Treatment Guidelines
from The Medical Letter®

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Drugs for Tuberculosis

RECOMMENDATIONS: The standard treatment for latent tuberculosis is nine months of isoniazid taken daily, or twice weekly under direct observation by a healthcare worker. Taking isoniazid and rifapentine once weekly for 12 weeks under direct observation is an alternative for patients ≥12 years old.

Initial therapy for patients with active or suspected tuberculosis should include isoniazid, rifampin, pyrazinamide and ethambutol until susceptibility is known. In patients with drug-susceptible pulmonary tuberculosis, the continuation phase of treatment should be a combination of isoniazid and either rifampin or rifapentine, taken for 4 or 7 months depending on risk factors.

Confirmed multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis should be treated with directly observed therapy in collaboration with a clinician familiar with management of these conditions. Treatment must include at least 4 drugs to which the organism is susceptible; the duration of therapy should usually be 18-24 months.

Directly observed therapy by a healthcare worker should be offered to all patients with active tuberculosis to minimize treatment failure, relapse and the emergence of drug resistance.

Tuberculosis (TB) is still a common cause of death worldwide, and the prevalence of drug-resistant TB poses challenges to its treatment and control.[1-3] Guidelines with detailed management recommendations are available from the American Thoracic Society, Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA).[4]

DIRECTLY OBSERVED THERAPY (DOT)

Poor adherence to TB therapy is the most common cause of treatment failure and can lead to drug resistance. Medical Letter consultants recommend that most patients, including those with disease due to drug-susceptible strains, take drugs for active TB under direct observation. Directly observed therapy (DOT) services are available through most local and state health departments. DOT is particularly important for children, patients with disease due to drug-resistant strains, those with HIV infection or other causes of immunosuppression, and those receiving intermittent regimens.[5]

LATENT TB INFECTION (LTBI)

Treatment of latent TB infection (LTBI) is recommended for patients at increased risk for developing active disease, such as those co-infected with HIV or receiving immunosuppressive therapy, children <5 years old, those with diabetes or chronic renal failure on hemodialysis, close contacts of patients with recent pulmonary TB, or those who have converted from a negative to a positive tuberculin skin test (PPD) or interferon-gamma release assay (IGRA) within the previous 2 years.[6,7] The risk of serious disease, including miliary TB and tuberculous meningitis, is highest among patients with HIV infection. Infants, the elderly, and patients with other causes of severe immunosuppression are also at increased risk. Treatment for LTBI should be started only if clinical and radiographic evaluations exclude active TB infection.

Risk of Immunomodulating Drugs – Recent reports indicate that patients with LTBI who are treated with a **TNF-alpha inhibitor** such as infliximab *(Remicade)*, etanercept *(Enbrel)*, adalimumab *(Humira)*, certolizumab pegol *(Cimzia)* or golimumab *(Simponi)* are at high risk for development of active TB disease.

These reports include cases of extrapulmonary and disseminated disease and death. Infliximab and adalimumab appear to be associated with a higher risk than etanercept, and with a shorter time to onset of active disease.[8-10] Patients should be screened for LTBI before starting a TNF inhibitor; if found to have LTBI, they should begin antituberculosis treatment before starting the TNF inhibitor. Whether antituberculosis treatment needs to be completed before TNF inhibitor therapy can begin is controversial.

Patients preparing to receive a **solid organ transplant** should also be screened for TB infection. Treatment for LTBI should be considered for patients with a positive PPD or IGRA once active TB is ruled out by clinical evaluation and chest radiograph.[11] Treatment should start before transplantation and, if not completed, be continued afterward. However, given the risk of drug interactions and hepatotoxicity, it is often preferable to complete LTBI treatment before transplantation.

Treatment – Isoniazid (INH) is the standard treatment for LTBI presumed to be due to drug-susceptible strains. It can be given daily, or intermittently by DOT.[7] The preferred duration of treatment with isoniazid is 9 months. Six months' treatment may be effective and could be considered for adult patients unable to take the drug for 9 months. Isoniazid taken for 9 months is the preferred regimen for children 2-11 years old.

