Reprinted from *The PRN Notebook*,® DECEMBER 2001.
Dr. James F. Braun, Editor-in-Chief. Tim Horn, Executive Editor.
Published in New York City by the Physicians' Research Network, Inc.,®
John Graham Brown, Executive Director. For further information and other articles available online, visit **http://www.PRN.org**

Double Scourge: Tuberculosis and HIV Coinfection

Wafaa El-Sadr, MD, MPH
Director, Division of Infectious Diseases, Harlem Hospital Center, New York, NY

SUMMARY BY TIM HORN
EDITED BY SHELDON BROWN, MD, AND JAY DOBKIN, MD

"If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infections such as bubonic plague, Asiatic cholera, must rank far behind tuberculosis"

—ROBERT KOCH, 1882

TUBERCULOSIS (TB) HAS, FROM ANCIENT times, ranked among the most feared and dreaded of the many diseases that afflict mankind. Over a century since *Mycobacterium tuberculosis* was discovered and more than 50 years after effective drug treatment was introduced, TB remains a major public health problem. It is now five years since the World Health Organization (WHO) took the unprecedented step of declaring TB a "global emergency." And yet more people died of TB last year than in recorded history—2 to 3 million deaths, or 1 death every 10 seconds.

Eradicating TB, even within the borders of industrialized nations, continues to be a significant challenge. In 1989, the U.S. Public Health Service Advisory Council on the Elimination of Tuberculosis was established and proposed the TB Elimination Strategy—defined as a case rate less than 1 per 1,000,000 people—to be completed by the year 2010. With only eight years remaining, thousands of TB cases continue to be reported annually in the United States. In turn, new recommendations toward the goal have been established, including more aggressive screening and early treatment approaches, particularly among those at the greatest risk for TB: persons living with HIV and AIDS.

TB in the U.S.: Better but Not Gone

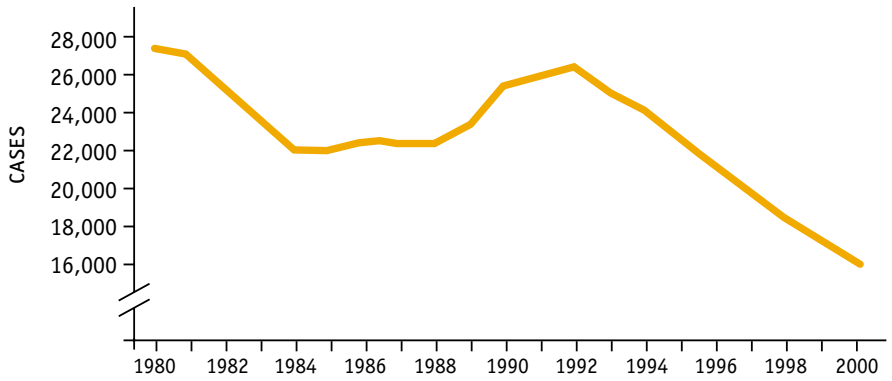
DURING THE 19TH CENTURY, TB CLAIMED more lives in the United States than any other disease. With improvements in nutrition, housing, sanitation, and medical care in the first half of the 20th century—along with the introduction of effective antibiotic therapies in the 1940s and '50s—the disease was finally in retreat. In 1985, however, the decline ended and the number of active TB cases in the United States began to rise again, a trend that was undeniably associated with the rapidly growing AIDS epidemic. Over a seven-year period, the number of new TB cases soared by 20%, from 22,201 cases in 1985 to 26,673 cases in 1992 (see Figure 1).

Fortunately, this dramatic climb was again reversed with the restrengthening of TB control activities, including aggressive screening and treatment of those considered to be at risk for symptomatic disease. In 2000, a total of 16,377 cases of active TB were reported to the U.S. Centers for Disease Control (CDC). This represents a 45% drop since 1992, from 10.5 cases per 100,000 people in 1992 to 5.8 cases per 100,000 in 2000. But the United States is not out of the red just yet: The CDC estimates that 10 to 15 million people in the U.S. have latent TB infection, and about 10% of them will go on to develop active TB at some point in their lives unless more aggressive steps are taken to lower these odds.

The ten states that led the nation with the highest TB rates in 2000 were (in ranking order) Alaska, Hawaii, California, New York, Georgia, Arkansas, Louisiana, Florida, Texas, and South Carolina (see Table 1). Seven of these states had a decrease in TB rates between 1999 and 2000, but three states—Alaska, Arkansas and Georgia—reported increases in rates. Alaska had the most dramatic rise in rates, from 9.9 in 1999 to 17.2 in 2000. TB rates in Arkansas climbed from 7.1 to 7.4, and the rates in Georgia increased slightly from 8.5 to 8.6.

As for TB rates in New York City, 1,332 new cases of active TB were reported in

FIGURE 1. Reported TB Cases, United States, 1980–2000



Source: Centers for Disease Control. Adapted from: *Reported Tuberculosis in the United States*, 2000.
Accessed at: http://www.cdc.gov/nchstp/surv/surv2000/default.htm

2000—a whopping 65% decrease from 1992. The case rate for 2000—16.6 per 100,000 people—is the lowest the city has ever recorded, although it is significantly higher than the national average. Epidemiological data from the New York City Department of Health (NYC DOH) also show a decrease in the number of new TB cases among foreign-born and U.S.-born New Yorkers. However, the decline in TB rates was actually sharper among U.S.-born residents, thus yielding a rather unsavory trend among foreign-born people residing in the Big Apple: 57.7% of new TB cases in 2000 were among foreign-born persons, up from 55.6% in 1999. In 1992, only 17.7% of TB cases were reported among foreign-born persons. The highest numbers of active TB cases were among those born in China, the Dominican Republic, Haiti, Ecuador, India and Mexico. These findings mirror national statistics reported by the CDC (See Figures 2A, 2B and 2C).

Drug-Resistant Tuberculosis

WHILE THERAPEUTIC EFFORTS TO CURB TB-related morbidity and mortality have certainly paid off in the United States, improper use of antibiotics—both now and in the past—has led to an epidemic unto itself: the emergence and spread of single-drug (usually isoniazid or rifampin) and multidrug-resistant (usually isoniazid *and* rifampin) TB (MDR-TB).

The mortality rate associated with MDR-TB is shockingly high. Even when treatment is initiated, death occurs in 40% to 60% of patients, usually within the first few months after the TB is diagnosed.

