

MYCOBACTERIAL INFECTIONS

I. INTRODUCTION

Mycobacterium tuberculosis infects one third of the world's population, and tuberculosis (TB) remains one of the most common infectious diseases among humans. Each year, more than 8 million new cases and 2 million deaths are reported worldwide, with 95% of them occurring in the developing world. TB is one of the most common HIV-related opportunistic infections. The annual number of new TB cases in the United States exhibited a steady decline for decades, until 1985 when the number of TB cases reached a plateau. By the late 1980s, incident TB cases began to increase steadily and peaked in 1992 with more than 26,000 cases reported that year. From 1993-2003, there has been a 44 % decline in cases reported annually. Of the 15,078 cases of TB reported in the United States in 2002, 1,434 cases (9.5%) occurred in New York State; of these cases, 75% were reported in New York City. Factors that contributed to the resurgence of TB in the United States included homelessness, nosocomial transmission resulting from poor infection control programs in hospitals, and inadequate support of both the public health infrastructure and TB control programs.¹ Arguably, however, the most important factor responsible for the increased rates of TB was the HIV epidemic.

HIV has had a profound impact on the epidemiology, natural history, and clinical presentation of TB. HIV infection increases a person's susceptibility to both primary progressive TB and reactivation of latent infection. The risk of primary progressive TB in HIV-infected persons is as high as 40% compared with approximately 5% in non-HIV-infected populations. HIV-infected patients with untreated latent infection have a 5% to 10% annual risk of developing active disease, a risk that approximates the lifetime risk in non-HIV-infected persons with latent TB. In addition, exogenous TB reinfection has been documented among patients with advanced AIDS, but it is unclear how often this occurs. Although there were initial concerns that HIV-infected patients with TB might be more infectious than non-HIV-infected patients with TB, a considerable amount of data suggests that both groups are similarly infectious.

The AIDS epidemic has also led to a much greater understanding and appreciation of the pathogenic potential of mycobacteria other than *M. tuberculosis*, especially the *M. avium* complex (MAC). MAC, composed of the two closely related species, *M. avium* and *M. intracellulare*, has become one of the most common systemic bacterial infections in patients with AIDS, affecting 20% to 40% of patients. The most important risk factor for the development of disseminated MAC infection is severe immunosuppression (CD4 cell count <50 cells/mm³). Antiretroviral (ARV) therapy and advances in the treatment and prevention of MAC infection have resulted in a significant decline in the incidence and clinical presentation of this infection.

Although many of the more unusual non-tuberculous mycobacteria are commonly isolated as laboratory contaminants or colonizers rather than true pathogens, in the setting of severe immunosuppression, isolation of these organisms may represent true infection. Among the mycobacterial organisms that have been associated with disease are *M. kansasii*, *M. haemophilum*, *M. genavense*, *M. goodii*, and *M. xenopi*.

II. PRESENTATION OF TB DISEASE

The clinical, radiographic, and laboratory features of TB in HIV-infected persons vary, depending on the patient's degree of immunosuppression. Pulmonary TB often develops early during the course of HIV and may be the initial manifestation.

Persons with relatively intact cellular immune function, as evidenced by higher CD4 cell counts, positive response to purified protein derivative (PPD) antigen skin testing, and no previous AIDS-associated illness, present with signs and symptoms of reactivation TB comparable with those observed in non-HIV-infected patients. Disease generally remains localized to the lungs. Fever, productive cough, night sweats, weight loss, and malaise are common. Chest x-rays frequently reveal typical apical infiltrates and cavitary disease; sputum smears generally demonstrate acid-fast bacilli (AFB).

In the setting of advanced HIV infection, TB often presents atypically, with extrapulmonary disease being a prominent feature. In extrapulmonary TB, the symptoms are usually constitutional and may not be localized to a particular organ or site. Alternatively, symptoms may relate more to the site of extrapulmonary involvement. In atypical pulmonary TB, chest x-rays may reveal adenopathy (hilar, mediastinal, or paratracheal), atypical infiltrates, pleural effusions, or miliary disease, or they may reveal no abnormality at all.

III. DIAGNOSIS OF TB DISEASE

RECOMMENDATIONS:

Clinicians should obtain a series of at least three sputum specimens collected on different days to establish the diagnosis. When diagnosis cannot be established from three expectorated sputum samples, induced sputum or bronchoscopy may be necessary. (I)

Clinicians should send sputum specimens from HIV-infected patients suspected of having TB to a microbiology laboratory for AFB staining and mycobacterial cultures. Sputum should be induced when an expectorated specimen cannot be produced. Results of AFB sputum smears should be available within 24 hours of obtaining a specimen. (I)

In addition to sending specimens to the microbiology laboratory, clinicians should send other tissue specimens (e.g., blood, urine, stool, cerebrospinal fluid, pleural and pericardial fluid, biopsy specimens), when available, to the anatomic pathology laboratory for histopathology and special staining (i.e., AFB stains). (I)

Key Points:

- Pulmonary TB should be included in the differential diagnosis of any HIV-infected patient with unexplained fever and cough.
- Both pulmonary and extrapulmonary TB should be included in the differential diagnosis of any HIV-infected patient with otherwise unexplained fever, weight loss, and/or signs and symptoms of systemic or localized infection.

A. Culture

The definitive diagnosis of TB requires isolation of *M. tuberculosis* by culture from a specimen. Given the high rate of pulmonary disease in TB, sputum is often the most appropriate initial specimen to send for AFB staining and culture. For patients with pulmonary disease who are unable to produce sputum, induction or even bronchoscopy may be helpful in obtaining suitable specimens for culture. However, because TB can occur at almost any anatomic site, and it is much more likely to be isolated from an extrapulmonary site in an immunocompromised HIV-infected patient than in a non-HIV-infected patient, clinical specimens other than sputum (e.g., urine, blood, cerebrospinal fluid, pleural and pericardial fluid, biopsy specimens) should be submitted for pathology and mycobacterial cultures when extrapulmonary TB is suspected.

B. Staining

The detection of AFB on stained smears varies widely, with sensitivities ranging from 22% to 78%. The degree of sensitivity depends on factors such as specimen type, number of specimens examined, observer experience, clinical conditions, and number of AFB present. In general, HIV-infected patients have lower frequencies of positive sputum smears, partly due to a lower incidence of cavitory disease. The fluorochrome stain is generally more sensitive than the traditional Kinyoun or Ziehl-Neelsen stains, but any of these methods is acceptable. Stained smears, however, are not useful for species identification. Moreover, because even non-viable bacilli will stain, a positive smear does not necessarily indicate the presence of live organisms.

C. Nucleic Acid Amplification Tests

Diagnostic tests that rely on gene amplification, such as polymerase chain reaction (PCR) and the *Mycobacterium tuberculosis* direct (MTD) tests, have been extensively evaluated on clinical specimens. These technologies are promising for supplementing the limitations of currently available microbiologic methods.

