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Prevention and Treatment of Tuberculosis Among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Prevention and Treatment of Tuberculosis Among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations

Summary

These guidelines update previous CDC recommendations for the diagnosis, treatment, and prevention of tuberculosis (TB) among adults and children coinfected with human immunodeficiency virus (HIV) in the United States. The most notable changes in these guidelines reflect both the findings of clinical trials that evaluated new drug regimens for treating and preventing TB among HIV-infected persons and recent advances in the use of antiretroviral therapy. In September 1997, when CDC convened a meeting of expert consultants to discuss current information about HIV-related TB, special emphasis was given to issues related to coadministration of TB therapy and antiretroviral therapy and how to translate this information into management guidelines. Thus, these guidelines are based on the following scientific principles:

- *Early diagnosis and effective treatment of TB among HIV-infected patients are critical for curing TB, minimizing the negative effects of TB on the course of HIV, and interrupting the transmission of* Mycobacterium tuberculosis *to other persons in the community.*
- *All HIV-infected persons at risk for infection with* M. tuberculosis *must be carefully evaluated and, if indicated, administered therapy to prevent the progression of latent infection to active TB disease and avoid the complications associated with HIV-related TB.*
- *All HIV-infected patients undergoing treatment for TB should be evaluated for antiretroviral therapy, because most patients with HIV-related TB are candidates for concurrent administration of antituberculosis and antiretroviral drug therapies. However, the use of rifampin with protease inhibitors or nonnucleoside reverse transcriptase inhibitors is contraindicated.*

Ideally, the management of TB among HIV-infected patients taking antiretroviral drugs requires a) directly observed therapy, b) availability of experienced and coordinated TB/HIV care givers, and in most situations, c) use of a TB treatment regimen that includes rifabutin instead of rifampin. Because alternatives to the use of rifampin for antituberculosis treatment are now available, the previously recommended practice of stopping protease inhibitor therapy to allow the use of rifampin for TB treatment is no longer recommended for patients with HIV-related TB. The use of rifabutin-containing antituberculosis regimens should always include an assessment of the patient's response to treatment to decide the appropriate duration of therapy (i.e., 6 months or 9 months). Physicians and patients also should be aware that paradoxical reactions might occur during the course of TB treatment when antiretroviral therapy

restores immune function. Adding to CDC's current recommendations for administering isoniazid preventive therapy to HIV-infected persons with positive tuberculin skin tests and to HIV-infected persons who were exposed to patients with infectious TB, this report also describes in detail the use of new short-course (i.e., 2 months) multidrug regimens (e.g., a rifamycin, such as rifampin or rifabutin, combined with pyrazinamide) to prevent TB in persons with HIV infection. A continuing education component for U.S. physicians and nurses is included.

INTRODUCTION

These guidelines update previous CDC recommendations for treating and preventing active tuberculosis (TB) among adults and children coinfected with human immunodeficiency virus (HIV) (*1–3*). The most notable changes in these guidelines reflect both the recent advances in the use of antiretroviral therapy and the findings of clinical trials that evaluated new drug regimens for the treatment and prevention of TB among HIV-infected persons. Antiretroviral therapy is discussed in the context of TB treatment only; more detailed information about antiretroviral therapy is published elsewhere (*4*).

In September 1997, CDC convened a meeting of expert consultants who reviewed and considered background information about HIV-related TB in the United States and the scientific principles of therapy for both diseases (Part I of this report). The consultants then used this review as the basis for updating the recommendations for HIV-infected patients with TB (Part II). During their review of the scientific principles of therapy, the expert consultants focused on epidemiologic and clinical interactions between *Mycobacterium tuberculosis* infection and HIV infection, considering the frequency of coexisting TB and HIV infection and rates of drug-resistant TB among patients infected with HIV in the United States; the copathogenicity of TB and HIV disease; the potential for a poorer outcome of TB therapy and paradoxical reactions to TB treatment among HIV-infected patients; drug interactions between rifampin used for TB therapy and agents commonly used in antiretroviral therapy; use of TB treatment regimens that do not contain rifampin; and results of clinical trials of therapies to prevent TB among HIV-infected persons. Thus, in addition to CDC's current recommendations, these new guidelines include information about the following topics:

- directly observed therapy for all patients with HIV-related TB;
- rifabutin-containing antituberculosis regimens (or a streptomycin-based alternative regimen that does not contain rifamycin) for treating TB among patients taking antiretroviral drugs that have interactions with rifampin;
- monitoring responses to antituberculosis treatment to decide about the appropriate duration of TB therapy;
- occurrence and management of paradoxical reactions during TB treatment, when immune function is restored because of antiretroviral therapy;
- use of 9 months of isoniazid daily or twice weekly for the treatment of *M. tuberculosis* infection;

- short-course multidrug therapy for latent *M. tuberculosis* infection; and
- special considerations that apply to children and pregnant women with HIV-related TB.

Health-care professionals need to be familiar with these new guidelines to ensure the use of the most effective management strategies for TB patients infected with HIV, while concurrently promoting optimal antiretroviral therapy for these patients. To help clinicians make informed treatment decisions based on the most current research results, the expert consultants have given each recommendation an evidence-based rating similar to the ratings used in previously issued guidelines (*4,5*). However, these recommendations are not intended to substitute for the judgment of an expert physician. When possible, the treatment of TB in HIV-infected persons should be directed by (or done in consultation with) a physician with extensive experience in the care of patients with TB and HIV disease. The implementation of these recommendations will help prevent cases of drug-resistant TB, reduce TB treatment failures, and diminish the adverse effects that TB has on HIV replication. Moreover, these guidelines will contribute to efforts to control TB and eliminate it from the United States by minimizing the likelihood of *M. tuberculosis* transmission, which will prevent the occurrence of new cases of TB.

In future years, health-care professionals can expect changes in the recommendations regarding the therapeutic options used to prevent and treat TB among patients infected with HIV. These changes will reflect the availability of new antiretroviral and antituberculosis agents, new information about existing agents, and subsequent changes in CDC's guidelines for the use of antiretroviral therapy for persons infected with HIV. Multiple copies of this report and all updates are available from the Office of Communications, National Center for HIV, STD, and TB Prevention, CDC, 1600 Clifton Road, Mail Stop E-06, Atlanta, GA 30333. The report also is posted on the CDC Division of TB Elimination Internet website at <http://www.cdc.gov/nchstp/tb> and the MMWR website at <http://www.cdc.gov/epo/mmwr/mmwr.html>. Readers should consult these sources regularly for updates in the guidelines.

PART I. BACKGROUND AND SCIENTIFIC RATIONALE

Frequency of Coexisting TB and HIV Infection and Disease in the United States

In the United States, epidemiologic evidence indicates that the HIV epidemic contributed substantially to the increased numbers of TB cases in the late 1980s and early 1990s (*6,7*). Overlap between the acquired immunodeficiency syndrome (AIDS) and TB epidemics continues to result in increases in TB morbidity. Analysis of national HIV-related TB surveillance data is limited by incomplete reporting of HIV status for persons with TB. As an alternative, state health department personnel have compared TB and AIDS registries to help estimate the proportion of persons reported with TB who are also infected with HIV. In the most recent comparison conducted by the 50 states and Puerto Rico, 14% of persons with TB in 1993–1994 (27% among those aged 25–44 years) also appeared in the AIDS registry (*8*). This proportion of TB patients with AIDS is believed to be a minimum estimate for the United States and might represent an increase in the proportion of TB patients identified as having TB and AIDS in 1990 (9%) (*6*). During 1993–1994, most persons with TB and AIDS (80%) were found in eight reporting areas: New York City, California, Florida, Georgia, Illinois, New Jersey, New York, and Texas (*8*).

In prospective epidemiologic studies, investigators have estimated that the annual rate of TB disease among untreated, tuberculin skin-test (TST)-positive, HIV-infected persons in the United States ranges from 1.7 to 7.9 TB cases per 100 person-years (Table 1) (*9–11*). The variability observed in these studies mirrors the differences in TB prevalence observed for different U.S. populations (i.e., the highest case rate was found in a study of a New York City population of intravenous drug users at a time when the incidence of TB was high and increasing [*9*]; and the lowest case rate was evident in a community-based cohort of persons enrolled in a study of the pulmonary complications of HIV infection at a time and in a population in which the incidence of TB was relatively low [*11*]). However, in all of these studies, the rate of TB disease among HIV-infected, TST-positive persons was approximately 4–26 times higher than the rate among comparable HIV-infected, TST-negative persons, and it was approximately 200–800 times higher than the rate of TB estimated for the U.S. population overall (0.01%) (*12*). Therefore, activities to control and eliminate TB in the United States must include aggressive efforts to identify HIV-infected persons with latent

TABLE 1. Annual rates* of tuberculosis among persons with human imunodeficiency virus infection, by tuberculin skin-test (TST) status — selected years and U.S. areas

Location and source	Rate among persons with positive TSTs	Rate among persons with negative TSTs	Rate ratio
New York City	7.9	0.3	26.3
Selwyn et al., 1989 (*9*)			
San Francisco	5.0	1.0	5.0
Daley et al., 1998 (*10*)			
Multiple sites			
Markowitz et al., 1997 (*11*)			
East Coast	4.6	1.3	3.5
West/Midwest	1.7	0.2	8.5
All sites	4.5	0.4	11.3

*Cases per 100 person-years.

TB infection and to provide them with therapy to prevent progression to active TB disease.

Rates of Drug-Resistant TB Among HIV-Infected Persons in the United States

Resistance to antituberculosis drugs is an important consideration for some HIV-infected persons with TB. According to the results of a study of TB cases reported to CDC from 1993 through 1996, the risk of drug-resistant TB was higher among persons with known HIV infection compared with others (*13*). During this 4-year period, among U.S.-born persons aged 25–44 years with TB, HIV test results were reported as positive for 32% of persons, negative for 23%, and unknown for 45%. Using univariate analysis that excluded patients known to have had a previous episode of TB, investigators found that patients known to be HIV seropositive had a significantly higher rate of resistance to all first-line antituberculosis drugs, compared with HIV-seronegative patients and patients with unknown HIV serostatus (Table 2). Moreover, using a multivariate model that included age, history of previous TB, birth country, residence in New York City, and race/ethnicity, the investigators confirmed HIV-positive serostatus as a risk factor for resistance to at least isoniazid, for both isoniazid and rifampin resistance (multidrug-resistant [MDR] TB) and for rifampin monoresistance (TB resistant to rifampin only). In some areas of the United States with a low level of occurrence of MDR TB, however, differences in MDR TB related to HIV status have not been found (*8*). Reasons for the increased risk for TB drug resistance among HIV-seropositive persons might reflect a higher proportion of TB disease resulting from recently acquired *M. tuberculosis* infection (*14,15*) and thus an increased risk of disease caused by drug-resistant strains in areas with high community and institutional transmission of drug-resistant strains of *M. tuberculosis* (*16*). Several well-described outbreaks of

TABLE 2. Percentage of tuberculosis (TB) patients* with drug-resistant isolates,† by drug and human immunodeficiency virus (HIV) serostatus — United States, 1993–1996

	HIV serostatus (%)		
Drug§	HIV positive (n=5,112)	HIV negative (n=3,754)	HIV status unknown (n=7,186)
Isoniazid	11.3	5.5	6.8
Rifampin	8.9	1.6	2.5
Pyrazinamide	5.1	1.8	2.2
Streptomycin	6.7	4.1	5.0
Ethambutol	3.9	1.5	2.0
Isoniazid and rifampin	6.2	1.3	1.5
Rifampin only¶	2.4	0.2	0.8

* Patients were born in the United States, were aged 22–44 years, and were not known to have had a previous episode of TB. All TB cases reported from California are included in the HIV-unknown category.

† The patient's *Mycobacterium tuberculosis* isolate had resistance to at least the specified drug but may have had resistance to other drugs as well.

§ The differences in drug-resistance rates among patients with TB known to be HIV-seropositive, compared with those known to be HIV-seronegative or of unknown status, are statistically significant (Chi-square test statistic, $p<0.05$).

¶ These figures were calculated for patients with *M. tuberculosis* isolates tested for isoniazid and rifampin always and streptomycin sometimes. Monoresistant isolates were resistant to rifampin but susceptible to the other first-line drugs tested.

Source: CDC, National Tuberculosis Surveillance System.

nosocomially transmitted MDR TB, primarily affecting persons with AIDS, support this association (*17–21*).

In the past decade, reports have increased of TB caused by strains of *M. tuberculosis* resistant to rifampin only, and growing evidence has indicated that this rare event is associated with HIV coinfection (*22–32*). In retrospective studies, nonadherence with TB therapy has been associated with acquired rifampin monoresistance (*22–24*); and among a small number of patients, the use of rifabutin as prophylaxis for *Mycobacterium avium* complex was associated with the development of rifamycin resistance (*31*). However, the occurrence of TB relapse with acquired rifampin monoresistance also has been documented among patients with TB who initially had rifampin-susceptible isolates and who were treated with a rifampin-containing TB regimen by directly observed therapy (DOT) (*30,32*). The mechanisms involved in the development of acquired rifampin monoresistance are not clearly understood but could involve the persistence of actively multiplying mycobacteria in patients with severe cellular immunodeficiency, selective antituberculosis drug malabsorption, and inadequate tissue penetration of drugs.

Thus, of critical importance for HIV-infected persons is implementation of TB prevention and control strategies such as a) appropriate use of therapy for latent *M. tuberculosis* infection, b) early diagnosis and effective treatment of active TB (i.e., administering four-drug antituberculosis regimens by DOT to all coinfected patients), and c) prompt compliance with requirements for reporting TB cases and drug-susceptibility test results. Implementing these strategies for persons coinfected with HIV will not only help reduce new cases of TB in general; it also could decrease further transmission of drug-resistant strains and new cases of drug-resistant TB.

Copathogenicity of TB and HIV Disease

Human immunodeficiency virus type 1 (HIV-1) and *M. tuberculosis* are two intracellular pathogens that interact at the population, clinical, and cellular levels. Initial studies of HIV-1 and TB emphasized the impact of HIV-1 on the natural progression of TB, but mounting immunologic and virologic evidence now indicates that the host immune response to *M. tuberculosis* enhances HIV replication and might accelerate the natural progression of HIV infection (*33*). Therefore, the interaction between these two pathogens has important implications for the prevention and treatment of TB among HIV-infected persons. Studies of the immune response in persons with TB disease support the biologic plausibility of copathogenesis in dually infected persons. The initial interaction between the host immune system and *M. tuberculosis* occurs in the alveolar macrophages that present mycobacterial antigens to antigen-specific CD4+ T cells (*34*). These T cells release interferon-gamma, a cytokine that acts at the cellular level to activate macrophages and enhance their ability to contain mycobacterial infection. The activated macrophages also release proinflammatory cytokines, such as tumor necrosis factor and interleukin (IL)-1, cytokines that enhance viral replication in monocyte cell lines in vitro (*35–38*). The mycobacteria and their products also enhance viral replication by inducing nuclear factor kappa-B, the cellular factor that binds to promoter regions of HIV (*39,40*).

When TB disease develops in an HIV-infected person, the prognosis is often poor, though it depends on the person's degree of immunosuppression and response to appropriate antituberculosis therapy (*41–43*). The 1-year mortality rate for treated,

HIV-related tuberculosis ranges from 20% to 35% and shows little variation between cohorts from industrialized and developing countries (*44–49*). The observed mortality rate for HIV-infected persons with TB is approximately four times greater than the rate for TB patients not infected with HIV (*44,46,49,50*). Although the cause of death in the initial period of therapy can be TB (*46*), death after the induction phase of antituberculosis therapy usually is attributed to complications of HIV other than TB (*45,51,52*). Epidemiologic data suggest that active TB accelerates the natural progression of HIV infection. In a retrospective cohort study of HIV-infected women from Zaire, investigators estimated the relative risk of death to be 2.7 among women with active TB compared with those without TB (*53*). In a retrospective cohort study of HIV-infected subjects from the United States, active TB was associated with an increased risk for opportunistic infections and death (*54*). The risk of death, or hazard rate, for persons with HIV-related TB follows a bimodal distribution, peaking within the first 3 months of antituberculosis therapy and then again after 1 year (*48*); the reasons for this distribution are not clear but might relate to the impact of TB on HIV disease progression. The observation that active TB increases deaths associated with HIV infection has been corroborated in studies of three independent cohorts in Europe (*55–57*).

