A Nonprofit Publication

Vol. 5 (Issue 55) March 2007

Published by The Medical Letter, Inc.
1000 Main Street
New Rochelle, N.Y. 10801
www.medicalletter.org

Treatment Guidelines from The Medical Letter®

Drugs for Tuberculosis

Even though the incidence continues to decline, tuberculosis (TB) is still a problem in the United States.[1] Treatment of TB can be divided into treatment of latent infection and treatment of active disease. A table listing the first-line drugs used for treatment of TB with their doses and adverse effects can be found on page 16. Other guidelines with more detailed management recommendations are available.[2,3]

DIRECTLY OBSERVED THERAPY

Poor adherence to TB therapy is the most common cause of treatment failure and is associated with emergence of drug resistance. Medical Letter consultants recommend that almost all patients, including those with disease due to susceptible strains, take drugs for active TB disease under direct observation. Compared to self-administered regimens, directly observed therapy (DOT) has been shown to decrease drug resistance, relapse and mortality rates, and to improve cure rates.[4,5] Due to the complexity and duration of TB treatment regimens, DOT is particularly important for treatment of patients with drug-resistant infections and for those on intermittent regimens because these are more susceptible to failure. Patients with latent infection who are at high risk for developing active TB or are taking an intermittent regimen should also be considered for DOT. DOT services are available through most local and state health departments.

LATENT TB INFECTION

The risk of patients with latent TB infection developing active TB disease is extremely high in those who are co-infected with HIV or are receiving immunosuppressive therapy. It is also high in children, in close contacts of patients with recent pulmonary TB, in previously untreated patients with radiographic evidence of prior TB, during the first 2 years after development of a positive tuberculin test, and in immigrants from countries with a high incidence of TB.[6,7]

The risk of serious disease, including miliary TB and tuberculous meningitis, is highest in infants, the elderly, and in patients with HIV infection or other causes of severe immunosuppression. Recent reports also indicate high risk for development of active TB disease in persons with latent TB infection who are treated with the TNF-alpha inhibitors infliximab *(Remicade)*, etanercept *(Enbrel)*, and adalimumab *(Humira)* for rheumatoid arthritis or some other condition. These reports include cases of extrapulmonary and disseminated disease, and deaths. Before beginning therapy with these drugs, testing for latent TB infection is recommended.[8,9]

Diagnosis – The tuberculin skin test (purified protein derivative, PPD) has been in clinical use for over a century. Recently, interferon-gamma release assays

First-Line Drugs

Drug/formulation	Adult dosage Daily	Adult dosage Intermittent[1]	Pediatric dosage Daily	Pediatric dosage Intermittent[1]	Main adverse effects
Isoniazid (INH)[2] 100, 300 mg tabs, 50 mg/5mL syrup, 100 mg/mL inj	5 mg/kg (max 300 mg) PO, IM or IV	15 mg/kg (max 900 mg) 2-3x/wk	10-20 mg/kg (max 300 mg)	20-30 mg/kg (max 900 mg) 2x/wk	Hepatic toxicity, rash, peripheral neuropathy
Rifampin *(Rifadin, Rimactane)* 150, 300 mg caps, 600 mg inj powder	10 mg/kg (max 600 mg) PO or IV	10 mg/kg (max 600 mg) 2-3x/wk	10-20 mg/kg (max 600 mg)	10-20 mg/kg (max 600 mg) 2x/wk	Hepatic toxicity, rash, flu-like syndrome, pruritis, drug interactions
Rifabutin[3] *(Mycobutin)* 150 mg caps	5 mg/kg (max 300 mg) PO	5 mg/kg (max 300 mg) 2-3x/wk	10-20 mg/kg (max 300 mg)	No data available	Hepatic toxicity, flu-like syndrome, uveitis, neutropenia, drug interactions
Rifapentine *(Priftin)* 150 mg tabs	—	10-15 mg/kg/wk (max 600-900 mg) PO	No data available	No data available	Similar to rifampin
Pyrazinamide 500 mg tabs	20-25 mg/kg PO (max 2 g)	30-50 mg/kg 2x/wk (max 3 g); 3x/wk (max 4 g)	15-30 mg/kg (max 2 g)	50 mg/kg (max 2 g) 2x/wk	Arthralgias, hepatic toxicity, pruritis, rash, hyperuricemia, GI upset
Ethambutol[4] *(Myambutol)* 100, 400 mg tabs	15-25 mg/kg PO (max 1.6 g)	25-50 mg/kg 2x/wk (max 2.4 g); 3x/wk (max 4 g)	15-25 mg/kg (max 1 g)	50 mg/kg (max 2.5 g) 2x/wk	Decreased red-green color discrimination, decreased visual acuity