The MTD test can be used for rapid identification of AFB, which allows for differentiation between TB and atypical mycobacteria. It can also be used to diagnose TB in patients who have symptoms that are highly suggestive of TB but whose AFB smears are negative. In New York State, these assays are now part of the management of specimens submitted from smear-positive patients; however, cost and required technical skill make these technologies largely unavailable to many institutions outside of New York State.

IV. DIRECTLY OBSERVED THERAPY

RECOMMENDATION:

Clinicians should enroll all HIV-infected patients with TB into a directly observed therapy (DOT) program. (I) For patients who refuse DOT, clinicians should carefully monitor therapy. (III)

Directly observed therapy (DOT), the practice of observing patients as they take each dose of anti-TB medication, has become the standard of care in New York State and in many other parts of the United States.² In the event that home- or field-based DOT fails, New York State law

empowers local public health authorities to issue any order that protects the public health, such as a DOT order, an isolation order, or, in rare instances, a long-term detention order.

Key Point:

Most patients will adhere to anti-TB therapy when adequate social services and either home- or field-based DOT are provided.

V. TREATMENT OF NON-DRUG-RESISTANT ACTIVE TB DISEASE

RECOMMENDATIONS:

HIV-infected patients with TB should ideally be treated in consultation with an HIV Specialist who has expertise in treating TB. (I)

Even if the results of definitive cultures are not yet available, anti-TB chemotherapy should be initiated in HIV-infected patients when TB is suspected and AFB are present in clinical specimens (see Figure 1). A macrolide should be added for MAC coverage if the patient has a CD4 count less <50 cells/mm³, pending culture results. (III)

Rifapentine should not be used in HIV-infected patients because of its association with acquired rifamycin resistance in these patients. (I)

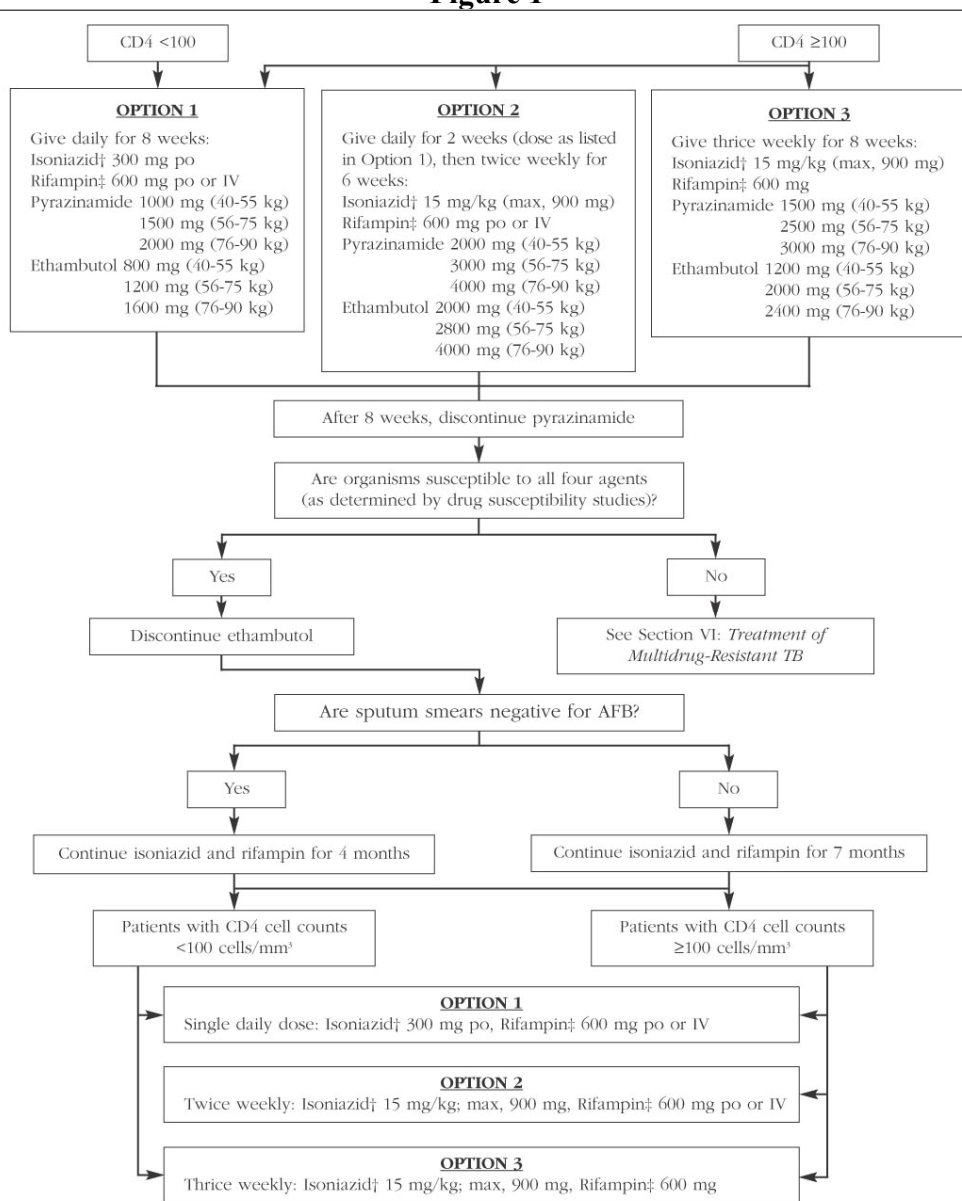
Streptomycin should not be used in pregnant women because it has been documented to cause congenital deafness in the human fetus. (I)

In addition to ordering AFB smears and cultures, clinicians should order susceptibility testing to the five first-line anti-TB agents (isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin) once *M. tuberculosis* is identified. (III)

For patients with drug-susceptible TB, clinicians should prescribe treatment for a minimum of 6 months. In patients with a delayed response (failure to convert to sterile cultures after 2 months of anti-TB therapy), treatment should be prolonged to either 9 months, or 4 months after culture conversion, whichever is greater. (II)

Because of the relatively high proportion of patients with isoniazid-resistant TB, four drugs are necessary in the initial 2-month treatment regimen. In the majority of situations, this consists of isoniazid, rifampin, pyrazinamide, and ethambutol using doses listed in Figure 1. If the organisms are susceptible to all four of the above agents, ethambutol can be safely discontinued. Rifabutin should be used instead of rifampin in patients receiving PIs (see Section VII: Considerations for Administering Simultaneous HAART and Anti-TB Therapy). This initial phase can be given daily for 2 weeks, then twice weekly for 6 weeks; daily for 8 weeks; or thrice weekly for 8 weeks. Pyrazinamide should be discontinued after 2 months. For the continuation phase of treatment for patients with susceptible organisms, isoniazid and rifampin are generally given for 18 weeks. This can be given daily or twice weekly, or for those with a thrice weekly initial phase, 3 times weekly (see Figure 1).

