

Update on the Treatment of Tuberculosis and Latent Tuberculosis Infection

Henry M. Blumberg, MD

Michael K. Leonard, Jr, MD

Robert M. Jasmer, MD

TUBERCULOSIS (TB) HAS EMERGED as a global public health epidemic. The World Health Organization estimates that there will be approximately 9 million individuals who develop active TB disease and more than 2 million deaths due to TB this year.^{1,2} The global epidemic of TB has affected the United States where the majority of cases now occur among non-US-born persons. In the United States, there were 14 511 cases reported in 2004 (4.9 cases per 100 000 individuals).³ Despite decreasing numbers of cases since 1992, TB remains a serious public health problem among certain patient populations and is highly prevalent in many urban areas.⁴ Given the decline in TB cases in the United States, there has been renewed interest in the treatment of those with latent TB infection as a TB-control strategy for eliminating the large reservoir of individuals at risk for progression to TB.

The treatment of TB and the treatment of latent TB infection in the United States are reviewed in this article. National evidence-based guidelines for the treatment of TB⁵ and latent TB infection^{6,7} have been developed in collaboration by the American Thoracic Society, the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America. Additional

CME available online at
www.jama.com

Tuberculosis (TB) has emerged as a global public health epidemic. Despite decreasing numbers of cases in the United States since 1992, TB remains a serious public health problem among certain patient populations and is highly prevalent in many urban areas. The responsibility for prescribing an appropriate drug regimen and ensuring that treatment is completed is assigned to the public health program or the clinician not to the patient. The initial prescribed regimen for the treatment of TB usually consists of 4 drugs: isoniazid, rifampin, pyrazinamide, and ethambutol. The minimum length for the treatment of drug-susceptible TB with a rifampin-based regimen is 6 to 9 months. Providing medications directly to the patient and watching him/her swallow the anti-TB drugs, which is termed *directly observed therapy*, is recommended for all patients diagnosed with TB and can help ensure higher completion rates, prevent the emergence of drug resistant TB, and enhance TB control. There has been renewed interest in the treatment of those with latent TB infection as a TB-control strategy in the United States for eliminating the large reservoir of individuals at risk for progression to TB. The 2 broad categories of persons who should be tested for latent TB infection are those who are likely to have been recently infected (such as contacts to infectious TB cases) and persons who are at increased risk of progression to TB disease following infection with *Mycobacterium tuberculosis* (eg, human immunodeficiency virus infection and selected medical conditions; recent immigrants to the United States from high TB-burden countries). The preferred regimen for the treatment of latent TB infection is 9 months of isoniazid. There is now renewed interest in and great need for the development of new drugs to treat TB and latent TB infection.

JAMA. 2005;293:2776-2784

www.jama.com

guidelines for the treatment of latent TB infection in children and adolescents have also been published.⁸

TB Treatment

Successful treatment of TB depends on more than the science of chemotherapy and should be provided within a clinical and social framework based on the patient's circumstances.⁵ The responsibility for prescribing an appropriate drug regimen and ensuring that treatment is completed is assigned to

the public health program or the clinician not to the patient.⁵ The initial prescribed regimen usually consists of iso-

Author Affiliations: Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Ga (Drs Blumberg and Leonard); Epidemiology Department, Grady Memorial Hospital, Atlanta, Ga (Dr Blumberg); and Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco (Dr Jasmer).

Corresponding Author: Henry M. Blumberg, MD, Division of Infectious Diseases, Emory University School of Medicine, 49 Jesse Hill Jr Dr, Atlanta, GA 30303 (henry.m.blumberg@emory.edu).

niazid, rifampin, pyrazinamide, and ethambutol. Providing medications directly to the patient and watching him/her swallow the anti-TB drugs, which is termed *directly observed therapy*, is recommended for all patients diagnosed with TB and can help ensure higher completion rates (FIGURE 1), prevent the emergence of drug-resistant disease, and enhance TB control.^{5,9} The infrastructure to provide directly observed therapy is generally only available through public health agencies. Tuberculosis should never be treated with a single drug and a single drug should never be added to a failing regimen because of the risk of emergence of drug-resistant disease. Thus, multidrug therapy is required. The minimum length of therapy for the treatment of drug-susceptible TB is 6 to 9 months (often termed *short-course therapy*) with a rifampin-based regimen.

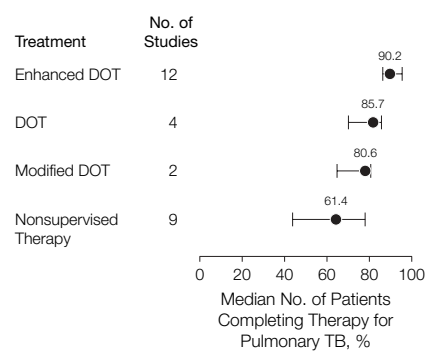
Indications for Initiating Therapy. The decision to initiate combination

anti-TB chemotherapy (eg, 4-drug therapy) should be based on epidemiological information; clinical, pathological, and radiographic findings; and the results of microscopic examination of acid-fast bacilli (AFB)-stained sputum smears as well as other appropriately collected diagnostic specimens and cultures for mycobacteria.⁵ Empirical therapy with an appropriate multidrug regimen (TABLE 1) needs to be initiated when there is a high clinical suspicion for active disease prior to culture confirmation and in some cases before AFB smear microscopy results are known. The use of nucleic acid amplification tests may be useful in selected cases in providing an immediate definitive diagnosis (eg, confirmation of AFB smear-positive respiratory specimens).¹¹ The threshold for initiating empirical therapy should be low for patients with potentially rapid, life-threatening conditions such as tuberculous meningitis, pericarditis, or miliary disease.

Principles of Multidrug Treatment.