Early in the HIV epidemic, researchers postulated that the immune activation resulting from concurrent infection with parasitic or bacterial pathogens might alter the natural progression of HIV infection (*58*). Subsequent observations have demonstrated that immune activation from TB enhances both systemic and local HIV replication. In some patients with active TB, the plasma HIV RNA level rises substantially before TB is diagnosed (*59*). Moreover, TB treatment alone leads to reductions in the viral load in these dually infected patients. TB and HIV also interact in the lungs, the site of primary infection with *M. tuberculosis*. In a recently published study of HIV-infected patients with TB, researchers found that the viral load was higher in the bronchoalveolar lavage fluid from the affected versus the unaffected lung and was correlated with levels of tumor necrosis factor in bronchoalveolar fluid (*60*). Researchers used V3 loop viral sequences to construct a phylogenetic tree and observed that the HIV quasispecies from the affected lung differed from those in the plasma within the same patient. These data suggest that pulmonary TB might act as a potent stimulus for the cellular-level replication of HIV. In summary, recent research findings have improved clinicians' understanding of how HIV affects the natural progression of TB and how TB affects the clinical course of HIV disease, and these findings support the recommendation for prevention, early recognition, and effective treatment for both diseases.

TB Therapy Outcomes Among Patients with HIV-Related TB

Among patients treated for TB, early clinical response to therapy and the time in which *M. tuberculosis* sputum cultures convert from positive to negative appear to be similar for those with HIV infection and those without HIV infection (*30,61,62*). However, the data are less clear about whether rates of TB relapse (recurrence of TB following successful completion of treatment) differ among patients with or without HIV infection (*63*). Current CDC and American Thoracic Society guidelines recommend a 6-month treatment regimen for drug-susceptible TB disease for patients coinfected with HIV (*2*) but suggest prolonged treatment for patients who have a delayed clinical and bacteriologic response to antituberculosis therapy. Some experts

have suggested that to ensure an optimal antituberculosis treatment outcome, all patients with HIV-related TB should be treated with a longer course of therapy (i.e., 9 months), regardless of evidence of early response to therapy (*64,65*).

To make a recommendation on duration of therapy for HIV-related TB, expert consultants at the September 1997 CDC meeting considered the results of prospective studies that ascertained the posttreatment relapse rate following 6-month TB therapy regimens among patients with HIV infection (Table 3) (*29,30,49,66,67*). Differences in the study designs, including those pertaining to eligibility for enrollment in the study and to the definition of TB relapse, limited the analysis of combined results from the five studies. Despite this limitation, the expert consultants were able to make the following observations: a) the studies had a posttreatment follow-up duration that ranged from 8 to 22 months (median duration: 18 months); b) in three studies (*30,49,67*), investigators found that 6-month TB regimens were associated with a clinically acceptable (≤5.4%) TB relapse rate; and c) in two studies (*29,66*), researchers

TABLE 3. Posttreatment relapse rates and CD4+ T-cell counts among patients enrolled in prospective studies of 6-month* tuberculosis (TB) treatment regimens, by human immunodeficiency virus (HIV) serostatus

Location and source	HIV status	Posttreatment relapses (%)	CD4+ T-cell counts (median)	Comments
Zaire Perriens et al., 1995 (*66*)	HIV positive (n=124)	9.0	338 cells/μL^3	• All cases of TB confirmed by culture at baseline. • DOT except for ½ doses in continuation phase. • Posttreatment follow-up = 12 months. • Culture-based relapse definition; however, relapse vs. reinfection not assessed by DNA fingerprinting.
	HIV negative (n=183)	5.3		
Côte d'Ivoire Kassim et al., 1995 (*49*)	HIV-1 positive (n=106)	3.0	Data not available	• Includes culture-positive and clinically diagnosed cases of TB. • Self-administered therapy. • Posttreatment follow-up = 18 months. • Relapse definition includes both culture-confirmed and clinically diagnosed TB. • Relapse vs. reinfection not assessed by DNA fingerprinting.
	HIV negative (n=194)	3.0		
Haiti Chaisson et al., 1996 (*67*)	HIV positive (n=177)	5.4	475 cells/μL^3	• Includes culture-positive and clinically diagnosed cases of TB. • DOT. • Posttreatment follow-up = 22 months. • Relapse definition includes both culture-confirmed and clinically diagnosed cases of TB. • Relapse vs. reinfection not assessed by DNA fingerprinting.
	HIV negative (n=250)	2.7		

found a high (≥9%) TB relapse rate associated with the use of 6-month TB regimens. In the Zaire study (*66*), TB patients coinfected with HIV had almost twofold higher posttreatment relapse rates than patients not infected with HIV who received the same TB treatment regimen; however, the authors did not investigate whether the relapses were the result of a recurrence of disease with the same strain of *M. tuberculosis* or reinfection (new disease) with a different strain. In the other study (*29*), which enrolled HIV-seropositive patients from 21 different sites in the United States, in all three patients who relapsed, the strain of *M. tuberculosis* isolated during the relapse episode matched, by DNA fingerprint, the strain of *M. tuberculosis* that was isolated during the initial episode of TB; this finding ruled out the possibility of reinfection.

The expert consultants who reviewed the available data agreed that short-course (i.e., 6-month) regimens should be used for the treatment of HIV-related pansusceptible TB (i.e., susceptible to all first-line antituberculosis drugs) in the United States, where patients are usually treated with DOT and where response to antituberculosis

TABLE 3. Posttreatment relapse rates and CD4+ T-cell counts among patients enrolled in prospective studies of 6-month* tuberculosis (TB) treatment regimens, by human immunodeficiency virus (HIV) serostatus — Continued

Location and source	HIV status	Posttreatment relapses (%)	CD4+ T-cell counts (median)	Comments
United States U.S. Public Health Service Rifapentine Trial Group et al., 1998 (*29*)	HIV positive (n=30)	10	137 cells/μL^3	• All cases of TB confirmed by culture at baseline. • DOT. • Posttreatment follow-up = 8 months. • All relapses confirmed by culture and had identical DNA fingerprints that matched baseline.
United States† El-Sadr et al., 1998 (*30*)	HIV positive (n=50)	3.9	70 cells/μL^3	• All cases of TB confirmed by culture at baseline. • DOT. • Posttreatment follow-up = 18 months. • Relapses confirmed by culture. Of the two relapse isolates, one matched and one did not match the DNA fingerprint of the respective baseline isolate.

DOT=Directly observed therapy.

* TB regimens mostly consisted of a 2-month, four-drug (isoniazid, rifampin, pyrazinamide, and ethambutol) daily induction regimen followed by a continuation regimen of 4-month intermittent isoniazid and rifampin. The exceptions are that a) ethambutol was not used during the induction phase in Côte d'Ivoire, and b) half of patients in one of the U.S. studies (*30*) received levofloxacin in addition to the other four drugs during the induction phase. During the continuation phase, patients in Côte d'Ivoire received drugs daily, patients in Haiti received drugs three times a week, and patients in all other studies received drugs twice a week.

† Also in this study, 51 comparable patients with HIV-related TB were randomly assigned to a treatment arm in which the duration of the continuation phase was prolonged from 4 months to 7 months. The culture-confirmed posttreatment relapse rate (2%) in this study arm was not significantly different from the rate in the 6-month study arm (p=1.00); however, an isolate was not available for DNA fingerprinting.

drugs can be monitored. This approach limits the use of lengthier multidrug antituberculosis therapies to the minimum possible number of patients with TB and HIV disease. Some experts believe the risk of TB treatment failure is increased among patients with advanced HIV-related immunosuppression and therefore advocate greater caution (or longer duration of therapy) when treating such patients for TB. The available data do not permit CDC to make a definitive recommendation regarding this issue. However, the experts recommended that clinicians treating TB in patients with HIV infection should consider the factors that increase a person's risk for a poor clinical outcome (e.g., lack of adherence to TB therapy, delayed conversion of *M. tuberculosis* sputum cultures from positive to negative, and delayed clinical response) when deciding the total duration of TB therapy.

Paradoxical Reactions Associated with Initiation of Antiretroviral Therapy During the Course of TB Therapy

The temporary exacerbation of TB symptoms and lesions after initiation of antituberculosis therapy — known as a paradoxical reaction — has been described as a rare occurrence (*68–74*) attributed to causes such as recovery of the patient's delayed hypersensitivity response and an increase in exposure and reaction to mycobacterial antigens after bactericidal antituberculosis therapy is initiated (*75*). Recently, a similar phenomenon was reported among patients with HIV-related TB (*76*). These reactions appear to be related more often to the concurrent administration of antiretroviral and antituberculosis therapy and occur with greater frequency than do paradoxical reactions associated primarily with the administration of antituberculosis therapy. Patients with paradoxical reactions can have hectic fevers, lymphadenopathy (sometimes severe), worsening of chest radiographic manifestations of TB (e.g., miliary infiltrates, pleural effusions), and worsening of original tuberculous lesions (e.g., cutaneous and peritoneal). However, these reactions are not associated with changes in *M. tuberculosis* bacteriology (i.e., no change from negative to positive culture and smear), and patients generally feel well and have no signs of toxicity.

In a prospective study, paradoxical reactions were more common among 33 patients with HIV-related TB who received TB treatment and combination antiretroviral therapy (36%) than among 55 patients not infected with HIV who received antituberculosis drugs alone (2%) and among 28 HIV-infected patients (historical control patients during pre-zidovudine era) who received antituberculosis drugs alone (7%) (*76*). Furthermore, among patients treated for both diseases, the paradoxical reactions were more temporally related to the initiation of combination antiretroviral therapy (mean +/- standard deviation [SD]: 15 +/- 11 days afterward) than to the initiation of antituberculosis treatment (mean SD: 109 +/- 72 days afterward). Researchers investigated potential causes for these symptoms and lesions (i.e., TB treatment failure, antituberculosis drug resistance, nonadherence with TB therapy, drug fever, development of conditions not related to TB or HIV) but considered such causes unlikely because these evaluations produced negative results, and TB was cured in patients who remained on unmodified antituberculosis regimens. Among patients in this study who received combination antiretroviral therapy, which usually included a protease inhibitor, the paradoxical reactions corresponded with a concurrent drop in HIV viral loads after antiretroviral therapy began and, in all but one patient, occurred while peripheral blood CD4+ T-cell counts were <200 cells/μL (*76*). In the historical control group (i.e.,

patients who were treated for TB but not for HIV), two (7%) of the 28 patients had a paradoxical reaction after antituberculosis therapy was initiated. This finding indicates that treatment of TB alone might sometimes decrease HIV viral load substantially and improve immune function (*40,59,68,76*).

After reviewing information about paradoxical reactions occurring during the course of TB therapy, expert consultants at the September 1997 CDC meeting concluded that exacerbation of TB signs and symptoms in patients with HIV-related TB can occur soon after combination antiretroviral therapy is initiated. Clinicians should always conduct a thorough investigation to eliminate other etiologies before making a diagnosis of paradoxical treatment reaction. For patients with paradoxical reactions, rarely are changes in antituberculosis or antiretroviral therapy needed. If the lymphadenopathy or other lesions are severe, one option is to continue with appropriate antituberculosis therapy and administer short-term steroids that suppress the enhanced immune response.

In the prospective study (*76*), despite having low CD4+ T-cell counts, six (86%) of seven TB patients who were initially tuberculin skin-test (TST)-negative had positive TST results after combination antiretroviral therapy was started. The reaction sizes of postantiretroviral TSTs ranged from 7 to 67 mm of induration. Clinicians must be aware of the potential public health and clinical implications of restored TST reactivity among persons who have not been diagnosed with active TB but who might be latently infected with *M. tuberculosis*. Persons previously known to have negative TST results might benefit from repeat tuberculin testing if they have evidence of restored immune function after antiretroviral therapy is initiated, because TB preventive therapy is recommended for TST-positive HIV-infected persons.

Considerations for TB Therapy for HIV-Infected Patients Treated with Antiretroviral Agents

Drug Interactions Between Rifamycins Used for TB Therapy and Antiretroviral Drugs Used for HIV Therapy

Widely used antiretroviral drugs available in the United States include protease inhibitors (saquinavir, indinavir, ritonavir, and nelfinavir) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, delavirdine, and efavirenz). Protease inhibitors and NNRTIs have substantive interactions with the rifamycins (rifampin, rifabutin, and rifapentine) used to treat mycobacterial infections (*3,77*). These drug interactions principally result from changes in the metabolism of the antiretroviral agents and the rifamycins secondary to induction or inhibition of the hepatic cytochrome CYP450 enzyme system (*78,79*). Rifamycin-related CYP450 induction decreases the blood levels of drugs metabolized by CYP450. For example, if protease inhibitors are administered with rifampin (a potent CYP450 inducer), blood concentrations of the protease inhibitors (all of which are metabolized by CYP450) decrease markedly, and most likely the antiretroviral activity of these agents declines as well. Conversely, if ritonavir (a potent CYP450 inhibitor) is administered with rifabutin, blood concentrations of rifabutin increase markedly, and most likely rifabutin toxicity increases as well.

Of the available rifamycins, rifampin is the most potent CYP450 inducer; rifabutin has substantially less activity as an inducer; and rifapentine, a newer rifamycin, has

intermediate activity as an inducer (*80–82*). The four currently approved protease inhibitors and amprenavir (141W94, an investigational agent in Phase III clinical trials) are all, in differing degrees, inhibitors of CYP450 (*83,84*). The rank order of the agents in terms of potency in inhibiting CYP450 is ritonavir (the most potent); amprenavir, indinavir, and nelfinavir (with approximately equal potencies); and saquinavir (the least potent). The magnitude of the effects of coadministering rifamycins and protease inhibitors has been evaluated in limited pharmacokinetic studies (Table 4) (*85–91*). The three approved NNRTIs have diverse effects on CYP450: nevirapine is an inducer, delavirdine is an inhibitor, and efavirenz is both an inducer and an inhibitor. The magnitude of the effects of coadministering rifamycins and NNRTIs has also been evaluated in pharmacokinetic studies or has been predicted on the basis of what is known about their potential for inducing or inhibiting CYP450 (Table 5) (*92–96*).

In contrast to the protease inhibitors and the NNRTIs, the other class of antiretroviral agents available, nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine, didanosine, zalcitabine, stavudine, and lamivudine) are not metabolized by CYP450. Rifampin (and to a lesser degree, rifabutin) increases the glucuronidation of zidovudine and thus slightly decreases the serum concentration of zidovudine (*97–100*). The effect of this interaction probably is not clinically important, and the concurrent use of NRTIs and rifamycins is not contraindicated (*77*). Also, no contraindication exists for the use of NRTIs, NNRTIs, and protease inhibitors with isoniazid, pyrazinamide, ethambutol, or streptomycin. These first-line antituberculosis medications, in contrast to the rifamycins, are not CYP450 inducers.

Coadministration of Antituberculosis and Antiretroviral Therapies

According to 1998 U.S. Department of Health and Human Services guidelines on the use of antiretroviral agents among HIV-infected adults and adolescents (*4*), to improve the length and quality of patients' lives, all persons with symptomatic HIV infection should be offered antiretroviral therapy. HIV-infected patients with TB fall in this category. When used appropriately, combinations of potent antiretroviral agents can effect prolonged suppression of HIV replication and reduce the inherent tendency of HIV to generate drug-resistant viral strains. However, as antiretroviral therapeutic regimens have become increasingly effective, they also have become increasingly complex in themselves as well as in the problems they cause for the treatment of other HIV-associated diseases.

At present, regimens that include two NRTIs combined with a potent protease inhibitor (or, as an alternative, combined with an NNRTI) are the preferred choice for combination antiretroviral therapy for the majority of patients. Each of the antiretroviral drug combination regimens must be used according to optimum schedules and doses (*4*) because the potential for resistant mutations of HIV decreases if serum concentrations of the multiple antiretroviral drugs are maintained steadily. Because rifampin markedly lowers the blood levels of these drugs and is likely to result in suboptimal antiretroviral therapy, the use of rifampin to treat active TB in a patient who is taking a protease inhibitor or an NNRTI is always contraindicated. Rifabutin is a less potent inducer of the CPY450 cytochrome enzymes than is rifampin and, when used in appropriately modified doses, might not be associated with a clinically significant reduction of protease inhibitors or nevirapine (Table 6). Thus, the substitution of rifabutin for rifampin in TB treatment regimens has been proposed as a practical

TABLE 4. Effects of coadministering rifamycins and protease inhibitors (PIs) on the systemic exposure (area-under-the-concentration-time curve [AUC]) of each drug*

	Rifampin (RIF)		Rifabutin (RFB)	
PI and source	**RIF's effect on PI**	**PI's effect on RIF**	**RFB's effect on PI**	**PI's effect on RFB**
Saquinavir† Sahai et al., 1996 (*85*)	80% decrease	Data not reported	45% decrease	Data not reported
Ritonavir Cato et al., 1996 (*86*) Abbot Laboratories, 1997 (*87*)	35% decrease	Unchanged§	Data not reported	293% increase
Indinavir Indinavir (MK 639) Pharmacokinetic Study Group, 1996 (*88*)	92% decrease	Data not reported	34% decrease	173% increase
Nelfinavir Kerr et al., 1997 (*89*)	82% decrease	Data not reported	32% decrease	200% increase
Amprenavir Polk et al., 1998 (*90*) Sadler et al., 1998 (*91*)	81% decrease	Unchanged	14% decrease	200% increase¶

* Effects are expressed as a percentage change in AUC of the concomitant treatment relative to that of the drug-alone treatment. No data are available regarding the magnitude of these bidirectional interactions when rifamycins are administered two or three times a week instead of daily.
† Hard-gel formulation (Invirase™).
§ Data from only two subjects.
¶ Percentages reflect increases in minimum concentrations; values for the AUC are not reported.