1. Intermittent therapy is usually begun after a few weeks or months of treatment with a daily regimen.
2. Pyridoxine 25-50 mg should be given to prevent neuropathy in malnourished or pregnant patients and those with HIV infection, alcoholism or diabetes.
3. For use with amprenavir, fosamprenavir, nelfinavir or indinavir, the rifabutin dose is 150 mg/day or 300 mg 3 times a week. For use with atazanavir, ritonavir alone or ritonavir combined with other protease inhibitors, and lopinavir/ritonavir *(Kaletra)*, the rifabutin dose is further decreased to 150 mg every other day or 3 times weekly. For use with efavirenz, the rifabutin dose is increased to 450 mg/day or 600 mg 2-3 times weekly. Not recommended with saquinavir alone or delavirdine.
4. Usually not recommended for children when visual acuity cannot be monitored. Some clinicians use 25 mg/kg/day during first one or two months or longer if organism is isoniazid-resistant. Decrease dosage if renal function is diminished.

(IGRAs) that measure host cell-mediated immune response to *Mycobacterium tuberculosis* have become available for diagnosis of latent TB infection. Unlike PPD skin testing, IGRA results are not affected by prior immunization with Bacille Calmette-Guerin (BCG) or exposure to most nontuberculous mycobacteria, which gives them higher specificity than skin testing.

Currently, the only FDA-approved IGRA is the QuantiFERON-TB Gold (QFT-G) assay.[10] QFT-G detects the immune response to two *M. tuberculosis* antigens that are absent from all BCG vaccine preparations and most nontuberculous mycobacteria (exceptions are *M. kansasii*, *M. marinum* and *M. szulgai*). It has not been well studied in high-risk groups such as children, healthcare workers, and HIV-infected and other immunocompromised persons. An enzyme-linked immunospot IGRA assay, T-SPOT. *TB*, is available in Europe.[11]

Treatment – Isoniazid (INH) is the drug of choice for treatment of latent TB infection presumed to be due to susceptible strains. It should be given daily or intermittently for 9 months.[12] Monthly follow-up visits, patient education, and identification of barriers to adherence can all promote completion of therapy for latent TB. Directly observed therapy (DOT) should be considered for high-risk patients such as children or patients co-infected with HIV and for all patients taking intermittent regimens.

An alternative regimen for treatment of latent TB, particularly for persons intolerant to isoniazid or those found to be tuberculin-positive after exposure to patients with organisms resistant to isoniazid, is daily rifampin alone for 4 months (6 months in children).[13,14] One meta-analysis found short-course therapy with 3 months of isoniazid plus rifampin equivalent to the standard 9 months of isoniazid.[15] The combination of rifampin and pyrazinamide for 2 months, which formerly was used as an alternative to isoniazid treatment of latent infection, is no longer recommended because of its association with potentially lethal hepatotoxicity.[16,17]

Drug-Resistant Latent TB Infection – There are no data-based recommendations for treatment of latent TB infection in high-risk patients with known exposure to multi-drug resistant TB (MDRTB), defined as isolates with resistance to at least isoniazid and rifampin. Regimens with two drugs to which the

organism is susceptible (e.g., pyrazinamide plus either ethambutol or a fluoroquinolone for 9-12 months) have been used, but are poorly tolerated, can be hepatotoxic and are of uncertain efficacy.[18,19]

Extensively drug-resistant TB (XDRTB), now defined as isolates with resistance not only to isoniazid and rifampin but also to any fluoroquinolone and either capreomycin, kanamycin or amikacin (see table on page 18), is an increasing problem worldwide; there are no data-based recommendations for treatment of latent TB following exposure to XDRTB.[20-22]

Medical Letter consultants recommend that treatment of patients with drug-resistant latent TB be provided by or in collaboration with a clinician experienced in treatment of these infections. Whatever treatment is chosen, such patients should be observed for up to 2 years following exposure.

ACTIVE TB DISEASE

All initial isolates of *M. tuberculosis* should be tested for antimicrobial susceptibility, but results generally do not become available for at least 2-4 weeks.[23] Standard treatment of active TB includes a 2-month initial phase and a continuation phase of either 4 or 7 months, depending on the presence or absence of cavitary disease at the time of diagnosis and the results of sputum cultures taken at 2 months (see table). Patients should be monitored monthly to assess for adverse reactions, adherence and response to treatment. Medical Letter consultants recommend that patients on self-administered therapy receive no more than a 1-month supply of medication at each visit.