Figure 1



* Rifampentine is contraindicated for use in HIV-infected patients.

† Patients should receive oral pyridoxine therapy 25 mg per day when receiving INH.

‡ Rifampin has interactions with numerous medications including PIs, antifungal azoles, oral contraceptives, and methadone. See Appendix A for dose adjustments required when patient is prescribed HAART. For substance users, at the first sign of narcotic withdrawal following initiation of rifampin therapy, increase methadone by 5 to 10 mg on a daily or every-other-day basis, until the symptoms of withdrawal and craving resolve. When rifampin is discontinued, the methadone dosage should be lowered to avoid over-sedation. Rifabutin may be used instead of rifampin at a lower dose (see Appendix A).

Streptomycin has been documented to cause congenital deafness in the human fetus and, therefore, should not be used in pregnant women. Although detailed teratogenicity data are not available, pyrazinamide can probably be used safely during pregnancy and is recommended by

the World Health Organization and the International Union against Tuberculosis and Lung Disease. The minimum duration of therapy is 9 months when pyrazinamide is not included in the initial treatment regimen.

Drugs for the treatment of TB are available free of charge in New York State through the local health departments. The updated [American Thoracic Society Guidelines](#) for treatment of TB also provide a range of total doses of medication required for completion of treatment (available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm).³ Reliable data addressing the efficacy of non-standard anti-TB regimens are not currently available.

Duration of Therapy

The length of treatment for drug-susceptible TB remains somewhat controversial. Many clinicians treat drug-susceptible TB with a 6-month course of therapy. Two randomized studies have compared various durations of treatment using rifampin-containing regimens for HIV-related pulmonary TB. In one study conducted in Zaire, HIV-infected patients with pulmonary TB who completed 6 months of therapy were randomly chosen to receive either placebo or 6 more months of biweekly isoniazid and rifampin. The relapse rate was significantly higher among HIV-infected patients who received only 6 months of therapy (9.9%) compared with those who received 12 months of therapy biweekly (1.9%). An NIH-funded randomized study compared 6- and 9-month courses of therapy. The failure/relapse rate in both groups was less than 5%. Three non-randomized, prospective studies also evaluated short-course rifampin-containing regimens in HIV-infected persons. One study conducted in Haiti used an intermittent, supervised regimen, and the other two (one in Tanzania and the other in the Ivory Coast) evaluated daily therapy. These three 6-month short-course therapy trials demonstrated relapse rates of between 0% and 5.4%.

Some experts recommend longer therapy (9-12 months) for meningeal, bone, joint, or miliary TB. In patients with a delayed response to therapy (failure to convert to sterile cultures after 2 months of anti-TB therapy), treatment should be prolonged to at least 9 months. Obtaining a pre-treatment chest x-ray can provide a comparison by which to evaluate the response to treatment. Following patient weight is also useful for assessing response to therapy.

When clinicians decide to initiate anti-TB chemotherapy in patients who have signs and symptoms that are suggestive of TB but in whom repeated smears and cultures remain negative and other causes have been excluded, a four-drug initial regimen is indicated. If there is a clinical and/or radiographic response within 2 months of initiation of therapy, treatment should be continued with an additional 2 months of isoniazid and rifampin to complete a total of 4 months of treatment.

VI. TREATMENT OF MULTIDRUG-RESISTANT TB (MDRTB)

RECOMMENDATIONS:

When treating patients with TB, clinicians should consider the possibility of drug-resistant TB, including MDRTB, in the following populations: (III)

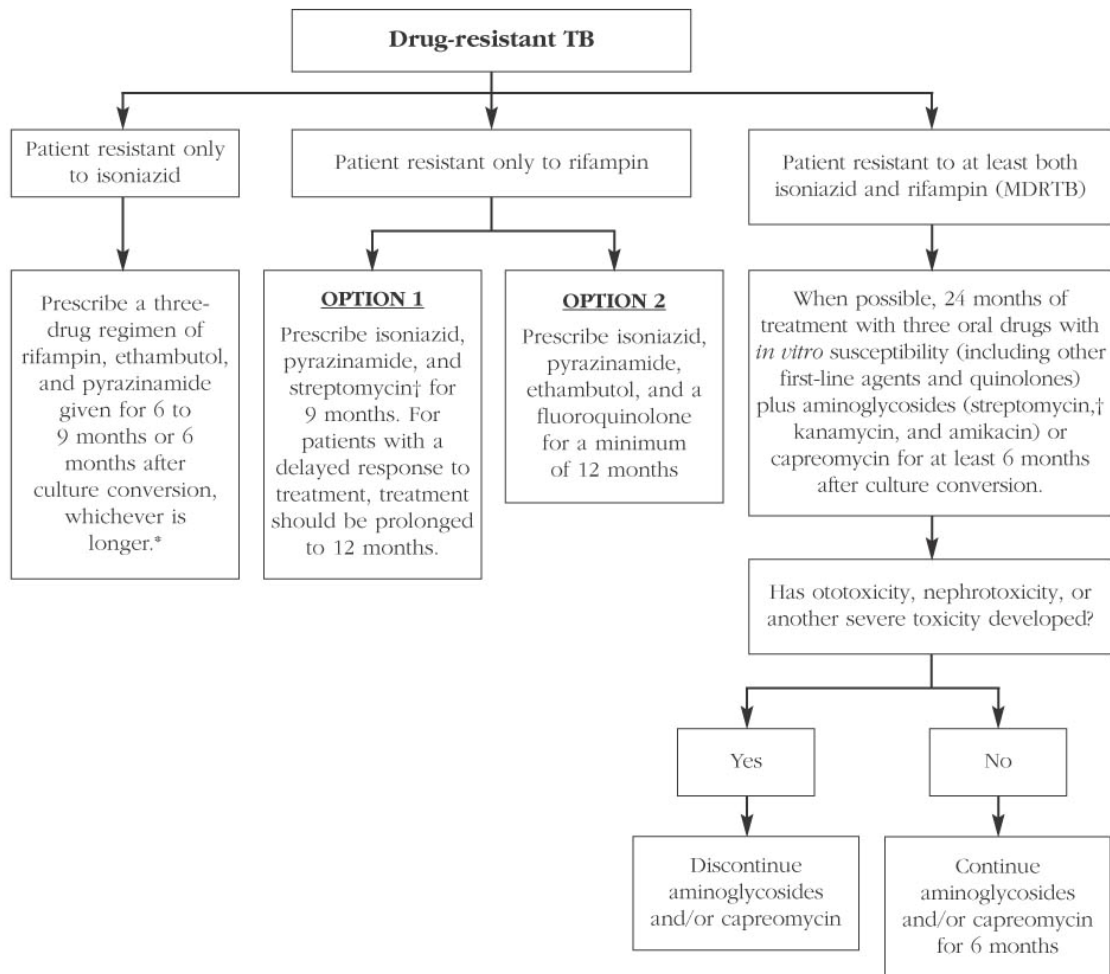
- **patients who have a previous history of treatment for TB**
- **patients who have been exposed to an individual with resistant TB**
- **patients who fail to exhibit the expected clinical or mycobacteriologic response to a standard four-drug anti-TB regimen**
- **patients who have lived in a country with a high rate of resistant TB**