TABLE 5. Known and predicted effects of coadministering rifamycins and nonnucleoside reverse transcriptase inhibitors (NNRTIs) on the systemic exposure (area-under-the-concentration-time curve [AUC]) of each drug*

	Rifampin (RIF)		Rifabutin (RFB)	
NNRTI and source	**RIF's effect on NNRTI**	**NNRTI's effect on RIF**	**RFB's effect on NNRTI**	**NNRTI's effect on RFB**
Nevirapine Roxane Laboratories, 1997 (*92*)	37% decrease	Unchanged†	16% decrease	Decrease†
Delavirdine Borin et al., 1997 (*93*) Borin et al., 1997 (*94*) Cox et al., 1998 (*95*)	96% decrease	Unchanged†	80% decrease	342% Increase†
Efavirenz Benedek et al., 1998 (*96*)	13% decrease	Unchanged†	Decrease†	Decrease†

* Effects are expressed as a percentage change in AUC of the concomitant treatment relative to that of the drug-alone treatment. No data are available regarding the magnitude of these bidirectional interactions when rifamycins are administered two or three times a week instead of daily.
† Predicted effect based on knowledge of metabolic pathways for the two drugs.

TABLE 6. Feasibility of using different antiretroviral drugs and rifabutin

Antiretroviral agent	Can be used in combination with rifabutin?	Comments
Saquinavir (soft-gel formulation)	Probably	Use of the soft-gel formulation (Fortovase™) in higher-than-usual doses might allow adequate serum concentrations of this drug despite concurrent use of rifabutin.* However, the pharmacokinetic data for this combination are limited in comparison with other protease inhibitors. Because of the expected low bioavailability of the hard-gel formulation (Invirase™) the concurrent use of this agent with rifabutin is not recommended.
Ritonavir	No	Ritonavir increases concentrations of rifabutin by 35-fold and results in increased rates of toxicity (arthralgia, uveitis, skin discoloration, and leukopenia). These adverse events have been noted in studies of high-dose rifabutin therapy, when rifabutin is administered with clarithromycin (another CYP450 inhibitor) — an indication that these events might result from high serum concentrations of rifabutin.
Indinavir	Yes	Data from drug interaction studies (unpublished report, Merck Research Laboratories, West Point, PA, 1998) suggest that the dose of indinavir should be increased from 800 mg every 8 hours to 1,200 mg every 8 hours if used in combination with rifabutin.*
Nelfinavir	Yes	Some clinical experts suggest that the dose of nelfinavir should be increased from 750 mg three times a day to 1,000 mg three times a day if used in combination with rifabutin.*
Amprenavir	Probably	The drug interactions between amprenavir and rifabutin (and thus potential for rifabutin toxicity) are reported to be similar to those of ritonavir with rifabutin. However, potential advantages of using this combination are that a) rifabutin has a minimal effect on reducing the levels of amprenavir and b) even though it has not been studied, rifabutin toxicity is not expected if the daily dose of rifabutin is reduced when used in combination with amprenavir.
NRTIs†	Yes	Not expected to have clinically significant interaction.
Nevirapine	Yes	Not known whether nevirapine or rifabutin dose adjustments are necessary when these drugs are used together.*
Delavirdine	No	Not recommended on the basis of marked decreases in concentrations of delavirdine when administered with rifamycins.
Efavirenz	Probably	Newly approved agent. Preliminary drug interaction studies suggest that when rifabutin is used concurrently with efavirenz, the dose of rifabutin for both daily and twice weekly administration should be increased from 300 mg to 450 mg.

*Daily dose of rifabutin should be reduced from 300 mg to 150 mg if used in combination with amprenavir, nelfinavir, or indinavir. It is unknown whether the dose of rifabutin should be reduced if used in combination with saquinavir (Fortovase™) or nevirapine.

†Nucleoside reverse transcriptase inhibitiors, including zidovudine, didanosine, zalcitabine, stavudine, and lamivudine.

choice for patients who are also undergoing therapy with protease inhibitors (with the exception of ritonavir [*86,87,101–103*] or hard-gel capsule saquinavir [Invirase™ (*85*)]) or with the NNRTIs nevirapine or efavirenz (but not delavirdine [*93,94*]). Currently, more clinical and pharmacokinetic data are available on the use of indinavir or nelfinavir with rifabutin than on the use of amprenavir or soft-gel saquinavir (Fortovase™) with rifabutin. Rifapentine is not recommended as a substitute for rifampin because its safety and effectiveness have not been established for the treatment of patients with HIV-related TB. As an alternative to the use of rifamycin for the treatment of TB, the use of streptomycin-based regimens that do not contain rifamycin can be considered for the treatment of TB in patients undergoing antiretroviral therapy with protease inhibitors or NNRTIs.

Use of Rifabutin-Based Regimens for the Treatment of HIV-Related TB

At present, TB drug regimens that include rifabutin instead of rifampin appear to offer the best alternative for the treatment of active TB among patients taking antiretroviral therapies that include protease inhibitors or NNRTIs. This recommendation is based on findings from studies of equivalent in vitro antituberculosis activity of rifabutin and rifampin (*104,105*) and the results of three clinical trials (*106–108*). These trials demonstrated that 6-month rifabutin-containing regimens (at a daily dose of either 150 mg or 300 mg) were as effective and as safe as similar control regimens containing rifampin for the treatment of TB (Table 7). The smallest (n=49) of these

TABLE 7. Results from clinical trials* that compared rifabutin (RFB) with rifampin (RIF) in treatment for pulmonary tuberculosis (TB)

Location and source	No. of patients	Treatment* regimen	Bacteriologic conversion	Posttreatment relapses	No. of patients with clinically significant adverse events
Brazil **Argentina** **Thailand** Gonzalez-Montaner et al., 1994 (*106*)	RFB_{150} (n=174) RFB_{300} (n=171) RIF (n=175)	2 months of NH, RFB_{150}, PZA, EMB; daily/ 4 months of INH, RFB_{150}; daily *or* 2 months of INH, RFB_{300}, PZA, EMB; daily/ 4 months of INH, RFB_{300}; daily	*At 3 months:* RFB_{150} = 86% RFB_{300} = 83% RIF = 86%	*At 2 years:* RFB_{150} = 3.4% RFB_{300} = 3.5% RIF = 1.8%	RFB_{150} = 1 RFB_{300} = 4 RIF = 6
South Africa McGregor et al., 1996 (107)	$RFB_{300,}$ (n=107) RIF (n=118)	2 months of INH, RFB_{300}, PZA, EMB; daily/ 4 months of INH, RFB_{300}, EMB; two times a week	*At 2 months:* RFB_{300} = 92% RIF = 88%	*At 2 years:* RFB_{300} = 5.1% RIF = 3.8%	RFB_{300} = 6 RIF = 4
Uganda Schwander et al., 1995 (*108*)	RFB_{300} (n=24)† RIF (n=25)†	2 months of INH, RFB_{300}, PZA, EMB; daily/ 4 months of INH, RFB_{300}; daily	*At 2 months:* RFB_{300} = 81% RIF = 48%	Data not available	RFB_{300} = 0 RIF = 0

EMB=ethambutol; INH=isoniazid; PZA=pyrazinamide.
* Comparison regimens included INH, PZA, and EMB with the same doses and intervals of administration as in the study regimens; however, comparison regimens included RIF (600 mg daily or twice a week) instead of RFB (150 mg daily, 300 mg daily, or 300 mg twice a week).
† All patients were known to be HIV-1 seropositive.

three trials was conducted in Uganda (*108*) and is the only one to include HIV-coinfected patients (who were not undergoing antiretroviral therapy at the time of the study). This study indicated that 81% of patients taking a TB treatment regimen containing daily rifabutin converted their sputum from *M. tuberculosis* positive to negative after 2 months of treatment, compared with a 48% sputum conversion rate among patients taking a TB regimen containing daily rifampin ($p<0.05$). However, when the researchers controlled for differences in baseline characteristics (a greater proportion of patients in the rifampin group had cavitary disease), they found no difference in the time to sputum conversion between the two study groups.

Studies are under way to evaluate the use of rifabutin administered daily (at a dose of 150 mg) or twice a week (at a dose of 300 mg) for the treatment of TB in HIV-infected patients who take protease inhibitors. Physicians at a state tuberculosis hospital in Florida have treated or consulted on the treatment of approximately 30 HIV-infected patients who received a protease inhibitor while undergoing treatment for TB with rifabutin. Patients have been treated for TB primarily with administration of rifabutin (150 mg daily) as part of four-drug therapy for 2–4 weeks, followed by rifabutin (300 mg twice weekly) as part of four-drug therapy to complete 8 weeks of induction, and then a continuation phase consisting of twice-weekly isoniazid and rifabutin (300 mg) to complete 6 months of treatment. To date, patients treated with this regimen have not experienced clinically significant increases in rifabutin serum levels, have had a minimal incidence of adverse reactions from rifabutin (one patient developed a case of uveitis), and have had a good clinical response to TB and HIV therapies. Approximately 80% of the patients attained sputum conversion by the second month of treatment, most have attained and maintained suppression of HIV replication, and no TB relapses have occurred with up to 1 year of posttreatment follow-up (David Ashkin, M.D., and Masahiro Narita, M.D., A.G. Holley State Tuberculosis Hospital, Lantana, Florida, personal communication, 1998).

In previous reports, CDC and the American Thoracic Society jointly recommended the use of rifampin-containing short-course regimens for the initial treatment of HIV-related TB (*2*). The inclusion of rifampin in regimens to treat TB was supported by data collected from approximately 90 controlled clinical trials conducted from 1968 to 1988 (*109*). Excluding rifampin from the TB treatment regimen was not recommended because regimens not containing rifampin a) had not been proven to have acceptable efficacy (i.e., have been associated with higher rates of TB treatment failure and death and with slower bacteriologic responses to therapy leading to potential increases in the likelihood of *M. tuberculosis* transmission) and b) require prolonging duration of therapy from 6 months to 12–15 months. Presently, available data suggest that rifabutin in short-course (i.e., 6 months) multidrug regimens to treat TB provides the same benefits as the use of rifampin. Three additional reasons support the use of rifabutin for treating HIV-related TB: a) observations suggest that rifabutin might be more reliably absorbed than rifampin in patients with advanced HIV disease (*110,111*); b) the use of rifabutin appears to have been better tolerated in patients with rifampin-induced hepatotoxicity (David Ashkin, M.D., and Masahiro Narita, M.D., A.G. Holley State Tuberculosis Hospital, Lantana, Florida, personal communication, 1998); and c) the use of rifabutin might lessen the possibility of interactions with other medications commonly prescribed for patients with HIV infection (e.g., azole antifungal drugs, anticonvulsant agents, and methadone) (*77*).

Use of Alternative TB Treatment Regimens that Contain Minimal or No Rifamycin

TB treatment regimens that contain no rifamycins have been proposed as an alternative for patients who take protease inhibitors or NNRTIs. Several clinical trials conducted in Hong Kong and Africa by the British Medical Research Council and published from 1974 through 1984 provide information about nonrifamycin and minimal-rifamycin regimens for the treatment of TB in patients who were not likely to be infected with HIV (Table 8) (*112–115*). Most of these studies demonstrated high relapse rates when regimens not containing streptomycin were used and when the duration of therapy was less than 9 months. However, in a large (n=404) randomized controlled clinical trial in Hong Kong that evaluated the use of six TB treatment regimens consisting of streptomycin, isoniazid, and pyrazinamide either daily, three times a week, or two times a week for 6 or 9 months (*112*), almost all patients treated with any of the study regimens achieved rapid sputum conversions (86%–94% of patients converted within 3 months of therapy). In this study, the 30-month posttreatment follow-up relapse rates were high (18%–24%) among patients treated with 6-month regimens, but the relapse rates among patients treated with 9-month regimens (5%–6%) were similar to the relapse rates expected following the use of rifampin-based TB treatments. Thus, the expert consultants who developed these guidelines concluded that treatment of TB without rifamycin always requires longer-duration (at least 9 months) regimens that include streptomycin (or an injectable antituberculosis drug

TABLE 8. Posttreatment relapse rates associated with tuberculosis treatment regimens containing minimal or no rifampin among patients not known to be coinfected with human immunodeficiency virus

Location and source	Treatment regimens	Posttreatment relapses (%)
Hong Kong Hong Kong Chest Service/British Medical Research Council, 1977 (*112*)	• 6 months of SM, INH, PZA; daily	18
	• 6 months of SM, INH, PZA; three times a week	24
	• 6 months of SM, INH, PZA; two times a week	21
	• 9 months of SM, INH, PZA; daily	5
	• 9 months of SM, INH, PZA; three times a week	6
	• 9 months of SM, INH, PZA; two times a week	6
Algeria Algerian Working Group/British Medical Research Council, 1984 (*113*)	• 2 months of INH, RIF, PZA, EMB; daily/ 4 months of INH, RIF; daily	3
	• 1 month of SM, INH, EMB; daily/ 11 months of INH, EMB; daily	17
East Africa East African/British Medical Research Council, 1974 (*114*)	• 6 months of SM, INH, RIF; daily	2
	• 6 months of SM, INH, PZA; daily	11
	• 6 months of SM, INH; daily	29
East Africa East African/British Medical Research Council, 1980 (*115*)	• 1 month of SM, INH, RIF, PZA; daily/ 5 months of SM, INH, PZA; two times a week	9
	• 1 month of SM, INH, RIF, PZA; daily/ 7 months of SM, INH, PZA; two times a week	2

EMB=ethambutol; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; SM=streptomycin.

such as capreomycin, amikacin, or kanamycin) (*63*). However, these TB regimens have not been studied among patients with HIV infection.

Streptomycin is highly bactericidal against *M. tuberculosis*, but it is rarely used in the United States to treat drug-susceptible TB because of problems associated with its administration by injection that can be intensified in patients with low body mass or wasting and because of potential ototoxicity and nephrotoxicity. The associated potential toxicities and increased duration of therapy and the patient's difficulty in adhering to an injectable-drug–based TB regimen can compromise the effectiveness of streptomycin-based TB regimens, and these limitations should be considered by physicians and patients.

Treatment of Latent M. tuberculosis *Infection in Patients with HIV Infection*

Scientific Rationale

Preventive therapy for TB is essential to controlling and eliminating TB in the United States (*116,117*). Treatment for HIV-infected persons who are latently infected with *M. tuberculosis* is an important part of this strategy and is also an important personal health intervention because of the serious complications associated with active TB in HIV-infected persons (*118–120*). Expert consultants attending the September 1997 CDC meeting and additional consultants attending a September 1998 meeting sponsored by the American Thoracic Society and CDC considered findings from multiple studies (*121–130*) before developing recommendations about the optimal duration of isoniazid preventive therapy regimens; frequency of administration (intermittency) of preventive therapy; new short-course multidrug regimens; and preventive therapy for anergic HIV-infected adults with a high risk of *M. tuberculosis* infection.

A key difference in most preventive therapy trials conducted before and after the beginning of the HIV epidemic is that the earlier trials focused on 12-month regimens of isoniazid, whereas five of seven trials (*122–126*) conducted in HIV-infected populations assessed 6-month regimens of isoniazid (Table 9). Four of these 6-month isoniazid regimens (*122-125*) were chosen for study on the basis of the operational feasibility of providing therapy in countries with limited resources where preventive therapy programs were not available; the fifth study (*126*), a U.S. trial conducted among anergic patients, used a 6-month regimen because of the absence of previous data about optimal duration of therapy for TST-negative, HIV-infected patients. Despite these variations, the expert consultants concluded that the findings from these different preventive therapy studies should apply to most persons with latent *M. tuberculosis* infection, regardless of their HIV serostatus, because similar levels of protection have been observed when identical preventive therapy regimens have been administered to persons infected with HIV and those not infected.