Initial Therapy – Until susceptibility results are available, empiric initial treatment should consist of a 4-drug regimen of isoniazid, rifampin, pyrazinamide and ethambutol.[24] Patients in areas with low rates of drug-resistant TB who cannot take pyrazinamide, such as those who have severe liver disease or gout, should receive empiric initial therapy with isoniazid, rifampin and ethambutol.

When TB disease proves to be caused by a fully susceptible strain, the initial phase of treatment should consist of isoniazid, rifampin and pyrazinamide for 2 months.

Continuation Therapy – Two factors increase the risk of treatment failure and relapse: cavitary disease at presentation and a positive sputum culture taken at 2 months. For patients with one or no risk factors, the continuation phase of treatment should be with isoniazid and rifampin for 4 months. For patients with both risk factors, and for those who could not take pyrazinamide as part of the initial regimen, the continuation phase is extended to 7 months.

Duration of Continuation Therapy[1]

Cavity on Chest X-ray	Drugs	Sputum culture taken at 2 mos	Duration (months)[2]
No	INH/RIF	Negative	4
	or INH/RPT[3]		4
No	INH/RIF	Positive[4]	4
	or INH/RPT[3]		7
Yes	INH/RIF	Negative	4
Yes	INH/RIF	Positive	7

INH = Isoniazid; RIF = rifampin; RPT = rifapentine
1. For treatment of drug-susceptible disease after two months of initial therapy.
2. Always 7 months for patients who could not take pyrazinamide as part of the initial regimen. Can be shortened to 2 months in non-HIV patients with culture-negative pulmonary TB.
3. RPT is a treatment option only for non-pregnant, HIV-negative adults without cavitary or extrapulmonary disease who are smear-negative at 2 months.
4. If the culture is positive and the patient is taking INH/RPT, some Medical Letter consultants would switch to INH/RIF.

For selected patients with neither cavitary disease nor a positive smear after 2 months of therapy, the long-acting rifamycin rifapentine, given once-weekly by DOT is an additional option for continuation therapy.[24] Rifapentine should not be used if the patient has extrapulmonary TB or co-infection with HIV, is younger than 12 years of age or pregnant, or if drug susceptibility is unknown. If the culture taken at 2 months proves to be positive and rifapentine is being used, some Medical Letter consultants would switch to rifampin.

If sputum cultures remain positive after 4 months of treatment, nonadherence to treatment or infection with drug-resistant TB must be considered. Only after these are excluded should other causes (e.g., malabsorption) be considered as possible explanations of poor response. Treatment duration should be prolonged in such patients.

TB osteomyelitis is usually treated for 6-9 months. Tuberculous meningitis is usually treated for a total of 9-12 months. Addition of a corticosteroid for 1-2 months is recommended for tuberculous pericarditis or meningitis.[25]

Culture-Negative TB – Patients with pulmonary disease who have no positive cultures for *M. tuberculosis* before treatment and after 2 months of therapy have "culture-negative TB"; in these patients, the continuation phase with isoniazid and rifampin can generally be shortened to 2 months. Exceptions are patients with extrapulmonary TB or those co-infected with HIV, who should be treated for 6 months or longer.

Some Second-Line Drugs

Drug	Daily adult dosage	Daily pediatric dosage	Main adverse effects
Streptomycin[1]	15 mg/kg IM (max 1 g)	20-40 mg/kg	Vestibular and auditory toxicity, renal damage
Capreomycin *(Capastat)*	15 mg/kg IM (max 1 g)	15-30 mg/kg	Auditory and vestibular toxicity, renal damage
Kanamycin (*Kantrex,* and others)	15 mg/kg IM or IV (max 1 g)	15-30 mg/kg	Auditory toxicity, renal damage
Amikacin *(Amikin)*	15 mg/kg IM or IV (max 1 g)	15-30 mg/kg	Auditory toxicity, renal damage
Cycloserine[2] (*Seromycin)*	10-15 mg/kg in 2 doses (max 500 mg bid) PO	10-15 mg/kg	Psychiatric symptoms, seizures
Ethionamide *(Trecator-SC)*	15-20 mg/kg in 2 doses (max 500 mg bid) PO	15-20 mg/kg	GI and hepatic toxicity, hypothyroidism
Levofloxacin *(Levaquin)*	500-1000 mg PO or IV	See footnote 3	GI toxicity, CNS effects, rash, dysglycemia
Moxifloxacin *(Avelox)*	400 mg PO or IV	See footnote 3	GI toxicity, CNS effects, rash, dysglycemia
Aminosalicylic acid (PAS; Paser)	8-12 g in 2-3 doses PO	200-300 mg/kg, in 2-4 doses	GI disturbance