The goals of anti-TB therapy include ensuring a cure without relapse, preventing death, stopping transmission of *Mycobacterium tuberculosis*, and preventing the emergence of drug-resistant disease.¹ Therapy is initiated with a multidrug regimen to kill tubercle bacilli

Figure 1. Treatment Completion Rates for Pulmonary Tuberculosis



Error bars indicate range. DOT indicates directly observed therapy; TB, tuberculosis. Source: Chauk et al.⁹

Table 1. Drug Regimens for Culture-Positive Pulmonary TB Caused by Drug-Susceptible Organisms⁵

| Initial Phase | | Continuation Phase | | Range of Total Doses (Minimum Duration) | Rating/Evidence Level ^{†‡} | |
|---|---|----------------------------|---|---|-------------------------------------|--------------|
| Regimen | Interval and Dose (Minimum Duration)* | Regimen | Interval and Dose (Minimum Duration)*† | | HIV Negative | HIV Positive |
| Isoniazid, rifampin, pyrazinamide, and ethambutol | 7 d/wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)§ | Isoniazid and rifampin | 7 d/wk for 126 doses (18 wk) or 5 d/wk for 90 doses (18 wk)§ | 130-182 (26 wk) | A/I | A/II |
| | | Isoniazid and rifampin | 2 d/wk for 36 doses (18 wk) | 76-92 (26 wk) | A/I | A/II |
| | | Isoniazid and rifapentine¶ | 1 d/wk for 18 doses (18 wk) | 58-74 (26 wk) | B/I | E/I |
| Isoniazid, rifampin, pyrazinamide, and ethambutol | 7 d/wk for 14 doses (2 wk)# | Isoniazid and rifampin | 2 wk/d for 36 doses (18 wk) | 58-62 (26 wk) | A/II | B/III |
| | | Isoniazid and rifapentine¶ | 1 d/wk for 18 doses (18 wk) | 40-44 (26 wk) | B/I | E/I |
| Isoniazid, rifampin, pyrazinamide, and ethambutol | 3 d/wk for 24 doses (8 wk) | Isoniazid and rifampin | 3 d/wk for 54 doses (18 wk) | 78 (26 wk) | B/I | B/II |
| Isoniazid, rifampin, and ethambutol | 7 d/wk for 56 doses (8 wk) or 5 d/wk for 40 doses (8 wk)§ | Isoniazid and rifampin | 7 d/wk for 217 doses (21 wk) or 5 d/wk for 155 doses (31 wk)§ | 195-273 (39 wk) | C/I | C/II |
| | | Isoniazid and rifampin | 2 d/wk for 62 doses (31 wk) | 102-118 (39 wk) | C/I | C/II |

Abbreviations: HIV, human immunodeficiency virus; TB, tuberculosis.

*When directly observed therapy is used, drugs may be taken 5 d/wk and the necessary number of doses adjusted accordingly. No studies compare regimens taken 5 d/wk with regimens taken 7 d/wk, but this should be effective.

†Patients with cavitation on initial chest radiograph and positive cultures at completion of 2-month therapy should receive a 7-month continuation phase (31 weeks; either 217 doses if taken daily or 62 doses if taken twice weekly).

‡Rating level: A indicates preferred regimen; B, acceptable alternative; C, offer when A and B cannot be given; D, generally should not be given; E, should never be given. Evidence level: I indicates based on data from a randomized trial with clinical end points; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

§Five days per week administration is always given by directly observed therapy. The rating and evidence level is A/III.

¶Not recommended for HIV-infected patients with CD4 cell counts lower than 100/μL.

#Should be used only in HIV-negative patients who have negative sputum smears at the time of completion of 2-month therapy and who do not have cavitation on initial chest radiograph. For patients started on this regimen and found to have a positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

#Then twice weekly for 12 doses (6 wk) or 5 d/wk for 10 doses (2 wk), which is always given by directly observed therapy, and then twice weekly for 12 doses (6 wk).

Box 1. First- and Second-Line Anti-TB Drugs**First-Line Drugs**

Isoniazid
Rifampin
Rifapentine
Rifabutin*
Pyrazinamide
Ethambutol

Second-Line Drugs

Cycloserine
Ethionamide
Levofloxacin*
Moxifloxacin*
Gatifloxacin*
P-Aminosalicylic acid
Streptomycin
Amikacin/kanamycin*
Capreomycin

*Not approved by the Food and Drug Administration for use in the treatment of tuberculosis (TB).

rapidly, to minimize or prevent development of drug resistance in *M tuberculosis*, and to eliminate persistent organisms from the host's tissue to prevent relapse. The first randomized trial was published in 1946 and explored the use of streptomycin for the treatment of TB.¹² Subsequent randomized trials performed by the British Medical Research Council, the US Public Health Service, and other investigators have helped to define regimens for the treatment of TB including rifampin-based short-course therapy regimens, which are now the standard of care.¹²⁻¹⁷

BOX 1 lists the first- and second-line drugs available for the treatment of TB. TABLE 2 lists the recommended doses and adverse effects for first-line drugs.

There are 2 phases of treatment for patients with TB—the initiation phase (bactericidal or intensive phase), which consists of 2 months of therapy, and the continuation phase (subsequent sterilizing phase), which lasts 4 to 7 months for patients with drug-susceptible dis-

ease. Therapy for TB should be initiated with a 4-drug regimen consisting of isoniazid, rifampin, pyrazinamide, and ethambutol because of concerns about the prevalence of drug resistance (Table 1). Appropriate clinical specimens should be obtained to make a definitive diagnosis and recover *M tuberculosis* from a culture so that susceptibility testing may be performed.

For patients with drug-susceptible disease, pyrazinamide should be discontinued after 2 months of therapy, which is the end of the initiation phase. Ethambutol can also be discontinued after 2 months of therapy or as soon as drug susceptibility is confirmed. Isoniazid and rifampin are continued for an additional 4 months during the continuation phase to complete a minimum of 6 months of therapy for drug-susceptible disease. Patients at high risk for relapse after 6 months of therapy are those with cavitary pulmonary TB who continue to have positive TB cultures after 2 months of therapy.¹⁷ Such patients should have