According to data from the CDC, the percentage of persons with *M. tuberculosis* strains resistant to either isoniazid or isoniazid and rifampin has dropped somewhat over the past eight years. In 1993, the total number of active TB cases in the United States—including both foreign-born and U.S.-born persons—with primary resistance to isoniazid was 1,400 (8.4%); in 2000, isoniazid resistance was documented in 851 (7.5%) of active TB cases (see Table 2A). As for TB cases involving *M. tuberculosis* strains with primary resistance to isoniazid and rifampin, 410 (2.5%) cases were reported to the CDC in 1993 and 120 cases (1.1%) in 2000 (see Table 2B).

TABLE 1. Top Ten States: TB Cases and Case Rates per 100,000 Population, 2000 and 1999.

	Cases		Case Rates		Rank According to Rate	
State	**2000**	**1999**	**2000**	**1999**	**2000**	**1999**
Alaska	108	61	17.2	9.8	1	4
Hawaii	136	184	11.2	15.5	2	1
California	3,297	3,606	9.7	10.9	3	2
New York	1,744	1,837	9.2	10.1	4	3
Georgia	703	665	8.6	8.5	5	5
Arkansas	199	181	7.4	7.1	6	12
Louisiana	331	357	7.4	8.2	7	8
Florida	1,171	1,277	7.3	8.5	8	6
Texas	1,506	1,649	7.2	8.2	9	7
South Carolina	286	315	7.1	8.1	10	9
United States	16,377	17,531	5.8	6.4	—	—

Source: Centers for Disease Control. Adapted from: *Reported Tuberculosis in the United States*, 2000. Accessed at: http://www.cdc.gov/nchstp/surv/surv2000/default.htm

Pathogenesis of TB

M. TUBERCULOSIS, LIKE HIV, IS AN INTRACELLULAR pathogen. Once the bacillus enters the body via inhalation, it is engulfed by alveolar macrophages. While most of the mycobacteria are destroyed or inhibited, a small number continue to replicate within the macrophages—how they are able to evade the normal processes by which macrophages kill microorganisms is not entirely understood—and are released when the macrophages die. The mycobacteria then spread through the lymphatic channels to regional lymph nodes and through the bloodstream to more distant tissues and organs, including areas in which TB disease is most likely to develop: the apices of the lungs, the kidneys, the brain, and bone. Once again, the mycobacteria are ingested by macrophages, this time resulting in the presentation of *M. tuberculosis* antigens to circulating CD4+ cells. An inflammatory immune response to *M. tuberculosis* is then initiated: Activated CD4+ cells release interferon-gamma to jump-start additional macrophages to contain the mycobacteria, whereas the macrophages release the proinflammatory cytokines tumor necrosis factor and interleukin-1. Once an immune response has been mounted, *M. tuberculosis* infection can be detected by tuberculin skin testing (TST), usually within two to 12 weeks after infection.

The result of this inflammatory response is the entrapment of *M. tuberculosis*-infected macrophages, activated macrophages, and CD4+ cells within granulomas. In approximately 5% of individuals infected with *M. tuberculosis*, these granulomas expand and cavitate, gradually leading to symptomatic disease within two years of infection. This is sometimes referred to as primary TB disease.

The vast majority of persons infected with *M. tuberculosis* go on to develop latent TB infection (LTBI)—the granulomas calcify, resulting in prolonged containment of the mycobacteria. However, approximately 5% of persons with LTBI, if not treated for the latent infection, go on to experience active tuberculosis sometime later in life (reactivation TB disease).

In other words, in approximately 10% of all persons infected with *M. tuberculosis*, active disease occurs at some point, whether as primary or reactivation TB

The HIV Factor

THERE HAS BEEN NO SHORTAGE OF DATA demonstrating that HIV-infected patients are at higher risk of developing active TB, particularly in the setting of continual immune suppression. According to two published papers, the risk of active TB is 7% to 10% annually for persons coinfected with

FIGURE 2A. Number of TB Cases in U.S.-Born vs. Foreign-Born Persons, United States, 1980–2000

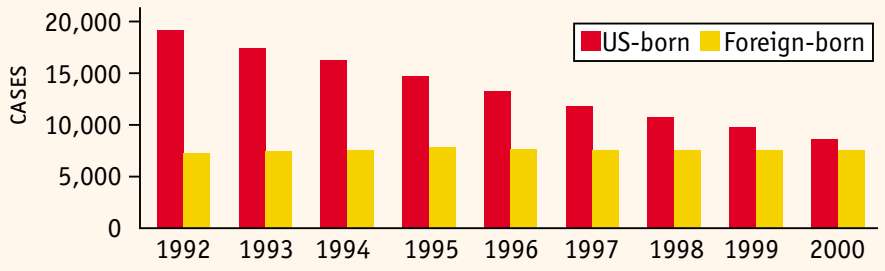


FIGURE 2B. Percentage of TB Cases Among Foreign-Born Persons

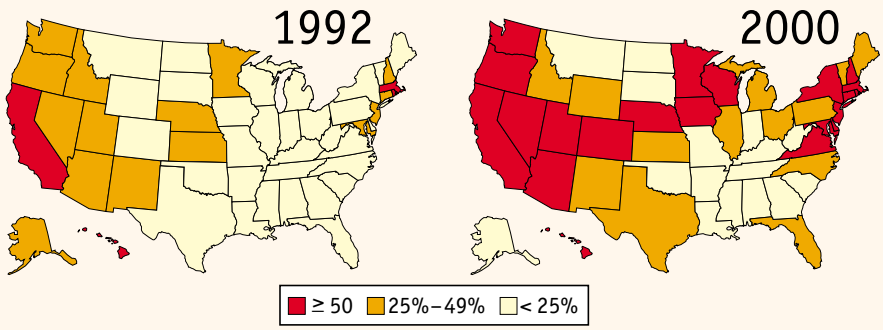
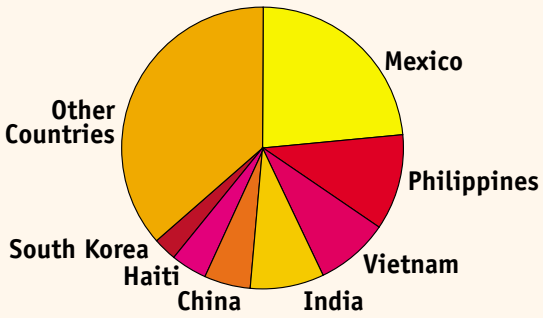


FIGURE 2C. Countries of Birth for Foreign-Born Persons Reported with TB, United States,2000



Source: Centers for Disease Control. Adapted from: *Reported Tuberculosis in the United States*, 2000. Accessed at: http://www.cdc.gov/nchstp/surv/surv2000/default.htm

M. tuberculosis and HIV, compared with 10% over a lifetime for persons infected only with *M. tuberculosis* (Selwyn, 1989; 1992).

