

Treatment Guidelines

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Drugs for Tuberculosis

Tuberculosis (TB) is still a problem in the United States, even though the incidence continues to decline in most of the country ([MMWR Morbid Mortal Wkly Rep 2004; 53:209](#)). Treatment of TB can be divided into treatment of latent infection diagnosed by a positive PPD and treatment of active clinical TB. Guidelines with detailed management recommendations are available from the US Centers for Disease Control and Prevention (CDC) ([MMWR Morbid Mortal Wkly Rep 2003; 52RR-11:1](#)).

TREATMENT OF LATENT TB INFECTION

The risk of developing clinical tuberculosis is greatest in patients with latent TB who are also infected with HIV or are receiving immunosuppressive therapy. It is also high in close contacts of patients with recent pulmonary tuberculosis, in those with radiographic evidence of prior TB, during the first 2 years after development of a positive tuberculin test, and in recent immigrants ([CR Horsburgh Jr, N Engl J Med 2004; 350:2060](#); [K Khan et al, N Engl J Med 2002; 347:1850](#)).

The risk of serious disease, including miliary tuberculosis and tuberculous meningitis, is highest in infants, the elderly, and in patients with HIV infection or other causes of severe immunosuppression. Recent studies also indicate high risk for development of clinical TB, including life-threatening and miliary disease, in persons with latent TB who are treated with the TNF-

alpha inhibitors infliximab (*Remicoid*), etanercept (*Enbrel*), and adalimumab (*Humira*). Before beginning therapy with these drugs, tuberculin skin testing and, if positive, initiation of treatment for latent TB infection, is recommended ([MMWR Morbid Mortal Wkly Rep 2004; 53:683](#); [KL Wintrop and JN Siegel, Clin Infect Dis 2004; 39:1256](#)).

Isoniazid – Isoniazid is the drug of choice for treatment of latent TB infection. It should be given for 9 months in a single daily dose of 300 mg for adults and 10 mg/kg (max 300 mg/day) for children, or twice weekly as 10-15 mg/kg (max 900 mg/dose) in adults and 20-30 mg/kg (max 900 mg/dose) in children ([MMWR Morb Mortal Wkly Rep 2000; 49 RR-6:1](#)). It is safe for treatment of latent TB in pregnancy ([G Bothamley, Drug Saf 2001; 24:553](#)).

Alternatives – Another possible regimen for treatment of latent TB is daily rifampin alone for 4 months, which may be useful in persons intolerant to isoniazid or those found to be tuberculin-positive after exposure to patients with organisms resistant to isoniazid ([LB Reichman et al, Am J Respir Crit Care Med 2004; 170:832](#)). The combination of rifampin and pyrazinamide for 2 months, which formerly was used as an alternative to isoniazid treatment of latent infection, should not be given because of its association with potentially lethal hepatotoxicity ([MMWR Morbid Mortal Wkly Rep 2003; 52:735](#)).

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First-Line Drugs

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

*Intermittent therapy is usually begun after a few weeks or months of treatment with a daily regimen.

1. Pyridoxine 10 to 25 mg should be given to prevent neuropathy in malnourished or pregnant patients and those with HIV infection, alcoholism or diabetes.
2. For use with amprenavir, fosamprenavir, nelfinavir or indinavir, the rifabutin dose is 150 mg/day or 300 mg 2-3 times a week. For use with atazanavir, ritonavir alone or combined with other protease inhibitors and lopinavir/ritonavir, 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 450-600 mg/day or 600 mg 2-3 times weekly. No dose adjustment is needed for use with nevirapine.
3. 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 diminished.

MDR-TB – For patients with known exposure to multi-drug resistant TB (MDR-TB) and a high risk of developing active TB, there are no data-based recommendations. Regimens with two drugs to which the organism is susceptible (e.g., pyrazinamide plus ethambutol or a fluoroquinolone for 9 to 12 months) have been used, but may be poorly tolerated ([J Papastavros et al, CMAJ 2002; 167:131](#); [R Ridzon et al, Clin Infect Dis 1997; 24:1264](#)).

DIRECTLY OBSERVED THERAPY

In treating TB, poor adherence to therapy is the most important cause of treatment failure and is associated with emergence of drug resistance. Medical Letter consultants recommend that almost all patients, including those with infection due to susceptible strains, take drugs for TB under direct observation (“directly observed therapy” or DOT). DOT has been shown to improve cure rates when compared to self-administered regimens ([RM Jasmer et al, Am J Respir Crit Care Med 2004; 170:561](#)). Due to the complexity and duration of treatment regimens, DOT is particularly important for treatment of patients with MDR-TB and for patients on intermittent regimens. DOT services are available through most local and state health department TB programs.

