aminotransferase increases are expected and usually do not require that treatment be stopped. However, treatment should be stopped and not resumed for any of these findings: aminotransferase greater than five times the upper limit of normal range in an asymptomatic person, aminotransferase greater than normal range when accompanied by symptoms of hepatitis, or a serum bilirubin greater than normal range.

The following considerations are crucial in deciding whom to test and treat for latent tuberculosis infection:

1. The purpose of targeted testing is to find and treat persons who have both latent tuberculosis infection and high risk for tuberculosis disease (e.g., recent exposure to a contagious case). Persons at low risk for developing tuberculosis and who have had a tuberculin skin test for other reasons, such as baseline tuberculin skin test of health-care workers, are not necessarily candidates for treatment if found to be infected.
2. Treatment is recommended for foreign-born persons from countries with a high prevalence of tuberculosis who have latent tuberculosis infection and who have been in the United States <5 years [as indicated below]. After 5 years, treatment decisions should be made on the same basis as other patients.
3. Because sporadic severe isoniazid-associated liver injury still occurs, patients taking isoniazid should be monitored as recommended [below].

CDC is collecting reports of severe liver injury (i.e., leading to hospital admission or death) in persons receiving any regimen for latent tuberculosis infection. Reports are being analyzed to assess contributing factors. Report possible cases to the Division of Tuberculosis Elimination; telephone (404) 639-8125.

Note from the National Guideline Clearinghouse:

The following recommendations, issued on June 9, 2000 by the Centers for Disease Control, have been superseded by revised recommendations issued on August 31, 2001 [see above].

Changes from Prior Recommendations on Tuberculin Testing and Treatment of Latent Tuberculosis Infection (LTBI)

Tuberculin Testing

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

Treatment of Latent Tuberculosis Infection

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

Clinical and Laboratory Monitoring

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

Targeted Tuberculin Testing

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

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

Treatment of Latent Tuberculosis Infection

In the guideline, 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 latent tuberculosis infection.

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

Drugs	Interval and Duration	Comments	<u>Rating (Evidence)</u>	
			HIV-	HIV+
Isoniazid	Daily for 9 mos ^{#&}	In human immunodeficiency virus (HIV)-infected patients, isoniazid may be administered concurrently with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs)	A (II)	A (II)
	Twice weekly for 9 mos ^{#&}	Directly observed therapy (DOT) must be used with twice-weekly dosing	B (II)	B (II)
Isoniazid	Daily for 6 mos ^{&}	Not indicated for HIV-infected persons, those with fibrotic lesions on chest radiographs, or children	B (I)	C (I)
	Twice weekly for 6 mos ^{&}	Directly observed therapy must be used with twice-weekly dosing	B (II)	C (I)
Rifampin plus pyrazinamide	Daily for 2 mos	May also be offered to persons who are contacts of pyrazinamide patients with isoniazid-resistant, rifampin-susceptible tuberculosis In HIV-infected patients, protease	B (II)	A (II)

inhibitors or NNRTIs should generally not be administered concurrently with rifampin; rifabutin can be used as an alternative for patients treated with indinavir, nelfinavir, amprenavir, ritonavir, or efavirenz, and possibly with nevirapine or soft-gel saquinavir**

	Twice weekly for 2-3 mos	Directly observed therapy must be used with twice-weekly dosing	C (II)	C (I)
Rifampin	Daily for 4 mos	For persons who cannot tolerate pyrazinamide	B (II)	B (III)
		For persons who are contacts of patients with Isoniazid-resistant, rifampin-susceptible tuberculosis who cannot tolerate pyrazinamide		

Recommended regimen for children younger than 18 years of age.
 & Recommended regimens for pregnant women. Some experts would use rifampin and pyrazinamide for 2 months as an alternative regimen in HIV-infected pregnant women, although pyrazinamide should be avoided during the first trimester.

** Rifabutin should not be used with hard-gel saquinavir or delavirdine. When used with other protease inhibitors or NNRTIs, dose adjustments or rifabutin may be required (see Table 8 in the guideline document).

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

Although a 9 month regimen of isoniazid is the preferred regimen for the treatment of latent tuberculosis infection, a 6 month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations, treatment for 6 months rather than 9 months may provide a more favorable outcome from a cost-effectiveness standpoint. Thus, based on local conditions, health departments or providers may conclude that a 6 month rather than a 9 month course of isoniazid is preferred.