In consultation with an HIV Specialist who has experience treating MDRTB, clinicians should prescribe a regimen of three or more drugs to which the strain is susceptible, if possible (see Figure 2). An injectable drug should be used for at least 6 months. (I)

Clinicians should add at least two new drugs to a treatment regimen that is failing. (I) A regimen is considered failing when the patient is not improving clinically within 2 weeks of the collection of the initial sputum samples, or the AFB smears and cultures are positive after 4 months of therapy.

For patients with TB resistant only to isoniazid, clinicians should prescribe a three-drug regimen of rifampin, ethambutol, and pyrazinamide given for 6 to 9 months, or 6 months after culture conversion, whichever is longer. (I)

Figure 2



* This regimen could be further strengthened with initial use of an aminoglycoside or fluoroquinolone.

† Streptomycin should not be used in pregnant women.

For patients with rifampin- or rifabutin-resistant tuberculosis, treatment should include isoniazid, pyrazinamide, and streptomycin given for 9 months or isoniazid, pyrazinamide, ethambutol, and a fluoroquinolone for a minimum of 12 months. For patients with a delayed response to treatment, the former treatment should be prolonged to 12 months.

For HIV-infected patients, MDRTB strains that are resistant to at least both isoniazid and rifampin require a minimum of 24 months of treatment after culture conversion.

Aminoglycosides (streptomycin, kanamycin, and amikacin) or capreomycin should be used for at least 6 months after culture conversion unless ototoxicity, nephrotoxicity, or other severe toxicity develops. Clinicians should consult with an HIV Specialist who has experience treating MDRTB to discuss whether parenteral agents should be continued for longer than 6 months after culture conversion if sputum conversion is slow or disease is extensive.

The guidelines in this section should be considered only as suggested regimens. Opinions vary about both the optimal drug regimens and the necessary duration of therapy. If there is any doubt about optimal therapy, expert consultation is advised.

Decisions concerning initial therapy for suspected MDRTB should take into account both individual and institutional factors. While awaiting susceptibility data for both first- and second-line anti-TB agents at institutions where outbreaks may be ongoing, it is prudent to initiate empiric therapy that optimizes treatment for the outbreak strain, using six- or seven-drug regimens until susceptibility data are available. At institutions where no known outbreaks have occurred but where drug resistance has been encountered, the recommended four-drug regimen is indicated.

Individual patient characteristics also play a role in deciding whether to initiate empiric treatment for MDRTB. The following factors should be considered to optimize empiric treatment:

- Detailed history of TB, including previous susceptibility data and treatment
- Contact with persons who have documented TB and their susceptibility data, if available
- Exposure to MDRTB at an institution (e.g., hospital, prison, or shelter)
- Immigration from a country where MDRTB is endemic

For individuals deemed to be at high risk for MDRTB, a drug regimen might include more than the four currently recommended drugs, including at least two drugs not included in previous regimens. Table 1 lists reasonable medications by order of efficacy for empiric therapy. In general, the optimal drugs for treating MDRTB should include the other first-line anti-TB drugs and the quinolones when susceptibility tests indicate no resistance. Among the fluoroquinolones, levofloxacin is the preferred agent for TB; however, based on *in vitro* data, gatifloxacin or moxifloxacin may be used.

TABLE 1
RECOMMENDED DRUG DOSAGES FOR TREATMENT OF MULTIDRUG RESISTANT
M. TUBERCULOSIS* BY ORDER OF EFFICACY

Medication	Usual Dosage
Rifampin	600 mg po qd
Rifabutin	300 mg po qd
Isoniazid	300 mg po qd
Pyrazinamide	25 mg/kg/d po
Ethambutol	15 mg/kg/d po
Streptomycin (amikacin kanamycin) <i>or</i> Capreomycin	15 mg/kg/d IM/IV; 10 mg/kg/day for patients >50 years of age 15 mg/kg/d IM/IV
Levofloxacin	1000 mg po qd
Ethionamide	0.5-1.0 g/d po Give 250 mg po bid to qid (or 500 mg bid, if tolerated)
Cycloserine	0.5-1.0 g/d po Give 250 mg po bid to qid (or 500 mg qd to bid, if tolerated)
Para-aminosalicylic acid (PAS)	4 g packet bid

* See Appendix A for information on contraindications and drug interactions when co-administering anti-TB and ARV therapy.

VII. CONSIDERATIONS FOR ADMINISTERING SIMULTANEOUS HAART AND ANTI-TB THERAPY

RECOMMENDATIONS:

For HIV-infected ARV-naïve patients with CD4 cell counts >200 cells/mm³, clinicians should consider delaying HAART until a minimum of 2-6 months of a standard anti-TB regimen is completed. (III) For patients with CD4 counts <200 cells/mm³, clinicians should initiate HAART 4-8 weeks after anti-TB medications are initiated. (III)

Clinicians should not use rifampin with indinavir, nelfinavir, lopinavir, saquinavir, or atazanavir, either alone or in dual-PI combinations using low-dose ritonavir (<200 mg twice daily).

When HAART cannot be delayed, clinicians should consider using rifampin or rifabutin with efavirenz or, if a PI is required, substituting rifabutin for rifampin. The rifabutin dose should be adjusted depending on which PI or NNRTI is used (see Appendix A).

Key Point:

Rifabutin may be used with PIs. Although dose adjustments may be necessary, it is associated with fewer problematic drug interactions than rifampin (see Appendix A).

In general, clinicians should avoid the simultaneous initiation of both HAART and anti-TB therapy. Delaying the initiation of HAART for 4–8 weeks after starting anti-TB therapy has the potential advantages of being better able to ascribe a specific cause for a drug side effect, decreasing the severity of paradoxical reactions or IRIS, and decreasing the adherence challenge for the patient. Several controlled studies are in development or being conducted to evaluate the optimal time for starting HAART in patients with HIV-1-associated TB disease. The decision on when to start HAART should be individualized on the basis of the patient’s initial response to TB therapy, occurrence of side effects, and acceptance of HAART. Initiation of anti-TB therapy should not be delayed given the risk of airborne transmission and the acute effects of untreated TB on the patient. For patients with CD4 counts <200 cells/mm³, HAART should be initiated as soon as anti-TB medications are tolerated. For patients with higher CD4 counts, delaying initiation of HAART for at least 8 weeks or until a 6-month course of anti-TB therapy is completed is a reasonable approach.