1. Streptomycin is generally given 5-7 times per week (15 mg/kg, or a maximum of 1 g per dose) for an initial 2 to 12 week period, and then (if needed) 2 to 3 times per week (20 to 30 mg/kg, or a maximum of 1.5 g per dose). For patients >59 years old, dosage is reduced to 10 mg/kg/d (max 750 mg/d). Dosage should be decreased if renal function is diminished.
2. Some authorities recommend pyridoxine 50 mg for every 250 mg of cycloserine to decrease the incidence of adverse neurological effects.
3. According to the American Academy of Pediatrics, although fluoroquinolones are generally contraindicated in children <18 years old, their use may be justified in special circumstances. Medical Letter consultants would use these drugs to treat children with MDRTB.

Drug Intolerance – For patients who cannot tolerate rifamycins, alternative regimens include 9-12 months of isoniazid, ethambutol and pyrazinamide, with or without a fluoroquinolone (levofloxacin or moxifloxacin). Levofloxacin has been safe for long-term use in patients with drug-resistant TB or those intolerant to isoniazid or a rifamycin. Moxifloxacin is currently in clinical trials for use in TB treatment and may be more active than levofloxacin against *M. tuberculosis*, but clinical data are limited.

Isoniazid plus ethambutol for 18 months has also been used for patients intolerant of rifamycins. Rifabutin has been substituted for rifampin in standard regimens for some patients who could not take rifampin because of drug interactions (such as HIV co-infected patients on a protease inhibitor). Patients who cannot take pyrazinamide in the initial phase of treatment should receive continuation therapy with isoniazid and rifampin for 7 months (a total course of 9 months).

Intermittent Treatment – Intermittent 4-drug regimens with 2 or 3 doses per week are also effective for treatment of TB, but must be given by DOT. Intermittent therapy is most commonly used in the continuation phase, after at least 2 months of daily (or 5x/wk) therapy during the initiation phase. It should never be used for treatment of drug-resistant TB. A once-weekly continuation-therapy regimen of isoniazid plus rifapentine (instead of rifampin), started after 2 months of standard initial therapy, is also effective for susceptible TB in selected patients.[2,24] This regimen has, however, been associated with development of rifamycin resistance in HIV-infected patients and should not be used in these individuals.[26-28]

Twice-weekly intermittent regimens have also been associated with rifamycin resistance in HIV co-infected patients with low CD4 counts; such patients should receive daily or 3x/wk therapy.

Fixed-Dose Combinations – A combination formulation of rifampin, isoniazid and pyrazinamide *(Rifater)* is approved by the FDA for the initial 2 months of daily anti-tuberculosis therapy. A combination of rifampin and isoniazid *(Rifamate)* has been available in the US since 1975. Fixed-dose combinations may be particularly useful for patients self-administering their therapy.[29]

Combination Drugs

Drug	Daily adult dosage
Rifamate[1] (isoniazid 150 mg, rifampin 300 mg)	2 capsules
Rifater[1] (isoniazid 50 mg, rifampin 120 mg, pyrazinamide 300 mg)	≤44 kg: 4 tablets 45-54 kg: 5 tablets 55-90 kg: 6 tablets >90 kg: 6 tablets plus additional pyrazinamide[2]

1. Pyridoxine 25-50 mg should be given to prevent neuropathy in malnourished or pregnant patients and those with HIV infection, alcoholism or diabetes.
2. Six tablets provide 1800 mg of pyrazinamide. Patients should take additional pyrazinamide tablets to achieve a total dose of 20-25 mg/kg/d.

DRUG-RESISTANT TB DISEASE

Resistance to Isoniazid – TB that is resistant to isoniazid can be treated with rifampin, pyrazinamide and ethambutol for 6-9 months. If the organism is susceptible, streptomycin is an alternative to ethambutol. Patients who cannot tolerate pyrazinamide can take rifampin and ethambutol for 12 months. A fluoroquinolone or an injectable drug (capreomycin, amikacin, kanamycin or streptomycin) is sometimes added, especially if the patient cannot tolerate pyrazinamide or if there is extensive disease.