Optimal Duration of Isoniazid Regimens for Treatment of Latent M. tuberculosis *Infection*

The American Thoracic Society and CDC have previously recommended a regimen of 12 months of isoniazid alone for treatment of latent *M. tuberculosis* infection in HIV-infected adults (*2*). The recommended duration of TB preventive therapy for persons not infected with HIV was a minimum of 6 months. When considering the

optimal duration of isoniazid preventive therapy, the consultants reviewed findings from two studies conducted in populations not known to be infected with HIV (*128,129*). One of these studies, a controlled trial conducted in seven European countries, compared the efficacy of three durations (3, 6, and 12 months) of isoniazid preventive treatment for TST-positive persons with stable, fibrotic lesions on chest radiographs (*128*). In this study, compliant patients who received medication for

TABLE 9. Results from studies of tuberculosis (TB) preventive therapy among persons coinfected with human immunodeficiency virus

Location and source	TST status of study subjects	Preventive therapy regimen	Rate of TB per 100 person-years	Relative risk of TB (95% CI)
Haiti				
Pape et al., 1993 (*121*)	TST positive (n=25)	12 months of placebo; daily	10.0	5.8 (1.2–28.7)
	TST positive (n=38)	12 months of INH; daily	1.7	1
	TST negative (n=35)	12 months of placebo; daily	5.7	1.8 (0.4–9.2)
	TST negative (n=20)	12 months of INH; daily	3.2	1
Haiti				
Halsey et al., 1994 (*122*)	TST positive (n=370)	6 months of INH; two times a week	1.7	1
	TST positive (n=380)	2 months of RIF, PZA; two times a week	1.8	1.1 (CI not available)
Uganda				
Whalen et al., 1997 (*123*)	TST positive (n=464)	6 months of placebo; daily	3.4	1
	TST positive (n=536)	6 months of INH; daily	1.1	0.3 (0.1–0.8)
	TST positive (n=556)	3 months of INH, RIF; daily	1.3	0.4 (0.2–0.9)
	TST positive (n=462)	3 months of INH, RIF, PZA; daily	1.7	0.4 (0.2–0.9)
	Anergic (n=323)	6 months of placebo; daily	3.1	1
	Anergic (n=395)	6 months of INH; daily	2.5	0.7 (0.3–1.9)
Zambia				
Mwinga et al., in press (*124*)	TST positive (n=60)	6 months of placebo; two times a week	9.8	1
	TST positive (n=52)	6 months of INH; two times a week	2.3	0.3 (0.05–1.4)
	TST positive (n=49)	3 months of RIF, PZA; two times a week	2.7	0.3 (0.05–1.4)
	TST negative (n=166)	6 months of placebo; two times a week	3.1	1
	TST negative (n=178)	6 months of INH; two times a week	2.5	0.9 (0.31–2.4)
	TST negative (n=173)	3 months of RIF, PZA; two times a week	3.8	1.3 (0.50–3.2)
Kenya				
Hawken et al., 1997 (*125*)	TST positive (n=67)	6 months of placebo; daily	8.0	1
	TST positive (n=69)	6 months of INH; daily	5.6	0.6 (0.2–1.6)
	TST negative (n=235)	6 months of placebo; daily	2.7	1
	TST negative (n=224)	6 months of INH; daily	3.3	1.2 (0.6–2.7)
United States				
Gordin et al., 1997 (*126*)	Anergic (n=257)	6 months of placebo; daily	0.9	1
	Anergic (n=260)	6 months of INH; daily	0.4	0.5 (0.1–1.9)
United States, Haiti, Mexico, and Brazil				
Gordin et al., 1998 (*127*)	TST positive (n=792)	12 months of INH; daily	1.2	1
	TST positive (n=791)	2 months of RIF, PZA; daily	1.2	1.0 (0.6–1.7)

CI=confidence interval; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin.
TST=tuberculin skin test.

12 months had better protection against TB (93%) than those who received medication for 6 months (69%). The other study was conducted among the Inuits in the Bethel area of Alaska, where participants received 0–24 months of isoniazid preventive therapy (*129*). In an assessment of observed posttherapy case rates of TB relative to the amount of isoniazid ingested (expressed as a percentage of a 12-month regimen), researchers found that higher amounts of therapy corresponded with lower TB rates among participants who had received 0–9 months of isoniazid therapy; after 9 months of therapy, participants had no additional benefits in terms of decreased TB case rates.

Four studies of HIV-infected persons have evaluated 6-month and 12-month regimens of daily isoniazid (*121,123,125,127*). Both of the studies that evaluated a 6-month regimen included a placebo comparison group and demonstrated reductions in the incidence of TB among persons in the treatment group — 70% in Uganda (*123*) and 75% in Kenya (*125*). A study of the 12-month regimen (*121*), which was conducted in Haiti and also included a placebo comparison group, demonstrated an 83% reduction in the incidence of TB among persons in the treatment group. A multicenter trial conducted in the United States, Mexico, Brazil, and Haiti (*127*) demonstrated that the magnitude of protection obtained from a regimen of isoniazid administered daily for 12 months was similar to that obtained from a regimen of rifampin and pyrazinamide administered daily for 2 months. Isoniazid preventive therapy regimens of 6 and 12 months' duration have not been compared with each other in the same study conducted among HIV-infected persons. In summary, these data indicate that a) the optimal duration of isoniazid preventive therapy should be >6 months to provide the maximum degree of protection against TB; b) therapy for 9 months appears to be sufficient; c) therapy for >12 months does not appear to provide additional protection.

Frequency of Administering Isoniazid Preventive Therapy

Two clinical trials (*122,124*) have evaluated 6-month twice-weekly isoniazid regimens for the prevention of active TB in HIV-infected persons (Table 9). Participants enrolled in the twice-weekly 6-month isoniazid arm of a study conducted in Zambia had a 40% reduction in the rate of TB compared with persons who took a placebo for 6 months (*124*). The findings of a trial conducted in Haiti (*122*) suggest that the magnitude of protection obtained from isoniazid administered twice a week for 6 months is equivalent to that obtained from rifampin and pyrazinamide regimens administered twice a week for 2 months. Preventive therapy trials that include twice-weekly isoniazid regimens for >6 months or comparisons of the same drugs administered daily versus intermittently have not been conducted. However, in a Baltimore demonstration project in which isoniazid was administered twice a week (10–15 mg/kg, with a maximum dose of 900 mg) to a cohort of injecting-drug users under directly observed preventive therapy (DOPT), the findings support the efficacy of twice-weekly isoniazid preventive therapy (*130*). Twice-weekly regimens with DOPT were used in Baltimore because the project staff expected that supervised delivery of therapy would enhance adherence with and completion of the preventive therapy regimen. Thus, the available data suggest that the protection obtained from isoniazid preventive therapy regimens should be the same whether the drug is administered daily or twice a week.

Short-Course Multidrug Regimens for TB Preventive Therapy

Four clinical trials (*122–124,127*) conducted among HIV-infected populations have evaluated courses of preventive therapy that are shorter than 6 months and that include rifampin in combination with isoniazid or pyrazinamide (Table 9). The largest and most recent of these trials was a multicenter, randomized TB prevention study conducted from 1992 through 1998 (*127*). Researchers found identical rates of TB (1.2 per 100 person-years) in two groups of TST-positive, HIV-infected persons: those who primarily self-administered isoniazid daily for 12 months and those who primarily self-administered rifampin and pyrazinamide daily for 2 months. Both study groups had similar adverse events and mortality rates; persons taking rifampin and pyrazinamide for 2 months were significantly more likely (80%) to complete therapy than were persons taking isoniazid for 12 months (68%) ($p<0.001$). Two other trials conducted in Haiti and Zambia (*122,124*) have also evaluated regimens of rifampin and pyrazinamide for the prevention of TB but have not included comparison arms of 12-month isoniazid regimens. The study in Haiti (*122*) compared patients receiving rifampin and pyrazinamide administered twice a week for 2 months with patients receiving isoniazid twice a week for 6 months; in both arms of the study, one of the twice-weekly doses was administered by DOPT. Investigators observed no difference in TB risk or mortality among participants enrolled in the two treatment arms (*122*). The placebo-controlled trial in Zambia demonstrated comparable protection from 3 months of rifampin and pyrazinamide versus 6 months of isoniazid; both regimens were self-administered twice a week (*124*). In the multicenter trial (*127*) and in the Haiti and Zambia studies (*122,124*), regimens that included rifampin and pyrazinamide were well tolerated. In a study conducted in Uganda (*123*), investigators observed no statistically significant reduction in TB rates but a high rate of toxicity and drug intolerance among persons who took three drugs (isoniazid, rifampin, and pyrazinamide) daily for 3 months compared with persons who took a placebo (Table 9); 3 months of daily self-administered rifampin and isoniazid provided protection similar to that of 6 months of daily self-administered isoniazid. Thus, short-course multidrug regimens (i.e., two drugs for 2–3 months) have been shown to be effective for the prevention of active TB in HIV-infected persons. The use of three drugs for preventive therapy, however, can be associated with unacceptably high rates of toxicity, and the use of a 3-month regimen of rifampin and isoniazid is not being considered for use in the United States. Available data indicate that in the United States, a regimen of rifampin and pyrazinamide administered daily for 2 months is a reasonable treatment option for HIV-infected adults with latent *M. tuberculosis* infection. The available data do not permit CDC to make a definitive statement regarding the intermittent (i.e., twice a week) administration of a 2-month regimen of rifampin and pyrazinamide.

Preventive Therapy for Anergic HIV-Infected Adults with a High Risk of Latent **M. tuberculosis** *Infection*

Isoniazid preventive therapy has not been found to be useful or cost-effective in preventing TB when administered to anergic, HIV-infected persons (*123,126*) (Table 9). The anergic subjects who received isoniazid in the Uganda trial had a statistically insignificant (17%) reduction in the rate of TB (2.5 cases per 100 person-years) compared with patients in the placebo group (3.1 cases per 100 person-years) (*123*). Similarly, anergic HIV-infected persons with a high risk for tuberculous infection who

were enrolled in a U.S. multicenter trial and treated with isoniazid daily for 6 months had a rate of TB (0.4 cases per 100 person-years) that was 50% less than, but not statistically different from, the rate observed among patients treated with placebo (0.9 cases per 100 person-years) (*126*). In both of these studies, HIV-infected persons with anergy tolerated isoniazid well, as suggested by the low rates of adverse reactions and high rates of therapy completion. These study findings do not support the routine use of preventive therapy in anergic, HIV-infected persons. Preventive therapy for TST-negative, HIV-infected persons also has not been proven effective (*121,124, 125*) (Table 9); however, some experts recommend primary preventive therapy (to prevent *M. tuberculosis* infection) for TST-negative or anergic HIV-infected residents of institutions that pose an ongoing high risk for exposure to *M. tuberculosis* (e.g., prisons, jails, homeless shelters).

Implications of Results of TB Preventive Therapy Trials

The effects of TB preventive therapy on mortality and progression of HIV infection appear to be limited, with the exception that such therapy can protect against the development of TB disease and its associated consequences. Moreover, the duration of this protective effect has not been clearly established for HIV-infected persons. Despite these limitations and uncertainties, preventive therapy is recommended because its benefits in preventing TB disease are thought to be greater than the risks of serious treatment-related adverse events, and such therapy benefits society by helping to prevent the spread of infection to other persons in the community.

The implementation of TB preventive therapy programs should be facilitated by the use of newly recommended short-course multidrug regimens and twice-weekly isoniazid regimens, especially among patients for whom DOPT is feasible. Because of the drug interactions between rifampin and protease inhibitors or NNRTIs, the use of shorter regimens containing rifampin is contraindicated for patients taking these antiretroviral drugs. Although preventive therapy trials evaluating rifabutin use among TST-positive, HIV-infected persons have not been conducted, the expert consultants reviewed available data and agreed that the use of rifabutin instead of rifampin is valid on the basis of the same scientific principles that support the use of rifabutin for the treatment of active TB.

PART II. RECOMMENDATIONS

This section of the report provides clinicians with recommendations for diagnosing, treating, and preventing TB among persons coinfected with HIV while concurrently promoting optimal antiretroviral care for these patients. The recommendations reflect the current state of knowledge regarding the use of antiretroviral agents, but this field of science is rapidly evolving. As new antiretroviral agents and new data regarding existing agents alter therapeutic options and preferences for antiretroviral therapy, these changes might affect future recommendations for the treatment of TB infection and disease among patients coinfected with HIV and the treatment of HIV infection among persons with TB. Expert consultants updated these recommendations after a September 1997 CDC meeting, where they reviewed and considered available information about the scientific principles of therapy for TB and HIV.

To help clinicians make informed treatment decisions based on the most current research results, the expert consultants have given the recommendations evidence-based ratings (general recommendations have no rating). The ratings include a letter and a Roman numeral (Table 10), similar to the ratings used in previously issued guidelines (*4,5*). The letter indicates the strength of the recommendation, and the Roman numeral indicates the nature of the evidence supporting the recommendation. Thus, clinicians can use the ratings to differentiate between recommendations based on data from clinical trials versus those based on the opinions of experts familiar with the relevant clinical practice and scientific rationale for such practice (when clinical trial data are not available). However, these recommendations are not intended to substitute for the judgment of an expert physician. Management of HIV-related TB disease is complex, and clinical and public health consequences associated with treatment failure are serious. When possible, treatment of TB among HIV-infected persons should be directed by, or conducted in consultation with, a physician with extensive experience in the care of patients with these two diseases.

The objectives of implementing these recommendations are to reduce TB treatment failures, prevent drug-resistant TB, and diminish the adverse effects that TB has on HIV replication. Moreover, these guidelines contribute to efforts to control and eliminate TB from the United States by minimizing the likelihood of *M. tuberculosis* transmission, which will prevent the occurrence of new cases of TB. Multiple copies of this report and all updates are available from the Office of Communications, National

TABLE 10. System used to rate the strength of recommendations and the quality of supporting evidence

Rating	
	Strength of the recommendation
A	Strong; should always be offered
B	Moderate; should usually be offered
C	Optional
D	Should generally not be offered
E	Should never be offered
	Quality of evidence supporting the recommendation
I	At least one randomized trial with clinical endpoints
II	Clinical trials with laboratory endpoints only or conducted only in populations not infected with human immunodeficiency virus
III	Expert opinion

Center for HIV, STD, and TB Prevention, CDC, 1600 Clifton Road, Mail Stop E-06, Atlanta, GA 30333. The report also is posted on the CDC Division of TB Elimination Internet website at <http://www.cdc.gov/nchstp/tb> and the MMWR website at <http://www.cdc.gov/epo/mmwr/mmwr.html>. Readers should consult these sources regularly for updates in the guidelines.

Active Tuberculosis

Clinical and Public Health Principles

Prompt initiation of effective antituberculosis treatment increases the probability that a patient with HIV infection who develops TB will be cured of this disease (*45,131*). TB treatment also quickly renders patients noninfectious (*30*), with the resulting reduction in the amount of *M. tuberculosis* transmitted to others, and it minimizes the patient's risk of death resulting from TB (*41–43,132*). Therefore, clinicians must immediately and thoroughly investigate the possibility of TB when a patient infected with HIV has symptoms consistent with TB. Persons suspected of having current TB disease should immediately be started on appropriate treatment, ideally with directly observed therapy (DOT) (*133–135*), and placed in TB isolation as necessary (*136,137*). Patients with TB and unknown HIV-infection status should be counseled and offered HIV testing. HIV-infected patients undergoing treatment for TB should be evaluated for antiretroviral therapy. Most patients with HIV-related TB are candidates for concurrent administration of antituberculosis and antiretroviral drug therapies (*4*).

Health-care providers, administrators, and TB controllers must strive to promote coordinated care for patients with TB and HIV and remove existing barriers to information-sharing between TB control programs and HIV/AIDS programs. TB control programs are responsible for setting TB treatment standards for physicians in the community, promoting the awareness and use of recommended TB infection-control practices, and enforcing state and local health department requirements concerning TB case notification and early reporting of drug-susceptibility test results. Because of the complexity of managing HIV-related TB disease and the serious public health consequences of mismanagement, care for persons with HIV-related TB should be provided by, or in consultation with, experts in the management of both TB and HIV disease.

Diagnosis of HIV-Related Tuberculosis

The typical signs and symptoms of pulmonary TB are cough with or without fever, night sweats, weight loss, and upper-lobe infiltrates with or without cavitation on chest x-rays. The diagnosis of TB for some HIV-infected patients might be difficult because TB in an immunocompromised host can be associated with atypical symptoms, a lack of typical symptoms, and a paucity of findings in chest x-rays (*138–140*). Among persons with AIDS, the diagnosis of TB also can be complicated by the presence of other pulmonary infections such as *Pneumocystis carinii* pneumonia and *Mycobacterium avium* complex disease and by the occurrence of TB in extrapulmonary sites. For patients with unusual clinical and radiographic findings, the starting point for diagnosing active TB often is a positive tuberculin skin test (TST). All patients

with positive TSTs should be evaluated to rule out active TB (see Diagnosis of *M. tuberculosis* Infection Among HIV-Infected Persons).

