TABLE 1. Annual Rates* of Tuberculosis Among Persons with Human Immunodeficiency 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	
Selwyn et al., 1989 (*9*)			26.3
San Francisco	5.0	1.0	
Daley et al., 1998 (*10*)			5.0
Multiple sites			
Markowitz et al., 1997 (*11*)			
East Coast	4.6	1.3	
West/Midwest	1.7	0.2	
All sites	4.5	0.4	3.5 8.5 11.3

*Cases per 100 person-years.

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.

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) HIV negative (n=183)	9.0 5.3	338 cells/μL^3	• All cases of TB confirmed by culture at baseline. • DOT except for 1/2 doses in continuation phase. • Posttreatment follow-up = 12 months. • Culture-based relapse definition; however, relapse vs. reinfection not assessed by DNA fingerprinting.
Côte d'Ivoire Kassim et al., 1995 (*49*)	HIV-1 positive (n=106) HIV negative (n=194)	3.0 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.
Haiti Chaisson et al., 1996 (*67*)	HIV positive (n=177) HIV negative (n=250)	5.4 2.7	475 cells/μL^3	• Includes culture-positive and clinically diagnosed cases of TB. • DOT. • Relapse definition includes both culture-confirmed and clinically diagnosed cases of TB. • Relapse vs. reinfection not assessed by DNAfingerprinting. • Posttreatment follow-up = 22 months.
United States U.S. Public Health Service Rifapentine Trial Group et al., 1998 (*29*)	HIV positive (n=30)	10	137 cells/mL^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/mL^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 DNAfingerprinting.

TABLE 4. Effects of Coadministering Rifamycins and Protease Inhibitors (PIs) on the Systematic Exposure (area-under-the-concentration-time curve [AUC]) of Each Drug*

PI and Source	Rifampin (RIF)		Rifabutin (RFB)	
	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 Nonnucleosides Reverse Transcriptase Inhibitors (NNRTIs) on the Systematic Exposure (area-under-the-concentration-time curve [AUC]) of Each Drug*

NNRTI and Source	Rifampin (RIF)		Rifabutin (RFB)	
	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.

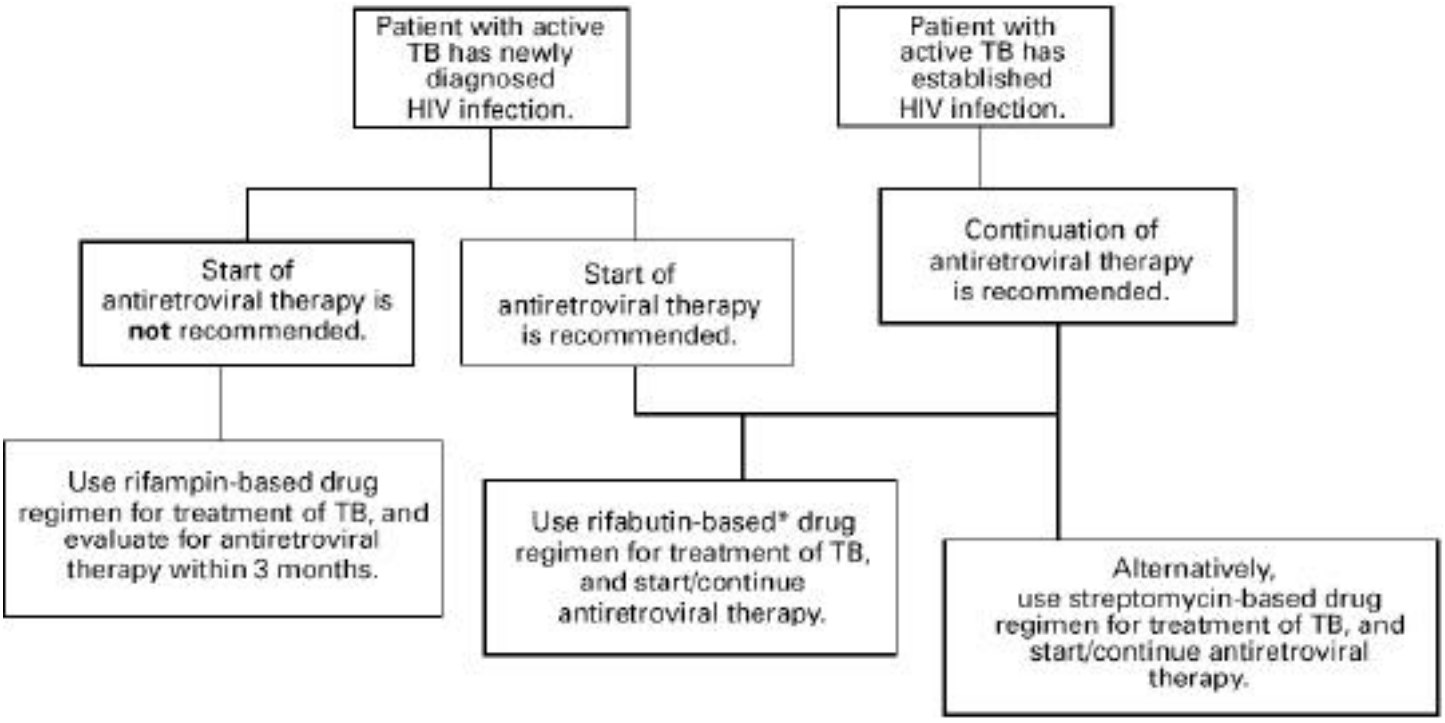
TABLE 6. Feasibility of Using Different Antiretroviral Drugs and Rifabutin

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, sta-vudine, and lamivudine.

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.

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 pre-viously 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 treat-ment, 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.

Chest X-Ray Examination

- Perform a chest x-ray examination. HIV-related immunosuppression reduces the inflam-matory 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).

BOX 2. Components of the Monthly Medical Evaluation for Human Immunodeficiency Virus-infected Patients Suspected 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**.**