Rifamycin drugs are an essential component of highly efficacious short-course anti-TB regimens and should not be excluded from the anti-TB treatment regimen because of interactions with some ARV agents.⁴ NRTIs and NtRTIs (zidovudine, didanosine, zalcitabine, stavudine, lamivudine, emtricitabine, abacavir, tenofovir) are not contraindicated and do not require dose adjustment when used with rifamycins (see Appendix A). For patients who require complex combinations of PIs or NNRTIs, clinicians may adopt an acceptable non-rifamycin-containing regimen for TB, consisting of isoniazid, pyrazinamide, and streptomycin thrice weekly for 9 months.

PIs complicate anti-TB therapy because of their significant interactions with rifamycins, especially rifampin. PIs are metabolized in the liver by the cytochrome P450 enzyme system. All PIs inhibit P450 to a variable extent. Rifampin is a potent inducer of the cytochrome P450 system; rifabutin induces it to a lesser extent. In addition, PIs increase serum levels of rifampin, thus increasing the toxicity of this drug. See Appendix A for dose adjustment information.

Because rifampin has interactions with numerous medications, rifabutin may be used in its place. The efficacy of rifabutin is probably equivalent to rifampin for treating TB; however, there are no head-to-head comparative trials. Rifabutin should not be preferentially used over rifampin because of anticipation of starting HAART.

With proper dose adjustments, rifampin can be safely used with the following drugs:

- NRTIs
- NtRTIs
- Enfuvirtide
- Efavirenz + NRTIs or NtRTIs
- Ritonavir + NRTIs or NtRTIs

With proper dose adjustments, rifabutin can be safely used with the following drugs:

- NRTIs
- NtRTIs
- Atazanavir
- Enfuvirtide
- Fosamprenavir
- Indinavir
- Tipranavir
- Lopinavir/r
- Nelfinavir
- Ritonavir
- Efavirenz when used with 2 NRTIs
- Nevirapine when used with 2 NRTIs
- Saquinavir* + ritonavir

* Saquinavir alone is contraindicated.

A recent USPHS study revealed five cases of anti-TB treatment failure as a result of acquired rifamycin resistance.⁵ In each of these cases, patients had a CD4 count <60 cells/mm³ at the time of initiation of anti-TB treatment. Four of the five patients received rifabutin twice weekly during the initial intensive phase (first 2 months of anti-TB treatment), and all five patients received twice-weekly dosing during the continuation phase. Therefore, CDC recommends that until additional data become available, persons with HIV-associated TB and CD4 cell counts <100 cells/mm³ should not be treated with highly intermittent regimens (less frequent than thrice-weekly). Rather, these patients should receive daily therapy during the initial intensive phase and daily or thrice-weekly therapy during the continuation phase. The total relapse rate in the group was low, suggesting that current recommendations concerning duration are sufficient.

On occasion, patients with TB may experience an increase in signs or symptoms of TB after beginning anti-TB therapy. Although treatment failure or another opportunistic infection should be excluded, these reactions may result from the reconstitution of the immune system achieved by ARV therapy or, less likely, by treatment of TB.⁶ Signs of a paradoxical reaction may include hectic fevers, enlarging and painful lymphadenopathy, and expanding or new pulmonary lesions. Although treatment of paradoxical reactions has not been systematically studied, mild reactions may generally be treated adequately with non-steroidal anti-inflammatory drugs (NSAIDs); more severe reactions often require a short course of high-dose steroids.

VIII. FOLLOW-UP DURING AND AFTER TUBERCULOSIS TREATMENT

RECOMMENDATIONS:

Clinicians should monitor patients receiving anti-TB chemotherapy monthly for response to treatment, adherence to treatment, and evaluation of medication toxicity. (III)

Clinicians should educate patients receiving anti-TB chemotherapy about the symptoms of hepatitis and should obtain serial serum liver enzyme levels, especially in patients with any one of the following: (I)

- **Elevated baseline serum liver enzymes**
- **Symptoms suggestive of hepatitis such as anorexia**
- **Other risk factors for hepatitis, such as older age (≥ 65 years), use of other potentially hepatotoxic drugs, alcoholism, or viral hepatitis**

Clinicians should order expectorated or induced sputum monthly for both AFB smear and culture for patients who have been diagnosed with pulmonary TB and are receiving treatment, until documentation of culture conversion has occurred. (III)

For patients with culture-negative TB, a chest x-ray should be obtained at 2 months and at the end of treatment. (III)

Clinicians should obtain repeat susceptibility testing if cultures remain positive after 3 months of treatment or earlier if the patient's condition is worsening while receiving an apparently adequate regimen. (III)

Clinicians should weigh patients monthly and follow weight as an indication of clinical response to therapy.

Clinicians should perform monthly vision tests in patients receiving ethambutol. (III)

A careful history and physical examination should be performed each month while the patient is receiving anti-TB chemotherapy. The clinician should pay particular attention to the specific side effects of certain anti-TB medications during these evaluations. For example, visual acuity and color vision should be checked during treatment with ethambutol. An expectorated or induced sputum should also be ordered monthly for both an AFB smear and a culture for those who are receiving treatment for pulmonary TB. In the absence of symptoms, ongoing chest x-rays are not indicated.

Serum liver enzyme levels do not need to be routinely assessed in asymptomatic patients with normal baseline serum liver enzyme levels. If LFTs are found to be abnormal, treatment with potentially hepatotoxic drugs may be continued unless transaminase levels exceed 5-fold the upper limit of the normal range. Other laboratory data should be obtained as required, based on clinical symptoms. Potential medication toxicities, such as renal toxicity as a result of aminoglycoside therapy, should likewise be considered. Table 2 lists side effects associated with anti-TB therapies.

There are no generally accepted guidelines for the long-term follow-up of patients with TB after completion of therapy. In the absence of symptoms, the accepted guidelines for HIV care and follow-up are adequate. Ongoing chest x-rays are not necessary in the absence of symptoms.