A combination of **isoniazid and rifapentine** given weekly for 12 weeks by DOT is an equal alternative to 9 months of isoniazid for treatment of LTBI in patients ≥12 years old, including HIV-infected patients not taking antiretrovirals.[12] It is not recommended for HIV-infected patients taking antiretroviral drugs, pregnant women (or those expecting to become pregnant), children <2 years old, or patients infected with suspected isoniazid- and/or rifampin-resistant isolates.[13,14]

Another alternative regimen, particularly for patients intolerant to isoniazid or those exposed to isoniazid-resistant organisms, is daily **rifampin** alone for 4 months (6 months in children). The efficacy of this shorter regimen compared to 9 months of isoniazid has not been established, but it has improved adherence and may have fewer adverse effects.[15,16]

Multidrug-Resistant LTBI – There are no data-based recommendations for treatment of LTBI in high-risk patients with known exposure to multidrug-resistant TB (MDRTB), defined as isolates with resistance to at least isoniazid and rifampin. Regimens with 2 drugs to which the organism is susceptible (e.g., pyrazinamide plus either ethambutol or a fluoroquinolone [levofloxacin or moxifloxacin] for 9-12 months) have been used.[7]

Table 1. Treatment of Latent Tuberculosis

Regimen	Adult Dosage[1]
Isoniazid	5 mg/kg/day (max 300 mg/day) or 15 mg/kg 2x/wk (max 900 mg/dose) x 9 months[2]
Isoniazid + rifapentine[3]	Isoniazid 15 mg/kg (max 900 mg/dose) + rifapentine 300-900 mg[4] weekly x 12 weeks
Rifampin[5]	10 mg/kg/day (max 600 mg/day) or 10 mg/kg 2x/wk (max 600 mg/dose) x 4 months[6]

1. All intermittent regimens should be administered by directly observed therapy (DOT).
2. 6 months' treatment may be effective and can be considered in patients unable to complete 9 months of therapy. Children should be treated for 9 months.
3. For patients ≥12 years old. Not recommended for HIV-infected patients taking antiretroviral drugs, pregnant women, children <2 years old or infection with suspected resistance to isoniazid and/or rifampin.
4. 10-14 kg patient: 300 mg; >14-25 kg: 450 mg; >25-32 kg: 600 mg; >32-<50 kg: 750 mg; ≥50 kg: 900 mg (MMWR 2011; 60:1650).
5. For patients intolerant to isoniazid or for those with exposure to patients with organisms resistant to isoniazid. Generally cannot be taken by HIV-infected persons taking protease inhibitors or certain NNRTIs.
6. For 6 months in children.

Extensively drug-resistant TB (XDRTB), defined as isolates with resistance not only to both isoniazid and rifampin, but also to any fluoroquinolone and at least one of 3 other injectable second-line drugs (i.e., capreomycin, kanamycin or amikacin), is an increasing problem worldwide; there are no data-based recommendations for treatment of LTBI following exposure to XDRTB.[17,18]

ACTIVE TB

Standard treatment of active pulmonary TB that is drug sensitive includes a **2-month initial phase** and a **continuation phase of either 4 or 7 months**, depending on risk factors. Patients should be monitored at least monthly for adverse reactions, adherence and response to treatment.

Initial Therapy – Until susceptibility results are available, empiric initial treatment should include 4 drugs: isoniazid, rifampin, pyrazinamide and ethambutol. When susceptibility to isoniazid, rifampin and pyrazinamide has been documented, ethambutol can be stopped.[4] Patients who cannot take pyrazinamide, such as those with severe liver disease or gout, should take isoniazid, rifampin and ethambutol.