Multidrug Resistance – Recommendations for treatment of MDRTB and XDRTB are based on limited data and should be undertaken in collaboration with someone familiar with the management of these conditions. MDRTB and XDRTB should be treated with ≥4 drugs to which the organism is susceptible. When MDRTB is likely, or in patients with a history of treatment for TB, some experienced clinicians start with combinations of 5-7 drugs before laboratory susceptibility data become available. Typically, empiric therapy for suspected MDRTB includes isoniazid, rifampin, ethambutol, pyrazinamide, an aminoglycoside (streptomycin, kanamycin or amikacin) or capreomycin, a fluoroquinolone and either cycloserine, ethionamide or aminosalicylic acid (PAS).[30-32] Drug selection is based on a hierarchy of drugs to which the isolate is susceptible. This involves inclusion of all active first-line drugs (pyrazinamide, ethambutol), a fluoroquinolone and one injectable drug.

Monthly bacteriologic results (AFB smear and culture) should be monitored and treatment continued for 18-24 months, or 12-18 months after the culture becomes negative. The parenteral drug should be continued for 6 months after culture conversion. Surgical resection has improved outcome in some patients and should be considered if cultures fail to convert to negative after 3-4 months of appropriate treatment.[33]

HIV-INFECTED PATIENTS

Testing for HIV infection is recommended for all patients with active TB. Persons with HIV, once infected, are at markedly increased risk of developing active TB disease. HIV-infected patients with a history of prior untreated or inadequately treated TB disease should be re-evaluated for active disease regardless of age or results of tests for latent TB infection. If active TB disease is ruled out, patients should receive treatment for latent TB infection. HIV-infected persons who have had recent close contact with a patient with active TB disease should receive empiric treatment for latent infection regardless of age, results of tests for TB infection, or history of previous treatment.

To minimize the emergence of drug-resistant TB, co-infected patients in the continuation phase of TB treatment should take medication once daily or three times weekly.[34] Twice-weekly regimens have been associated with acquisition of rifamycin resistance in patients with CD4 cell counts <100 cells/mm^3.[35] Once-weekly rifapentine is not recommended for TB treatment in HIV-infected patients because it has been associated with development of rifamycin resistance.[28]

Patients Not on HAART – For HIV-infected patients requiring TB treatment who are not currently being treated with highly active antiretroviral therapy (HAART), it may be prudent to delay HAART for 2-3 months in order to avoid a paradoxical worsening of TB due to immune reconstitution, decrease the risk of overlapping drug adverse effects and interactions, reduce pill burden, and enhance adherence to both drug regimens,[36-38] but the optimal timing for initiating HAART in patients with newly diagnosed TB is not known.

Patients on HAART – Rifamycins induce hepatic CYP enzymes, especially CYP3A4, and can accelerate metabolism of protease inhibitors and some non-nucleoside reverse transcriptase inhibitors (NNRTIs), decreasing their serum concentrations, possibly to ineffective levels. The degree to which each drug induces CYP3A4 differs: rifampin is the most potent and rifabutin the least. In addition, rifabutin is a substrate for CYP3A4; protease inhibitors decrease its metabolism, increasing serum concentrations and possibly toxicity.

Standard 4-drug treatment regimens including rifampin can be given to HIV-infected patients with active TB who are simultaneously receiving HAART if the HAART regimen consists of efavirenz *(Sustiva)* and two nucleoside reverse transcriptase inhibitors (NRTIs). Standard doses of rifampin can also be used in patients taking ritonavir *(Norvir)* as the only protease inhibitor, combined with 2 NRTIs.[39]

Two alternative TB/HAART regimens are based on **rifabutin**, which appears to be as effective as rifampin against TB and has less effect on protease inhibitor concentrations. The first substitutes low-dose rifabutin (150 mg once/day or 300 mg 3x/week) for rifampin in the standard TB regimen (i.e., isoniazid, rifabutin, pyrazinamide and ethambutol) and uses higher-than-usual doses of indinavir *(Crixivan)* or nelfinavir *(Viracept)*, or standard doses of amprenavir *(Agenerase)* or fosamprenavir *(Lexiva)* as the HIV protease inhibitor. The second decreases the rifabutin dose further to 150 mg every other day or 3 times weekly and the HAART regimen includes standard doses of atazanavir *(Reyataz)*, ritonavir/lopinavir *(Kaletra)* or

ritonavir alone or combined with other protease inhibitors. Saquinavir *(Invirase)* alone should not be used. Higher rifabutin doses (450 mg daily or 600 mg 2-3 times per week) are needed if the HAART regimen contains efavirenz.