HIV is by no means the only factor associated with an increased risk of progression to active TB. Other factors, including some that are prevalent in the HIV-infected community, include: substance abuse (particularly intravenous drug use), recent infection with *M. tuberculosis* (within the past two years), chest radiograph findings suggestive of previous TB, diabetes mellitus, silicosis, prolonged corticosteroid and other immune-suppressive therapies, cancer of the head and neck, hematologic and reticulo-endothelial diseases, intestinal bypass or gastrectomy, chronic malabsorption syndromes, and abnormal body weight (see Tables 3 and 4).

In the general population, extrapulmonary TB is unusual. Among HIV-positive patients with TB, however, extrapulmonary disease—whether the development of abscesses, splenomegaly, granulomas in other organs, or mycobacteremia—is frequently reported. Although most HIV-positive patients with TB have pulmonary involvement, it has been estimated that more than half of them will also have extrapulmonary complications of the infection.

Should active TB occur in HIV-positive people, the prognosis is dependent on the severity of immune suppression and the response to antibiotic treatment. The one-year mortality rate for treated, HIV-related TB ranges from 20% to 35% and shows little variation between cohorts from industrialized and developing countries. This mortality rate is actually four times greater than the rate for TB patients not infected with HIV. According to Dr. Wafaa El-Sadr, "the most likely cause of death during the first few months of anti-TB treatment, among HIV-positive patients, is usually TB. Thereafter, death is usually attributed to other opportunistic infections."

Complicating matters is the fact that HIV/*M. tuberculosis* coinfection is a two-way street—just as HIV can increase a person's risk of developing active TB, TB may also accelerate the progression of HIV disease, leading to worse outcomes and higher mortality. One possible reason for this is the pathogenic role of TB infection on HIV replication. As discussed above, the immune response to *M. tuberculosis* infection involves the production of proinflammatory cytokines, chiefly interferon-gamma, tumor necrosis factor, and interleukin-1. These cytokines have been shown to stimulate HIV production *in vitro*. It has also been suggested that mycobacteria, including *M. tuberculosis*, enhance viral replication by inducing nuclear factor kappa-β, the cellular factor that binds to promoter regions of HIV.

Dr. El-Sadr also hinted at a number of other mechanisms by which TB may have a deleterious effect on HIV disease outcomes. "Some of the atypical manifestations in advanced HIV disease may delay diagnosis," she said. "HIV-associated immune suppression may also affect the ability to control TB and can certainly render a patient more susceptible to other AIDS-related opportunistic infections. Another factor to consider is that malabsorption, which is sometimes seen in late-stage HIV disease, can reduce the bioavailability of antituberculous medications."

More concrete data indicating that TB has a detrimental effect on HIV-disease progression can be found in a number of cohort studies. In one retrospective study conducted in the United States, the incidence rate of new AIDS-defining opportunistic infections among HIV-positive patients with active TB was 4.0 per 100 person-months, compared with 2.8 per 100 person-months in matched HIV-positive patients without TB (Whalen, 1995). Pa-

TABLE 2. Resistance to Isoniazid with or without Rifampin Resistance in Reported TB Cases with No Previous TB (Primary Resistance) by Origin: United States, 1993–2000

	A. Resistant to Isoniazid?						B. Resistant to Isoniazid and Rifampin?					
	Total Cases		U.S.-Born		Foreign-Born			Total Cases		U.S.-Born		Foreign-Born	
YEAR	No.	%	No.	%	No.	%	YEAR	No.	%	No.	%	No.	%
1993	1,400	8.4	804	6.8	579	12.4	1993	410	2.5	302	2.6	105	2.3
1994	1,355	8.3	709	6.4	632	12.1	1994	352	2.2	238	2.2	109	2.1
1995	1,171	7.3	554	5.4	615	11.0	1995	252	1.6	168	1.6	84	1.5
1996	1,138	7.4	496	5.2	639	11.3	1996	206	1.3	104	1.1	101	1.8
1997	1,082	7.5	436	5.0	640	11.2	1997	156	1.1	75	0.9	80	1.4
1998	1,012	7.5	366	4.7	644	11.3	1998	130	1.0	55	0.7	74	1.3
1999	904	7.1	284	4.1	618	11.0	1999	128	1.0	39	0.6	89	1.6
2000	851	7.5	261	4.4	587	11.0	2000	120	1.1	38	0.6	82	1.5

1. Isolates may be resistant to other drugs.
2. Includes persons of unknown country of birth.
3. Includes persons born outside the United States, American Samoa, the Federated States of Micronesia, Guam, the Republic of the Marshall Islands, Midway Island, the Commonwealth of the Northern Mariana Islands, Puerto Rico, the Republic of Palau, U.S. Minor Outlying Islands, U.S. Miscellaneous Pacific Islands, and the U.S. Virgin Islands.

More than 85% of all cases in each group had drug susceptibility test results reported for an initial isolate.

Source: Centers for Disease Control. Adapted from: *Reported Tuberculosis in the United States*, 2000. Accessed at: http://www.cdc.gov/nchstp/surv/surv2000/default.htm

tients with HIV-associated TB also had a shorter overall survival rate than did the HIV-positive patients without TB. This translated into an increased risk of death (odds ratio = 2.17), even when controlling for age, intravenous drug use, previous opportunistic infection, baseline CD4+ count, and antiretroviral therapy.

More recently, a prospective study evaluated the impact of TB on survival among people infected with HIV in Uganda (Whalen, 2000). In the study, 230 HIV-positive patients with TB and 442 HIV-infected subjects without TB were followed for a mean duration of 19 months. During the follow-up period, 63/230 (28%) TB cases died, compared with 85/442 (19%) controls, with a crude risk ratio of 1.4. Most deaths occurred in patients with CD4+ counts below 200 cells/mm^3 at baseline and occurred with similar frequency in the TB cases (46%) and the controls (44%). When the CD4+ counts were greater than 200 cells/mm^3, however, the relative risk of death among HIV-positive patients with TB was 2.1, compared with subjects without TB. Interestingly, the one-year survival rate among patients with CD4+ counts greater than 200 cells/mm^3 was only slightly lower in those with TB than in those without the disease, but by the end of the second year of follow-up, the survival proportion was significantly lower among HIV-positive patients with TB than among those in the control group (0.84 versus 0.91). After adjusting for age, sex, TST status, CD4+ cell count, and history of HIV-related infections, the overall relative hazard for death associated with tuberculosis was 1.81. In a nested Cox regression model, the relative hazard for death was 3.0 for patients with CD4+ counts greater than 200 cells/mm^3 and 1.5 for patients with CD4+ counts below 200 cells/mm^3.