TABLE 2
SIDE EFFECTS AND TOXICITIES OF ANTI-TB MEDICATIONS

<p>Isoniazid Rash Hepatic enzyme elevation Hepatitis Peripheral neuropathy Mild CNS effects</p> <p>Rifampin/Rifabutin Rash Hepatitis Fever Thrombocytopenia Flu-like symptoms</p> <p>Pyrazinamide Gastrointestinal upset Hepatitis Rash Arthralgias Hyperuricemia Gout (rare)</p> <p>Ethambutol Optic neuritis (decreased red-green color discrimination) Decreased visual acuity Rash</p>	<p>Streptomycin Ototoxicity (hearing loss or vestibular function) Congenital deafness Nephrotoxicity Hypokalemia Hypomagnesemia</p> <p>Levofloxacin Abdominal cramps GI upset Insomnia Headache Photosensitivity</p> <p>Cycloserine Psychosis Seizures Headache Depression Other CNS effects Rash</p> <p>Ethionamide GI upset Bloating Hepatotoxicity Metallic taste Hypothyroidism (esp. with PAS)</p>	<p>Kanamycin/Amikacin Auditory and renal toxicity Hypokalemia Hypomagnesemia Vestibular toxicity (rare)</p> <p>Capreomycin Auditory, vestibular, and renal toxicity Eosinophilia Hypokalemia Hypomagnesemia</p> <p>Para-aminosalicylic acid GI disturbance Hypersensitivity Hepatotoxicity Hypothyroidism</p>
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IX. MANAGEMENT OF LATENT TB INFECTION

RECOMMENDATIONS:

For HIV-infected patients without a history of TB or a positive tuberculin skin test (TST), clinicians should order a 5-tuberculin unit (TU) PPD at the time of the initial evaluation and annually thereafter. (I) Induration of ≥ 5 mm is considered a positive test and an indication for treatment of latent TB infection (LTBI). (I)

Anergy testing is not recommended at the time of tuberculin skin testing. (I)

For HIV-infected patients with a new positive TST, clinicians should obtain a detailed history, perform a physical examination, and obtain a chest x-ray to determine whether active TB is present. (I)

HIV-infected persons with LTBI should receive treatment to prevent progression to TB disease; however, treatment for LTBI should not be initiated until active TB disease is excluded. (III) The preferred regimen for LTBI is 9 months of isoniazid 300 mg daily (or 900 mg twice weekly if directly observed) plus pyridoxine, 25 mg per day or 50 mg twice weekly, to prevent peripheral neuropathy. (I)

Clinicians should avoid using rifampin plus pyrazinamide to treat LTBI because of the risk of severe liver injury and death. (I) If there are no other alternatives, an expert in the management of TB should be consulted prior to use of this regimen. (I)

Directly observed therapy for latent TB infection should be offered to patients when it is available. (I)

HIV-infected patients have consistently shown lower rates of reactivity to TST when compared with demographically similar non-HIV-infected individuals. This phenomenon is due primarily to the failure of the delayed-type hypersensitivity (DTH) response in patients with advanced HIV infection. Induration of ≥ 15 mm in response to an intradermal injection of 5 TU defines a positive skin test in the general population and is thus considered diagnostic of latent infection in non-HIV-infected persons, whereas induration of only ≥ 5 mm to 5 TU is considered positive in HIV-infected persons.⁷ This lower threshold for HIV-infected persons exists for two reasons: 1) the elevated risk of TB for HIV-infected persons with advanced disease ($CD4 \leq 200$ cells/mm³) with induration of 5 to 9 mm following TST, and 2) the high incidence of TB in HIV-infected persons.

Cutaneous anergy is more common in HIV-infected persons, and the prevalence of anergy increases relative to the degree of immunosuppression. Cutaneous anergy as a functional measure of cellular immunity has been used to determine whether negative tuberculin skin tests are valid in the presence of HIV immunosuppression. Anergy testing is no longer recommended because skin test anergy has been found to be both inconsistent and difficult to standardize and reproduce. In addition, two large prospective trials found low rates of active TB among anergic HIV-infected individuals, regardless of whether they received isoniazid chemoprophylaxis.

Isoniazid has repeatedly been shown to be effective in preventing the development of TB in patients with LTBI. In addition, chemoprophylaxis should be given to those HIV-infected individuals who have radiographic evidence of previous TB or have had a close exposure to a known case of TB. In the latter situation, regimens should be based on the susceptibility of the isolate from the index patient.

For known exposure to MDRTB, there are no clearly proven therapeutic options; consultation with a TB expert and/or local department of health is strongly advised. Pyrazinamide with ethambutol, and pyrazinamide with levofloxacin are two possible preventive regimens which have yet to be studied. When the infecting strain is partially susceptible to either isoniazid or

rifampin, these drugs should be used in combination with other oral agents. Therapy should last a minimum of 12 months.

Regimens that are usually well-tolerated may occasionally result in severe adverse effects. Idiosyncratic liver injury has been recognized as a potential toxicity of isoniazid, and fatal hepatotoxicity has recently been described with rifampin and pyrazinamide for treatment of LTBI. Therefore, rifampin plus pyrazinamide should generally not be offered. Healthcare providers should instruct patients about the initial symptoms of hepatitis (e.g., nausea, anorexia, abdominal pain, and fatigue) and the importance of discontinuing medication if symptoms develop.

X. INFECTION CONTROL ISSUES

RECOMMENDATIONS:

Clinicians should use airborne precautions and specialized rooms in situations that pose high risk for TB transmission, including sputum induction, bronchoscopy, and use of aerosolized pentamidine for prophylaxis of *Pneumocystis jirovecii* pneumonia (PCP). (I)

Clinicians should place any individual admitted to a hospital and suspected of having AFB smear-positive pulmonary or laryngeal TB in a code-compliant AFB isolation room until one of the following occurs: (I)

- **The indicated therapy has been initiated and the patient has had a clinical and bacteriologic response to therapy (three consecutive negative AFB sputum smears)**
- **Disease due to *M. tuberculosis* has been excluded**

Clinicians should not transfer patients receiving therapy for pulmonary TB to a non-isolation room until they have resolution of signs and symptoms (especially cough) and they have had three consecutive negative AFB sputum smears on different days. (I) Smear-positive patients should receive a minimum of 2 weeks of anti-TB therapy before additional AFB smears are obtained. (III)

Staff members who enter the rooms of, or who have contact with, smear-positive patients with TB should wear properly fitted disposable particulate respirators capable of filtering small (1-5 microns) aerosolized particles. Common surgical masks are not effective. (I)

Clinicians should not discharge patients with smear-positive pulmonary TB from the hospital unless they meet all of the following criteria: (III)

- **Their symptoms and signs, especially the cough, are resolved or near resolution**
- **They are receiving therapy to which the strain is known to be, or very likely to be, susceptible**
- **They are highly likely to adhere to the prescribed course of anti-TB therapy (e.g., DOT)**
- **They are not being discharged to congregate living environments or households where immunocompromised people or young children live.**

The principles of infection control to limit intra-institutional transmission of TB in the United States apply to both HIV-infected and non-HIV-infected populations who are infected with drug-resistant or drug-susceptible strains of TB. Nevertheless, transmission to HIV-infected patients and employees is of particular concern because of the high likelihood of developing active TB if they become infected with *M. tuberculosis*. These straightforward principles include effective isolation of suspected or known cases of TB until they are no longer infectious, rapid confirmation of diagnosis, and implementation of anti-TB chemotherapy medications.