TB IN PREGNANCY

Active TB disease during pregnancy requires treatment. The treatment of **latent TB infection** during pregnancy is more controversial because of the risk of isoniazid hepatotoxicity. In general, it is recommended that treatment of latent TB be delayed until 2 or 3 months after delivery. However, for women who are HIV-positive or have been infected with TB recently, initiation of therapy should not be delayed because of pregnancy.

Treatment of **active TB disease** should be initiated in pregnancy when there is moderate to high suspicion of disease because the risk to the fetus is much greater than the risk of adverse drug effects. The initial regimen should include isoniazid, rifampin and ethambutol. Each of these drugs crosses the placenta, but none is teratogenic. Pyrazinamide has not been extensively studied in pregnancy, but some Medical Letter consultants would use it in addition to isoniazid, rifampin and ethambutol.[40] If pyrazinamide is not used, treatment should be continued for a total of at least 9 months. Pyrazinamide is always recommended as part of the initial regimen in pregnant women who are HIV co-infected or when drug resistance is suspected.

Limited data are available on the treatment of MDRTB in pregnancy. Regimens using various combinations of amikacin, ethionamide, PAS, cycloserine, capreomycin and fluoroquinolones have been successful without causing fetal adverse effects, even though these drugs are generally not considered safe in pregnancy.[41-43]

ADVERSE EFFECTS

Isoniazid – Serum aminotransferase activity increases in 10-20% of patients taking isoniazid, especially in the early weeks of treatment, but often returns to normal even when the drug is continued. Severe liver damage due to isoniazid is less common than previously thought. It is more likely to occur in patients more than 35 years old. Clinical monitoring should occur monthly; monitoring of serum transaminases is not routinely recommended except for patients with pre-existing liver disease and those at increased risk for isoniazid hepatotoxicity, such as those patients who drink alcohol regularly. Medical Letter consultants recommend stopping isoniazid when serum aminotransferase activity reaches five times the upper limit of normal or if the patient has symptoms of hepatitis. In patients with active TB disease it can sometimes be restarted later. Rechallenge with isoniazid is not recommended for patients with latent TB infection.

Peripheral neuropathy occurs rarely and can usually be prevented by supplementation with pyridoxine (vitamin B6, 25-50 mg/day), which is recommended for patients with chronic alcohol use, diabetes, chronic renal failure or HIV infection, and for those who are pregnant, breastfeeding or malnourished. Some Medical Letter consultants routinely use pyridoxine for all patients taking isoniazid. Pyridoxine does not need to be given to a nursing infant unless the baby is also being given isoniazid.

Rifamycins – Rifampin, like isoniazid, is potentially hepatotoxic, and gastrointestinal disturbances, morbilliform rash and thrombocytopenic purpura can occur. Whenever possible, rifampin should be continued despite minor adverse reactions such as pruritus and gastrointestinal upset. When taken erratically, the drug can cause a febrile "flu-like" syndrome and, very rarely, shortness of breath, hemolytic anemia, shock and acute renal failure. Patients should be warned that rifampin may turn urine, tears and other body fluids reddish-orange and can permanently stain contact lenses and lens implants.

Rifampin is an inducer of CYP isozymes 3A4, 2C9, 2C19, 2D6, 2B6, and 2C8. It can increase the metabolism and decrease the effect of many other drugs, including hormonal contraceptives (patients should be advised to use another method of contraception), sulfonylureas such as glyburide (*Diabeta*, and others), corticosteroids, warfarin (*Coumadin*, and others), quinidine, methadone (*Dolophine*, and others), delavirdine *(Rescriptor)*, clarithromycin (*Biaxin*, and others), ketoconazole (*Nizoral*, and others), itraconazole (*Sporanox*, and others) and fluconazole (*Diflucan*, and others), as well as protease inhibitors and most statins (such as atorvastatin and simvastatin).[44]

Rifabutin and **rifapentine** have adverse effects similar to those of rifampin. Rifabutin can also cause uveitis, skin hyperpigmentation and neutropenia, but is less likely than rifampin to interact with other drugs.