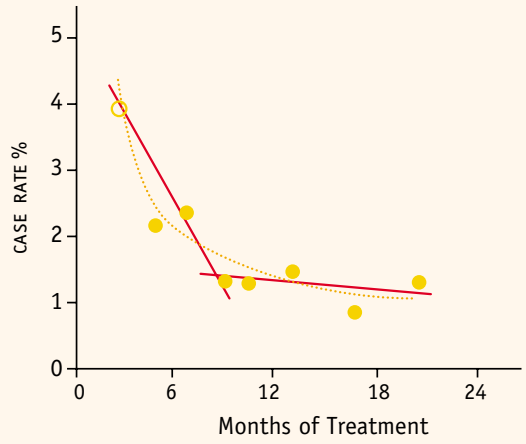
The conclusion of this study couldn't be clearer—active TB exerts its most profound effect on survival in the early stages of HIV infection (CD4+ counts greater than 200 cells/mm^3), when there is a reserve capacity of the host immune response. "These observations," the authors stated, "provide a theoretical basis for the treatment of latent tuberculosis infection in HIV-infected persons," not only to greatly reduce the risk of active TB, but also to reduce the likelihood of accelerated HIV disease progression in patients coinfected with HIV and *M. tuberculosis*. Dr. El-Sadr could not agree more.

Focusing on Latent Tuberculosis

IDENTIFICATION OF PERSONS WITH LTBI HAS previously been accomplished by widespread tuberculin skin testing of individuals or groups at variable risk for TB. In many situations, this screening was done with limited consideration of the risk for TB in the population(s) being tested. In turn, concerned infectious disease specialists and other TB experts have been working to shift the nomenclature away from the over-simplified "TB screening" to the more precise and aggressive "targeted tuberculin testing" in order to encourage directed clinical care.

Similarly, the terms "preventive therapy" and "chemoprophylaxis" are also considered to be too vague in terms of curbing the potential progression of LTBI. While these terms refer to the use of a simple regimen—usually isoniazid—to prevent the development of active TB in persons known or likely to be infected with *M. tuberculosis*, rarely does such a regimen result in true primary prevention (i.e., prevention of infection in persons exposed to others with *M. tuberculosis*). To describe the intended intervention more accurately, Dr. El-Sadr consistently referred to the "treatment of LTBI," a term she and others

FIGURE 3. Incidence of TB, Bethel Isoniazid LTBI Studies



TB case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; orange line, the calculated curve; and red lines, the calculated values based on the first four and the last five observations.

Source: Comstock, 1999. **How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults?** *Int J Tuberc Lung Dis* 3:847-50. Reprinted with permission of the International Union Against Tuberculosis and Lung Disease.

hope will promote greater understanding of the concept for both patients and providers, resulting in more widespread implementation of this essential TB control strategy.

Dr. El-Sadr is by no means alone in this effort to shift the medical establishment's thinking regarding LTBI. In April 2000, the American Thoracic Society—in concert with the CDC, the Infectious Disease Society of America, and the American Academy of Pediatrics—published guidelines focusing exclusively on targeted tuberculin testing and the treatment of LTBI (American Thoracic Society, 2000). As explained by Dr. El-Sadr, these guidelines were developed in recognition of the importance of treating LTBI as a vital component of eliminating TB in the United States, while at the same time realizing the differing risks and benefits of treatment for specific populations of patients. This requires identification and TST screening of those most at risk for active TB who, in turn, would most likely benefit from treatment. Conversely, screening persons who are at low risk for active TB is discouraged because it diverts resources away from higher priority TB control activities and because the likelihood of false-positive TST results increases among low-risk populations.

Based on the sensitivity and specificity of TST and the prevalence of TB in different groups, three cut-off levels are included in the American Thoracic Society guidelines for defining a positive tuberculin reaction: >5 mm, >10 mm, and >15 mm of induration. However, Dr. El-Sadr was careful to point out that a positive TST is not the only determinant in deciding which persons should receive treatment for LTBI. For some persons—any child under the age of five years or any adult or child who is HIV-infected or immune-compromised who has been in recent close contact with an infectious TB patient—treatment for LTBI is highly recommended, irrespective of the TST reaction. "Given the risk of active TB among particular persons and groups with presumed recent *M. tuberculosis* infection, even if the TST appears to be negative, treatment for LTBI should be considered," she added.

To help clarify the American Thoracic Society guidelines, the Charles P. Felton National Tuberculosis Center at Harlem Hospital—in collaboration with Columbia University, the Health and Hospitals Corporation, and the NYC DOH—has produced at-a-glance cue cards to provide key pieces of information regarding targeted TST and the treatment of LTBI. Three cue cards have been produced: one providing general information on the treatment of LTBI, a second providing an overview of the treatment of LTBI in children and adolescents, and a third illustrating the treatment of LTBI in pregnancy. The cue cards can be viewed or ordered through the World Wide Web (http://www.harlemtbcenter.org) or by telephone: (212) 939-8254.

The criteria for treating LTBI, depending on the induration of the TST reaction, are shown in Table 5. As stated above, children under the age of five or adults or children who are either HIV-infected or immune-suppressed, if they have been in recent contact with another person with active TB, should be treated for LTBI, as they are at high risk of both infection with *M. tuberculosis* and progression to active TB. A TST cut-off level of >5 mm induration is recommended for older children, adolescents, and adults who are immune-suppressed because of disease (e.g., HIV infection) or medications (e.g., systemic corticosteroids), as they have a high likelihood of developing active TB disease if they are infected with *M. tuberculosis*. Otherwise healthy persons who have had recent close contact with an infectious TB patient and those with fibrotic changes on chest X ray consistent with prior TB are at high risk for TB; the sensitivity provided by a >5 mm cut-off for a positive test is also appropriate for these individuals.

Persons with a TST reaction of >10 mm of induration should receive treatment for LTBI if they fall within the following categories: recent arrivals from an endemic country, injection drug users, residents/employees in an institutional setting, mycobacteria lab workers, persons with high-risk clinical conditions (see Note 3 in Table 5), children under the age of four, and persons under the age of 18 exposed to high-risk adults.

Routine tuberculin testing is not recommended for populations at low risk for LTBI. However, if these persons are tested (e.g., at entry into a work site where risk of exposure to TB is anticipated and a longitudinal tuberculin testing program is in place), a higher cut-off of >15 mm is recommended.

It's important to note that immune-suppressed HIV-positive patients may have a false-negative TST in spite of *M. tuberculosis* infection because of anergy to cutaneous antigens. While early studies suggested that anergy was associated with high rates of developing active TB, two studies reported in 1997—conducted in Uganda and in the United States—did not demonstrate a significant benefit of LTBI treatment in HIV-infected, anergic adults (Gordin, 1997; Whalen, 1997). Dr. El-Sadr also explained that the greatest risk to anergic, immune-suppressed patients is the development of primary TB disease after recent exposure to someone with symptomatic infection. In turn, anergy testing is not recommended in evaluating the risk of TB in immune-suppressed HIV-positive patients. But as stated above, any HIV-infected patient—regardless of his or her TST result—who has recently been exposed to *M. tuberculosis* should receive treatment for LTBI.