Medical Evaluation of Patients Suspected of Having Active TB

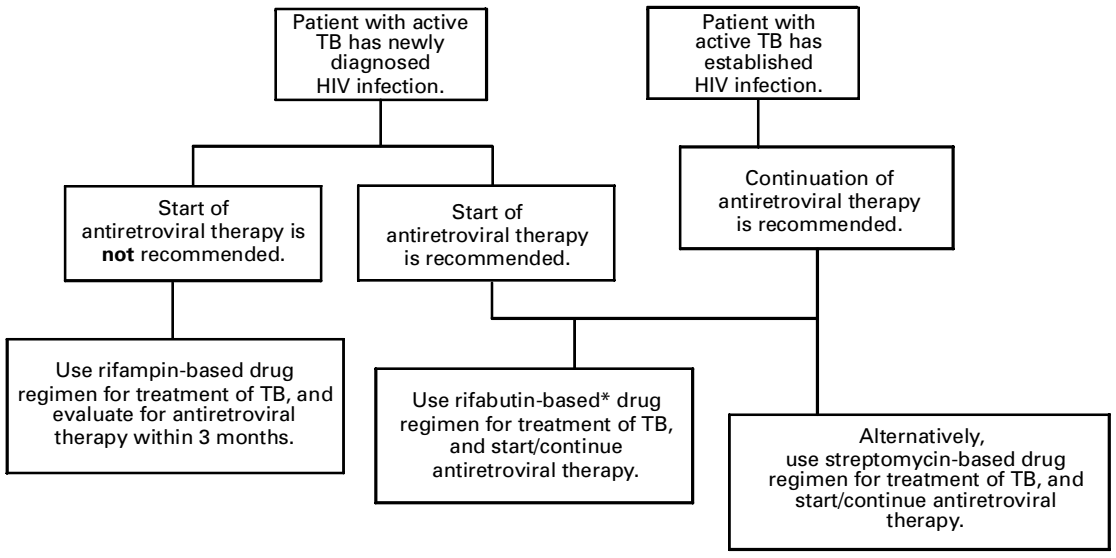
Rating	Recommendation
A.II	Every person suspected of having TB should undergo a thorough medical evaluation (see Box 1).
A.II	The evaluation should include HIV counseling and testing unless the person has documentation of a) a positive HIV antibody test or b) a negative result to an HIV antibody test conducted within the past 6 months.

Management of HIV-Infected Patients with Active TB

Coadministration of TB Treatment and Antiretroviral Therapy

The following management strategies are for patients with HIV-related pulmonary TB a) who are not known to have or who do not have risk factors for multidrug-resistant TB and b) for whom antiretroviral therapy is appropriate. When they first receive care for active TB disease, some patients might already be receiving antiretroviral therapy, whereas other patients might be newly diagnosed with HIV infection (Figure 1). For these newly diagnosed patients, in addition to the currently established recommendations for the immediate initiation of antituberculosis therapy, recently published guidelines (*4*) recommend the use of antiretroviral therapy. When treatments for HIV and TB disease are begun simultaneously, the optimal setting is one with experienced and coordinated care givers as well as accessible resources to provide a continuum of medical services (e.g., a reliable source of medications and social, psychosocial, and nutritional services).

FIGURE 1. Recommended management strategies for patients with human immunodeficiency virus (HIV) infection and tuberculosis (TB)



*Coadministration of rifabutin with ritonavir, saquinavir (Invirase™), or delavirdine is not recommended.

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MORBIDITY AND MORTALITY WEEKLY REPORT

October 30, 1998 / Vol. 47 / No. RR-20

Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Prevention and Treatment of Tuberculosis Among Patients Infected with Human Immunodeficiency Virus: Principles of Therapy and Revised Recommendations

OBJECTIVE

The objective of this *MMWR* is to inform the reader of recommendations and guidelines for the diagnosis, treatment, and prevention of tuberculosis (TB) among patients with human immunodeficiency virus (HIV). These recommendations and guidelines are based on a meeting of expert consultants convened in September 1997 by CDC. These recommendations should guide clinical practice and policy development related to appropriate management of patients with or at risk for HIV-related TB. Upon completion of this educational activity, the reader should possess a clear working knowledge of the diagnosis, treatment, and prevention of TB among patients with HIV.

ACCREDITATION

Continuing Medical Education (CME) Credit: This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education (ACCME) by CDC. CDC is accredited by the ACCME to provide continuing medical education for physicians. CDC awards 2.0 hours of category 1 credit toward the AMA Physician's Recognition Award for this activity.

Continuing Nursing Education (CNE) Credit: This activity for 2.4 contact hours is provided by CDC, which is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation.

EXPIRATION — October 30, 1999

The response form must be completed and returned electronically, by fax, or by mail, **postmarked no later than one year from the publication date of this report**, for eligibility to receive continuing education credit.

INSTRUCTIONS

1. Read this MMWR *(Vol. 47, RR-20)*, which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for Continuing Medical Education (CME) credit *or* Continuing Nursing Education (CNE) credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer *all* of the questions. Questions with more than one answer will instruct you to "indicate all that are true."
5. Sign and date the response form.
6. Return the response form, or a photocopy of the form, no later than **October 30, 1999**, to CDC by one of the following methods:

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   Centers for Disease Control and Prevention
   1600 Clifton Road, N.E.
   Atlanta, GA 30333

   If you answer all of the questions, you will receive an award letter for either 2.0 hours of CME credit or 2.4 hours of CNE credit within 90 days. No fees are charged for participating in this continuing education activity.

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES

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

1. Which of the following statements are true? ***(Indicate all that are true.)***

A. Human immunodeficiency virus (HIV) infection accelerates the natural progression of tuberculosis (TB).

B. Active TB accelerates the natural progression of HIV infection and disease.

C. The mortality rate for HIV-infected persons with TB is four times greater than the rate for TB patients not infected with HIV.

D. The toxicity associated with isoniazid TB preventive therapy significantly outweighs this therapy's benefits in preventing active TB in an HIV-infected person.

2. Which of the following strategies are recommended for patients with TB taking protease inhibitors for HIV therapy? ***(Indicate all that are true.)***

A. Stop protease inhibitor therapy to allow the use of rifampin for TB treatment.

B. Use an antituberculosis treatment regimen that includes rifabutin instead of rifampin.

C. Ensure that experienced and coordinated TB/HIV care givers are available.

D. Provide therapy for TB that is directly observed.

3. Which of the following strategies are recommended for HIV-infected patients with active TB? ***(Indicate all that are true.)***

A. Immediately and simultaneously begin treatment regimens that include a protease inhibitor for HIV therapy and drugs other than rifampin for antituberculosis therapy.

B. Immediately and simultaneously begin treatment regimens that include a protease inhibitor for HIV therapy and rifampin for antituberculosis therapy.

C. For patients who start antiretroviral therapy with a protease inhibitor, plan a 2-week period between the last dose of rifampin and the first dose of protease inhibitor.

D. For patients who are not on antiretroviral therapy when TB is diagnosed, plan to start antiretroviral therapy at the end of the induction phase of TB therapy (8 weeks) or when TB therapy is completed.

4. When rifabutin is administered with indinavir, nelfinavir, or amprenavir, the recommended dosage of rifabutin is: ***(Choose the one correct answer.)***

A. 300 mg daily or 150 mg twice weekly.

B. 300 mg daily or 300 mg twice weekly.

C. 150 mg daily or 300 mg twice weekly.

D. 150 mg daily or 150 mg twice weekly.

5. A paradoxical reaction during the course of TB and HIV treatment . . . ***(Indicate all that are true.)***

A. is a temporary exacerbation of symptoms and signs of TB in some patients who have restored immune function because of effective antiretroviral therapy.

B. is always associated with a positive *Mycobacterium tuberculosis* culture.

C. if suspected, calls for evaluating the patient to rule out other causes of the signs and symptoms (e.g., antituberculosis treatment failure).

D. might require hospitalization and possibly time-limited use of corticosteroids (e.g., prednisone therapy) if the patient has severe or life-threatening clinical manifestations.

6. When administered with rifamycins, which of the following drugs might require a dosage adjustment, the use of alternative therapies, or other changes because of drug interaction? ***(Indicate all that are true.)***

A. Methadone

B. Hormonal contraceptives

C. Beta-blockers

D. Fluconazole

E. Levofloxacin

7. Which of the following drugs is not recommended for patients receiving rifabutin? ***(Choose the one correct answer.)***

A. Indinavir

B. Nelfinavir

C. Ritonavir

D. Amprenavir

8. Which of the following statements are true for HIV-infected persons? *(Indicate all that are true.)*

A. Persons who have a positive tuberculin skin-test reaction (≥5 mm) are candidates for TB preventive therapy.

B. Persons with a negative tuberculin skin-test reaction (<5 mm) are never candidates for TB preventive therapy.

C. For persons with a negative tuberculin skin-test reaction (< 5 mm), a history of exposure to *M. tuberculosis* should be investigated and used as the basis for prescribing TB preventive therapy.

D. Persons with recent contact with an infectious TB patient should receive TB preventive therapy regardless of age, skin-test results, or history of previous TB preventive therapy.

9. Which of the following TB preventive therapy options are recommended for HIV-infected adults with a positive tuberculin skin-test reaction (≥5 mm), no evidence of active TB, and no history of exposure to isoniazid- and rifampin-resistant strains of *M. tuberculosis*? *(Indicate all that are true.)*

A. Isoniazid daily for 9 months.

B. Rifampin (or rifabutin) and pyrazinamide daily for 2 months.

C. Isoniazid 2 times per week for 9 months.

D. Isoniazid daily 6 months.

10. Each month, approximately how many patients with TB and HIV coinfection do you see?

A. None

B. 1–5

C. 6–15

D. 16–25

E. 25 or more

11. Please indicate the setting where you work.

A. City/county/state health department

B. Other public health agency

C. Hospital/managed care organization

D. Private practice/clinic

E. Academic institution

F. Other

12. How long did it take you to read the report and complete this exam?

A. ≤2 hours

B. >2 hours but <3 hours

C. ≥3 hours but <4 hours

D. ≥4 hours

The following questions will assess your perceptions of the readability and applicability of the material.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
13. Overall, this report met the stated objectives.	**A**	**B**	**C**	**D**	**E**
14. The tables and figures are useful.	**A**	**B**	**C**	**D**	**E**
15. Overall, the presentation of the report enhanced my ability to understand the material.	**A**	**B**	**C**	**D**	**E**
16. These recommendations will affect my practice.	**A**	**B**	**C**	**D**	**E**

Answer guide for questions 1–9

1.a,b,c; 2.b,c,d; 3.a,c,d; 4.c; 5.a,c,d; 6.a,b,c,d; 7.c; 8.a,c,d; 9.a,b,c

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BOX 1. Components of the medical evaluation for human immunodeficiency virus-infected patients suspected of having tuberculosis

The medical evaluation should include the following questions and assessments:

Medical History

- Ask all patients about their history of tuberculosis (TB) treatment. If the patient has previously received treatment, care providers must determine the antituberculosis drugs used, duration of treatment, history of adverse reactions, reasons for discontinuation of treatment, history of adherence with treatment, and previous antituberculosis drug-susceptibility test results.
- Question all patients about the following risk factors for drug-resistant TB: a) previous treatment for TB, especially if it was incomplete; b) previous residence in a country outside the United States where drug-resistant TB is common; c) close contact with a person who has drug-resistant TB or multidrug-resistant TB; and d) previous residence in an institution (i.e., hospital, prison, homeless shelter) with documented transmission of a drug-resistant strain of TB.
- Ask all patients about their history of antiretroviral therapy and their history of therapies to prevent opportunistic infections. If the patient has previously or is currently receiving these treatments, care providers should determine the drugs used, duration of treatment, history of adverse reactions, and reasons for discontinuation of treatment if treatment ended.
- Ask female patients whether they might be pregnant. Women of childbearing potential with menses more than 2 weeks late should receive a pregnancy test. (See TB Treatment for HIV-Infected Pregnant Women.)
- When clinical specimens for culture and susceptibility testing cannot be obtained from patients (e.g., young children, patients with skeletal or meningeal TB), the culture and drug-susceptibility results of the *Mycobacterium tuberculosis* strain isolated from the infecting source-patient should be investigated and reviewed if available so that TB treatment for the current patient can be tailored appropriately. (See TB Treatment for HIV-Infected Children.)
- If necessary, perform a Mantoux-method tuberculin skin test (TST) to help diagnose culture-negative TB.

Because of drug interactions, the use of rifampin to treat TB is not recommended for patients who a) will start treatment with an antiretroviral regimen that includes a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor (NNRTI) at the same time they begin treatment for TB (*4*) or b) have established HIV infection that is being maintained on such an antiretroviral regimen when TB is newly diagnosed and needs to be treated. Thus, two TB treatment options are currently recommended for these patients: a) a rifabutin-based regimen or b) an alternative nonrifamycin regimen that includes streptomycin (see Treatment Options for Patients with HIV Infection and Drug-Susceptible Pulmonary TB and Figure 1). Using a rifampin-based TB treatment regimen continues to be recommended for patients with HIV infection a) who have not started antiretroviral therapy, when both the patient and the clinician agree that waiting to start such therapy would be prudent or b) for whom antiretroviral management does not include a protease inhibitor or an NNRTI (*4*) (Figure 1).

BOX 1. Components of the medical evaluation for human immunodeficiency virus-infected patients suspected of having tuberculosis — Continued

Chest X-Ray Examination

- Perform a chest x-ray examination. HIV-related immunosuppression reduces the inflammatory reaction and cavitation of pulmonary lesions, and therefore HIV-infected patients with pulmonary TB can have atypical findings or normal chest x-rays. Children younger than age 5 years should undergo both a posterior-anterior and a lateral chest x-ray. All other persons should receive a posterior-anterior chest x-ray; additional chest x-ray examinations should be performed at the physician's discretion. Pregnant women who are being evaluated for active TB disease should undergo a chest x-ray (with the appropriate shielding) without delay, even during the first trimester of pregnancy. Patients suspected of having extrapulmonary TB should undergo a chest x-ray to rule out pulmonary TB.

Laboratory Tests

- Collect smears for acid-fast bacilli, cultures, and drug susceptibilities from expectorated or induced sputum samples on 3 consecutive days, preferably in the mornings. Children who are unable to produce sputum spontaneously or who cannot use the sputum induction machine should be admitted to the hospital for early morning gastric aspirates on 3 consecutive, separate days.
- Obtain a complete blood cell count, including platelets.
- Conduct chemistry panel tests, especially for liver enzyme levels (serum glutamic oxalacetic transaminase or aspartate aminotransferase [SGOT/AST] and serum glutamic pyruvic transaminase or alanine aminotransferase [SGPT/ALT]); total bilirubin; uric acid; blood urea nitrogen; and creatinine.

Other Procedures

- Perform a baseline visual acuity exam and test for red-green color perception for all patients who will be receiving ethambutol.
- Perform baseline audiometry tests if an aminoglycoside (e.g, streptomycin, amikacin, kanamycin) or capreomycin will be administered.
- Perform as necessary procedures such as bronchoscopies and bronchoalveolar lavage; biopsies and aspirates (e.g, of peripheral lymph nodes, visceral lymph nodes, liver, and bone marrow); mycobacterial culturing of nonrespiratory clinical specimens (e.g., blood, urine, pleural fluid); and radiologic evaluations other than chest x-rays (e.g., computerized tomographies, magnetic resonance imaging).

When determining the time to begin antiretroviral therapy for patients who are acutely ill with TB, clinicians and patients need to consider the existing clinical issues (e.g., drug interactions and toxicities, ability to adhere to two complex treatment regimens, and laboratory abnormalities). A staggered initiation of antituberculosis and antiretroviral treatments for patients not currently on antiretroviral therapy might promote greater adherence to the TB and HIV treatment regimens and reduce the associated drug toxicity of both regimens. This strategy might include starting antiretroviral therapy either at the end of the 2-month induction phase of TB therapy or after TB therapy is completed. When a decision is made to delay initiation of antiretroviral therapy, clinicians should monitor the patient's condition by measuring

plasma HIV RNA levels (viral load) and CD4+ T-cell counts and assessing the HIV-associated clinical condition at least every 3 months (*4*), because such information will assist in decisions regarding the timing for initiating such therapy. For some patients, switching from a rifampin-based TB regimen to either a rifabutin-based or a nonrifamycin-based TB regimen will be necessary if the decision is made to start antiretroviral therapy before completion of antituberculosis therapy. Clinicians and patients should be aware that the potent effect of rifampin as a CYP450 inducer (*77,80*), which lowers the serum concentration of protease inhibitors and NNRTIs, continues up to at least 2 weeks following the discontinuation of rifampin. Thus, they should consider planning for a 2-week period between the last dose of rifampin and the first dose of protease inhibitors or NNRTIs (see TB Drug Interaction and Absorption and Table 1A of Appendix).

Treatment Options for Patients with HIV Infection and Drug-Susceptible Pulmonary TB

A.II DOT and other strategies that promote adherence to therapy should be used for all patients with HIV-related TB.

A.II For patients who are receiving therapy with protease inhibitors or NNRTIs, the initial phase of a 6-month TB regimen consists of isoniazid, rifabutin, pyrazinamide, and ethambutol. These drugs are administered a) daily for 8 weeks or b) daily for at least the first 2 weeks, followed by twice-a-week dosing for 6 weeks, to complete the 2-month induction phase. The second phase of treatment consists of isoniazid and rifabutin administered daily or twice a week for 4 months (see Six-month RFB-based therapy in Table 1A of Appendix).