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

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

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

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

Special considerations for treatment of latent tuberculosis infection apply to the following populations:

- When isoniazid is chosen for treatment of latent tuberculosis infection in persons with HIV infection or those with radiographic evidence of prior tuberculosis, 9 months rather than 6 months is recommended.
- For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 months is recommended. For women at risk for progression of latent tuberculosis infection to disease, especially those who are infected with HIV or who have likely been infected recently, initiation of therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. For women whose risk for active tuberculosis is lower, some experts recommend waiting until after delivery to start treatment.
- For children and adolescents, isoniazid given either daily or twice weekly for 9 months is the recommended regimen.
- For contacts of patients with isoniazid-resistant, rifampin-susceptible tuberculosis, rifampin and pyrazinamide given daily for 2 months is

- recommended, and for patients with intolerance to pyrazinamide, rifampin given daily for 4 months is recommended.
- For persons who are likely to be infected with isoniazid- and rifampin-resistant (multidrug) tuberculosis and who are at high risk for developing tuberculosis, pyrazinamide and ethambutol or pyrazinamide and a quinolone (i.e., levofloxacin or ofloxacin) for 6 to 12 months are recommended. Immunocompetent contacts may be observed or treated for at least 6 months, and immunocompromised contacts (e.g., HIV-infected persons) should be treated for 12 months.

Clinical and Laboratory Monitoring

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

Baseline laboratory testing is not routinely indicated for all patients at the start of treatment for latent tuberculosis infection. Patients whose initial evaluation suggests a liver disorder should have baseline hepatic measurements of serum aspartate aminotransferase (serum glutamic oxaloacetic transaminase) (AST [SGOT]) or alanine aminotransferase (serum glutamic pyruvic transaminase) (ALT [SGPT]) and bilirubin. Baseline testing is also indicated for patients with HIV infection, pregnant women, and women in the immediate postpartum period (i.e., within 3 months of delivery), persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis, or cirrhosis), persons who use alcohol regularly, and persons at risk for chronic liver disease. Baseline testing is not routinely indicated in older persons. However, such testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid or pyrazinamide for treatment of latent tuberculosis infection.

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

Definitions:

Treatment recommendations use an adaptation of the rating system from recent U.S. Public Health Service documents that grades the strength of the recommendation and the quality of the evidence.

Strength of the recommendation

- A. Preferred; should generally be offered
- B. Alternative; acceptable to offer
- C. Offer when preferred (A) or alternative (B) regimens cannot be given
- D. Should generally not be offered
- E. Should never be offered

Quality of evidence supporting the recommendations

- I. At least one randomized trial with clinical endpoints
- II. Clinical trials that either are not randomized or were conducted in other populations
- III. Expert opinion

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for the treatment recommendations (See "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall

- Decreased incidence of active tuberculosis in high risk groups and in the general population and control of tuberculosis infection

Pharmacologic-specific

- Isoniazid in HIV-negative individuals

Many randomized, controlled clinical trials of isoniazid for the treatment of latent tuberculosis infection were conducted in the 1950s and 1960s. The effectiveness of treatment, as measured by the decrease in tuberculosis among all persons participating in these trials, varied from 25 to 92%. However, when analysis was restricted to persons who were compliant with the medication, the protective efficacy was approximately 90%. Substantial

protection was conferred even if pill taking was irregular but sustained, suggesting the possibility that intermittent treatment may be efficacious.

Only one trial, conducted by the International Union Against Tuberculosis (IUAT), was designed to evaluate various durations of isoniazid. In this trial, a placebo regimen was compared with isoniazid regimens lasting for 3, 6, and 12 months among persons with fibrotic pulmonary lesions consistent with inactive tuberculosis. The 5 year incidence rates of tuberculosis were 1.43% for placebo compared with 1.13, 0.50, and 0.36% for the 3-, 6-, and 12-month regimens, respectively. The rates indicated a 65% effectiveness for the 6-month isoniazid regimen and 75% effectiveness for the 12-month regimen; persons who received 6 months of isoniazid had a 40% higher risk for tuberculosis compared with those who received 12 months of therapy.

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

- Isoniazid in HIV-positive individuals

Seven randomized, controlled trials have evaluated different regimens for the treatment of latent tuberculosis infection in persons with HIV infection. Five of these studies evaluated isoniazid regimens using comparison groups that either received a placebo or were not actively treated.