Table 2. Recommended Dosages and Drug-Related Adverse Effects of First-Line Anti-TB Drugs Used for Initial Treatment in Children and Adults

| Drug | Type of Administration | Dosage Frequency* | | | Adverse Effects | |
|--------------|-------------------------------------|-------------------|-------------------------|----------------------|---|-------------|
| | | Daily | 2 d/wk† | 3 d/wk† | | |
| Isoniazid | Oral, intramuscular, or intravenous | | | | Hepatic enzyme elevation; hepatitis; peripheral neuropathy; CNS effects; rash | |
| | | Children | 10 mg/kg | 20-30 mg/kg | | ... |
| | | Adults | 5 mg/kg | 15 mg/kg | | 15 mg/kg |
| | | Maximum | 300 mg | 900 mg | | 900 mg |
| Rifampin | Oral or intravenous | | | | Orange discoloration of secretions and in urine (occurs in all patients); hepatitis; rash thrombocytopenia, flu-like symptoms; many drug interactions | |
| | | Children | 10-20 mg/kg | 10-20 mg/kg | | ... |
| | | Adults | 10 mg/kg | 10 mg/kg | | 10 mg/kg |
| | | Maximum | 600 mg | 600 mg | | 600 mg |
| Rifabutin | Oral | | | | Similar to rifampin; uveitis | |
| | | Adults | 5 mg/kg | 5 mg/kg | | 5 mg/kg |
| | | Maximum | 300 mg | 300 mg | | 300 mg |
| Pyrazinamide | Oral | | | | Gastrointestinal tract upset; hepatitis; hyperuricemia; arthralgias | |
| | | Children | 15-30 mg/kg | 50 mg/kg (2 g max) | | ... |
| | | Adults | 25 mg/kg | 50 mg/kg | | 35-40 mg/kg |
| | | Maximum | 2 g | 4 g | | 3 g |
| Ethambutol | Oral | | | | Optic neuritis | |
| | | Children | 15-20 mg/kg (1.0 g max) | 50 mg/kg (2.5 g max) | | ... |
| | | Adults | 15-25 mg/kg | 50 mg/kg | | 25-30 mg/kg |
| | | Maximum | 1600 mg | 2400 mg | | 4000 mg |

Abbreviations: CNS, central nervous system; TB, tuberculosis. Ellipses indicate no recommended dosage.

*Doses per weight are based on ideal body weight. Children weighing more than 40 kg should receive adult doses.

†Must be administered by directly observed therapy only.

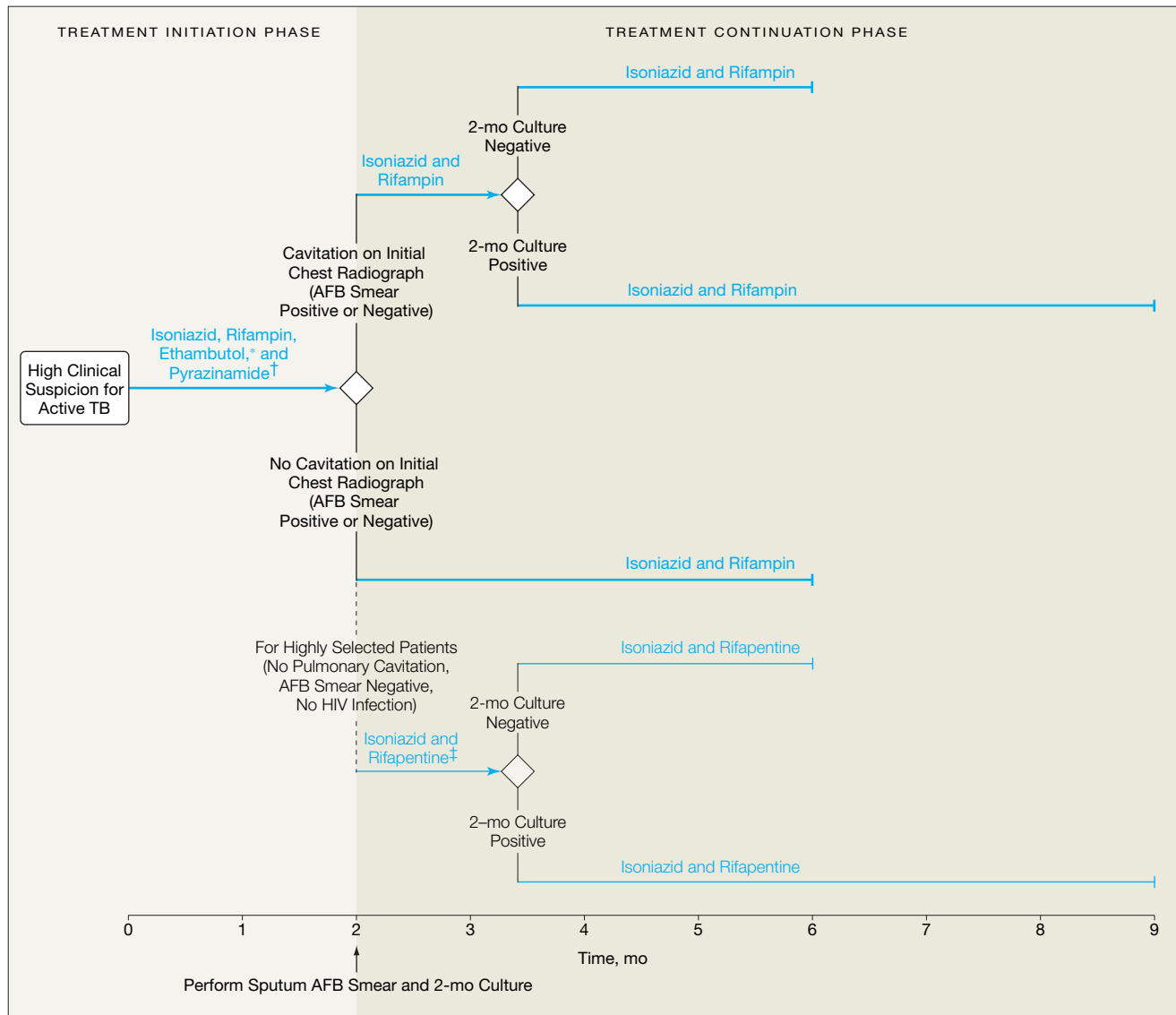
therapy extended for an additional 3 months during the continuation phase for a total of 9 months of therapy. A treatment algorithm for drug-susceptible pulmonary TB is shown in FIGURE 2.