Stopping Immunomodulating Drugs – Immunomodulators, such as TNF-alpha inhibitors, are usually stopped in patients who develop active TB. The timing of restarting the biologic agent while still on TB treatment is controversial; some clinicians wait until the disease improves before restarting.[9]

Continuation Therapy – A repeat sputum smear and culture should be performed when the initial 2 months

Table 2. First-Line Drugs for Treatment of Active Tuberculosis

		Adult Dosage		Pediatric Dosage	
Drug	**Formulations**	**Daily[1]**	**Intermittent[2]**	**Daily[1]**	**Intermittent[2]**
Isoniazid (INH)[3]	100, 300 mg tabs, 50 mg/5mL syrup, 100 mg/mL inj	5 mg/kg (max 300 mg)	15 mg/kg (max 900 mg) 1-3x/wk	10-15 mg/kg (max 300 mg)	20-30 mg/kg (max 900 mg) 2x/wk
Rifampin (*Rifadin, Rimactane*, and others)[4]	150, 300 mg caps, 600 mg inj powder	10 mg/kg (max 600 mg)	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
Rifabutin *(Mycobutin)*	150 mg caps	5 mg/kg (max 300 mg)[5]	5 mg/kg (max 300 mg) 2-3x/wk[5]	No data available	No data available
Rifapentine *(Priftin)*	150 mg tabs	—	10 mg/kg 1x/wk continuation phase (max 600 mg)	Not approved	Not approved
Pyrazinamide	500 mg tabs	40-55 kg: 1000 mg 56-75 kg: 1500 mg 76-90 kg: 2000 mg	2x/wk:[6] 40-55 kg: 2000 mg 56-75 kg: 3000 mg 76-90 kg: 4000 mg	15-30 mg/kg (max 2 g)	50 mg/kg (max 2 g) 2x/wk
Ethambutol (*Myambutol*, and others)	100, 400 mg tabs	40-55 kg: 800 mg 56-75 kg: 1200 mg 76-90 kg: 1600 mg	2x/wk:[7] 40-55 kg: 2000 mg 56-75 kg: 2800 mg 76-90 kg: 4000 mg	15-20 mg/kg[8] (max 1 g)	50 mg/kg (max 2.5 g) 2x/wk[8]

1. Or 5x/wk DOT. DOT is also recommended for children on daily therapy.
2. Intermittent therapy (administered by DOT) is usually begun after a few weeks or months of treatment with a daily regimen.
3. Pyridoxine 25-50 mg should be given to prevent neuropathy in malnourished or pregnant patients and those with HIV infection, renal failure, thyroid disease, alcoholism or diabetes.
4. Generally cannot be taken by HIV-infected persons taking protease inhibitors or certain NNRTIs.
5. When taken with efavirenz, the rifabutin dose is increased to 450 mg/day or 600 mg 2-3 times weekly. When taken with fosamprenavir, nelfinavir or indinavir, the rifabutin dose is 150 mg/day or 300 mg 3 times a week. With lopinavir/ritonavir *(Kaletra)*, ritonavir alone, atazanavir alone or ritonavir combined with other protease inhibitors, the rifabutin dose is 150 mg every other day or 3 times a week; some experts believe this dose to be subtherapeutic and recommend 150 mg daily with close monitoring for rifabutin toxicity, particularly uveitis. Updated recommendations are expected to become available soon from the CDC.
6. For 3x/wk regimen: dose for a 40-55 kg patient = 1500 mg; 56-75 kg = 2500 mg; 76-90 kg = 3000 mg.
7. For 3x/wk regimen: dose for a 40-55 kg patient = 1200 mg; 56-75 kg = 2000 mg; 76-90 kg = 2400 mg.
8. Usually not recommended for children when visual acuity cannot be monitored. Some clinicians use 15 mg/kg/day during first one or two months or longer if organism is isoniazid-resistant. Decrease dosage if renal function is diminished.

of therapy are completed. In patients with drug-susceptible TB, isoniazid and rifampin, taken daily or twice weekly, are generally used for the continuation phase of treatment.