Treatment of LTBI

AFTER AN INITIAL CLINICAL EVALUATION, including radiologic studies, to rule out active TB, treatment of LTBI should be initiated in all patients who have a positive TST according to the cut-offs described above.

Isoniazid remains the most widely recommended treatment for LTBI in both HIV-positive and HIV-negative patients. Since the mid-1950s, approximately 19 controlled clinical trials of isoniazid have been conducted in eleven countries, examining six- and 12-month regimens in both HIV-positive and HIV-negative persons. Although efficacy rates—including progression to primary TB disease, tuberculin conversion in uninfected contacts, and disease recurrence—varied considerably (25% to 92%), the general consensus was that 12 months of isoniazid therapy, provided that a high level of adherence was maintained, yielded a protective benefit in excess of 90%. Six-month regimens, again depending on the level of adherence, were associated with a protective benefit of up to 70% in both HIV-positive and HIV-negative persons.

According to a recent analysis of data from a community-based study conducted in Bethel, Alaska, the maximal benefit of isoniazid for LTBI is achieved by the ninth month of treatment and there is minimal additional benefit in extending treatment to 12 months (see Figure 3) (Comstock, 1999). Although a nine-month course of isoniazid has not been compared with a six-month or 12-month course in prospective clinical trials, it is now widely believed that nine months of therapy is more effective than the six-month course and equally effective as the 12-month course in both HIV-positive and HIV-negative patients.

Based on this consensus, the preferred drug for the treatment of LTBI is isoniazid for nine months, regardless of HIV serostatus. As shown in Table 6, isoniazid can be administered either once a day (300 mg) or twice weekly (900 mg) over a nine-month period. However, the criteria for completion involve the actual number of doses administered, not the duration of treatment. If isoniazid is taken daily, a total of 270 doses must be taken in no fewer than nine months but no more than 12 months. If isoniazid is taken twice weekly, a total of 76 doses must be taken in no fewer than nine months but no more than 12 months. Directly observed therapy (DOT) is not required for the daily isoniazid dosing schedule, but it is highly recommended; for those employing the twice-weekly schedule, says Dr. El-Sadr, DOT is vital.

TABLE 3. Incidence of Active TB in Persons with a Positive TST, By Selected Risk Factors

Risk Factor	TB Cases/1,000 Person-Years
Recent TB infection	
Infection <1 year past	12.9
Infection 1–7 years past	1.6
Human immunodeficiency virus	
HIV infection	35.0–162
Injection drug use	
HIV-positive	76.0
HIV-negative or unknown	10.0
Silicosis	68
Radiographic findings consistent with prior TB	2.0–13.6
Weight deviation from standard	
Underweight by 10–14%	2.0
Underweight by 5%–9%	2.2
Weight within 5% of standard	1.1
Overweight by ≥5%	0.7

Source: American Thoracic Society, 2000.

TABLE 4. Relative Risk* for Developing Active TB, By Selected Clinical Conditions

Clinical Condition	Relative Risk
Silicosis	30
Diabetes mellitus	2.0–4.1
Chronic renal failure/hemodyalisis	10.0–25.3
Gastrectomy	2–5
Jejunoileal bybass	27–63
Solid organ transplantation	
Renal	37
Cardiac	20–74
Carcinoma of head or neck	16

*Relative to control population; independent of TST status.

Source: American Thoracic Society, 2000.

The American Thoracic Society lists a dual combination of rifampin and pyrazinamide as a possible regimen for the treatment of LTBI. This recommendation is based on the results of a clinical trial in which a two-month course of rifampin/pyrazinamide was compared to a 12-month course of isoniazid in HIV-infected patients (Gordin, 2000). As highlighted in Table 6, rifampin (600 mg) plus pyrazinamide (2,000 mg) should be taken every day for a total of 60 doses in no less than two months but no more than three months. While a twice-weekly regimen is permissible, it is not as effective as either the nine-month isoniazid or the two-month daily rifampin/pyrazinamide regimens. If twice-weekly rifampin/pyrazinamide is employed, DOT must be used.

While the shorter duration of rifampin/pyrazinamide therapy is certainly desirable—especially for persons who have been exposed to patients with isoniazid-

TABLE 5. Candidates for Treatment of LTBI

Category of Person Tested	TST <5 mm	TST ≥5 mm	TST ≥10 mm	TST ≥15 mm
Child <5 yrs and *recent contact*[1]	TREAT	TREAT	TREAT	TREAT
HIV-infected and *recent contact*[1]	TREAT	TREAT	TREAT	TREAT
Immune-suppressed and *recent contact*[1]	TREAT	TREAT	TREAT	TREAT
HIV-infected	DON'T TREAT	TREAT	TREAT	TREAT
Immune-suppressed	DON'T TREAT	TREAT	TREAT	TREAT
Recent contact of TB case	DON'T TREAT	TREAT	TREAT	TREAT
Fibrotic changes on chest X-ray	DON'T TREAT	TREAT	TREAT	TREAT
Recent arrival from endemic country	DON'T TREAT	DON'T TREAT	TREAT	TREAT
Injection drug user	DON'T TREAT	DON'T TREAT	TREAT	TREAT
Resident/Employee institutional setting[2]	DON'T TREAT	DON'T TREAT	TREAT	TREAT
Mycobacteria lab personnel	DON'T TREAT	DON'T TREAT	TREAT	TREAT
High-risk clinical conditions[3]	DON'T TREAT	DON'T TREAT	TREAT	TREAT
Child <4 years of age	DON'T TREAT	DON'T TREAT	TREAT	TREAT
Persons <18 exposed to high-risk adults	DON'T TREAT	DON'T TREAT	TREAT	TREAT
No risk factors (TST discouraged)	DON'T TREAT	DON'T TREAT	DON'T TREAT	TREAT

[1] Contacts should receive a TST immediately. Even if TST is 00 mm, these groups should be treated and TST placed again 12 weeks after exposure to TB case. Treatment can be discontinued in a healthy child if second TST is negative.

[2] TST Conversion: An increase in reaction size of ≥10 mm induration within two years should be considered a TST conversion indicative of recent infection with *M. tuberculosis*.

[3] Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head and neck or lung), weight loss of >10% of ideal body weight, gastrectomy, jejunoileal bypass.

Pregnancy: Treat during pregnancy if either HIV-infected or recent *M. tuberculosis* infection.