TB Treatment in Special Circumstances

HIV-Infected Persons. All patients diagnosed with TB should be strongly encouraged to undergo human immu-

nodeficiency virus (HIV) testing.⁵ Tuberculosis may be the first disease that brings an HIV-infected person into the health care system. Treatment of TB among HIV-infected persons is simi-

Figure 2. Treatment Algorithm for Drug-Susceptible Pulmonary TB⁵



Patients in whom tuberculosis (TB) is proved or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol for the initial 2 months of treatment. A repeat acid-fast bacilli (AFB) smear and culture should be performed when the initial 2 months of drug treatment has been completed. If cavitation was present on the initial chest radiograph and the TB culture was positive after 2 months of therapy, the continuation phase should be extended to 7 months (total treatment: 9 months). If cavitation was present on the initial chest radiograph but the TB culture was negative at 2 months, the total length of therapy should be 6 months (2 months of initial therapy and 4 months in the continuation phase). If a patient was infected with human immunodeficiency virus (HIV) and his/her CD4 cell count was lower than 100/ μ L, the continuation phase should consist of isoniazid and rifampin daily or 3 times weekly. In patients without HIV, without cavitation on chest radiograph, and negative AFB smears at completion of initial 2-month treatment, the continuation phase may consist of either (1) once-weekly isoniazid and rifapentine or (2) isoniazid and rifampin daily or twice weekly (total treatment: 6 months). In patients who took isoniazid and rifapentine and whose 2-month cultures were positive, treatment should be extended 3 months (total treatment: 9 months). Asterisk indicates ethambutol may be discontinued when results of drug susceptibility testing indicate no drug resistance. Dagger indicates pyrazinamide may be discontinued after it has been taken for 2 months. Double dagger indicates rifapentine should not be used in patients who have HIV and TB or in patients with extrapulmonary TB. Section symbol indicates therapy should be extended to 9 months if the 2-month culture was positive. Source: Blumberg et al.⁵

lar to that in those not infected with HIV with 2 exceptions. One exception is that HIV-infected patients should not be treated with a once-weekly isoniazid and rifampine regimen during the continuation phase because of an unacceptably high increased risk of relapse with this regimen, which occurs frequently with organisms that have acquired rifamycin resistance.¹⁸ Second, HIV-infected patients with CD4 cell counts lower than 100/ μ L should not receive twice-weekly intermittent regimens (eg, isoniazid and rifampin or isoniazid and rifabutin during the continuation phase) because acquired rifamycin resistance has also been reported in this setting.¹⁹ It has been recommended that HIV-infected patients with low CD4 cell counts should receive therapy daily or 3 times weekly.^{5,19} Patients infected with HIV who have drug-susceptible TB can generally be treated for 6 months (Table 1). For those HIV-infected patients with TB who are slow to respond to therapy or who have a suboptimal response (eg, cultures are still positive after 2 months of therapy), prolongation of the continuation phase to 7 months for a total of 9 months of treatment is suggested.

The use of antiretroviral therapy among HIV-infected patients with TB is complicated by overlapping toxicity profiles of some anti-TB and antiretroviral drugs, complex drug interactions, and the occurrence of immune reconstitution reactions.²⁰ The use of antiretroviral therapy during TB treatment is complex for both the patient and the physician.²¹ Thus, there needs to be close coordination of care between HIV and TB clinicians. A long list of clinically significant drug interactions involving rifamycins has been published.^{5,20} Rifamycins induce the hepatic cytochrome P450 3A system. Rifampin is the most potent inducer and cannot be given with most protease inhibitors and some non-nucleoside reverse transcriptase inhibitors because it results in low serum levels of these drugs. Rifabutin has less of an effect and therefore can be used with certain protease inhibitors. Updated recommendations on the use of antiretro-

viral regimens among patients undergoing treatment for TB have been published²² and are available from the CDC at http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm.

Persons infected with HIV who begin taking antiretroviral agents early in the course of their anti-TB therapy are more likely to experience the immune reconstitution syndrome, which is characterized by exacerbation of symptoms and signs or by radiographic manifestations of TB.²³ There are no data to indicate the optimal timing of initiation of antiretroviral therapy among HIV-infected patients with TB. However, to try to reduce the risk of immune reconstitution reactions from occurring, it has been recommended to delay initiation of antiretrovirals until after 2 months of anti-TB therapy if possible.⁵

Extrapulmonary TB. The basic principles that underlie the treatment of pulmonary TB also apply to extrapulmonary forms of the disease. A 6-month course of therapy is recommended for treating drug-susceptible TB involving any site with the exception of the meninges for which a 9- to 12-month regimen is recommended.⁵ Prolongation of therapy also should be considered for patients with extrapulmonary TB that is slow to respond to treatment. The addition of corticosteroids is strongly recommended for patients with TB pericarditis and meningitis to improve outcomes and decrease mortality.^{5,24}

Drug-Resistant TB. Treatment of drug-resistant TB, especially multidrug-resistant TB, which is defined by resistance to at least isoniazid and rifampin, is quite challenging and should only be performed by or in close consultation with an expert in the management of drug-resistant disease. Treatment guidelines for multidrug-resistant TB have been published.⁵

Response to Treatment. For patients undergoing treatment for pulmonary TB, it is recommended that a sputum specimen for an AFB smear and culture should be obtained at least monthly until 2 consecutive specimens are culture-negative.⁵ It is crucial to obtain a sputum specimen for an

AFB smear and culture after 2 months of therapy because this result is an important risk predictor of relapse. Drug-susceptibility tests should always be performed on the initial positive culture and should be repeated on *M tuberculosis* isolates from patients who have positive cultures after 3 months of treatment. All patients undergoing treatment for TB should be seen on a monthly basis and have a clinical evaluation to identify possible adverse effects of the anti-TB medications and to assess adherence.

New Drugs for TB Treatment

Following decades of neglect, there is now renewed hope and interest in the development of drugs to treat TB.²⁵ The effort for drug development is in large part being coordinated by the Global Alliance for TB Drug Development,²⁶ a recently established organization that has been building public-private partnerships with the objective of creating a portfolio of new TB drugs and bringing a new TB drug to the market in the next decade. There has been considerable excitement about the potential of a newly discovered novel diarylquinoline that considerably reduces the time necessary to treat TB in mice.²⁷ Further studies are needed to determine if this potential will be met in the treatment of humans with TB.

Latent TB Infection

As cases of TB have decreased in the United States,³ there has been renewed interest and focus on the treatment of latent TB infection as an important TB-control strategy.^{28,29} Two broad categories of candidates for latent TB infection testing are persons who are likely to have been recently infected (such as contacts to infectious TB cases) and persons who are at increased risk of progression to TB disease following infection with *M tuberculosis* because of certain clinical conditions (eg, HIV infection and selected medical conditions; recent immigrants to the United States from high TB-burden countries).⁶ Prior to beginning treatment for latent TB infection,

it is essential that active TB be excluded by a chest radiograph and symptom review in all persons suspected of having latent TB infection.