The advances in isolation procedures have improved the prevention of hospital-acquired infection, contributing substantially to the decrease in the total number of cases of both drug-susceptible and drug-resistant TB. Failure to adhere to effective isolation and control programs has resulted in a large number of institutional outbreaks and cases of nosocomial TB that have affected both patients and employees.

The isolation of suspected or known cases of TB in an institutional setting is a labor-intensive process and has had varying degrees of success. Placement of patients into rooms with negative pressure and a minimum of six air exchanges per hour is currently recommended. Other supplemental environmental interventions include the use of masking devices and high-efficiency filtration systems. However, given the difficulty in adhering to rigorous respiratory isolation algorithms and procedures, some institutions have advocated widespread use of ultraviolet irradiation as an adjunctive measure. At present, no controlled studies exist to support widespread use of this intervention.

XI. MYCOBACTERIUM AVIUM COMPLEX INFECTIONS

Disseminated MAC infection is a common late complication of untreated HIV infection. It occurs in patients who are severely immunosuppressed, with CD4 cell counts generally <50 cells/mm³.

A. Presentation

Bacteremia is usually present by the time of clinical presentation and accompanies widespread dissemination involving the liver, spleen, bone marrow, and lymph nodes. Patients generally complain of fever, anorexia, night sweats, and weight loss. Abdominal pain and diarrhea may also occur. Anemia and pancytopenia are common as a result of bone marrow infiltration. Elevated serum alkaline phosphatase levels are common signs of liver infiltration. In contrast, MAC disease in immunocompetent hosts is rare and usually localized to the lungs or less commonly to lymph nodes. The prevalence of disseminated MAC infection has declined dramatically with the advent of ART. At the same time, syndromes of localized infection due to MAC, including scrofula, osteomyelitis, and pneumonitis (occasionally with cavitation), have been seen soon after the initiation of effective ARV therapy; these manifestations are likely the consequence of immune reconstitution superimposed on pre-existing subclinical localized MAC infection. Similarly, MAC osteomyelitis may occur as a late manifestation of IRIS.

B. Diagnosis

RECOMMENDATIONS:

Clinicians should consider a diagnosis of disseminated MAC infection in any severely immunosuppressed patient with AIDS who presents with otherwise unexplained persistent fever, sweats, weight loss, and/or pancytopenia. (III)

Clinicians should obtain blood culture to diagnose disseminated MAC infection. (I) Sputum and stool cultures are generally not diagnostic of disease.

In patients suspected of having disseminated MAC, a blood specimen should be obtained for mycobacterial culture. Mycobacteremia is continuous and often high grade when symptoms are moderate or severe, so that one blood culture is usually sufficient for diagnosis. However, because transient mycobacteremia also occurs, additional cultures are warranted when symptoms persist despite a negative culture. It usually takes 5 days to 4 weeks for cultures to become positive depending on the culture system used and the degree of the mycobacteremia.

Deep-tissue infection of macrophages in organs of the reticulo-endothelial system precedes the development of continuous bacteremia in disseminated MAC. Culture of a biopsy specimen from a normally sterile site (e.g., bone marrow, liver, or lymph node) may therefore lead to an earlier diagnosis in individuals with negative blood cultures. Tissue biopsy and culture may be of increasing importance in diagnosing localized MAC disease associated with immune reconstitution due to ART.

Respiratory and stool specimens are not recommended to diagnose disseminated disease because many people are colonized with MAC in the respiratory and GI tracts. The presence of the organism in these specimens, therefore, is not diagnostic of disseminated MAC. However, MAC infection in the setting of immune reconstitution may localize to the lungs. Sequential cultures of MAC from serial sputum specimens in the setting of compatible radiographic and clinical findings may be due to localized MAC pneumonitis. The guidelines of the [American College of Respiratory Physicians](#) should be followed for diagnosis and treatment of pulmonary disease due to MAC.⁸

C. Treatment

RECOMMENDATIONS:

Clinicians should treat all patients with disseminated MAC infection. (I) Treatment regimens should include at least two drugs to increase efficacy and prevent the emergence of resistance. (I)

Clinicians should include a macrolide antibiotic (either clarithromycin or azithromycin) and ethambutol in all regimens for treatment of disseminated MAC infection. (I)

The clinician should initiate effective ART in HIV-infected patients with disseminated MAC infection who are not already receiving ART. (I)

A three-drug regimen against MAC should be considered for patients not able to be prescribed effective ART. (II)

MAC bacteremia has been independently associated with an increased risk of death, and anti-TB therapy has been associated with prolonged survival. The macrolides, clarithromycin and azithromycin, demonstrate excellent clinical and microbiologic activity in a number of single-drug and combination-drug studies.⁹ Because treatment of MAC with high dose clarithromycin (1000 mg twice a day) is associated with decreased survival compared with 500 mg twice daily, the lower dose should be used.

Ethambutol is the most commonly recommended second drug. One randomized clinical trial demonstrated improved survival with the addition of rifabutin to the combination of clarithromycin and ethambutol. Two other randomized clinical trials demonstrated that 3-drug combinations reduced emergence of drug resistance; therefore, in individuals not initiating HAART or able to be prescribed an effective HAART regimen, it is preferable to treat with a three-drug combination.

Other antibiotics with activity against MAC include the rifamycins (rifampin and rifabutin), quinolones (especially levofloxacin), and amikacin. One study suggests benefit from regimens including clofazimine, but its use remains controversial.

PIs complicate anti-TB therapy because of their significant interactions with rifamycins, especially rifampin. PIs are metabolized in the liver by the cytochrome P450 enzyme system. All PIs inhibit P450 to a variable extent. Rifampin is a potent inducer of the cytochrome P450 system; rifabutin induces it to a lesser extent. In addition, PIs increase serum levels of rifampin, thus increasing the toxicity of this drug. Appendix A lists the agents used for MAC prophylaxis and treatment and their potentially significant interactions with other drugs.

Anti-MAC therapy may be discontinued in patients who have achieved all of the following:

- 1) a sustained rise in CD4 count to >100 cells/mm³ for 6 or more months in response to HAART
- 2) completion of at least 12 months of treatment for disseminated MAC
- 3) absence of MAC symptoms

D. Prevention

RECOMMENDATIONS:

Clinicians should administer chemoprophylaxis against disseminated MAC to HIV-infected patients with CD4 cell counts <50 cells/mm³. (I)

Clinicians should use one of the following regimens for primary prevention of disseminated MAC: (I)

- clarithromycin 500 mg bid
- azithromycin 1200 mg per week

If neither clarithromycin nor azithromycin are tolerated, rifabutin (300 mg each day) should be used as an alternative agent for primary prevention. (III)

Before initiating prophylaxis, clinicians should exclude disseminated MAC disease by clinical evaluation, which may include obtaining a blood culture. (III)

Strategies to prevent disseminated MAC have been studied; however, prevention of exposure to these ubiquitous organisms is highly impractical.¹⁰ Consequently, numerous chemoprophylaxis trials have been completed. Three agents that have been well studied, both singly and in combination, are clarithromycin, azithromycin, and rifabutin. Clarithromycin and azithromycin have been shown to be more effective and better tolerated than rifabutin.