The Charles P. Felton National Tuberculosis Center at Harlem Hospital, based on official guidelines published by the American Thoracic Society (2000).

resistant/rifampin-sensitive active TB—a few significant caveats must be considered before prescribing this regimen. First, rifampin should not be administered concurrently with protease inhibitors or nonnucleoside reverse transcriptase inhibitors in patients with LTBI. [NOTE: *This is not necessarily the case in HIV-positive patients with active TB, as discussed in the next section.*] If HAART involving either of these classes must be continued, rifabutin should be used instead of rifampin. However, rifabutin is still contraindicated in patients receiving either hard-gel saquinavir (Invirase) or delavirdine (Rescriptor) and requires decrease of dose if combined with either ritonavir (Norvir) or lopinavir/ritonavir (Kaletra) or increase of dose if combined with efavirenz (Sustiva) (see Table 6, note 1). Second, at least 21 cases of severe hepatotoxicity have been associated with this two-month regimen in recent months; five of these patients receiving rifampin/pyrazinamine therapy for LTBI died of liver failure (CDC, 2001).

All things considered, rifampin/pyrazinamide remains an option for the treatment of LTBI in the eyes of the American Thoracic Society, provided that careful clinical and laboratory parameters are monitored (e.g., transaminases). Across the board, however, the Society stresses that the nine-month course of isoniazid remains the first-line approach.

Other possible drug regimens are listed in Table 6. These include a six-month course of isoniazid, either 300 mg a day for a total of 180 doses or 900 mg twice weekly for a total of 52 doses. However, this is not indicated for HIV-positive patients (the nine-month isoniazid regimen is preferred), nor for any persons with evidence of fibrotic lesions on X ray or for children. Also listed is a four-month course of rifampin monotherapy (600 mg QD), intended only for persons who may have been exposed to isoniazid-resistant *M. tuberculosis* and are unable to tolerate pyrazinamide.

Treatment of Active TB

OFFICIAL RECOMMENDATIONS REGARDING THE treatment of HIV-associated active TB have been somewhat contradictory over the past five years. According to American Thoracic Society and CDC treatment guidelines drafted in 1994, both HIV-positive and HIV-negative persons with active TB should receive a rifampin-based combination, given the effectiveness of regimens containing

TABLE 6. Recommended Drug Regimens for Treatment of LTBI in Adults

Drug	Interval and Duration	Adult Dosage (max)	Criteria for Completion	Comments
INH	Daily for 9 months	5 mg/kg (300 mg)	270 doses within 12 months	**Preferred regimens for all persons.** Use for HIV-infected persons when completion of treatment can be assured. INH may be administered concurrently with NRTIs, PIs, or NNRTIs.
	Twice-weekly for 9 months	15 mg/kg (900 mg)	76 doses within 12 months	**DOT must be used with twice-weekly dosing.**
INH	Daily for 6 months	5 mg/kg (300 mg)	180 doses within 9 months	Not indicated for persons with HIV infection or fibrotic lesions. Not indicated for children.
	Twice-weekly for 6 months	15 mg/kg (900 mg)	52 doses within 9 months	**DOT must be used with twice-weekly dosing.**
RIF*	Daily for 4 months	RIF 10 mg/kg (600 mg)	120 doses within 6 months	Alternate to longer regimens, also for persons who who are contacts of patients with INH-resistant/ RIF-susceptible TB.
RIF* plus PZA	Daily for 2 months	RIF 10 mg/kg (600 mg); PZA 15-20 mg/kg (2.0 g)	60 doses within 3 months	**Use when completion of longer treatment courses is unlikely and when patients can be monitored closely; also for contacts of patients with INH-resistant, RIF-susceptible TB.** Use with caution in patients on hepatotoxic agents or with history of alcoholism. NOT recommended for persons with liver disease or with INH-associated liver injury. Dispense no more than a two-week supply of RIF-PZA to facilitate periodic clinical assessments.
	Twice-weekly for 2 to 3 months	RIF 10 mg/kg (600 mg); PZA 50 mg/kg (4.0 g)	16-26 doses within 3-4 months	**DOT must be used with twice-weekly dosing.**

Abbreviations: INH = isoniazid, RIF = rifampin, PZA = pyrazinamide; DOT = directly observed therapy.

Pregnancy: INH regimens preferred for pregnant women. Some experts would use RIF plus PZA as alternate in HIV-infected pregnant women. PZA should be avoided during first trimester.

MDRT-TB exposure: For persons who are likely to be infected with INH and RIF (multidrug) resistant-TB and at high risk of reactivation, PZA and ethambutol or PZA and a quinolone for 6-12 months are recommended. (Consult expert.)

***HIV coinfection**: PIs or NNRTIs should not be administered concurrently with RIF; an alternative is rifabutin 300 mg daily. Rifabutin should not be used with hard-gel saquinavir (Invirase) or delavirdine (Rescriptor). Dose adjustment of rifabutin may be required: to 150 mg BIW with ritonavir (Norvir) or lopinavir/ritonavir (Kaletra), to 150 mg QD or 300 mg BIW with other protease inhibitors, or to 450–600 mg QD or 600 mg BIW with efavirenz (Sustiva).

Source: The Charles P. Fenton National Tuberculosis Center at Harlem Hospital, based on official guidelines published by the American Thoracic Society (American Thoracic Society, 2000) and recently updated to reflect toxicity concerns associated with the coadministration of rifabutin and pyrazinamide for the treatment of latent tuberculosis infection (LTBI) (Centers for Disease Control, 2001).

both isoniazid and rifampin for the treatment of uncomplicated, drug-sensitive TB (see Table 7) (American Thoracic Society, 1994). Soon after these guidelines were published, the first wave of PIs and NNRTIs became available and were incorporated into the clinical care of HIV-positive patients with symptomatic disease, including active TB. However, rifampin was contraindicated in patients receiving any of the PIs or NNRTIs, given the significant interactions between antiretroviral drugs metabolized by the cytochrome P450 enzyme system and the rifamycins.

In 1998, the CDC produced guidelines

AS WE WENT TO PRESS...

Quantiferon TB Test Approved

QUANTIFERON, A ONE-STEP BLOOD TEST FOR LATENT TUBERCULOSIS infection (LTBI), received approval from a U.S. Food and Drug Administration (FDA) panel in October. Like tuberculin skin testing (TST), the results of Quantiferon are read quantitatively, with cut-off points established to designate whether the test is read as positive or not. Unlike the TST, Quantiferon subjects do not have to return a second time for a reading.

The test was first developed by an Australian veterinarian to detect latent TB infection in cattle. The assay was purchased by Cellestis, which has been collaborating with the U.S. Centers for Disease Control (CDC) to closely evaluate Quantiferon in phase III clinical trials.