For more than 100 years, the only test to identify latent TB infection was the tuberculin skin test. Diagnostic criteria for what constitutes a positive tuberculin skin test appear in **BOX 2**.⁶ Limitations of the tuberculin skin test include (1) reader variability; (2) false-positive test results due to cross-reactivity with environmental mycobacteria and with previous BCG vaccination; and (3) false-negative test results due to anergy in immunosuppressed individuals, emphasizing the need for new and better diagnostic tests for latent TB infection.²⁹ In recent years, peripheral blood T-cell–based interferon γ (IFN- γ) assays have been developed and investigated. There are 2 commercially available tests: a whole-blood IFN- γ release assay (QuantiFERON-TB Gold, Cellestis Ltd, Victoria, Australia), which has been recently approved by the Food and Drug Administration; and an enzyme-linked immunospot assay (T SPOT-TB, Oxford Immunotec, Oxford, England), which is approved for use in Europe. The CDC has published guidelines on the use of the first generation QuantiFERON-TB assay, which is no longer available,³⁰ and will be publishing guidelines for use of second generation QuantiFERON-TB Gold, which uses TB-specific antigens, in selected patient populations. These T-cell–based assays offer hope for improved sensitivity and specificity for the diagnosis of infection with *M tuberculosis*.^{31–35} However, prospective studies are needed to determine (1) whether IFN- γ responses are predictive of those who have a high risk of progression to active TB, (2) the utility of such tests in specialized subgroups of patients (including children and HIV-infected persons), and (3) whether treating latent TB infection based on IFN- γ results will reduce the TB burden in low-incidence countries such as the United States.

Isoniazid remains the drug of choice for treatment of latent TB infection

Box 2. Criteria for a Positive Tuberculin Skin Test by Risk Group

Response With \geq 5-mm Induration

Positive test result for human immunodeficiency virus (HIV)
 Contact with someone who has tuberculosis (TB)
 Fibrotic changes on chest radiograph consistent with prior TB
 Organ transplant recipients, patients receiving tumor necrosis factor α inhibitors (eg, infliximab, etanercept, adalimumab) or other immunosuppression (receiving the equivalent of >15 mg/d of prednisone for ≥ 1 month)*

Response With \geq 10-mm Induration

Recent immigrant from high-prevalence country
 Injection drug use
 Resident or employee† of a prison or jail, nursing home or other long-term facility for the elderly, hospital or other health care facility, residential facility for patients with AIDS, or a homeless shelter
 Works at mycobacteriology laboratory
 Person at high risk due to having silicosis, diabetes mellitus, chronic renal failure, some hematologic disorder, other specific malignancy (eg, carcinoma of the head or neck and lung), weight loss higher than 10% of ideal body weight, gastrectomy, or jejunioileal bypass
 Child younger than 4 years; and infant, child, or adolescent exposed to an adult at high risk

Response With \geq 15-mm Induration

Anyone (including a person without risk factors for TB)

Source: American Thoracic Society.⁶

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

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

(TABLE 3).^{6,7} The effectiveness of isoniazid for treatment of latent TB infection has been reported to range from 25% to 92%.⁶ However, when the analysis was restricted to persons who were compliant with the medication, the protective efficacy was approximately 90%. The preferred duration of treatment with isoniazid for latent TB infection in all patient populations is 9 months because clinical trial data suggest that the maximal benefit is achieved by this period (Table 3).^{6,36} Treatment with isoniazid for 6 months is an alternative for HIV-seronegative adults.

The most important adverse effect of isoniazid is hepatitis. The rate of symptomatic isoniazid-related hepatitis has been estimated to be 1 to 3 per 1000 persons.^{37,38} However, asymptomatic liver enzyme abnormalities are rela-

tively common.^{39,40} The most important cofactor for the development of isoniazid-induced hepatitis is alcohol consumption. All persons taking isoniazid should be educated about the symptoms of hepatitis so that they can be evaluated before hepatitis becomes severe. In an effort to prevent the development of neuropathy, 25 to 50 mg/d of pyridoxine should be given concurrently with isoniazid to persons predisposed to neuropathy (such as patients with diabetes, uremia, malnutrition, and HIV infection), pregnant women, and persons with seizure disorders.

Treatment with rifampin alone for 4 months is an alternative choice for treatment of latent TB infection (Table 3). However, rifampin for treatment of latent TB infection has not been exten-

sively studied. In the only large randomized trial evaluating its use, 10% of the patients taking rifampin alone for 3 months developed TB within 5 years of completing therapy.⁴¹ Rifampin is best used in patients who are presumed to have infection with isoniazid-resistant strains of *M tuberculosis*. Data regarding toxicity in patients taking rifampin alone for latent TB infection are limited. However, rifampin alone appeared to be well-tolerated and had a very low rate of hepatotoxicity in 3 published studies.⁴¹⁻⁴³

For patients being treated for latent TB infection, baseline and monthly laboratory testing of liver enzymes are not routinely recommended by the guidelines from the American Thoracic Society and the CDC.⁶ Baseline and monthly laboratory testing of liver enzymes is recommended for HIV-infected persons; pregnant women and those women who are within 3 months postpartum; persons with a chronic liver disease; and persons who consume alcohol regularly.⁶ Baseline and

monthly monitoring of liver enzymes should also be performed for patients with comorbid illnesses who are also taking other medications that can be hepatotoxic. Isoniazid or rifampin should not be given if a symptomatic patient's serum transaminase level is higher than 3 times the upper limit of normal or if an asymptomatic patient's serum transaminase level is higher than 5 times the upper limit of normal.^{6,7} Recommendations on doses and length of therapy for latent TB infection are summarized in Table 3.