In the first study, conducted in Haiti during 1986-1992, 12 months of daily isoniazid resulted in a substantial reduction in tuberculosis (83%) among tuberculin-positive persons. Protection was constant over the 4 year of follow-up after treatment. Two other studies, which evaluated 6 months of isoniazid taken daily by tuberculin-positive persons, had differing results: the drug provided a significant level of protection in Uganda (68%) but did not provide a significant level of protection in Kenya (40%). A fourth study evaluated a 6-month, twice-weekly regimen of isoniazid in both tuberculin-positive and -negative persons in Zambia. The overall level of protection was minimal but significant (38%). Although the level of protection among tuberculin-positive persons was higher (70%), it was not significant because of the limited number of persons in this group.

- Short-course regimens in HIV-negative persons

The only randomized clinical trial to evaluate rifampin-containing regimens among HIV-seronegative persons was conducted in tuberculin-positive persons with silicosis in Hong Kong. In this study, daily regimens of 6 months of isoniazid, 3 months of rifampin, or 3 months of isoniazid and rifampin were compared with a 6-month placebo control. Analyzing only those patients who were assumed to be compliant yielded an estimate of efficacy in preventing tuberculosis of 63% for the 3-month rifampin regimen, 48% for the 6-month isoniazid regimen, and 41% for the 3-month isoniazid-rifampin regimen. All of these differences were significantly different from the placebo regimen but were not statistically different from each other. The annual incidence rate was about 7% per year in the placebo group and about 4% per year in the three active-treatment regimens combined.

- Short-course regimens in HIV-positive persons

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

- Adherence

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

POTENTIAL HARMS

- Isoniazid

Hepatitis is the most severe toxic effect and alcohol consumption may increase toxicity. In a comprehensive study conducted by the PHS (Public Health Service), the overall rate of probable isoniazid hepatitis was 1%. Other side effects are peripheral neuropathy and mild central nervous system effects.

Interaction of isoniazid and phenytoin increases the serum concentration of both drugs.

- Rifampin

The most common adverse reaction is gastrointestinal upset. Other reactions include skin eruptions, hepatitis, and, rarely, thrombocytopenia.

Because rifampin induces hepatic microsomal enzymes, it may accelerate clearance of drugs metabolized by the liver (e.g., methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin). By accelerating the metabolism of estrogen, rifampin may interfere with the effectiveness of oral contraceptives

Intermittent administration of doses of rifampin >10 mg/kg may be associated with thrombocytopenia, an influenza-like syndrome, hemolytic anemia, and acute renal failure.

- Pyrazinamide

The most common side effect of pyrazinamide is gastrointestinal upset. The most severe adverse reaction is liver injury. No substantial increase in hepatotoxicity results from adding 15–30 mg/kg of pyrazinamide to a regimen of rifampin during 2 months of therapy for active tuberculosis (tuberculosis). Hyperuricemia also occurs, but acute gout is uncommon.

- Rifampin-Pyrazinamide

On August 8, 2003, the CDC reported on an analysis of data collected from patients taking rifampin-pyrazinamide (RZ) regimen for treatment of latent tuberculosis infection (LTBI). The analysis found high rates of hospitalization and death from liver injury associated with use of RZ. Based on the analysis, previous recommendations were changed: RZ is generally not to be offered to persons with LTBI. If the regimen is prescribed by a tuberculosis (TB)/LTBI expert, special monitoring is necessary. Refer to the 2003 guideline addendum for details.

During February 12 to August 24, 2001, a total of 21 cases of liver injury associated with a two-month rifampin-pyrazinamide regimen for treatment of latent tuberculosis infection was reported to the Centers for Disease Control. These 21 cases are in addition to two previously reported rifampin-pyrazinamide-associated cases. Cases of liver injury have occurred each year since 1999. [A case was defined as liver injury (i.e., clinical and laboratory findings consistent with hepatitis) leading to hospital admission or death of a patient being treated for latent tuberculosis infection with rifampin-pyrazinamide.]