The duration of treatment for pulmonary TB is determined by two factors that can increase the risk of treatment failure and relapse: cavitary disease at presentation and a positive sputum culture taken at 2 months (see Table 4 on page 32). For patients with drug-susceptible isolates and one or none of these risk factors, the duration of the continuation phase should be 4 months. For patients with both risk factors or those unable to take pyrazinamide as part of the initial regimen, the continuation phase should be extended to 7 months.

If sputum cultures remain positive after 4 months of treatment, malabsorption, nonadherence to treatment, or infection with drug-resistant TB should be considered. Treatment duration should be prolonged in such patients. Consultation with local or state public health departments should be sought.

TB **osteomyelitis** is usually treated for at least 6-9 months and tuberculous **meningitis** for at least 9-12 months. Addition of a corticosteroid for 1-2 months should be considered for tuberculous pericarditis or meningitis.[4,19]

Intermittent Treatment – Intermittent 4-drug regimens (isoniazid, pyrazinamide, rifampin, ethambutol) with **2 or 3 doses per week** are effective for treatment of active pulmonary TB. Intermittent therapy is most commonly used in the continuation phase, after 2 months of daily (or 5x/wk) therapy during the initiation phase. It should never be used for treatment of drug-resistant TB. Intermittent regimens should be given by DOT.

A **once-weekly** continuation-therapy regimen of isoniazid plus rifapentine, started after 2 months of standard initial therapy, can be used for HIV-negative patients with non-cavitary drug-susceptible TB.[4,20] This regimen has been associated with development of rifamycin resistance in patients with HIV and should not be used in such patients.[4] It is also not recommended for use in children, pregnant women, patients with extrapulmonary TB, or in those with unknown drug susceptibility.

Twice-weekly intermittent regimens have also been associated with rifamycin resistance in HIV co-infect-

Table 3. Duration of Continuation Therapy[1]

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

INH = Isoniazid; RIF = rifampin; RPT = rifapentine
1. For treatment of drug-susceptible disease after two months of initial therapy.
2. 7 months for patients who could not take pyrazinamide as part of the initial regimen.
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 taken at 2 months is positive and the patient is taking INH/RPT, some expert clinicians would switch to INH/RIF.

ed patients with low CD4 counts; such patients should receive daily TB therapy initially and continuation therapy with a daily or 3x/wk regimen.[21] **Three-times-weekly** continuation regimens may be preferable for other immunocompromised patients and for patients with cavitary disease.[22]

Culture-Negative TB – In the absence of another diagnosis, patients with evidence of pulmonary TB, 3 negative sputum cultures for *Mycobacterium tuberculosis* before treatment, and clinical improvement or radiographic response with treatment can be considered to have "culture-negative TB". In these patients, the continuation phase with isoniazid and rifampin can be shortened to 2 months.

Drug Intolerance – Adverse effects from first-line anti-TB drugs are common, particularly during the first few weeks of treatment.[4] Drug-induced hepatitis is the most common serious adverse effect of the first-line drugs. Pyrazinamide is probably the most hepatotoxic.[23] If hepatitis (serum AST ≥3x the upper limit of normal with symptoms or ≥5x the upper limit of normal with or without symptoms) occurs during the initial phase of treatment, isoniazid, pyrazinamide and rifampin should be stopped. When serum AST levels decrease to <2x the upper limit of normal and symptoms improve, rifampin, isoniazid, pyrazinamide can be restarted sequentially, one week apart.[4,24]

Rifabutin has been substituted for rifampin in standard regimens for some patients who could not take rifampin because of intolerance or unacceptable drug interactions (such as HIV co-infected patients on a protease inhibitor or some non-nucleoside reverse transcriptase inhibitors [NNRTIs], or patients with solid organ transplants).[11,25]

Patients who are unable to tolerate isoniazid or a rifamycin should receive the same regimen used to treat strains resistant to those drugs (see Drug-Resistant Active TB below). When patients are unable to tolerate ≥2 first-line drugs, they should be treated as if they have MDRTB.