TREATMENT OF SUSCEPTIBLE TB

All isolates of *Mycobacterium tuberculosis* should be tested for antimicrobial susceptibility, but results generally do not become available for at least 2 weeks and sometimes much longer ([GL Woods, Infect Dis Clin North Am 2002; 16:127](#)). Standard therapy for TB includes a 2-month initial phase of treatment and a continuation phase of either 4 or 7 months, depending on the results of sputum cultures at 2 months. Among the drugs used for treatment of TB, effectiveness is best documented for regimens containing isoniazid and rifampin.

Empiric Initial Therapy – Until susceptibility results are available, empiric initial treatment consists of a 4-drug regimen of isoniazid, rifampin, pyrazinamide and ethambutol ([ED Chan and MD Iseman, BMJ 2002; 325:1282](#)). Patients who cannot take pyrazinamide, such as those who have severe liver disease or gout, should receive empiric initial therapy with isoniazid, rifampin and ethambutol.

Susceptible Organisms – When infection proves to be caused by a fully susceptible strain of TB, the initial phase of treatment should include isoniazid, rifampin and pyrazinamide. If pulmonary cavitation is not pres-

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ent on the initial chest X-ray and the patient has a negative AFB smear at 2 months, isoniazid plus rifampin or rifapentine, a long-acting rifamycin, can be given for the next 4 months (continuation phase) to complete a total of 6 months. For patients with a positive AFB culture at 2 months and cavitary lung disease, continuation therapy with isoniazid and rifampin is extended to 7 months (for a total duration of therapy of 9 months). Rifampin, not rifapentine, should be used for continuation therapy if there is cavitary lung disease, a positive AFB smear at 2 months, coinfection with HIV, extrapulmonary disease, or infection in children.

Disseminated TB, tuberculous meningitis and infections in children are usually treated for a total of 9-12 months. Osteomyelitis is usually treated for 6-9 months. Addition of a corticosteroid for 1-2 months is recommended for tuberculous pericarditis or meningitis (GE Thwaites et al, N Engl J Med 2004; 351:1741).

Duration of Continuation Therapy

Cavity on Chest X-ray	Results at 2 mos		Drugs	Duration (months)
	AFB smear	AFB culture		
No	-	-	INH/RIF	4
		+	INH/RIF or INH/RPT	4 7
No	-	+	INH/RIF	4
		+	INH/RIF	4
Yes	+	-	INH/RIF	4
Yes	+	+	INH/RIF	7

INH = isoniazid; RIF = rifampin; RPT = rifapentine

Drug Intolerance – For patients who cannot tolerate rifampin, alternative regimens include 9-12 months of isoniazid, ethambutol and pyrazinamide, with or without a fluoroquinolone (usually levofloxacin, moxifloxacin, or gatifloxacin); 18 months of isoniazid plus ethambutol has also been given. Rifabutin has been substituted for rifampin in standard regimens for some patients who could not take rifampin because of drug interactions (SV Goldberg et al, Clin Infect Dis 2003; 37:607; A Lopez-Montes et al, Am J Kidney Dis 2004; 44:e59). Patients who cannot take pyrazinamide in the initial phase of treatment should receive continuation therapy with isoniazid and rifampin for a total of 7 months.

Intermittent Treatment – Intermittent 4-drug regimens with 2 or 3 doses per week after at least 2 weeks of daily therapy are also effective for treatment of TB and should always be given by DOT. Once-weekly continuation-therapy regimens including rifapentine (instead of rifampin), started after 2 months of standard initial therapy, may also be effective for susceptible TB

(Tuberculosis Trials Consortium, Lancet 2002; 360:528), but the optimal rifapentine dose is not clear, and these regimens have been associated with development of resistance (M Weiner et al, Am J Respir Crit Care Med 2004; 169:1191; FM Gordin, Am J Respir Crit Care Med 2004; 169:1176). Intermittent treatment should never be used for treatment of drug-resistant TB.

Combination Drugs

Drug	Daily adult dosage
<i>Rifamate</i> ¹ (isoniazid 150 mg, rifampin 300 mg)	2 capsules
<i>Rifater</i> 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 10 to 25 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 total daily dose of 20-25 mg/kg/d.

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 (B Blomberg and B Fourie, Drugs 2003; 63:535).

TREATMENT OF RESISTANT TB

Resistance to Isoniazid – The most common pattern of resistance is isolated resistance to isoniazid, which can be treated with rifampin, pyrazinamide and ethambutol for 6-9 months. A quinolone is often added if there is extensive disease; streptomycin is an alternative to ethambutol. Patients who cannot tolerate pyrazinamide can take rifampin and ethambutol for 12 months.