Other Drugs – Pyrazinamide can cause gastrointestinal disturbances, hepatotoxicity, morbilliform rash, arthralgias and asymptomatic hyperuricemia, and can block the hypouricemic action of allopurinol (*Zyloprim*, and others). **Ethambutol** can cause optic neuritis, but only very rarely when using a dosage of 15 mg/kg daily. Testing of visual acuity and color per-

ception should be performed at the start of therapy, and monthly thereafter. The decision to use ethambutol in children too young to have visual acuity monitored must take into consideration the risk/benefit for each particular patient.[45]

Streptomycin causes ototoxicity (usually vestibular disturbance) and, less frequently, renal toxicity. **Amikacin** and **kanamycin** can cause tinnitus and high-frequency hearing loss. These drugs and **capreomycin** can also cause renal and vestibular toxicity. **Cycloserine** can cause psychiatric symptoms and seizures. **Ethionamide** has been associated with gastrointestinal, hepatic and thyroid toxicity. A delayed-release granular formulation of **aminosalicylic acid** (PAS) has better gastrointestinal tolerability than older formulations. **Fluoroquinolones** are usually well-tolerated, but can cause gastrointestinal and CNS disturbances, and dysglycemia can occur, particularly in the elderly and in patients with diabetes.

CONCLUSION

All initial isolates of *M. tuberculosis* should be tested for antimicrobial susceptibility. Initial therapy for most patients with active TB should include at least isoniazid, rifampin, pyrazinamide and ethambutol until susceptibility is known. Directly observed therapy (DOT) by a healthcare worker is the standard of care and should be offered to all patients with active TB to minimize failure rates, relapse and the emergence of drug resistance. Confirmed multidrug-resistant tuberculosis (MDRTB) should be treated with DOT in collaboration with a clinician familiar with the management of the disease. Regimens for MDRTB must include at least 4 drugs to which the organism is susceptible; the duration of therapy usually should be 18-24 months.

1. Centers for Disease Control and Prevention (CDC). Trends in tuberculosis — United States, 2005. MMWR Morb Mortal Wkly Rep 2006; 55:305.
2. American Thoracic Society; CDC; Infectious Diseases Society of America. Treatment of tuberculosis. MMWR Recomm Rep 2003; 52 (RR-11):1.
3. PC Hopewell et al. International standards for tuberculosis care. Lancet Infect Dis 2006; 6:710.
4. TR Frieden and SS Munsiff. The DOTS strategy for controlling the global tuberculosis epidemic. Clin Chest Med 2005; 26:197.
5. K DeRiemer et al. Does DOTS work in populations with drug-resistant tuberculosis? Lancet 2005; 365:1239.
6. CR Horsburgh Jr. Priorities for the treatment of latent tuberbulosis infection in the United States. N Engl J Med 2004; 350:2060.
7. KP Cain et al. Tuberculosis among foreign-born persons in the United States: achieving tuberculosis elimination. Am J Respir Crit Care Med 2007; 175:75.
8. Centers for Disease Control and Prevention (CDC). Tuberculosis associated with blocking agents against tumor necrosis factor-alpha—California, 2002-2003. MMWR Morb Mortal Wkly Rep 2004; 53:683.
9. KL Winthrop. Risk and prevention of tuberculosis and other serious opportunistic infections associated with the inhibition of tumor necrosis factor. Nat Clin Pract Rheumatol 2006; 2:602.
10. Centers for Disease Control and Prevention (CDC). Guidelines for using the QuantiFERON®-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR Recomm Rep 2005;54 (RR-15):49.
11. M Pai et al. New tools and emerging technologies for the diagnosis of tuberculosis: part I. Latent tuberculosis. Expert Rev Mol Diagn 2006; 6:413.
12. Centers for Disease Control and Prevention (CDC). Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recomm Rep 2000; 49 (RR-6):1.
13. KR Page et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch Intern Med 2006; 166:1863.
14. A Lardizabal et al. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest 2006; 130:1712.
15. J Ena and V Valls. Short-course therapy with rifampin plus isoniazid, compared with standard therapy with isoniazid, for latent tuberculosis infection: a meta-analysis. Clin Infect Dis 2005; 40:670.
16. Centers for Disease Control and Prevention (CDC); American Thoracic Society. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection – United States, 2003. MMWR Morb Mortal Wkly Rep 2003; 52:735.
17. PD McElroy et al. National survey to measure rates of liver injury, hospitalization, and death associated with rifampin and pyrazinamide for latent tuberculosis infection. Clin Infect Dis 2005; 41:1125.
18. T Papastavros et al. Adverse events associated with pyrazinamide and levofloxacin in the treatment of latent multidrug-resistant tuberculosis. CMAJ 2002; 167:131.
19. R Ridzon et al. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. Clin Infect Dis 1997; 24:1264.
20. Centers for Disease Control and Prevention (CDC). Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs — worldwide, 2000-2004. MMWR Morb Mortal Wkly Rep 2006; 55:301.
21. Centers for Disease Control and Prevention (CDC). Revised definition of extensively drug-resistant tuberculosis. MMWR Morb Mortal Wkly Rep 2006; 55:1176.
22. NR Gandhi et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006; 368:1575.
23. GL Woods. The mycobacteriology laboratory and new diagnostic techniques. Infect Dis Clin North Am 2002; 16:127.
24. H Blumberg et al. Update on the treatment of tuberculosis and latent tuberculosis infection. JAMA 2005; 293:2776.
25. GE Thwaites et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med 2004; 351:1741.
26. M Weiner et al. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. Am J Respir Crit Care Med 2004; 169:1191.
27. FM Gordin. Rifapentine for the treatment of tuberculosis: is it all it can be? Am J Respir Crit Care Med 2004; 169:1176.
28. A Vernon et al. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. Lancet 1999; 353:1843.
29. B Blomberg and B Fourie. Fixed-dose combination drugs for tuberculosis: application in standardised treatment regimens. Drugs 2003; 63:535.
30. JA Caminero. Treatment of multidrug-resistant tuberculosis: evidence and controversies. Int J Tuberc Lung Dis 2006; 10:829.