The FDA panel put no restrictions on how the test could be used, other than to note that data are still lacking on test performance in certain groups, including HIV-positive people, transplant patients, pregnant women and children. One condition attached to the approval was that the test should not be used within 30 days of applying a tuberculin skin test (TST) because the tuberculin antigen in the TST sometimes provides a transient immune reaction that might render a false positive result from Quantiferon.

The U.S. Centers for Disease Control has not yet determined how best to interpret results in clinical settings and for TB control purposes. What's more, as a condition of its approval, Cellestis must provide additional sensitivity and specificity data and develop an extensive educational component on how to use the test. *prn*

Source: Cellestis; U.S. Food and Drug Administration

Longer Treatment Recommended for HIV/TB Coinfected Patients

PATIENTS COINFECTED WITH TB AND HIV HAVE A HEIGHTENED RISK of TB relapse, according to recent research by Dr. Cynthia Driver and her colleagues from the New York City Department of Health Tuberculosis Control Program. In their report, published in the November 15, 2001 issue of *Clinical Infectious Diseases*, Dr. Driver's team suggested that coinfected patients receive longer treatment regimens or be checked regularly for TB recurrence.

The study evaluated therapy outcomes in a cohort of 4,571 patients, both with and without HIV infection, who had received at least 24 weeks of standard 4-drug TB treatment: isoniazid, rifampin, pyraxinamide and ethambutol (or streptomycin). None of the patients had drug-resistant TB. "Recurrence" was defined as having a positive culture less than 30 days after the last treatment date; "relapse" was defined as having a positive culture more than 30 days after the last treatment.

The study found that patients infected with HIV were more likely than those who were uninfected to have recurrence or relapse (2.0 vs. 0.4 per 100 person-years; P >0.001). Patients infected with HIV who received <36 weeks of treatment were more likely than those who received >36 weeks to have a recurrence (7.9% vs. 1.4%; P <0.001).

The authors stressed that clinicians should be aware of the possibility of recurrence of TB six to nine months after the start of treatment. If the standard nine-month regimen is used, Dr. Driver's team also urges that sputum be evaluated after three months of treatment. *prn*

Source: Driver CR, Munsiff JL, Kundamal N, et al. **Relapse in Persons Treated for Drug-susceptible Tuberculosis in a Population with High Coinfection with Human Immunodeficiency Virus in New York City.** *Clin Infect Dis* 33(10):1762-9, 2001.

describing anti-TB regimens that included rifabutin instead of rifampin as the preferable alternative for the treatment of active TB among patients taking PIs or NNRTIs. More recently, the pendulum has swung back in favor of rifampin (Centers for Disease Control, 1998). New data described in a CDC update produced in 2000 indicated that rifampin can be used for the treatment of active TB in three situations: 1) in a patient whose antiretroviral regimen includes the NNRTI efavirenz and two NRTIs; 2) in a patient whose antiretroviral regimen includes the protease inhibitor ritonavir and one or more NRTIs; or 3) in a patient whose antiretroviral regimen includes the combination of two protease inhibitors (ritonavir and either versions of saquinavir [Invirase or Fortovase]) (Centers for Disease Control, 2000). [NOTE: *These three conditions for the use of rifampin do not apply to individuals with LTBI who are taking either a PI or NNRTI. The advantage of using rifampin in a regimen to treat active TB far outweighs the risk of drug-drug interactions that may retard antiretroviral efficacy down the road, whereas the risk of these efficacy-limiting drug-drug interactions in LTBI likely outweighs the potential advantages of the rifampin/pyrazinamide treatment duration.*]

If rifampin is substituted with rifabutin, the updated CDC guidelines recommend substantially reducing the dose of rifabutin (150 mg two or three times per week) when it is administered to patients taking ritonavir and increasing the dose of rifabutin (either 450 mg or 600 mg daily or 600 mg two or three times per week) when rifabutin is used concurrently with efavirenz—adjustments similar to those adopted for the treatment of LTBI.

The American Thoracic Society TB treatment guidelines are reviewed in Table 7. The CDC recommendations for coadministering different antiretroviral drugs with either rifampin or rifabutin are listed in Table 8.

The Impact of HAART on the Incidence and Clinical Manifestations of TB

THE AVAILABILITY AND WIDESPREAD USE OF HAART, at least in the United States and other industrialized nations, has led to significant reductions in the risk of TB among HIV-positive persons, as well as the likelihood of developing atypical manifestations of the disease. With respect to the risk factors and incidence of TB in the era of HAART, a team of CDC investigators analyzed data from the Adult/Adolescent Spectrum of HIV Disease project, collected from January 1996 through June 1998 (Jones, 2000). During this period, 80 cases of TB occurred

TABLE 7. American Thoracic Society Guidelines for Short-Course Treatment for Active TB (Pulmonary)—1994 Recommendations

Regimen Isoniazid + rifampin (or rifabutin) + pyrazinamide + ethambutol for two months, followed by isonazid + rifampin for an additional four months

Qualifications Ethambutol may be omitted:

- If the drug resistance in the community is <4%, or
- As soon as the organism is shown to be sensitive to isoniazid, rifampin and pyrazinamide

- Same regimen for HIV-positive and HIV-negative patients
- Same regimen for children
- Treat extrapulmonary TB for longer (usually 12 months)
- Extended therapy for pulmonary TB is recommended for patients with slow clinical responses or prolonged sputum culture positivity (> 3 months)
- If pyrazinamide not usable, treat with isoniazid + rifampin (+ ethambutol) for nine months

Adult Dosages	Daily (DOT Strongly Recommended)		Twice Weekly (DOT Required)	
	Dose	Not to Exceed	Dose	Not to Exceed
Isoniazid	5mg/kg	300mg	15mg/kg	900mg
Rifampin or Rifabutin	See Table 8	See Table 8	See Table 8	See Table 8
Pyrazinamide	15-30mg/kg	2g	50-70mg/kg	4g
Ethambutol	15-25mg/kg	—	50mg/kg	—

Source: American Thoracic Society, 1994.

in 16,032 person-years (5.0 cases/1000 person-years). In multivariate analysis, the risk of TB was much lower among persons prescribed HAART (relative risk = 0.2), and also lower among persons prescribed less potent antiretroviral therapy (RR = 0.6), than the risk in persons not prescribed antiretroviral therapy.

With respect to the changes in clinical presentations and outcomes of HIV-associated TB in the HAART era, a team of Italian investigators reviewed clinical charts of HIV-infected patients with culture-confirmed pulmonary TB in two referral centers in Rome (Girardi, 2000). The 67 patients diagnosed in 1995 and 1996 were compared with 51 patients diagnosed in 1997 and 1998.