- Rifabutin

Side effects attributed to rifabutin include rash, gastrointestinal intolerance, neutropenia, myalgias, and dysgeusia. Hepatotoxicity is rare, but rifabutin can cause drug-induced hepatitis. Rates of side effects increase when rifabutin is administered with a CYP (cytochrome P-450)-3A4 inhibitor (e.g., clarithromycin); side effects that have been noted under these circumstances

include uveitis and abnormal skin pigmentation. Similar to rifampin, rifabutin can also decrease concentrations and clinical efficacy of methadone, coumadin derivatives, glucocorticoids, hormonal contraceptives, oral hypoglycemic agents, digitalis, anticonvulsants, dapsone, ketoconazole, and cyclosporin, as well as itraconazole, Å-blockers, and theophylline. Doses of these medications may have to be increased when administered with rifabutin.

- Fluoroquinolones

Side effects of pyrazinamide and fluoroquinolones include gastrointestinal symptoms and hepatic transaminase elevations

Subgroups Most Likely to be Harmed:

- Isoniazid

Isoniazid-related hepatitis is more frequent in persons aged 35 years or older. Alcohol consumption may increase toxicity.

The largest and most comprehensive study of isoniazid hepatitis, conducted by the Public Health Service (PHS) during 1971-1972, reported higher rates of hepatitis among Asian males compared with white males.

A comprehensive analysis of deaths from isoniazid-associated hepatitis in the United States found that women may be at increased risk of death. Other reports have suggested that the risk for isoniazid-associated hepatitis may be increased by the administration of the drug to pregnant women in the third trimester and the immediate postpartum period or by the concomitant administration of acetaminophen.

In a Hong Kong study of patients with silicosis, patients receiving isoniazid had a higher incidence of abnormal liver function tests during treatment.

- Rifampin

By accelerating the metabolism of estrogen, rifampin may interfere with the effectiveness of oral contraceptives.

One study revealed that 3% of 446 fetuses exposed in utero to rifampin had abnormalities (i.e., limb reductions, central nervous system abnormalities, and hypoprothrombinemia) compared with 2% for ethambutol and 1% for both isoniazid and controls. Hemorrhagic disease of the newborn has been described following the use of rifampin in the mother.

- Pyrazinamide

In clinical trials involving HIV-infected persons, a trend of increased adverse reactions occurred among persons taking a daily regimen that included pyrazinamide.

Pyrazinamide should be avoided in pregnancy but may be given after the first trimester.

- Rifampin-Pyrazinamide

The 2-month rifampin-pyrazinamide treatment regimen for latent tuberculosis infection should never be offered to patients who are concurrently taking other medications associated with liver injury; drink excessive amounts of alcohol, even if alcohol use is discontinued during treatment; have underlying liver disease; or have a history of isoniazid (INH)-associated liver disease.

- Rifabutin

When administered with rifabutin, protease inhibitors, used for the treatment of HIV infection, may lead to increased levels of rifabutin and decreased levels of the protease inhibitor; however, these effects are generally less than those that occur with rifampin and can be accommodated by dose adjustments. Non-nucleoside reverse transcriptase inhibitors, used for the treatment of HIV infection, may also necessitate rifabutin dose adjustment.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Isoniazid

Active hepatitis and end-stage liver disease are relative contraindications to the use of isoniazid for treatment of latent tuberculosis infection (latent tuberculosis infection).

- Rifampin

In persons with HIV infection who are taking HIV protease inhibitors, rifampin is usually contraindicated because drug interactions between rifampin and these agents can lead to increased rifampin levels and decreased protease-inhibitor levels, resulting in increased risk for rifampin toxicity and decreased protease-inhibitor efficacy. Rifampin is also contraindicated or should be used with caution in HIV-infected patients who are taking non-nucleoside reverse transcriptase inhibitors (NNRTIs).

- Pyrazinamide

Active hepatitis and end-stage liver disease are relative contraindications to the use of pyrazinamide for treatment of latent tuberculosis infection.

- Rifabutin

Rifabutin is contraindicated for HIV-infected patients taking hard-gel saquinavir or delavirdine; caution is also advised if rifabutin is administered with soft-gel saquinavir.

DESCRIPTION OF IMPLEMENTATION STRATEGY

From the 2003 guideline addendum:

For progression to tuberculosis (TB) disease to be prevented, persons with latent tuberculosis infection (LTBI) should be identified in contact investigations and targeted screening programs and should complete treatment with safe and effective regimens. The successful treatment of LTBI is an essential component of the TB elimination strategy in the United States. In addition to the guideline addendum published in the Morbidity and Mortality Weekly Report (MMWR) [hereinafter referred to as the report], the Centers for Disease Control and Prevention (CDC) and its partners are sending a letter to TB-control programs in 12 large cities and all 50 states and organizations active in TB control (e.g., the National Coalition to Eliminate Tuberculosis). To reach clinicians who are treating patients with LTBI, primary care medical associations (e.g., the American Medical Association and the American College of Physicians) are distributing the report to their members. The report and the letter are available at www.cdc.gov/tb. The letter is being added to the April 2000 CDC Targeted Tuberculin Testing and Treatment of Latent TB Infection Guidelines, and existing provider educational materials are being revised.