In 2000, guidelines from the American Thoracic Society and the CDC recommended a third option for the treatment of latent TB infection in adults: a 2-month regimen of rifampin and pyrazinamide.⁶ This recommendation was based on studies performed in HIV-infected persons that suggested this regimen was as effective and safe as isoniazid.⁴⁴⁻⁴⁶ Unfortunately, following the initial recommendation for the wider use of rifampin and pyrazinamide for latent TB infection among all adults,⁶

48 cases of severe liver injury and/or death were reported to the CDC among patients treated with the regimen of rifampin and pyrazinamide.⁷ The CDC estimated the rate of hospitalization from liver injury related to the regimen of rifampin and pyrazinamide to be 3 per 1000 persons treated for latent TB infection and the rate of death from liver injury to be 0.9 per 1000 persons treated, which is substantially higher than the risk of death reported in the literature for isoniazid (0-0.3 per 1000 persons; median, 0.04 per 1000 persons).⁷ As a result, revised guidelines that rifampin plus pyrazinamide should not be used to treat latent TB infection in either HIV-infected or uninfected persons were published by the American Thoracic Society and the CDC in 2003 and were endorsed by the Infectious Diseases Society of America.⁷

Several additional studies have examined the risk of hepatic toxicity of treatment with rifampin and pyrazinamide for latent TB infection.⁴⁶⁻⁵⁶ These studies demonstrate an increased rate

Table 3. Recommended Regimens for the Treatment of Latent TB Infection*

| Drug and Regimen | Dosage and Duration | | Rating/Evidence Level† ⁹ | | Comment |
|------------------|---------------------|----------------------|-------------------------------------|--------------|--|
| | Adults | Children | HIV Negative | HIV Positive | |
| Isoniazid | | | | | Preferred regimen for adults and children; should be given to HIV-infected persons and those with fibrotic lesions on chest radiograph; concomitant administration of antiretrovirals is permissible |
| Daily | 5 mg/kg for 9 mo | 10-15 mg/kg for 9 mo | A/II | A/II | |
| Maximum | 300 mg | 300 mg | | | |
| 2 d/wk | 900 mg for 9 mo | 20-30 mg/kg for 9 mo | B/II | B/II | Directly observed therapy must be used |
| Maximum | | 900 mg | | | |
| Isoniazid | | | | | Alternative regimen for HIV-negative adults |
| Daily | 5 mg/kg for 6 mo | NA | B/I | C/I | |
| Maximum | 300 mg | NA | | | |
| 2 d/wk | 900 mg for 6 mo | NA | B/II | C/I | Directly observed therapy must be used |
| Rifampin‡ | | | | | Alternative regimen for the treatment of latent TB infection; should be used to treat contacts of patients with isoniazid-resistant TB |
| Daily | 10 mg/kg for 4 mo | 10-20 mg/kg for 6 mo | B/II | B/III | |
| Maximum | 600 mg | 600 mg | | | |

Abbreviations: HIV, human immunodeficiency virus; NA, not recommended for children for 6 months; TB, tuberculosis.

*The use of rifampin and pyrazinamide for the treatment of latent TB infection is not recommended (D/II) for any patients because of reports of high rates of severe hepatotoxicity with this regimen. Sources: American Thoracic Society,⁶ Centers for Disease Control and Prevention,⁷ and the Pediatric Tuberculosis Collaborative Group.⁸

†Rating level: A indicates preferred regimen; B, acceptable alternative; C, offer when A and B cannot be given; D, generally should not be given; E, should never be given. Evidence level: I indicates based on data from a randomized trial with clinical end points; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.

‡Cannot be taken by HIV-infected persons taking protease inhibitors or certain nonnucleoside reverse transcriptase inhibitors. These persons should take rifabutin. Current data are available at: http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm or <http://www.aidsinfo.nih.gov/guidelines>. Many drug interactions can result in decreased levels of other concomitantly administered drugs (eg, antiretrovirals, warfarin, methadone).

of hepatotoxicity for patients not infected with HIV and treated with rifampin and pyrazinamide for latent TB infection. Combining results from all of these studies results in a rate of moderate-to-severe liver injury of 7.3%. The reason for the increased rate of hepatotoxicity among those taking this regimen for latent TB infection is not known.

A major limitation of the treatment of latent TB infection is poor completion rates for self-administered therapy.^{57,58} Nearly 40 years after isoniazid was introduced into clinical practice for the treatment of latent TB infection, little progress has been made in the identification of new, shorter, and safer regimens for the treatment of latent TB infection.^{58,59} Currently, the CDC-funded TB Trials Consortium is performing a randomized, multicenter study to compare a 3-month regimen of isoniazid and rifapentine given once weekly with a 9-month regimen of isoniazid given daily. Results from that study will not be available for several years.

Conclusions

Updated recommendations on the treatment of TB and latent TB infection exist. Prescribing an appropriate treatment regimen for TB and ensuring completion of therapy is best achieved with directly observed therapy, which is essential for curing patients with the disease, minimizing the risk of emergence of drug-resistant disease, and for enhancing TB control. Thus, treatment of TB often requires close collaboration between the public and private sectors. New drugs are needed for the treatment of multidrug-resistant TB and to shorten treatment regimens to less than 6 months for those with drug-susceptible TB. Better diagnostic tests for latent TB infection and shorter, safe, and efficacious treatment regimens are needed to enhance the use of detection and treatment of latent TB infection as a TB-control strategy.

Financial Disclosures: None reported.

Funding/Support: This work was supported in part by grant K07 HL03078 from the National Institutes

of Health and the National Heart, Lung, and Blood Institute and grant D43TW007124 from the National Institutes of Health and the Fogarty International Center.

Role of the Sponsor: The National Institutes of Health had no role in the preparation, review, or approval of the manuscript.