DRUG-RESISTANT ACTIVE TB

Resistance to Isoniazid – Patients with pulmonary TB resistant to isoniazid can be treated with rifampin, pyrazinamide and ethambutol for 6 months. Those who cannot tolerate pyrazinamide can take rifampin and ethambutol for 12 months. A fluoroquinolone (levofloxacin or moxifloxacin) is sometimes added, especially if the patient cannot tolerate pyrazinamide or if there is extensive disease. Fluoroquinolones are well tolerated in patients with drug-induced hepatic dysfunction.[26] Moxifloxacin may be more active *in vitro* than levofloxacin against *M. tuberculosis*, but clinical data are limited, and levofloxacin has a longer safety record.[4]

Resistance to Rifamycins – For patients with rifamycin resistance, at least 12 months of treatment with isoniazid, ethambutol and a fluoroquinolone (levofloxacin or moxifloxacin) can be used. Pyrazinamide, with or without an injectable drug, should also be used during the initial 2 months of therapy.

Multidrug Resistance – Recommendations for treatment of MDRTB (isolates with resistance to at least isoniazid and rifampin) and XDRTB (isolates with resistance not only to isoniazid and rifampin, but also to any fluoroquinolone and at least one of three injectable second-line drugs [i.e., amikacin, kanamycin or capreomycin]) are based on limited data. MDRTB and XDRTB should be treated with daily (not intermittent) DOT therapy.

Empiric therapy for suspected MDRTB often includes isoniazid, rifampin, ethambutol, pyrazinamide, an aminoglycoside (streptomycin, kanamycin or amikacin) or capreomycin, a fluoroquinolone and, if needed, cycloserine, ethionamide and/or p-aminosalicylic acid (PAS).[27] Once susceptibility data are available, the regimen should include all active first-line drugs (e.g., pyrazinamide, ethambutol), a fluoroquinolone and one injectable drug (≥4 drugs total).[28]

Treatment options for XDRTB are even more limited and usually all drugs to which the organism is susceptible are used.[29] Linezolid *(Zyvox)*, used in combination with other anti-TB drugs, appears to have some efficacy, but clinical trial data are lacking and adverse effects, particularly myelosuppression, peripheral neuropathy and optic neuropathy, can occur with prolonged use.[30]

Table 4. Some Second-Line Drugs for Active Tuberculosis

Drug	Daily Adult Dosage[1]	Daily Pediatric Dosage	Main Adverse Effects
Streptomycin[2]	15 mg/kg IM or IV (max 1 g)	20-40 mg/kg (max 1 g)	Vestibular and ototoxicity, renal damage
Capreomycin *(Capastat)*[2]	15 mg/kg IM or IV (max 1 g)	15-30 mg/kg (max 1 g)	Auditory and vestibular toxicity, renal damage, electrolyte disturbances
Kanamycin (*Kantrex,* and others)[2]	15 mg/kg IM or IV (max 1 g)	15-30 mg/kg (max 1 g)	Ototoxicity, renal damage
Amikacin (*Amikin,* and others)[2]	15 mg/kg IM or IV (max 1 g)	15-30 mg/kg (max 1 g)	Ototoxicity, renal damage
Cycloserine (*Seromycin*)[3]	10-15 mg/kg PO (max 500 mg bid)	10-15 mg/kg (max 1 g)	Psychiatric symptoms, seizures
Ethionamide *(Trecator)*	15-20 mg/kg in 1 or 2 divided doses PO (max 500 mg bid)	15-20 mg/kg (max 1 g)	GI and hepatic toxicity, neurotoxicity, hypothyroidism, optic neuritis
Levofloxacin (*Levaquin,* and others)	500-1000 mg PO or IV	See footnote 4	GI toxicity, CNS effects, rash, dysglycemia, tendonitis or tendon rupture, QT prolongation
Moxifloxacin *(Avelox)*	400 mg PO or IV	See footnote 4	GI toxicity, CNS effects, rash, tendonitis or tendon rupture, QT prolongation, dysglycemia
Para-aminosalicylic acid (PAS; *Paser*)	8-12 g in 2-3 doses PO	200-300 mg/kg, divided in 2-4 doses (max 10 g)	GI disturbance, hepatitis, hypothyroidism

1. Dosage may need to be adjusted for renal impairment.
2. Generally given 5-7 times per week (15 mg/kg, or a maximum of 1 g per dose) for an initial 2 to 4 months, 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 (max 750 mg per dose). Dosage should be decreased if renal function is diminished.
3. Some authorities recommend pyridoxine 50 mg for every 250 mg of cycloserine to decrease the incidence of adverse neurological effects.
4. 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, such as MDRTB. The optimal dose is not known.