Multidrug Resistance – Treatment of MDRTB is based on limited data; patients should be referred, if possible, to clinicians who have experience in treating such cases. MDRTB (resistant at least to isoniazid and rifampin) should be treated with ≥ 4 drugs to which the organism is susceptible. Three drugs are usually given by mouth, the fourth by injection. When MDRTB is likely, or in patients with a history of previous treatment for TB, some clinicians start with combinations of 5, 6 or 7 drugs before laboratory susceptibility data are available.

Typically, empiric therapy for suspected MDRTB includes isoniazid, rifampin, ethambutol, pyrazi-

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 (<i>Capastat</i>)	15 mg/kg IM (max 1 g)	15-30 mg/kg	Auditory and vestibular toxicity, renal damage
Kanamycin (<i>Kantrex</i> , and others)	15 mg/kg IM, IV (max 1 g)	15-30 mg/kg	Auditory toxicity, renal damage
Amikacin (<i>Amikin</i>)	15 mg/kg IM, IV (max 1 g)	15-30 mg/kg	Auditory toxicity, renal damage
Cycloserine ² (<i>Seromycin</i> , and others)	10-15 mg/kg in 2 doses (max 500 mg bid) PO	10-15 mg/kg	Psychiatric symptoms, seizures
Ethionamide (<i>Trecator-SC</i>)	15-20 mg/kg in 2 doses (max 500 mg bid) PO	15-20 mg/kg	GI and hepatic toxicity, hypothyroidism
Ciprofloxacin (<i>Cipro</i> , and others)	750-1500 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Ofloxacin (<i>Floxin</i>)	600-800 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Levofloxacin (<i>Levaquin</i>)	500-1000 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Gatifloxacin ³ (<i>Tequin</i>)	400 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Moxifloxacin ³ (<i>Avelox</i>)	400 mg PO, IV	Not recommended	Nausea, abdominal pain, restlessness, confusion
Aminosalicylic acid (<i>PAS</i> ; <i>Paser</i>)	8-12 g in 2-3 doses PO	200-300 mg/kg, in 2-4 doses	GI disturbance

1. When oral drugs are given daily, streptomycin is generally given 5 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. No published clinical data on dosage for tuberculosis.

namide, an aminoglycoside (streptomycin, kanamycin or amikacin) or capreomycin, a fluoroquinolone (usually levofloxacin, moxifloxacin or gatifloxacin), and either cycloserine, ethionamide or aminosalicylic acid (PAS) (JB Nachega and RE Chaisson, *Clin Infect Dis* 2003; 36 suppl 1:S24; JS Mukherjee et al, *Lancet* 2004; 363:474). Even when susceptibility is confirmed, the regimen should include at least 4 active drugs.

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 (ED Chan et al, *Am J Respir Crit Care Med* 2004; 169:1103).

HIV-INFECTED PATIENTS

Because TB therapy is complicated by co-infection with HIV, testing for HIV infection is recommended for all patients with active tuberculosis. To minimize the risk of resistance, treatment in the continuation phase should be given once daily or three times weekly (MMWR Morbid Mortal Wkly Rep 2002; 51:214). Twice weekly regimens should not be given to patients with CD4 cell counts <100 cells/mm³ because they

have been associated with rifamycin resistance (RE Nettles et al, *Clin Infect Dis* 2004; 38:731). Rifapentine is not recommended for TB treatment in HIV-infected patients because it has been associated with development of rifamycin resistance (A Vernon et al, *Lancet* 1999; 353:1843).

Patients Not on HAART – For HIV-infected patients requiring TB treatment who are not currently being treated with highly active anti-retroviral therapy (HAART), it may be prudent to delay HAART (particularly in patients with CD4 cell counts above 100 cells/mm³) for 2 or more months in order to avoid a paradoxical worsening of TB due to immune reconstitution, decrease the risk of overlapping drug adverse effects and interactions, and enhance adherence to both drug regimens (GL Dean et al, *AIDS* 2002; 16:75; DB Pedial-Sampaio et al, *AIDS* 2002; 16:1845). The optimal timing for initiating HAART in patients with newly diagnosed TB is not known.

Patients on HAART – Rifamycins induce hepatic CYP3A4 enzymes 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 activates CYP3A4 dif-

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fers: rifampin is the most potent and rifabutin the least. In addition, rifabutin is a substrate for CYP3A4; protease inhibitors slow its metabolism, increasing serum concentrations and possibly toxicity.