B.II For patients for whom the use of rifamycins is limited or contraindicated for any reason (e.g., intolerance to rifamycins, patient/clinician decision not to combine antiretroviral therapy with rifabutin), the initial phase of a 9-month TB regimen consists of isoniazid, streptomycin,* pyrazinamide, and ethambutol administered a) daily for 8 weeks or b) daily for at least the first 2 weeks, followed by twice-a-week dosing for 6 weeks, to complete the 2-month induction phase. The second phase of treatment consists of isoniazid, streptomycin,* and pyrazinamide administered 2–3 times a week for 7 months (see Nine-month SM-based therapy in Table 1A of Appendix).

A.I For patients who are not candidates for antiretroviral therapy, or for those patients for whom a decision is made not to combine the initiation of antiretroviral therapy with TB therapy, the preferred option continues to be a 6-month regimen that consists of isoniazid, rifampin, pyrazinamide, and ethambutol (or streptomycin). These drugs are administered a) daily for 8 weeks or b) daily for at least the first 2 weeks, followed by 2–3-times-per-week dosing for 6 weeks, to complete the 2-month induction phase. The

*Every effort should be made to continue administering streptomycin for the total duration of treatment or for at least 4 months after culture conversion (approximately 6–7 months from the start of treatment). Some experts suggest that in situations in which streptomycin is not included in the regimen for all of the recommended 9 months, ethambutol should be added to the regimen to replace streptomycin, and the duration of treatment should be prolonged from 9 months to 12 months. Alternatives to streptomycin are the injectable drugs amikacin, kanamycin, and capreomycin.

second phase of treatment consists of a) isoniazid and rifampin administered daily or 2–3 times a week for 4 months. Isoniazid, rifampin, pyrazinamide, and ethambutol (or streptomycin) also can be administered three times a week for 6 months (see Six-month RIF-based therapy in Table 1A of Appendix).

D.II TB regimens consisting of isoniazid, ethambutol, and pyrazinamide (i.e., three-drug regimens that do not contain a rifamycin, an aminoglycoside [e.g., streptomycin, amikacin, kanamycin], or capreomycin) should generally not be used for the treatment of patients with HIV-related TB; if these regimens are used for the treatment of TB, the minimum duration of therapy should be 18 months (or 12 months after documented culture conversion).

A.II Pyridoxine (vitamin B_6) (25–50 mg daily or 50–100 mg twice weekly) should be administered to all HIV-infected patients who are undergoing TB treatment with isoniazid, to reduce the occurrence of isoniazid-induced side effects in the central and peripheral nervous system.

E.II Because CDC's most recent recommendations for the use of antiretroviral therapy strongly advise against interruptions of therapy,* and because alternative TB treatments that do not contain rifampin are available, previous antituberculosis therapy options that involved stopping protease inhibitor therapy to allow the use of rifampin (Option I and Option II [*3*]) are no longer recommended.

Medications and Doses for Treatment of TB

No rating When rifabutin is used concurrently with indinavir, nelfinavir, or amprenavir, the recommended daily dose of rifabutin should be decreased from 300 mg to 150 mg (Table 2A of Appendix).

No rating The dose of rifabutin recommended for twice-weekly administration is 300 mg, and this dose recommendation does not change if rifabutin is used concurrently with indinavir, nelfinavir, or amprenavir (Table 2A of Appendix).

No rating Preliminary drug interaction studies suggest that when rifabutin is used concurrently with efavirenz, the dose of rifabutin for both daily and twice-weekly administration should be increased from 300 mg to 450 mg.

No rating Three-times-per-week administration of rifabutin used in combination with antiretroviral therapy has not been studied, and thus a recommendation for adjustment of dosages cannot currently be made.

No rating Experts do not know whether the daily dose of rifabutin should be reduced when this drug is used concurrently with either soft-gel saquinavir (Fortovase™) or nevirapine.

No rating No modifications in the usually recommended doses of isoniazid, ethambutol, pyrazinamide, or streptomycin (Table 2A of Appendix) are necessary if these drugs are used concurrently with protease inhibitors, NNRTIs, or nucleoside reverse transcriptase inhibitors (NRTIs).

*To minimize the emergence of drug-resistant HIV strains, if any antiretroviral medication must be temporarily discontinued for any reason, clinicians and patients should be aware of the theoretical advantage of stopping all antiretroviral agents simultaneously, rather than continuing the administration of one or two of these agents alone (*4*).

No rating The safety and effectiveness of rifapentine (Priftin®), a rifamycin newly approved by the U.S. Food and Drug Administration for the treatment of pulmonary tuberculosis, have not been established for patients infected with HIV. Administration of rifapentine to patients with HIV-related TB is not currently recommended.

Duration of TB Treatment

A.II The minimum duration of short-course rifabutin-containing TB treatment regimens is 6 months, to complete a) at least 180 doses (one dose per day for 6 months) or b) 14 induction doses (one dose per day for 2 weeks) followed by 12 induction doses (two doses per week for 6 weeks) plus 36 continuation doses (two doses per week for 18 weeks) (see Six-month RFB-based therapy in Table 1A of Appendix).

A.II The minimum duration of short-course rifampin-containing TB treatment regimens is 6 months, to complete a) at least 180 doses (one dose per day for 6 months) or b) 14 induction doses (one dose per day for 2 weeks) followed by 12–18 induction doses (two to three doses per week for 6 weeks) plus 36–54 continuation doses (two to three doses per week for 18 weeks) (see Six-month RIF-based therapy in Table 1A of Appendix).

A.II Three-times-per-week rifampin regimens should consist of at least 78 doses administered over 26 weeks.*

A.II The final decision on the duration of therapy should consider the patient's response to treatment. For patients with delayed response to treatment (see Box 2), the duration of rifamycin-based regimens should be prolonged from 6 months to 9 months (or to 4 months after culture conversion is documented).

A.II The minimum duration of nonrifamycin, streptomycin-based TB treatment regimens is 9 months, to complete a) at least 60 induction doses (one dose per day for 2 months) or b) 14 induction doses (one dose per day for 2 weeks) followed by 12–18 induction doses (two to three doses per week for 6 weeks) plus either 60 continuation doses (two doses per week for 30 weeks) or 90 continuation doses (three doses per week for 30 weeks).

A.II When making the final decision on the duration of therapy, clinicians should consider the patient's response to treatment. For patients with delayed response to treatment (see Box 2), the duration of streptomycin-based regimens should be prolonged from 9 months to 12 months (or to 6 months after culture conversion is documented).

A.III Interruptions in therapy because of drug toxicity or other reasons should be taken into consideration when calculating the end-of-therapy date for individual patients. Completion of therapy is based on total number of medication doses administered and not on duration of therapy alone.

A.III Reinstitution of therapy for patients with interrupted TB therapy might require a continuation of the regimen originally prescribed (as long as needed to complete the recommended duration of the particular regimen)

*Three-times-per-week rifabutin regimens, used in combination with antiretroviral therapy, have not been studied.

BOX 2. Components of the monthly medical evaluation for human immunodeficiency virus-infected patients undergoing treatment for active tuberculosis

For patients infected with human immunodeficiency virus (HIV) who are undergoing treatment for active tuberculosis (TB), clinicians should include the following components in the monthly evaluation:

- Once a month, evaluate symptoms and signs of TB (response to treatment) by conducting a) a physical examination (the nature and extent of this evaluation will depend on the patient's symptoms and the site of disease) and b) for patients with pulmonary TB, an examination by smear and culture of an expectorated or induced sputum specimen until cultures are no longer positive for *Mycobacterium tuberculosis*.
- Perform as necessary for individual patients laboratory tests such as: complete blood cell count, platelet count, and tests for serum glutamic oxalacetic transaminase or aspartate aminotransferase (SGOT/AST) and serum glutamic pyruvic transaminase or alanine aminotransferase (SGPT/ALT), alkaline phosphatase, total bilirubin, uric acid, blood urea nitrogen, and creatinine.
- To assist in the decision about the duration of TB treatment, investigate the possibility of a delayed response to treatment (Table 1A of Appendix). Delayed response to treatment should be suspected (and in most cases treatment duration should be prolonged) if by the end of the 2-month induction phase of therapy, patients a) continue to be culture-positive for *M. tuberculosis* or b) do not experience resolution of signs or symptoms of TB or do experience progression of signs or symptoms of TB (e.g., persistent fever, progressive weight loss, or increase in size of lymph nodes, abscesses, or other tuberculous lesions, none of which can be accounted for by a disease other than TB). (See Duration of TB Treatment.)
- Some factors potentially associated with TB treatment failure are a large mycobacterial load and extensive lung cavitation at baseline, nonadherence with the drug regimen (even among patients assumed to be on DOT), inappropriately low medication doses, and impaired absorption of drugs. Immediately institute corrective measures for those factors amenable to intervention.
- Because patients with HIV-infection often are treated with multiple drugs in addition to antituberculosis drugs, at each visit, review all medications that the patient is taking and assess any change in medications for potential drug interactions with TB medications. Efforts to manage these potential problems related to drug interactions require the coordinated efforts of care givers for HIV and TB disease. (See TB Drug Interaction and Absorption.)
- Because several antituberculosis drugs have hepatotoxicity as a potential side effect (Table 2A of Appendix), advise all persons taking TB medications about the symptoms consistent with hepatitis (e.g., anorexia, nausea, vomiting, abdominal pain, jaundice) and instruct them to discontinue all TB medications immediately and seek medical attention promptly if they exhibit such symptoms. These patients usually will need an examination by a physician, liver function tests, and a planned strategy for restarting TB treatment.
- If ethambutol is administered, perform a monthly visual acuity exam and test for red-green color perception.
- If streptomycin is administered, perform audiometry and renal function tests as needed.

or a complete renewal of the regimen. In either situation, when therapy is resumed after an interruption of ≥2 months, sputum samples (or other clinical samples as appropriate) should be taken for smear, culture, and drug-susceptibility testing.

Management of the Coadministration of TB and HIV Therapies, Including the Potential for Paradoxical Reactions

When antituberculosis treatment has been started, all patients should be monitored for response to antituberculosis therapy, drug-related toxicity, and drug interactions. Detailed recommendations for managing antiretroviral therapy are published elsewhere (*4*), and consultation with experts in this area is highly recommended.

The frequency and type of most TB medication side effects are similar among TB patients with and without HIV infection (*30,65,67*). When caring for HIV-infected persons, clinicians must be aware of the following problems that can result from the administration of TB medications: a) patients might have a higher predisposition toward isoniazid-related peripheral neuropathy; b) evaluation of dermatologic reactions related to TB medications might be complicated because HIV-infected patients are subject to several dermatologic diseases related to HIV disease or to medications used for other treatment or prophylaxis reasons; and c) patients undergoing concurrent therapy with rifabutin and protease inhibitors or NNRTIs are at risk for rifabutin toxicity associated with increased serum concentrations of this drug. The reported adverse events associated with rifabutin toxicity include arthralgias, uveitis, and leukopenia (*86,101–103*). Detailed recommendations for managing these adverse reactions are published elsewhere and should be consulted (*2,64*).

Paradoxical reactions — temporary exacerbation of symptoms, signs, or radiographic manifestations of TB (e.g., recurrence of fever, enlarged lymph nodes, appearance of cavitation in previously normal chest x-ray) among patients who have experienced a good clinical and bacteriologic response to antituberculosis therapy — have been reported among patients coinfected with HIV who have restored immune function because of antiretroviral therapy (*76*). The synchronization and severity of paradoxical reactions associated with antiretroviral therapy are not well understood; therefore, experts do not know whether the occurrence of these reactions should affect the timing of initiating or changing antiretroviral therapy when such therapy is indicated for a patient with HIV infection. However, because an association between paradoxical reactions and initiation of antiretroviral therapy has been noted, clinicians should be aware of this possibility and discuss the risks with patients undergoing therapy for active TB.

Monthly Medical Evaluation and the Diagnosis and Management of Paradoxical Reactions

A.II All patients should receive a monthly clinical evaluation (see Box 2) to monitor their response to treatment, adherence to treatment, and medication side effects (Table 2A of Appendix). During the early days of therapy, the interval between these evaluations might be shorter (e.g., every 2 weeks).

A.II Patients suspected of having paradoxical reactions should be evaluated to rule out other causes for their clinical presentation (e.g., TB treatment failure) before attributing their signs and symptoms to a paradoxical reaction.

C.III Some experts recommend that to avoid paradoxical reactions, clinicians should delay the initiation of or changes in antiretroviral therapy until the signs and symptoms of TB are well controlled (possibly 4–8 weeks from the initiation of TB therapy).

No rating For patients with a paradoxical reaction in whom the symptoms are not severe or life-threatening, the management of these reactions might consist of symptomatic therapy and no change in antituberculosis or antiretroviral therapy. For patients with a paradoxical reaction associated with severe or life-threatening clinical manifestations (e.g., uncontrollable fever, airway compromise from enlarging lymph nodes, enlarging serosal fluid collections [pleuritis, pericarditis, peritonitis], sepsis-like syndrome), the management might include hospitalization and possibly a time-limited use of corticosteroids (e.g., prednisone started daily at a dose of 60–80 mg and reduced after 1 or 2 weeks, with the resolution of symptoms as a guide; in most cases, corticosteroid therapy should last no more than 4–6 weeks).

TB Drug Interaction and Absorption

E.II Given the expected drug interactions that would result in markedly decreased serum levels of antiretroviral agents, and given the overlapping toxicities, the coadministration of *rifampin* with any of the protease inhibitors or with NNRTIs, as well as the coadministration of *rifabutin* with ritonavir, hard-gel saquinavir (Invirase™), or delavirdine, is contraindicated.

A.II The potent effect of rifampin as a CYP450 inducer, which lowers the serum concentration of protease inhibitors and NNRTIs, is expected to continue up to at least 2 weeks following the discontinuation of rifampin. Therefore, to diminish the likelihood of adverse effects on drug metabolism, clinicians should plan the start of therapy with protease inhibitors or NNRTIs at least 2 weeks after the date of the last dose of rifampin.

A.II Rifabutin is a less potent CYP450 inducer than rifampin and thus can be used (with adjustments in dosages) concurrently with the NNRTIs nevirapine or efavirenz or with certain protease inhibitors (e.g., indinavir, nelfinavir, and possibly soft-gel saquinavir [Fortovase™] and amprenavir).

No rating Indinavir serum concentrations are decreased by rifabutin-related induction of the hepatic cytochrome P450; therefore, when indinavir is used in combination with rifabutin, the dose of indinavir usually is increased from 800 mg every 8 hours to 1,200 mg every 8 hours.

No rating Nelfinavir serum concentrations are also decreased when nelfinavir is used in combination with rifabutin (Table 1A of Appendix); however, the resultant metabolite of nelfinavir is known to be active against HIV. Nevertheless, some experts suggest increasing the dose of nelfinavir from

750 mg three times per day to 1,000 mg three times per day when used in combination with rifabutin.

No rating Experts do not know whether dose-modifications are needed for soft-gel saquinavir (Fortovase™), amprenavir, nevirapine, or efavirenz if these agents are used in combination with rifabutin.

No rating Many other medications commonly used by patients with HIV infection have drug interactions with the rifamycins (rifampin or rifabutin) of sufficient magnitude to require interventions such as dose adjustments or use of alternative therapies. Some examples of these drugs are hormonal contraceptives, dapsone, ketoconazole, fluconazole, itraconazole, narcotics (including methadone), anticoagulants, corticosteroids, cardiac glycosides, hypoglycemics (sulfonylureas), diazepam, beta-blockers, anticonvulsants, and theophylline.

No rating Malabsorption of antituberculosis drugs has been demonstrated in some patients with HIV infection, and in some cases, it has been associated with TB treatment failures and the selection of drug-resistant *M. tuberculosis* bacilli (*141–145*). Therapeutic drug monitoring has been advocated by some experts as an adjunct in the management of HIV-related TB (*146*). This approach might be useful when evaluating patients with TB treatment failure or relapse and in the treatment of multidrug-resistant (MDR) TB. However, the role of therapeutic drug monitoring in the routine management of TB among HIV-infected patients has not been established and is not presently recommended.

Treatment of TB in Special Situations

The following general treatment recommendations address special situations such as drug-resistant forms of HIV-related TB, TB among HIV-infected pregnant women, TB among HIV-infected children, and extrapulmonary HIV-related TB. Detailed recommendations for managing these patients are published elsewhere (*2,64,147–150*), and consultation with experts in these areas is highly recommended.

Treatment of Drug-Resistant TB

A.II **TB disease resistant to isoniazid only.** The treatment regimen should generally consist of a rifamycin (rifampin or rifabutin), pyrazinamide, and ethambutol for the duration of treatment. Intermittent therapy administered twice weekly can be used following at least 2 weeks (14 doses) of daily induction therapy (see Duration of TB Treatment). The recommended duration of treatment is 6–9 months or 4 months after culture conversion. Isoniazid is generally stopped when resistance (>1% of bacilli resistant to 1.0 μg/mL of isoniazid) to this drug is discovered; however, when low-level resistance is discovered (>1% of bacilli resistant to 0.2 μg/mL of isoniazid, but no resistance to 1.0 μg/mL of isoniazid), some experts suggest continuing to use isoniazid as part of the treatment regimen. Because the development of acquired rifamycin resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.