From the 2000 original guideline:

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

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

Identification and Access to High-risk Groups

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

Role of the Health Department

In this community-based approach to targeted testing and treatment of latent tuberculosis infection, the health department tuberculosis program should be instrumental in planning and coordination, setting performance standards, and overseeing quality of service. The health department is responsible for assessing the community's tuberculosis problem, identifying high-risk groups based on the local epidemiology of tuberculosis, and ascertaining the sites of most convenient access to those groups. In addition, the health department should assume responsibility for organizing the community-based approach, recruiting health professionals, educating such professionals about tuberculosis, and motivating them to institute targeted testing and treatment programs. The health department should also serve as advisor, consultant, and facilitator to community providers and institutions that conduct testing and treatment programs. The health department should assist in identifying potential funding sources and ensure linkages with essential clinical and consultation sources. It should provide in-service training on tuberculin skin testing and treatment, written protocols for activities including patient tracking and skin testing, and patient and provider educational material translated into appropriate languages. The health department may also need to provide chest radiography and subsidize the supply of antituberculosis drugs. Finally, the health department should be responsible for providing or facilitating the ongoing evaluation of community-based targeted testing and treatment programs, including development and monitoring of program indicators (e.g., rates of skin tests administered that are read, proportion of tests read that are positive, and initiation and completion rates of treatment). The health department should also routinely collect and review these data to determine yield and relative effectiveness of targeted testing and treatment of latent tuberculosis infection in the community.

To achieve a high rate of acceptance of testing and completion of treatment in a community-based program, barriers to success should be anticipated, identified, and managed. The concept of taking drugs to treat a latent infection that is not causing current health problems is unfamiliar to most persons, and education of the patient is essential. Other known barriers include culturally derived health beliefs that differ from those of Western medicine, inability to communicate with medical providers in one's primary language, inability to afford the costs of medical evaluation and treatment, and lack of access to medical care. Patients should not be expected to pay directly for public health interventions (e.g., testing, evaluation, and treatment of latent tuberculosis infection). The more

convenient this process of testing and treatment, the more likely patients will adhere to therapy, especially as targeted testing and treatment of latent tuberculosis infection are extended beyond the province of public health tuberculosis clinics to sites where primary health care is delivered.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep 2000 Jun; 49(RR-6): 1-54. [169 references]

Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection--United States, 2003. MMWR Morb Mortal Wkly Rep 2003 Aug 8; 52(31): 735-9. [16 references] [PubMed](#)

Update: fatal and severe liver injuries associated with Rifampin and Pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations--United States 2001. MMWR Recomm Rep 2001 Aug 31; 50(34): 733-5.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies:

- The original guideline is available in [HTML format](#) and [PDF format](#) from the Centers for Disease Control and Prevention (CDC) Web site.
- The August 2001 Update: Fatal and Severe Liver Injuries Associated with Rifampin and Pyrazinamide for Latent Tuberculosis Infection, and Revisions in American Thoracic Society/CDC Recommendations--United States, 2001 is also available at the [CDC Web site](#).
- The August 2003 Update: Adverse Event Data and Revised American Thoracic Society/CDC Recommendations Against the Use of Rifampin and

Pyrazinamide for Treatment of Latent Tuberculosis Infection--United States, 2003 is also available at the [CDC Web site](#).

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection. Am J Respir Crit Care Med 2000; 161:S221-47.

Electronic copies: Available from the [American Journal of Respiratory Care Medicine Web site](#).

- Continuing education activity sponsored by CDC: Targeted tuberculosis testing and treatment of latent tuberculosis infection. MMWR Morbid Mortal Wkly Rep 2000 Jun; 49(RR-6):CE1-7.

Electronic copies: Available from the [Centers for Disease Control and Prevention \(CDC\) Web site](#).

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

PATIENT RESOURCES

None available

NGC STATUS

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