Monthly bacteriologic results (smear and culture) should be monitored and treatment continued for 18-24 months, or at least for 18 months after the culture becomes negative. Most experts recommend that the parenteral drug be continued for at least 6 months after culture conversion. Surgical resection has improved outcomes in some patients and should be considered if cultures fail to become negative after 3-4 months of appropriate treatment.[31]

HIV-INFECTED PATIENTS

Testing for HIV infection is recommended for all patients with TB. Persons with HIV, once infected with *M. tuberculosis*, are at markedly increased risk of developing active TB disease. HIV-infected patients with a history of prior untreated or inadequately treated TB should be evaluated for active disease regardless of results of tests for LTBI. If active TB disease is ruled out, patients should receive treatment for LTBI. HIV-infected persons who have had recent close contact with a patient with active TB disease should receive empiric treatment for LTBI regardless of results of tests for TB infection or history of previous treatment.[7]

Daily isoniazid for 9 months is the preferred treatment for **LTBI** in co-infected patients. Once-weekly isoniazid/rifapentine for 12 weeks is an alternative for HIV-infected patients who are not taking antiretroviral drugs.[13]

Patients on Antiretroviral Therapy (ART) – A rifamycin-based anti-TB regimen should be used if at all possible for treatment of **active disease**. However, rifamycins induce hepatic CYP450 enzymes, especially CYP3A4, and can accelerate the metabolism of protease inhibitors and some NNRTIs, possibly decreasing their serum concentrations to ineffective levels. The degree to which each drug induces CYP3A4 differs: rifampin is the most potent and rifabutin the least. In general, rifampin should not be used with protease inhibitors.[4,32]

Alternative regimens are based on rifabutin, which appears to be as effective as rifampin against TB and has less effect on protease inhibitor concentrations. Rifabutin is, however, a substrate of CYP3A4; protease inhibitors can decrease its metabolism, possibly increasing serum concentrations of rifabutin to toxic levels. CYP3A4 inducers, such as efavirenz, can increase rifabutin's metabolism, possibly resulting in loss of efficacy.[32]

To minimize the emergence of drug-resistant TB, co-infected patients in the **continuation phase** of TB treat-

ment should take medication once daily, or three times weekly with DOT. In patients with CD4 cell counts <100 cells/mm^3, twice-weekly regimens have been associated with acquisition of rifamycin resistance.[33]

Patients Not on ART – Starting ART during anti-TB therapy can improve survival and virologic outcome.[34] In patients with CD4 counts <50 cells/mm^3, initiation of ART as soon as possible after initiation of TB treatment can decrease the risk of HIV-associated infections or death,[35] but the incidence of adverse events and the risk of immune reconstitution inflammatory syndrome (IRIS) are increased during early co-administration.[36-39] Patients with higher CD4 counts (>50 cells/mm^3) or TB meningitis should probably wait until after the initial phase of TB treatment to begin ART in order to reduce the risk of adverse events and IRIS.[40] Using fixed-dose combinations in the ART regimen along with fixed-dose anti-TB drugs may facilitate adherence.

Table 5. Fixed-Dose Combinations

Drug	Strength
Isoniazid/pyrazinamide/rifampin *Rifater*[1] (Sanofi)	50/300/120 mg tabs
Isoniazid/rifampin *Rifamate* (Sanofi),[2] and others	150/300 mg caps

1. FDA-approved for daily use during initial 2 months of treatment for active TB.
2. FDA-approved for daily use after initial 2 months of treatment for active TB.