REFERENCES

- Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C. Tuberculosis. *Lancet*. 2003;362:887-899.
- World Health Organization. *Global Tuberculosis Control: Surveillance, Planning, Financing*. Geneva, Switzerland: World Health Organization; 2004.
- Centers for Disease Control and Prevention. Trends in tuberculosis—United States—2004. *MMWR Morb Mortal Wkly Rep*. 2005;54:245-249.
- Sotir MJ, Parrott P, Metchock B, et al. Tuberculosis in the inner city. *Clin Infect Dis*. 1999;29:1138.
- Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167:603-662.
- American Thoracic Society; Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161:S221-S247.
- Centers for Disease Control and Prevention. 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;52:735-739.
- Pediatric Tuberculosis Collaborative Group. Targeted tuberculin skin testing and treatment of latent tuberculosis infection in children and adolescents. *Pediatrics*. 2004;114:1175-1201.
- Chaulk CP, Kazdanzian VA. Directly observed therapy for the completion of tuberculosis: consensus statement of the Public Health Tuberculosis Guidelines Panel. *JAMA*. 1998;279:943-949.
- Gross PA, Barrett TL, Dellinger EP. Quality standard for the treatment of bacteremia. *Clin Infect Dis*. 1994;18:428-430.
- Brodie D, Schluger NW. The diagnosis of tuberculosis. *Clin Chest Med*. 2005;26:247-271.
- Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. *BMJ*. 1948;2:769-782.
- Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications. *Int J Tuberc Lung Dis*. 1999;3(suppl 2):S231-S279.
- Combs DL, O'Brien RJ, Geiter LJ. USPHS Tuberculosis Short-Course Chemotherapy Trial 21. *Ann Intern Med*. 1990;112:397-406.
- Cohn DL, Catlin BJ, Peterson KL, Judson FN, Sbarbaro JA. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. *Ann Intern Med*. 1990;112:407-415.
- Singapore Tuberculosis Service/British Medical Research Council. Longterm follow-up of a clinical trial of 6-month and 4-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis*. 1986;133:779-783.
- Benator D, Bhattacharya M, Bozeman L, et al; Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet*. 2002;360:528-534.
- Vernon A, Burman W, Benator D, Khan A, Bozeman L; Tuberculosis Trials Consortium. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet*. 1999;353:1843-1847.
- Centers for Disease Control and Prevention. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. *MMWR Morb Mortal Wkly Rep*. 2002;51:214-215.
- Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy in adults with tuberculosis: current status. *Int J Tuberc Lung Dis*. 2005;9:248-257.
- Burman WJ. Issues in the management of HIV-related tuberculosis. *Clin Chest Med*. 2005;26:283-294.
- Centers for Disease Control and Prevention. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. *MMWR Morb Mortal Wkly Rep*. 2004;53:37.
- Narita M, Ashkin D, Hollender ES, et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med*. 1998;158:157.
- Thwaites GE, Nguyen DB, Nguyen HD, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *N Engl J Med*. 2004;351:1741-1751.
- O'Brien RJ, Spigelman M. New drugs for tuberculosis. *Clin Chest Med*. 2005;26:327-340.
- TB Alliance. Global alliance for TB drug development. Available at: <http://www.tballiance.org>. Accessibility verified May 10, 2005.
- Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science*. 2005;307:223-227.
- Advisory Council for the Elimination of Tuberculosis. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. *MMWR Recomm Rep*. 1999(48)RR-9:1-13.
- Institute of Medicine. *Ending Neglect: The Elimination of Tuberculosis in the United States*. Washington, DC: National Academy Press; 2000.
- Mazurek GH, Villarino ME. Guidelines for using the QuantiFERON-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. *MMWR Recomm Rep*. 2003;52RR-2:15-18.
- Pai M, Riley LW, Colford JM Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. *Lancet Infect Dis*. 2004;4:761-776.
- Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. *Am J Respir Crit Care Med*. 2004;170:59-64.
- Barnes PF. Diagnosing latent tuberculosis infection: turning glitter to gold. *Am J Respir Crit Care Med*. 2004;170:5-6.
- Lalvani A, Pathan AA, Durkan H, et al. Enhanced contact tracing and spatial tracking of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Lancet*. 2001;357:2017-2021.
- Ewer K, Deeks J, Alvarez L, et al. Comparison of T-cell-based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak. *Lancet*. 2003;361:1168-1173.
- Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *Int J Tuberc Lung Dis*. 1999;3:847-850.
- Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA*. 1999;281:1014-1018.
- LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. *Am J Respir Crit Care Med*. 2003;168:443-447.
- Byrd RB, Horn BR, Solomon DA, Griggs GA. Toxic effects of isoniazid in tuberculosis chemoprophylaxis: role of biochemical monitoring in 1,000 patients. *JAMA*. 1979;241:1239-1241.

40. Mitchell JR, Zimmerman HJ, Ishak KG, et al. Isoniazid liver injury: clinical spectrum, pathology, and probable pathogenesis. *Ann Intern Med.* 1976;84:181-192.
41. Hong Kong Chest Service/Tuberculosis Research Centre; Madras/British Medical Research Council. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. *Am Rev Respir Dis.* 1992;145:36-41.
42. Polesky A, Farber HW, Gottlieb DJ, et al. Rifampin preventive therapy for tuberculosis in Boston's homeless. *Am J Respir Crit Care Med.* 1996;154:1473-1477.
43. Villarino ME, Ridzon R, Weismuller PC, et al. Rifampin preventive therapy for tuberculosis infection. *Am J Respir Crit Care Med.* 1997;155:1735-1738.
44. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS.* 1998;12:2447-2457.
45. Halsey NA, Coberly JS, Desormeaux J, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet.* 1998;351:786-792.
46. Gordin F, Chaisson RE, Matts JP, et al; Terry Bein Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. *JAMA.* 2000;283:1445-1450.
47. Gordin FM, Cohn DL, Matts JP, Chaisson RE, O'Brien RJ. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? *Clin Infect Dis.* 2004;39:561-565.
48. Lobato MN, Jasmer RM, Grabau JC, Bock NN, Shang N; 2RZ Study Group. Adverse events and treatment completion for latent tuberculosis in jail inmates and homeless persons. *Chest.* 2005;127:1296-1303.
49. Bock NN, Rogers T, Tapia JR, et al. Acceptability of short-course rifampin and pyrazinamide treatment of latent tuberculosis infection among jail inmates. *Chest.* 2001;119:833-837.
50. Jasmer RM, Saukkonen JJ, Blumberg HM, et al. Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann Intern Med.* 2002;137:640-647.
51. Lee AM, Mennone JZ, Jones RC, Paul WS. Risk factors for hepatotoxicity associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection. *Int J Tuberc Lung Dis.* 2002;6:995-1000.
52. Leung CC, Law WS, Chang KC, et al. Initial experience on rifampin and pyrazinamide vs isoniazid in the treatment of latent tuberculosis infection among patients with silicosis in Hong Kong. *Chest.* 2003;124:2112-2118.
53. McNeill L, Allen M, Estrada C, Cook P. Pyrazinamide and rifampin vs isoniazid for the treatment of latent tuberculosis. *Chest.* 2003;123:102-106.
54. Tortajada C, Martinez-Lacasa J, Sanchez F, et al. Is the combination of pyrazinamide plus rifampicin safe for treating latent tuberculosis infection in persons not infected by the human immunodeficiency virus? *Int J Tuberc Lung Dis.* 2005;9:276-281.
55. Chaisson RE, Armstrong J, Stafford J, Golub J, Bur S. Safety and tolerability of intermittent rifampin/pyrazinamide for the treatment of latent tuberculosis infection in prisoners. *JAMA.* 2002;288:165-166.
56. Priest DH, VJ, Sherfy EA, Hoy DP, Haley CA. Use of intermittent rifampin and pyrazinamide therapy for latent tuberculosis infection in a targeted tuberculin testing program. *Clin Infect Dis.* 2004;39:1764-1771.
57. Marks SM, Taylor Z, Qualls NL, et al. Outcomes of contact investigations of infectious tuberculosis patients. *Am J Respir Crit Care Med.* 2000;162:2033-2038.
58. Blumberg HM. Treatment of latent tuberculosis infection: back to the beginning. *Clin Infect Dis.* 2004;39:1772-1775.
59. Nolan CM. Isoniazid for latent tuberculosis infection: approaching 40 and reaching its prime. *Am J Respir Crit Care Med.* 2003;168:412-413.