Options with Rifampin – 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 either ritonavir (*Norvir*), ritonavir/saquinavir or ritonavir/lopinavir (*Kaletra*) as the protease inhibitor, combined with 2 NRTIs. Nevirapine (*Viramune*) with two NRTIs can also be given with standard dose rifampin (*MMWR Morbid Mortal Wkly Rep* 2004; 53:37).

Options with Rifabutin – Two alternative regimens are based on the fact that rifabutin appears to be as effective as rifampin against TB, and has less effect on protease inhibitor levels. The first substitutes low-dose rifabutin (150 mg once/day or 300 mg 3x/week) for rifampin in the standard 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 protease inhibitor. The second decreases the rifabutin dose further to 150 mg every other day or 3 times weekly and gives it with standard doses of atazanavir (*Reyataz*), ritonavir/lopinavir (*Kaletra*) or ritonavir alone or combined with other protease inhibitors. Saquinavir (*Fortovase, Invirase*) alone should not be used. If the HAART regimen contains nevirapine, the usual dose of rifabutin should be used. Higher rifabutin doses (450-600 mg daily) are needed if the HAART regimen contains efavirenz.

TB IN PREGNANCY

Treatment of TB should be initiated in pregnancy when there is moderate to high suspicion of disease because active infection during pregnancy poses a risk to the fetus that is 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 is also probably safe in pregnancy and some Medical Letter consultants would use it in addition to or as a substitute for ethambutol, depending on results of susceptibility testing (*G Bothamlen, Drug Saf* 2001; 24:553). If pyrazinamide is not used, treatment should be continued for at least 9 months.

Limited data is available on the treatment of MDRTB in pregnancy. Regimens using combinations of

amikacin, ethionamide, PAS, cycloserine, capreomycin and fluoroquinolones have been successful without causing fetal adverse effects, although these drugs are not generally considered safe in pregnancy (*S Shin et al, Clin Infect Dis* 2003; 36:996; *KD Lessnau and S Qarah, Chest* 2003; 123:953).

ADVERSE EFFECTS

Isoniazid – Serum aminotransferase activity increases in 10% to 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 (*CM Nolan et al, JAMA* 1999; 281:1014). It is more likely to occur in patients more than 35 years old, but can also occur in younger patients. Routine monitoring is not necessary except for patients with pre-existing liver disease. Medical Letter consultants recommend stopping isoniazid when serum aspartate aminotransferase activity reaches five times the upper limit of normal or if the patient has symptoms of hepatitis, but it can sometimes be restarted later.

Peripheral neuropathy occurs rarely and can usually be prevented by supplementation with pyridoxine (Vitamin B₆, 10-25 mg/day), which is recommended for patients with chronic alcohol use, diabetes, chronic renal failure or HIV infection, and for those who are pregnant, breast feeding or malnourished.

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 oral contraceptives (patients should be advised to use another method of contraception), sulfonyleureas such as glyburide (*Diabeta*, and others), corticosteroids, warfarin (*Coumadin*, and others), quinidine, methadone (*Dolophine*, and others), delavirdine (*Rescriptor*), clarithromycin (*Biaxin*), ketoconazole (*Nizoral*, and others), itraconazole (*Sporanox*) and fluconazole (*Diflucan*), as well as pro-

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tease inhibitors (Medical Letter Adverse Drug Interactions Program).

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

Other Drugs – Pyrazinamide can cause morbilliform rash, arthralgias and asymptomatic hyperuricemia, and blocks the hypouricemic action of allopurinol (*Zyloprim*, and others). Gastrointestinal disturbances and hepatotoxicity can occur. **Ethambutol** can cause optic neuritis, but this is very rare when using a dosage of 15 mg/kg daily. Testing of visual acuity should be performed at the start of therapy, and monthly if the drug is continued past 2 months. 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.

Streptomycin causes ototoxicity (usually vestibular disturbance) and, less frequently, renal toxicity. **Amikacin** and **kanamycin** commonly cause tinnitus and high frequency hearing loss. These drugs and **capreomycin** can also cause nephro- 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, *Paser*) is better tolerated than older formulations. **Fluoroquinolones** are usually well-tolerated, but can cause gastrointestinal and CNS disturbances.

CONCLUSION

All isolates of *M. tuberculosis* should be tested for antimicrobial susceptibility. Initial therapy for most patients with active TB should include at least isoniazid, a rifamycin, pyrazinamide and ethambutol until susceptibility is known. Directly observed therapy

(DOT) by a health care worker should be considered for all cases of active TB to minimize failure rates and the risk of emergence of drug resistance. Confirmed multidrug-resistant tuberculosis (MDRTB) should be treated with DOT and a regimen that includes at least 4 drugs to which the organism is susceptible; the total duration of therapy usually is 18 to 24 months.

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