TB IN PREGNANCY

The treatment of TB during pregnancy is problematic because of the risk of hepatotoxicity and the scarcity of data on the risk of teratogenicity. In general, it is recommended that treatment for **LTBI** be delayed until 2 to 3 months after delivery. However, for women who are HIV-positive or have been recently infected with TB (e.g. close contacts of infectious cases or recent PPD or IGRA convertors), initiation of therapy should not be delayed.

Treatment of **active TB** disease should be initiated during pregnancy when there is a moderate to high suspicion of disease because the risk of tuberculosis 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 are known to be teratogenic. Pyrazinamide has not been extensively studied in pregnancy, but is generally considered to be safe.[41,42] If pyrazinamide is not used, treatment should be extended for a total of at least 9 months.

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.[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 older patients. Clinical monitoring should occur at least monthly. Monitoring of serum transaminases is recommended for patients with pre-existing liver disease or abnormal baseline ALT, those who drink alcohol regularly or take other hepatotoxic drugs, HIV-infected patients treated with ART, and for women who are pregnant or <3 months postpartum. Some experts also recommend monitoring of otherwise healthy patients >35 years old and of all patients during initial therapy for active disease.

Isoniazid should be stopped if serum aminotransferase activity reaches five times the upper limit of normal or three times the upper limit of normal if the patient has symptoms of hepatitis. In patients with active TB disease, it can often be restarted later.[24,44] Rechallenge with isoniazid is not recommended for patients with LTBI.

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 reviewers 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 is potentially hepatotoxic. GI disturbances, morbilliform rash and thrombocytopenia 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 a potent inducer of multiple CYP isozymes (3A4, 2C9, 2C19, 2B6 and 2C8). It can increase the metabolism and decrease the effect of many other drugs. **Rifabutin** is less likely than rifampin to interact with other drugs.

Rifabutin and **rifapentine** have adverse effects similar to those of rifampin. At higher doses, rifabutin can also cause uveitis, skin hyperpigmentation and neutropenia.

Other Drugs – Pyrazinamide can cause severe and prolonged hepatotoxicity, gastrointestinal disturbances, arthralgias and hyperuricemia, and can block the hypouricemic action of allopurinol. It is the most common cause of drug rash among the first-line agents; some patients are able to continue the drug despite the rash.

Ethambutol can cause optic neuritis, but only very rarely when using a dosage of 15 mg/kg daily. Testing of visual acuity and color perception (differentiation between red and green) 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 ototoxicity. Capreomycin in particular can cause severe electrolyte disturbances.

Cycloserine can cause psychiatric symptoms and seizures. **Ethionamide** has been associated with gastrointestinal, hepatic, thyroid and neurological toxicity. A delayed-release granular formulation of **p-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. Fluoroquinolones are associated with an increased risk of tendonitis and tendon rupture; this risk is further increased in patients over 60 years of age, in patients taking corticosteroid drugs and in those with kidney, heart or lung transplants.[46] QT interval prolongation can occur, particularly with moxifloxacin.

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The expected outcome of the CME Program is to increase the participant's ability to know, or apply knowledge into practice after assimilating, information presented in materials contained in *Treatment Guidelines*.

The Medical Letter will strive to continually improve the CME program through periodic assessment of the program and activities. The Medical Letter aims to be a leader in supporting the professional development of healthcare professionals through Core Competencies by providing continuing medical education that is unbiased and free of industry influence. The Medical Letter is supported solely by subscription fees and accepts no advertising, grants or donations.

GOAL:
Through this program, The Medical Letter expects to provide the healthcare community with unbiased, reliable and timely educational content that they will use to make independent and informed therapeutic choices in their practice.