31. JB Nachega and RE Chaisson. Tuberculosis drug resistance: a global threat. Clin Infect Dis 2003; 36 suppl 1:S24.
32. JS Mukherjee et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004; 363:474.
33. ED Chan et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2004; 169:1103.
34. Centers for Disease Control and Prevention (CDC). Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. MMWR Morb Mortal Wkly Rep 2002; 51:214.
35. RE Nettles et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment: a comparison by HIV serostatus and rifamycin use. Clin Infect Dis 2004; 38:731.
36. W Manosuthi et al. Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. J Infect 2006; 53:357.
37. SA Shelburne et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS 2005; 14:399.
38. G Breton et al. Determinants of immune reconstitution inflammatory syndrome in HIV type 1-infected patients with tuberculosis after initiation of antiretroviral therapy. Clin Infect Dis 2004; 39:1709.
39. Centers for Disease Control and Prevention (CDC). Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. Available at www.cdc.gov/nchstp/tb/tb_hiv_drugs/toc.htm. Accessed February 13, 2007.
40. G Bothamley. Drug treatment for tuberculosis during pregnancy: safety considerations. Drug Saf 2001; 24:553.
41. S Shin et al. Treatment of multidrug-resistant tuberculosis during pregnancy: a report of 7 cases. Clin Infect Dis 2003; 36:996.
42. KD Lessnau and S Qarah. Multidrug-resistant tuberculosis in pregnancy: case report and review of the literature. Chest 2003; 123:953.
43. PC Drobac et al. Treatment of multidrug-resistant tuberculosis during pregnancy: long-term follow-up of 6 children with intrauterine exposure to second-line agents. Clin Infect Dis 2005; 40:1689.
44. Medical Letter Adverse Drug Interactions Program.
45. World Health Organization. Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children. Available at http://whqlibdoc.who.int/hq/2006/who_htm_tb_2006.365_eng.pdf, Accessed February 13, 2007.

Coming Soon in *Treatment Guidelines*:
Drugs for Pain – April 2007
Choice of Antibacterial Drugs – May 2007
Drugs for Cardiac Arrhythmias – June 2007

Subscription Services

Mailing Address
The Medical Letter, Inc.
1000 Main Street
New Rochelle, NY 10801-7537

Customer Service
Call: 800-211-2769 or 914-235-0500
M-F 8am-6pm Eastern Time
Fax: 914-632-1733
Email: custserv@medicalletter.org

Web Site
www.medicalletter.org

Back Issues
Back issues are $12 each.

Subscriptions
1 year - $98; 2 years - $167;
3 years - $235. $49.00 per year for students, interns, residents and fellows in the US and Canada.
All prices include print, full-text online access and handheld application.

Major credit cards accepted.

Bulk Subscriptions
Special reduced rates for bulk subscriptions. Contact Customer Service at 800-211-2769. Special Classroom rates are available.

Site license inquires to:
info@medicalletter.org or call 800-211-2769 x315

Permissions
To reprint any portion of this issue, e-mail your request to: permissions@medicalletter.org.

The Medical Letter is an independent nonprofit organization that provides health care professionals with unbiased drug prescribing recommendations. The editorial process used for its publications relies on a review of published and unpublished literature, with an emphasis on controlled clinical trials, and on the opinions of its consultants. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants or donations. The editors declare no conflict of interest. The members of the Advisory Board are required to disclose any potential conflict of interest.