Based on the current [USPHS/IDSA guidelines](#), discontinuation of primary prophylaxis in patients who have not developed disseminated MAC infection may be considered for patients who have sustained a rise in CD4 count to >100 cells/mm³ for 3 or more months in response to ART.¹⁰ Discontinuation of secondary prophylaxis may be considered for patients who have sustained a rise in CD4 cell count to >100 cells/mm³ for 6 months plus at least 12 months of treatment and absence of symptoms.⁹ It is critical to remember to re-initiate prophylaxis in individuals who once had MAC and then develop immunologic failure with CD4 counts <50 cells/mm³. Similarly, it is important to always consider the individual's nadir CD4 count in the differential diagnosis of atypical infections because unusual late manifestations of MAC IRIS have been reported.

XII. MYCOBACTERIA OTHER THAN TB AND MAC

RECOMMENDATION:

When mycobacteria other than TB or MAC are isolated and implicated in infection, the clinician should seek the advice of an expert to aid in the management of uncommon infections. (III)

Non-tuberculous mycobacteria are a diverse group of organisms that are differentiated on the basis of a variety of morphologic, physiologic, and biochemical characteristics. Unlike *M. tuberculosis* disease, in which the isolation of a single colony is always clinically significant, the isolation of non-tuberculous mycobacteria and subsequent discrimination among contamination, colonization, and disease is often difficult. Non-tuberculous mycobacteria species are ubiquitous in soil, water, dust, and foodstuffs and may colonize secretions or body surfaces for prolonged periods without causing disease. In addition, non-tuberculous mycobacteria may contaminate clinical specimens. Drug susceptibilities vary considerably among non-tuberculous mycobacteria, and treatments for some of these organisms are not standardized. Other mycobacteria that cause localized and/or disseminated infections include *M. gordonae*, *M. fortuitum*, *M. chelonae*, *M. haemophilum*, *M. xenopi*, and *M. marinum*.

M. kansasii is the second most frequently reported non-tuberculous mycobacteria to cause disease. The clinical presentation of *M. kansasii* is often similar to that of TB, but the organism is

generally less virulent. Pulmonary parenchymal disease and disseminated disease are the most common clinical presentations. Treatment is often complex. Higher doses of isoniazid may be required; pyrazinamide is ineffective. In addition, increasing rates of rifampin resistance have been reported. Most HIV-infected patients with *M. kansasii* infection have treatable disease, although a small proportion of these patients seem to have rapidly progressing and fatal disease.

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Appendix A
Clinically Significant Interactions Among HAART and Antimycobacterial Drugs

APPENDIX A CLINICALLY SIGNIFICANT INTERACTIONS AMONG HAART AND ANTIMYCOBACTERIAL DRUGS			
HAART	Rifampin (RM)*	Rifabutin (RB)†	Clarithromycin (CL)
NNRTIs			
Delavirdine (DLV)	↓DLV AUC 96% Contraindicated	↓DLV AUC 80% ↑RB AUC 100% Contraindicated	↑CL 100% Reduce CL dose in renal impairment
Efavirenz (EFV)	↓EFV AUC 22% Consider ↑EFV dose to 800 mg po qd No change in RM concentration	↓RB AUC 35% In regimens that do not include PIs: Consider ↑RB to 450-600 mg qd or 600 mg 3x/week	↓CL AUC 39% Monitor for efficacy or use alternative MAC therapy
Nevirapine (NVP)	↓NVP AUC 37%-58% Careful clinical and virologic monitoring is required. Use only if no other options exist.	↓NVP AUC 16% No dose adjustment for regimens that do not include PIs	↓CL AUC 31% Metabolite 14-OH-CL↑42% Monitor for efficacy or use alternative MAC therapy
PIs			
Atazanavir (ATZ)	Not recommended	↑RB AUC 250% ↓RB to 150 mg qod or 3x/week	↑CL AUC 94% and may cause QTc prolongation ↑ATZ AUC 28% Consider alternative therapy
Fosamprenavir (f-APV)	↓APV AUC 82% Not recommended	Comparable to APV ↓RB to 150 mg qd or 300 mg 2-3x/week‡	
Indinavir (IDV)	↓IDV AUC 89% Not recommended	↓IDV AUC 32% ↑RB AUC 204% ↑IDV to 1000 mg q8h, and ↓RB to 150	↑CL AUC 53% No dose adjustment

		mg qd or 300 mg 3x/week	
Lopinavir/ ritonavir (LPV/r)	↓LPV AUC 75% Not recommended‡	↑RB AUC 3-fold ↓RB to 150 mg qod§	RTV↑CL AUC 77% Pharmacokinetic effects of combined LPV and RTV on CL have not been studied. Adjust CL dose for moderate and severe renal impairment
Nelfinavir (NFV)	↓NFV AUC 82% Not recommended	↓NFV AUC 32% ↑RB AUC 207% ↑NFV to 1000 mg q8h, and ↓RB to 150 mg qd or 300 mg 3x/week	No data
Ritonavir (RTV)	↓RTV AUC 35% No dose changes Increased liver toxicity possible	↑RB AUC 430% No change in RTV concentration ↓RB to 150 mg qod or 150 mg 3x/week¶	↑CL AUC 77% Reduce CL dose in moderate and severe renal impairment
Saquinavir (SQV)	↓SQV AUC 84% Contraindicated	↓SQV AUC 43% Contraindicated without co- administration of RTV	↑CL 45% ↑SQV 177% No dose adjustment

* Rifampin increases concentrations of zidovudine and probably abacavir. Although the clinical significance of these changes is not clear, it is prudent to use rifabutin with triple NRTIs.

† Avoid twice-weekly rifabutin therapy in patients with CD4 counts <100 cells/mm³.

‡ 3x/week administration in patients with CD4 counts <100 cells/mm³.

§ When the dose of rifabutin is decreased, it is important to monitor adherence with ritonavir because discontinuation of ritonavir may result in underdosing with rifabutin.

¶ In one small study, an increased dose of LPV/r 800/200 mg was used to offset rifampin-inducing activity of LPV; the standard dose of rifampin was used. 28% of patients discontinued this regimen due to increases in LFTs. The safety of this combination has not been established and, if used, close monitoring, including measuring LPV concentrations, is recommended.