LEARNING OBJECTIVES:
The objective of this activity is to meet the need of healthcare professionals for unbiased, reliable and timely information on treatment of major diseases. The Medical Letter expects to provide the healthcare community with educational content that they will use to make independent and informed therapeutic choices in their practice. Participants will be able to select and prescribe, or confirm the appropriateness of the prescribed usage of the drugs and other therapeutic modalities discussed in *Treatment Guidelines* with specific attention to clinical evidence of effectiveness, adverse effects and patient management.

Upon completion of this program, the participant will be to:

1. Explain the current approach to the management of a patient with latent tuberculosis infection or active disease.
2. Discuss the pharmacologic options and treatment regimens available for patients with latent tuberculosis infection or active disease and compare them based on their efficacy, dosage and administration, potential adverse effects and drug interactions.
3. Determine the most appropriate therapy given the clinical presentation of an individual patient.

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Issue 116 Questions

1. Patients with latent TB infection at increased risk for developing active disease include:
   a. those co-infected with HIV
   b. children <5 years old
   c. those who have diabetes
   d. all of the above

   Issue 116

2. A 34-year-old man has recently been diagnosed with Crohn's disease. Before starting infliximab therapy, which of the following would you suggest?
   a. screening for latent TB infection prior to starting infliximab
   b. starting TNF-alpha inhibitor therapy before screening for latent TB infection
   c. starting antituberculosis treatment before screening for latent TB infection
   d. none of the above

   Issue 116

3. The drug of choice for treatment of latent TB infection is:
   a. pyrazinamide
   b. rifampin
   c. ethambutol
   d. isoniazid

   Issue 116

4. An equally effective alternative to 9 months of isoniazid for treatment of latent TB infection in otherwise healthy patients ≥12 years old is twelve weeks of once-weekly:
   a. isoniazid plus rifapentine
   b. ethambutol
   c. isoniazid plus pyrazinamide
   d. moxifloxacin

   Issue 116

5. Standard empiric initial treatment of active TB should include:
   a. rifampin
   b. pyrazinamide
   c. isoniazid
   d. all of the above

   Issue 116

6. A 59-year-old woman has evidence of pulmonary disease, but 3 sputum cultures that were taken before she started treatment for active TB were negative for *Mycobacterium tuberculosis*. She is improving on treatment and has no other diagnosis to explain her symptoms. She asks if she should receive 4 months of continuation therapy with isoniazid and rifampin. You could tell her that:
   a. she should receive 4 months of continuation therapy with isoniazid and rifampin
   b. she could have her continuation therapy shortened to 2 months
   c. she can stop taking all her medications after 2 months of initial therapy
   d. she should receive 8-12 months of isoniazid and rifampin

   Issue 116

7. Intermittent regimens for active TB disease:
   a. should only be administered during the initial phase of treatment
   b. should be used only for patients with HIV infection
   c. should be administered as directly observed therapy
   d. none of the above

   Issue 116

8. Active TB resistant to isoniazid can be treated with:
   a. rifampin, pyrazinamide and ethambutol for a total 2 months
   b. rifampin and ethambutol for a total of 6 months
   c. moxifloxacin for a total of 4 months
   d. rifampin, pyrazinamide and ethambutol for a total of 6 months

   Issue 116

9. Multidrug-resistant TB and extensively drug-resistant TB should be treated with at least:
   a. ≥6 drugs to which the organism is susceptible
   b. ≥4 drugs to which the organism is susceptible
   c. ≥2 drugs to which the organism is susceptible
   d. none of the above

   Issue 116

10. Which of the following intermittent treatment schedules is preferred for the continuation phase of active TB treatment in persons co-infected with HIV?
    a. three-times-weekly regimens administered as directly observed therapy
    b. twice-weekly regimens administered as directly observed therapy
    c. once-weekly regimens administered as directly observed therapy
    d. none of the above

    Issue 116

11. Treatment of active TB disease during pregnancy should include:
    a. isoniazid
    b. rifampin
    c. ethambutol
    d. all of the above

    Issue 116

12. Which of the following drugs causes severe and prolonged hepatotoxicity?
    a. pyrazinamide
    b. isoniazid
    c. rifampin
    d. streptomycin

    Issue 116

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