Author in the Room

Join the author of this article on Wednesday, June 15, 2005, from 2 to 3 PM Eastern time for Author in the Room, an interactive conference call aimed at closing the gap between knowledge—what is published in this article—and action—how much of this knowledge can be put into your actual practice. This call, facilitated by clinical experts, should help readers answer their questions and consider the implications of the study results for their practice. We will be studying the degree to which readers who participate report implementing this change within their practice, and participants will be asked to

complete 3 short surveys (at registration, immediately after the call, and 3 months after the call), which will assess clinical application.

Author in the Room is brought to you by JAMA and the Institute for Healthcare Improvement, with generous support from The Robert Wood Johnson Foundation.

Please register early for this innovative initiative because there is no fee for the first 200 callers. After the first 200 callers, a \$55 fee per line will apply. For more information or to register for Author in the Room, please visit <http://www.ihl.org/IHI/Programs/ConferencesAndTraining/Author+in+the+Room.htm>.

Financial Disclosures: None reported.

1. Wears RL, Berg M. Computer technology and clinical work: still waiting for Godot. *JAMA*. 2005;293:1261-1263.
2. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA*. 2005;293:1197-1203.
3. Norman DA. *Emotional Design: Why We Love (or Hate) Everyday Things*. New York, NY: Basic Books; 2004.
4. Mayhew DJ. *Principles and Guidelines in Software User Interface Design*. Englewood Cliffs, NJ: Prentice Hall; 1992.
5. Hackos JT, Redish JC. *User and Task Analysis for Interface Design*. New York, NY: John Wiley & Sons Inc; 1998.

In Reply: Drs Harrison and Young criticize the source of the estimate for IT project failures. This is understandable because most of what we hear about, and most publicly reported information including the research literature, tends to be biased in favor of successes.¹ In addition, when does a system “fail”—when it is rejected by users, when it does not perform as was promised, or when its implementation costs 3 times the budgeted figure? Good estimates are hard to find, and we opted for a conservative one. Other sources are comparable. Surveys of chief information officers conducted yearly since 1994 have suggested that only 15% to 30% of IT projects are completed successfully, on time, and within budget. About 30% are abandoned uncompleted, and the remainder have serious cost or time overruns (by a factor of 2-3) or are seriously deficient in their ultimate functionality.^{2,3} A Computer-based Patient Record Institute study in 1998 showed a dismal 95% failure rate in the case of electronic patient records.⁴ Finally, even if the proportion of successful systems is higher than we thought, that is no reason for comfort, because the system studied by Koppel et al⁵ would have been considered a “success” by most accounts. We agree, though, that more research is required into the area of success and failure. At the same time, we also argue that there is already much known about these failures, but that understanding is at risk of being ignored in the current climate of enthusiasm.

We agree with most of Dr Mitchell’s points. We do not believe that the development of useful computer-based aids to clinical work is completely impossible but, rather, that it is difficult and may be impossible using traditional development methods. Ethnographic techniques are superb tools to truly understand the nature of work processes, and we have frequently argued for such methods ourselves.

Most important is the awareness that a vision of organizational change has to precede IT systems implementation for beneficial results to be achieved. That vision should recognize that clinical IT projects are incredibly complex social endeavors in unforgiving environments that happen to

involve computers, as opposed to IT projects that happen to involve physicians.⁶ Throwing IT at a health care system to remedy high medication error rates will not be effective unless the organizational reasons for those failures also are addressed. These reasons are hidden in the “messy details” of clinical work⁷: complexity; uncertainty; conflicting goals; gaps in supplies, procedures, and coordination; brittleness of tools and organizational routines; and the lack of acceptance that high-risk work environments require “high-reliability” working routines and organizational structures. As long as these deeper issues remain unaddressed, introducing IT, particularly technologies focused on improving decision making by individual clinicians, will not advance us much further.

Robert L. Wears, MD, MS
wears@ufl.edu
Department of Emergency Medicine
University of Florida
Jacksonville

Marc Berg, MA, MD, PhD
Department of Social Medical Sciences
Institute of Health Policy and Management
Erasmus University
Rotterdam, the Netherlands

Financial Disclosures: None reported.

1. Denrell J. Vicarious learning, undersampling of failure, and the myths of management. *Organ Sci*. 2003;14:228-243.
2. The CHAOS Report (1994). 1994. Available at: http://www.standishgroup.com/sample_research/chaos_1994_1.php. Accessed March 27, 2005.
3. Xia W, Lee G. Grasping the complexity of IS development projects. *Commun ACM*. 2004;47:68-74.
4. Amatayakul M. The state of the computer-based patient record. *J AHIMA*. 1998; 69:34-36, 38, 40.
5. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA*. 2005;293:1197-1203.
6. Silverstein S. Sociotechnologic issues in clinical computing: common examples of healthcare IT failure. Available at: <http://home.aol.com/medinformaticsmid/failurecases.htm>. Accessed March 23, 2005.
7. Nemeth CP, Cook RI, Woods DD. The messy details: insights from the study of technical work in health care. *IEEE Trans Syst Man Cybern A Syst Hum*. 2004; 34:689-692.

CORRECTIONS

Error in Table: In the Original Contribution entitled “Secular Trends in Cardiovascular Disease Risk Factors According to Body Mass Index in US Adults” published in the April 20, 2005, issue of *JAMA* (2005;293:1868-1874), Table 1 contained an error. The row labeled “High school education, %” should have been labeled “Less than high school education, %.”

Incorrect Dosage: In the Special Communication entitled “Update on the Treatment of Tuberculosis and Latent Tuberculosis Infection” published in the June 8, 2005, issue of *JAMA* (2005;293:2776-2784), there was an incorrect dosage in Table 2. The daily isoniazid dosage for adults should be 5 mg/kg not 300 mg/kg.