A.II **TB disease resistant to rifampin only.** The 9-month treatment regimen should generally consist of an initial 2-month phase of isoniazid, streptomycin, pyrazinamide, and ethambutol (see Nine-month SM-based therapy in Table 1A of Appendix). The second phase of treatment should consist of isoniazid, streptomycin, and pyrazinamide administered for 7 months. Because the development of acquired isoniazid resistance would result in MDR TB, clinicians should carefully supervise and manage TB treatment for these patients.

A.III **Multidrug-resistant TB (resistant to both isoniazid and rifampin).** These patients should be managed by or in consultation with physicians experienced in the management of MDR TB. Findings from a retrospective study of patients with MDR TB strongly indicate that early aggressive treatment with appropriate regimens (based on the known or suspected drug-resistance pattern of the *M. tuberculosis* isolate) markedly decreases deaths associated with MDR TB (*63,151–153*). Most drug regimens currently used to treat MDR TB include an aminoglycoside (e.g., streptomycin, kanamycin, amikacin) or capreomycin, and a fluoroquinolone. The recommended duration of treatment for MDR TB in HIV-seropositive patients is 24 months after culture conversion, and posttreatment follow-up visits to monitor for TB relapse should be conducted every 4 months for 24 months. Because of the serious personal and public health concerns associated with MDR TB, health departments should always use DOT for these patients and take whatever steps are needed to ensure their adherence to therapy.

A.III ***TB Treatment for HIV-Infected Pregnant Women***

HIV-infected pregnant women who have a positive *M. tuberculosis* culture or who are suspected of having TB disease should be treated without delay. Choices of TB treatment regimens for HIV-infected pregnant women are those that include a rifamycin (Table 1A of Appendix). Routine use of pyrazinamide during pregnancy is recommended by international organizations but has not been recommended in the United States because of inadequate teratogenicity data (*2*). However, for HIV-infected pregnant women, the benefits of a TB treatment regimen that includes pyrazinamide outweigh potential pyrazinamide-related risks to the fetus. Aminoglycosides (e.g, streptomycin, kanamycin, amikacin) and capreomycin are contraindicated for all pregnant women because of potential adverse effects on the fetus. Considerations for antiretroviral therapy for pregnant HIV-infected women have been published elsewhere (*4*).

A.II ***TB Treatment for HIV-Infected Children***

HIV-infected children who are suspected of having TB disease should be treated without delay. For HIV-infected children, even those who are too young to be evaluated for visual acuity and red-green perception, ethambutol at a dosage of 15 mg/kg body weight (Table 2A of Appendix) should generally be included as part of the initial regimen, unless the infecting strain of *M. tuberculosis* is known or suspected of being susceptible to

isoniazid and rifampin. If drug-susceptibility results are not available, a four-drug regimen (e.g., isoniazid, rifamycin, pyrazinamide, and ethambutol) for 2 months, followed by intermittent administration of isoniazid and a rifamycin for 4 months, is recommended. Considerations for antiretroviral therapy for children and adolescents have been published elsewhere (*154*).

A.II ***TB Treatment for HIV-Infected Patients with Extrapulmonary TB***

The basic principles that support the treatment of pulmonary TB in HIV-infected patients also apply to extrapulmonary forms of the disease. Most extrapulmonary forms of TB (including TB meningitis, tuberculous lymphadenitis, pericardial TB, pleural TB, and disseminated or miliary TB) are more common among persons with advanced-stage HIV disease (*155,156*) than among patients with asymptomatic HIV infection. The drug regimens and treatment durations that are recommended for treating pulmonary TB in HIV-infected adults and children (Table 1A of Appendix) are also recommended for treating most patients with extrapulmonary disease. However, for certain forms of extrapulmonary disease, such as meningioma, bone, and joint TB, using a rifamycin-based regimen for at least 9 months is generally recommended.

Latent M. tuberculosis *Infection*

Clinical and Public Health Principles

When caring for persons with HIV infection, clinicians should make aggressive efforts to identify those who also are infected with *M. tuberculosis*. Because the reliability of the tuberculin skin test (TST) can diminish as the CD4+ T-cell count declines, TB screening with TST should be performed as soon as possible after HIV infection is diagnosed. Because the risk of infection and disease with *M. tuberculosis* is particularly high among HIV-infected contacts of persons with infectious pulmonary or laryngeal TB, these persons must be evaluated for TB as soon as possible after learning of exposure to a patient with infectious TB.

Health-care providers, administrators, and TB controllers must coordinate their work and establish TB screening initiatives in settings where a) the prevalence of infection with *M. tuberculosis* among persons with HIV-infection is expected to be high and b) referral for medical evaluation and TB preventive therapy can be accomplished. Such settings include prisons, jails, prenatal-care programs, drug treatment programs, syringe exchange programs, HIV specialty clinics, acute-care hospitals serving populations at high risk of TB, AIDS patient group residences, some community-health centers, psychiatric institutions, mental health residences, and homeless shelters. All HIV counseling and testing sites must have mechanisms in place to ensure that persons identified with HIV infection receive tuberculin skin testing. TB control programs in jurisdictions that have HIV reporting requirements should make efforts to ensure that all persons with HIV infection have TSTs.

Because of the complexity of problems associated with active TB disease in HIV-infected persons, and as part of the efforts to control and eliminate TB in the United States, all HIV-infected persons identified as latently infected with *M. tuberculosis*

should complete a full recommended course of preventive therapy unless such therapy is contraindicated. Public health programs should take an active role in ensuring that patients treated in outpatient settings complete TB preventive therapy. In certain outpatient and institutional settings, directly observed preventive therapy (DOPT) should be used whenever operationally feasible and when resources permit.

Diagnosis of M. tuberculosis *Infection Among HIV-Infected Persons*

The Mantoux-method TST, with 5 TU of purified protein derivative, is used to diagnose *M. tuberculosis* infection. A TST reaction size of ≥5 mm of induration is considered positive (i.e., indicative of *M. tuberculosis* infection) in persons who are infected with HIV. Persons with a TST reaction size of <5 mm but with a history of exposure to TB also could be infected with *M. tuberculosis*; this possibility should be investigated (*157*). Whenever *M. tuberculosis* infection is suspected in a patient, an evaluation to rule out active TB and assess the need for preventive therapy should be conducted (see Box 3). This evaluation should include HIV counseling and testing for persons whose HIV status is unknown but who are at risk for HIV infection.

Tuberculin Skin Testing Among HIV-Infected Persons

A.I As soon as possible after HIV infection is diagnosed, all persons should receive a TST unless previously tested and found to be TST-positive.

A.II As soon as possible (ideally within 7 days) after learning of an exposure to a patient with infectious TB, all HIV-infected persons should be evaluated for TB and receive a TST, regardless of any previous TST results.

B.III TSTs should be conducted periodically for HIV-infected persons who are TST-negative on initial evaluation and who belong to populations with a substantial risk of exposure to *M. tuberculosis* (e.g., residents of prisons, jails, or homeless shelters).

C.III Some experts recommend repeat TSTs for HIV-infected persons who are TST-negative on initial evaluation and whose immune function is restored because of effective antiretroviral therapy.

C.I Because results of anergy testing in HIV-infected populations in the United States do not seem useful to clinicians making decisions about preventive therapy, anergy testing is no longer recommended as a routine component of TB screening among HIV-infected persons (*157*). However, some experts support the use of anergy testing to help guide individual decisions regarding preventive therapy, and some recommend that a TST be performed on patients previously classified as anergic if evidence indicates that these patients' immune systems have responded to therapy with antiretroviral drugs.

Candidates for TB Preventive Therapy Among HIV-Infected Persons

A.I Persons with a TST reaction size of ≥5 mm who have not previously received treatment for *M. tuberculosis* infection should receive TB preventive treatment, regardless of their age.

A.II Persons who have had recent contact with an infectious TB patient should receive TB preventive treatment, regardless of their age, results of TSTs, or history of previous TB preventive treatment.

BOX 3. Components of the baseline medical evaluation for tuberculosis preventive treatment for patients infected with human immunodeficiency virus

When conducting a medical evaluation to rule out active tuberculosis (TB) and administer preventive treatment for patients infected with human immunodeficiency virus (HIV), clinicians should include the following questions and assessments:

Medical History

- Ask patients about their history of recent close contact with a person who has TB disease. If the infecting source-patient is known, his or her culture and drug-susceptibility results should be investigated and reviewed so that the preventive therapy regimen can be tailored appropriately (see Treatment of Latent *M. Tuberculosis* in Special Situations).
- Assess patients for their risk of increased toxicity associated with the medications used for TB preventive therapy (e.g., history of excessive alcohol ingestion, liver disease, hepatitis, chronic use of other medications).
- Assess patients for contraindications to TB preventive therapy (Table 3A of Appendix).
- When persons have previously received TB preventive treatment, determine what drugs were used, duration of treatment, and any history of adverse reactions (Table 2A of Appendix) and adherence to preventive therapy.
- Ask patients about their history of antiretroviral therapy and their history of therapies to prevent opportunistic infections. If a patient has ever received or is receiving any of these treatments, the care provider must determine the drugs used, duration of treatment, history of adverse reactions, potential for drug interactions with TB medications, and any reasons for discontinuation of treatment if treatment ended.

Chest X-Ray Examination

- A chest x-ray is indicated for all persons being considered for preventive therapy, to rule out active pulmonary TB disease. Children younger than 5 years old should undergo both a posterior-anterior and a lateral chest x-ray. All other individuals should receive a posterior-anterior chest x-ray only; additional x-rays should be performed at the physician's discretion. Pregnant women who have a positive TST or who have negative TST results but are recent contacts of a person who has infectious TB disease should undergo a chest x-ray (with appropriate shielding) without delay, even during the first trimester of pregnancy.

Laboratory Tests

- Obtain a complete blood cell count, and also obtain a platelet count if the patient will be treated with a rifamycin (rifampin or rifabutin).
- Conduct chemistry panel tests, especially for liver enzyme levels (serum glutamic oxalacetic transaminase or aspartate aminotransferase [SGOT/AST] and serum glutamic pyruvic transaminase or alanine aminotransferase [SGPT/ALT]) and total bilirubin. In addition, check uric acid levels if the patient will be treated with pyrazinamide.
- Obtain three consecutive sputum samples for smear, culture, and drug-susceptibility testing to rule out active TB disease in a) persons who have symptoms that indicate TB disease (e.g., cough, fever, night sweats, weight loss) and b) persons who have chest x-ray findings that indicate past, healed TB (e.g., noncalcified fibrotic lesions) and who have a history of no TB treatment or inadequate TB treatment.

A.II Persons with a history of prior untreated or inadequately treated past TB that healed and no history of adequate treatment for TB should receive TB preventive treatment, regardless of their age or results of TSTs.

C.III Primary prophylaxis for TST-negative, HIV-infected persons with an ongoing and unavoidable high risk of exposure to *M. tuberculosis* for the duration of the exposure time (e.g., residents of prisons, jails, or homeless shelters in which the current prevalence of TB is high) should be considered in some situations.

TB Preventive Therapy Regimens, Including Dosage Recommendations

The following recommendations are appropriate for adults with HIV infection who are likely to have latent *M. tuberculosis* infection with organisms susceptible to isoniazid and rifamycins. Updated recommendations for children are not yet available. Several TB preventive therapy regimens are currently recommended (Table 3A of Appendix). The TB medications used in these regimens have varying doses, toxicities, and monitoring requirements (Table 2A of Appendix). All patients on twice-a-week dosing regimens should receive DOPT; some experts also recommend DOPT for patients on 2-month preventive therapy regimens. The administration of TB preventive therapy regimens that contain rifampin is contraindicated for patients who take protease inhibitors or NNRTIs. For these patients, the substitution of rifabutin for rifampin in preventive therapy regimens is recommended; however, the substitution of rifapentine for rifampin is not currently recommended because rifapentine's safety and effectiveness have not been established for patients infected with HIV.

Recommended Preventive Therapy Regimens for Patients Receiving Protease Inhibitors or NNRTIs

A.II For HIV-infected adults, a 9-month regimen of isoniazid can be administered daily.

B.I For HIV-infected adults, a 9-month regimen of isoniazid can be administered twice a week (DOPT should be used with intermittant dosing regimens).

B.III For HIV-infected adults, a 2-month regimen of rifabutin and pyrazinamide can be administered daily.

No rating The concurrent administration of rifabutin is contraindicated with ritonavir, hard-gel saquinavir (Invirase™), and delavirdine.

Recommended Preventive Therapy Regimens for Patients Not Receiving Protease Inhibitors or NNRTIs

A.II For HIV-infected adults, a 9-month regimen of isoniazid can be administered daily.

B.I For HIV-infected adults, a 9-month regimen of isoniazid can be administered twice a week.

A.I For HIV-infected adults, a 2-month regimen of rifampin and pyrazinamide can be administered daily.

Duration of TB Preventive Therapy

A.II Daily isoniazid regimens should consist of at least 270 doses to be administered for 9 months or up to 12 months if interruptions in therapy occur.

A.III Twice-a-week isoniazid regimens should consist of at least 76 doses to be administered for 9 months or up to 12 months if interruptions in therapy occur.

A.II Daily regimens of rifamycin (rifampin or rifabutin) and pyrazinamide should consist of at least 60 doses to be administered for 2 months or up to 3 months if interruptions in therapy occur.

A.III When calculating the end-of-preventive-therapy date for individual patients, consider interruptions in therapy because of drug toxicity or other reasons. Completion of therapy is based on total number of medication doses administered and not on duration of therapy alone.

A.III When reinstituting therapy for patients with interrupted TB preventive therapy, clinicians might need to continue the regimen originally prescribed (as long as needed to complete the recommended duration of the particular regimen) or completely renew the entire regimen. In either situation, when therapy is restored after an interruption of ≥2 months, a medical examination to rule out TB disease is indicated.

Monthly Monitoring of Patients During TB Preventive Treatment

A.II All persons undergoing preventive treatment for TB should receive a monthly clinical evaluation of their adherence to treatment and medication side effects (see Box 4).

BOX 4. Components of the monthly medical evaluation for human immunodeficiency virus-infected patients undergoing preventive treatment for latent *Mycobacterium tuberculosis* infection

For patients infected with human immunodeficiency virus (HIV) who are undergoing preventive treatment for latent *Mycobacterium tuberculosis* infection, clinicians should include the following components in the monthly evaluation:

- At every monthly evaluation, review signs and symptoms potentially related to active tuberculosis (TB) disease as well as signs and symptoms of drug reactions potentially related to antituberculosis drugs (Table 2A of Appendix).
- At the start of preventive therapy and at each subsequent monthly visit, remind patients of the need to immediately discontinue preventive therapy and seek prompt medical attention if signs and symptoms of hepatotoxicity appear (e.g., anorexia, abdominal pain, nausea, vomiting, change in color of urine and feces, jaundice).
- Monthly liver function tests are advised only for a) persons whose pretreatment tests were abnormal (>3 times the upper level of normal); b) persons who are 35 years or older; and c) patients who are pregnant.
- Patients with HIV infection often are treated with multiple drugs in addition to antituberculosis drugs. At each visit, all medications that a patient is taking should be reviewed and assessed for potential drug interactions with TB medications. Some examples of these drugs are hormonal contraceptives, ketoconazole, fluconazole, itraconazole, narcotics (including methadone), anticoagulants, corticosteroids, cardiac glycosides, hypoglycemics (sulfonylureas), diazepam, beta-blockers, anticonvulsants, and theophylline. Efforts to manage these potential problems related to drug interactions require the coordinated efforts of HIV and TB patients' care givers.

Treatment of Latent* M. tuberculosis *Infection in Special Situations

A.I DOPT should always be used with intermittent dosing regimens.

B.III DOPT also should be used when operationally feasible, especially with 2-month preventive therapy regimens and in some special settings (e.g., in some institutional settings, in some community outreach programs, and for some persons who are candidates for preventive therapy because they are household contacts of patients with TB disease who are receiving home-based DOT).

A.III For persons who are known to be contacts of patients with isoniazid-resistant, rifamycin-susceptible TB, a 2-month preventive therapy regimen of a rifamycin (rifampin or rifabutin) and pyrazinamide is recommended. For patients with intolerance to pyrazinamide, a 4–6-month regimen of a rifamycin (rifampin or rifabutin) alone is recommended (*158–160*) (Table 3A of Appendix).