Patients seen in 1997 to 1998 were more likely to have TB diagnosed as the first AIDS-defining illness (78% versus 58%) within two months after learning of their HIV-positive serostatus (33% vs. 7%), to have typical chest radiograph pattern (45% vs. 25%), and to have higher CD4+ counts at the time of TB diagnosis (median 105 cells/mm^3 vs. 43 cells/mm^3). Survival at one year was 80% for patients diagnosed in 1997 to 1998 vs. 65% for those diagnosed in 1995 to 1996—a statistically significant finding suggesting that HAART confers a survival benefit, perhaps by reducing the risk of other life-threatening opportunistic infections. Age, CD4+ cell count (<25 CD4+ cells/mm^3), and AIDS-defining illnesses prior to the diagnosis of TB were all associated with a higher risk of death, whereas a decreased risk of death was observed in patients starting a triple-drug antiretroviral regimen after TB diagnosis (hazard ratio: 0.14).

Paradoxical Responses During the Treatment of TB

WHILE THERE'S MUCH TO BE SAID FOR THE role of HAART on TB-related morbidity and mortality rates, the immune restoration that accompanies antiretroviral therapy is not without potential downsides. Paradoxical reactions—temporary exacerbation of symptoms, signs, or even radiographic manifestations of TB—can occur in immune-suppressed patients, who initiate therapy for HIV and TB and experience a sudden jump in their delayed-type hypersensitivity.

A study published in 1998 evaluated the incidence of paradoxical responses in persons coinfected with HIV and TB who are treated with antituberculous therapy and subsequently with HAART (Narita, 1998). Enrolled in the study were 33 HIV-positive TB patients treated with standard anti-TB therapy and HAART (Group 1), 55 HIV-negative TB patients treated with anti-TB therapy (Group 2), and 28 HIV-positive TB patients who received anti-TB therapy without HAART (Group 3). In Group 1, paradoxical responses occurred in 12/33 (36%) patients, compared with 1/55 (2%) patients in Group 2 and 2/28 (7%) patients in Group 3. The majority of patients who experienced paradoxical responses and received TST (PPD) in Group 1 experienced a conversion from negative to strongly positive after initiating HAART. According to the authors, these observations—all of which were statistically significant—suggest that a para-

TABLE 8. Coadministration of Antiretrovirals with Rifabutin and Rifampin—2000 Recommendations

Antiretroviral	Use in combination with rifabutin	Use in combination with rifampin	Comments
Saquinavir[1]			
Invirase	Possibly,[2] if antiretroviral regimen also includes ritonavir	Possibly, if antiretroviral regimen also includes ritonavir	Coadministration of Fortovase with usual-dose rifabutin (300 mg/ daily or two or three times per week) is a possibility. However, the PK data and clinical experience for this combination are limited.
Fortovase	Probably[3]	Possibly, if antiretroviral regimen also includes ritonavir	The combination of Fortovase or Invirase and ritonavir, coadministered with 1) usual-dose rifampin (600 mg/daily or two or three times per week), or 2) reduced-dose rifampin (150 mg two or three times per week) is a possibility. However, the PK data and clinical experience for these combinations are limited. Coadministration of Invirase or Fortovase with rifampin (in the absence of ritonavir) is not recommended because rifampin markedly decreases concentrations of saquinavir.
Ritonavir	Probably	Probably	If the combination of ritonavir and rifabutin is used, then a substantial reduced-dose rifabutin regimen (150 mg two or three times per week) is recommended. Coadministration of ritonavir with usual-dose rifampin (600 mg/ daily or two or three times per week) is a possibility, though PK data and clinical experience are limited.
Indinavir	Yes	No	There is limited, but favorable, clinical experience with coadministration of indinavir with a reduced daily dose of rifabutin (150 mg) or with the usual dose of rifabutin (300 mg two or three times per week). Coadministration of indinavir[4] with rifampin is not recommended because rifampin markedly decreases concentrations of indinavir.
Nelfinavir	Yes	No	There is limited, but favorable, clinical experience with coadministration of nelfinavir[5] with a reduced daily dose of rifabutin (150 mg) or with the usual dose of rifabutin (300 mg two or three times per week). Coadministration of nelfinavir with rifampin is not recommended because rifampin markedly decreases concentrations of nelfinavir.
Amprenavir	Yes	No	Coadministration of amprenavir with a reduced daily dose of rifabutin (150 mg) or with the usual dose of rifabutin (400 mg two or three times per week) is a possibility, but there is no published clinical experience. Coadministration of amprenavir with rifampin is not recommended because rifampin markedly decreases concentrations of amprenavir.
Nevirapine	Yes	Possibly	Coadministration of nevirapine with usual-dose rifabutin (300 mg/daily or two or three times per week) is a possibility based on PK study data. However, there is no published clinical experience. Data are insufficient to assess whether dose adjustments are necessary when rifampin is coadministered with nevirapine. Therefore, rifampin and nevirapine should be used in combination only if clearly indicated and with careful monitoring.
Delavirdine	No	No	Contraindicated because of the marked decrease in concentrations of delavirdine when administered with either rifabutin or rifampin.

Antiretroviral	Use in combination with rifabutin	Use in combination with rifampin	Comments
Efavirenz	Probably	Probably	Coadministration of efavirenz with increased-dose rifabutin (450 mg or 600 mg daily, or 600 mg two or three times per week) is a possibility, though there is no published clinical experience. Coadministration of efavirenz[6] with usual-dose rifampin (600 mg/daily or two or three times per week) is a possibility, though there is no published clinical experience.

[1] Usual recommended doses are 500 mg BID for each of these PIs and 400 mg of ritonavir.

[2] Despite limited data and clinical experience, the use of this combination is potentially successful.

[3] Based on available data and clinical experience, the successful use of this combination is likely.

[4] Usual recommended doses is 800 mg q8h. Some experts recommend increasing the indinavir dose to 1000 mg q8h if indinavir is used in combination with rifabutin.

[5] Usual recommended dose is 750 mg TID or 1250 mg BID. Some experts recommend increasing the nelfinavir dose to 1000 mg if three-times-daily dosing is used and nelfinavir is used in combination with rifabutin.

[6] Usual recommended dose is 600 mg/daily. Some experts recommend increasing the efavirenz dose to 800 mg/daily if efavirenz is used in combination with rifampin.

Source: Centers for Disease Control, 2000.

doxical response associated with enhanced TST reactivity may occur after the initiation of HAART in HIV-infected TB patients.

It is important to note that paradoxical responses are not associated with bacteriological changes, such as changing from negative to positive smears or cultures. Symptoms of these reactions are usually self-limited—generally lasting between 10 and 40 days—but they should be evaluated to rule out other possible causes of treatment failure. In the event of severe paradoxical reaction, hospitalization or the use of corticosteroids may be warranted. prn

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