C.III The choices for preventive treatment for persons who are likely to be infected with a strain of *M. tuberculosis* resistant to both isoniazid and rifamycins are published elsewhere (*161*). In general, the recommended preventive therapy regimens for these persons include the use of a combination of at least two antituberculosis drugs that the infecting strain is believed to be susceptible to (e.g., ethambutol and pyrazinamide, levofloxacin and ethambutol). The clinician should review the drug-susceptibility pattern of the *M. tuberculosis* strain isolated from the infecting source-patient before choosing a preventive therapy regimen.

A.III For HIV-infected women who are candidates for TB preventive therapy, the initiation or discontinuation of preventive therapy should not be delayed on the basis of pregnancy alone, even during the first trimester. A 9-month regimen of isoniazid administered daily or twice a week is the only recommended option (Table 3A of Appendix).

No rating For HIV-infected children who are candidates for TB preventive therapy, a 12-month regimen of isoniazid administered daily is recommended by the American Academy of Pediatrics (*162*).

Follow-up of HIV-Infected Persons Who Have Completed Preventive Therapy

A.II Follow-up care — including chest x-rays and medical evaluations — is not necessary for patients who complete a course of TB preventive treatment, unless they develop symptoms of active TB disease or are subsequently reexposed to a person with infectious TB disease.

Follow-up of HIV-Infected Persons Who Are Candidates for, but Who Do Not Receive, TB Preventive Therapy

A.III These persons should be assessed periodically (in intervals of <6 months) for symptoms of active TB as part of their ongoing HIV infection management. Clinicians should educate these persons about the symptoms of TB disease (e.g., cough with or without fever, night sweats, weight loss) and advise them to seek immediate medical attention if they develop such

symptoms. If persons present with these symptoms, clinicians should always include TB disease in the differential diagnosis.

CONCLUSIONS

Implementing TB prevention and control strategies for persons infected with HIV has always been important and is even more critical now that a larger selection of new, more potent antiretroviral drugs has enabled clinicians to implement therapies that improve the health and prolong the lives of HIV-infected persons. These antiretroviral therapeutic strategies often include the use of drugs such as the protease inhibitors or the nonnucleoside reverse transcriptase inhibitors (NNRTIs), which because of drug interactions cannot be used concurrently with certain other drugs (e.g., rifampin). Thus, to improve the diagnosis and management of TB and HIV coinfection, TB control programs need to be prepared for the following challenges:

- Ensure that all patients with TB receive HIV counseling and testing either on site or elsewhere. Patients with latent *M. tuberculosis* infection who are at risk for HIV infection also should receive HIV counseling and testing.
- Initiate prompt and effective antituberculosis treatment (ideally with directly observed therapy) for all patients diagnosed with HIV-related TB.
- Promote optimal antiretroviral therapy for patients with *M. tuberculosis* and HIV infection.
- Become knowledgeable about the indications, potential dosing adjustments, and monitoring requirements of a rifabutin-containing regimen (or an alternative regimen that does not contain rifamycin) for the treatment of TB in patients who are undergoing antiretroviral therapy with protease inhibitors or NNRTIs.
- Identify potential risk factors for TB treatment failure or relapse as well as the potential for paradoxical treatment reactions, and learn how to recognize and manage these outcomes.
- Follow procedures to ensure early recognition and implementation of effective treatment for drug-resistant TB.
- Recognize that previous options that involved stopping protease inhibitor therapy to allow the use of rifampin for TB treatment are no longer recommended for two reasons: a) the most recent guidelines for the use of antiretroviral therapy advise against interrupting HIV therapy, and b) alternatives for TB therapy that do not contain rifampin are available.
- Coordinate efforts and establish TB screening initiatives in settings where a) the prevalence of infection with *M. tuberculosis* among persons with HIV-infection is expected to be high and b) referral for medical evaluation and therapy for active or latent TB is possible.
- Be aware of changes in options for TB preventive therapy. In addition to recommendations for using 9 months of isoniazid daily or twice a week, new short-course multidrug regimens (e.g., a 2-month course of a rifamycin such as

rifabutin or rifampin with pyrazinamide) can be prescribed for HIV-infected patients with latent *M. tuberculosis* infection.

When faced with treatment choices, TB controllers and clinicians can use these recommendations to make informed decisions based on the most current research results available, keeping in mind that as new antiretroviral and antituberculosis agents become available, these guidelines will likely change. The aim of these recommendations is to help reduce TB treatment failures, prevent cases of drug-resistant TB, diminish the adverse effects that TB has on HIV replication, and support efforts to not only control TB, but to eliminate it from the United States. Future research should include a) the development of methods for early and accurate diagnosis of *M. tuberculosis* infection in persons coinfected with HIV, b) strategies to help simplify treatment for active and latent TB and increase adherence to and completion of therapy, and c) basic research to define what host factors protect persons from infection with *M. tuberculosis* and HIV and from the development of TB and HIV disease.

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Appendix

Recommended Treatment Options for Persons with Human Immunodeficiency Virus-Related Tuberculosis Infection and Disease

TABLE 1A. Treatment regimens for human immunodeficiency virus (HIV)-related tuberculosis (TB)

Rating	Induction Phase		Continuation Phase		Considerations for HIV Therapy	Comments
	Drugs	Interval and Duration	Drugs	Interval and Duration		
Six-month RFB-based therapy (may be prolonged* to 9 months)						
A.II	•INH •RFB •PZA† •EMB†	Daily for 2 months (8 weeks)	•INH •RFB	Daily or 2 times/week for 4 months (18 weeks)	RFB should not be used concurrently with ritonavir, hard-gel saquinavir (Invirase™), or delavirdine. A 20%–25% increase in the dose of protease inhibitors or NNRTIs might be necessary.	If the patient also is taking indinavir, nelfinavir, or amprenavir, the daily dose of RFB is decreased from 300 mg to 150 mg. The twice-weekly dose of RFB (300 mg) remains unchanged if the patient is also taking these protease inhibitors.
		or		or		
	•INH •RFB •PZA† •EMB†	Daily for 2 weeks and then 2 times/week for 6 weeks	•INH •RFB	2 times/week for 4 months (18 weeks)	The patient should be monitored carefully for RFB drug toxicity (arthalgia, uveitis, leukopenia) if RFB is used concurrently with protease inhibitors or NNRTIs. Evidence of decreased antiretroviral drug activity should be assessed periodically with HIV RNA levels. No contraindication exists for the use of RFB with NRTIs.	If the patient also is taking efavirenz, the daily or twice weekly dose of RFB is increased from 300 mg to 450 mg. Three-times-a-week administration of RFB used in combination with antiretroviral therapy has not been studied.
Nine-month SM-based therapy (may be prolonged* to 12 months)						
B.II	•INH •SM •PZA •EMB	Daily for 2 months (8 weeks)	•INH •SM •PZA	2–3 times/week for 7 months (30 weeks)	Can be used concurrently with antiretroviral regimens that include protease inhibitors, NRTIs, and NNRTIs.	SM is contraindicated for pregnant women. Every effort should be made to continue administering SM for the total duration of treatment. When SM is not used for the recommended 9 months, EMB should be added to the regimen and the treatment duration should be prolonged from 9 months (38 weeks) to 12 months (52 weeks).
		or		or		
	•INH •SM •PZA •EMB	Daily for 2 weeks and then 2–3 times/week for 6 weeks	•INH •SM •PZA	2–3 times/week for 7 months (30 weeks)		

Six-month RIF-based therapy (may be prolonged* to 9 months)						
A.I	•INH •RIF •PZA§ •EMB§ (or SM)	Daily for 2 months (8 weeks) or	•INH •RIF	Daily or 2–3 times/week for 4 months (18 weeks) or	Protease inhibitors or NNRTIs should not be administered concurrently with RIF. NRTIs can be administered concurrently with RIF. If appropriate, patients should be assessed every 3 months to evaluate the decision to initiate antiretroviral therapy. A 2-week "P-450 induction washout" period may be necessary between the last dose of RIF and the first dose of protease inhibitors or NNRTIs.	SM is contraindicated for pregnant women.
	•INH •RIF •PZA§ •EMB§ (or SM)	Daily for 2 weeks and then 2–3 times/week for 6 weeks or	•INH •RIF	2–3 times/week for 4 months (18 weeks) or		
	•INH •RIF •PZA •EMB (or SM)	3 times/week for 2 months (8 weeks)	•INH •RIF •PZA •EMB (or SM)	3 times/week for 4 months (18 weeks)		

EMB=ethambutol; INH=isoniazid; PZA=pyrazinamide; RFB=rifabutin; RIF=rifampin; SM=streptomycin.
NNRTI=nonnucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor.

* Duration of therapy should be prolonged for patients with delayed response to therapy. Criteria for delayed response should be assessed at the end of the 2-month induction phase and include a) lack of conversion of the *Mycobacterium tuberculosis* culture from positive to negative or b) lack of resolution or progression of signs or symptoms of TB.
† Continue PZA and EMB for the total duration of the induction phase (8 weeks).
§ Continue PZA for the total duration of the induction phase (8 weeks). EMB can be stopped after susceptibility test results indicate *Mycobacterium tuberculosis* susceptibility to INH and RIF.

TABLE 2A. Antituberculosis medications: doses, toxicities, and monitoring requirements

Drug	Dose in mg/kg (*maximum dose*) Route of Administration: Daily – Children	Daily – Adults	Two times/week* – Children	Two times/week* – Adults	Three times/week* – Children	Three times/week* – Adults	Adverse Reactions	Monitoring	Comments
INH	10-20 *(300 mg)* PO or IM	5 *(300 mg)* PO or IM	20-40 *(900 mg)* PO or IM	15 *(900 mg)* PO or IM	20-40 *(900 mg)* PO or IM	15 *(900 mg)* PO or IM	•Rash •Hepatic enzyme elevation •Hepatitis •Peripheral neuropathy •Mild central nervous system effects •Drug interactions resulting in increased phenytoin (Dilantin) or disulfiram (Antabuse) levels	Liver function tests Repeat measurements if •baseline results are abnormal •patient is pregnant or at high risk for adverse reactions •patient has symptoms of adverse reactions	Hepatitis risk increases with age and alcohol consumption. Pyridoxine (Vitamin B_6) might prevent peripheral neuropathy and central nervous system effects.
RIF	10-20 *(600 mg)* PO or IV	10 *(600 mg)* PO or IV	10-20 *(600 mg)* PO or IV	10 *(600 mg)* PO or IV	10-20 *(600 mg)* PO or IV	10 *(600 mg)* PO or IV	•Rash •Hepatitis •Fever •Thrombocytopenia •Flu-like symptoms associated with intermittent dosing •Orange-colored body fluids (secretions, urine, tears)	Complete blood count, platelets, and liver function tests Repeat measurements if •baseline results are abnormal • patient has symptoms of adverse reactions	RIF use contraindicated for patients taking PIs or NNRTIs. Decreases levels of many drugs (e.g., methadone, dapsone, ketoconazole, hormonal contraceptives). Might permanently discolor soft contact lenses.
RFB[†]	10-20 *(300 mg)* PO or IV or NA[§] *(150 mg)* PO or IV or NA[¶] *(450 mg)* PO or IV	5 *(300 mg)* PO or IV or NA[§] *(150 mg)* PO or IV or NA[¶] *(450 mg)* PO or IV	10–20 *(300 mg)* PO or IV or 10-20[§] *(300 mg)* PO or IV or NA[¶] *(450 mg)* PO or IV	5 *(300 mg)* PO or IV or 5[§] *(300 mg)* PO or IV or NA[¶] *(450 mg)* PO or IV	Not known Not Known Not Known	Not known Not Known Not Known	•Rash •Hepatitis •Fever •Thrombocytopenia •Orange-colored body fluids (secretions, urine, tears) With increased levels of RFB: •Severe arthralgias •Uveitis •Leukopenia	Complete blood count, platelets, and liver function tests Repeat measurements if •baseline results are abnormal • patient has symptoms of adverse reactions Use adjusted daily dose of RFB,[§] and monitor for decreased antiretroviral activity and for RFB toxicity if RFB taken concurrently with PIs or NNRTIs.	RFB is contraindicated for patients taking ritonavir, saquinavir (Invirase™), or delavirdine. Reduces levels of many drugs (e.g., PIs, NNRTIs, methadone, dapsone, ketoconazole, hormonal contraceptives). Might permanently discolor soft contact lenses.

PZA	15-30 *(2.0 g)* PO	15-30 *(2.0 g)* PO	50-70 (3.5 g) PO	50-70 *(3.5 g)* PO	50-70 *(2.5 g)* PO	50-70 *(2.5 g)* PO	•Gastrointestinal upset •Hepatitis •Rash •Arthralgias •Hyperuricemia •Gout (rare)	Liver function tests and uric acid Repeat measurements if •baseline results are abnormal •patient has symptoms of adverse reactions	Treat hyperuricemia only if patient has symptoms. Might make glucose control more difficult in persons with diabetes.
EMB	15-25 *(1600 mg)* PO	15-25 *(1600 mg)* PO	50 *(4000 mg)* PO	50 *(4000 mg)* PO	25-30 *(2000 mg)* PO	25-30 *(2000 mg)* PO	•Optic neuritis (decreased red-green color discrimination), decreased visual acuity •Rash	Baseline and monthly tests of visual acuity and color vision	Optic neuritis might be unilateral; check each eye separately.
SM	20-40 *(1 g)* IM or IV	15 *(1 g)* IM or IV	25-30 *(1.5 g)* IM or IV	25-30 *(1.5 g)* IM or IV	25-30 *(1.5 g)* IM or IV	25-30 *(1.5 g)* IM or IV	•Ototoxicity (hearing loss or vestibular dysfunction) •Nephrotoxicity	Baseline and repeat as needed audiometry and renal function tests	Ultrasound and warm compresses to injection site might reduce pain. Maximum dose for patients ≥60 years is 1.0 g.

EMB=ethambutol; INH=isoniazid; PZA=pyrazinamide; RFB=rifabutin; RIF=rifampin; SM=streptomycin.
NNRTIs=nonnucleoside reverse transcriptase inhibitors; PI=protease inhibitor.
IM=intramuscular; IV=intravenous; PO=by mouth.

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

† The concurrent use of RFB is contraindicated with ritonavir, saquinavir (Invirase™), and delavirdine. Information regarding the use of rifabutin with saquinavir (Fortovase™), amprenavir, efavirenz, and nevirapine is limited.

§ Not applicable. If nelfinavir, indinavir, or amprenavir is administered with RFB, blood concentrations of these protease inhibitors decrease. Thus, when RFB is used concurrently with any of these three drugs, the daily dose of RFB is reduced from 300 mg to 150 mg (the twice-weekly dose of RFB is unchanged, however).

¶ NA=not applicable. If efavirenz is administered with RFB, blood concentrations of RFB decrease. Thus, when RFB is used concurrently with efavirenz, the dose of RFB for both daily and twice weekly administration should be increased from 300 mg to 450 mg.

TABLE 3A. Tuberculosis (TB) preventive therapy regimens for adults with human immunodeficiency virus (HIV) infection

Rating	Drug	Interval and Duration	Comments	Indications	Contraindications
A.II	INH	Daily for 9 months	INH can be administered concurrently with NRTIs, protease inhibitors, or NNRTIs.	HIV-infected persons who are candidates for TB preventive therapy.	History of an INH-induced reaction, including hepatic, skin, or other allergic reactions, or neuropathy.
B.I	INH	2 times/week for 9 months		DOPT must be used when twice-weekly dosing is used.	Known exposure to person who has INH-resistant TB.
					Chronic severe liver disease.
A.I	RIF and PZA*	Daily for 2 months	Protease inhibitors or NNRTIs should not be administered concurrently with RIF; in this situation, an alternative is the use of RFB† and PZA.	HIV-infected persons who are candidates for TB preventive therapy.	History of a rifamycin-induced reaction, including hepatic, skin, or other allergic reactions, or thrombocytopenia.
B.III	RFB and PZA*	Daily for 2 months	If RFB is administered, patient should be monitored carefully for potential RFB drug toxicity and potential decreased antiretroviral drug activity.	HIV-infected persons known to be contacts of patient who has INH-resistant, rifamycin-susceptible TB.	Pregnancy.
					Chronic severe hyperuricemia.
					Chronic severe liver disease.
			Dose adjustments, alternative therapies, or other precautions might be needed when rifamycins are used (e.g., patients using hormonal contraceptives must be advised to use barrier methods, and patients using methodone require dose adjustments).		

INH=isoniazid; PZA=pyrazinamide; RFB=rifabutin; RIF=rifampin.
DOPT=directly observed preventive therapy; NNRTI=nonnucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor.

* For patients with intolerance to PZA, some experts recommend the use of rifamycin (RIF or RFB) alone for preventive treatment. Most experts agree that available data support the recommendation that this treatment can be administered for as short a duration as 4 months, although some experts would treat for 6 months.

† The concurrent use of RFB is contraindicated with ritonavir, hard-gel saquinavir (Invirase™), and delavirdine. The information regarding the use of RFB with soft-gel saquinavir (Fortovase™), amprenavir, efavirenz, and nevirapine is limited.

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