[FDA] and the European Medicine Agency [EMA] in the case of bedaquiline; the EMA and the Pharmaceuticals and Medical Devices Agency of Japan in the case of delamanid).

REGIMENS

Standard short-course regimens are divided into an initial, or bactericidal, phase and a continuation, or sterilizing, phase. During the initial phase, the majority of the tubercle bacilli are killed, symptoms resolve, and usually the patient becomes noninfectious. The continuation phase is required to eliminate persisting mycobacteria and prevent relapse. The treatment regimen of choice for virtually all forms of drug-susceptible TB in adults consists of a 2-month initial (or intensive) phase of isoniazid, rifampin, pyrazinamide, and ethambutol followed by a 4-month continuation phase of isoniazid and rifampin **(Table 202-3)**. This regimen can cure TB in more than 90% of patients. In children, most forms of TB in the absence of HIV infection or suspected isoniazid resistance can be safely treated without ethambutol in the intensive phase. Treatment should be given daily throughout the course. However, daily treatment during the intensive phase and intermittently (three times weekly) during the continuation phase is an alternative for patients who can be directly supervised and properly supported. A fully supervised, three-times-weekly regimen throughout the course also can be offered in the absence of HIV infection, although the risk of acquired drug resistance is higher than that among patients treated daily for the full course. In addition, if the infecting strain is resistant to isoniazid, the risks of both acquired resistance and treatment failure are higher with three-times-weekly intensive therapy than with daily treatment in the intensive phase. HIV-infected patients should always receive their initial-phase regimen daily (see below). A continuation phase of once-weekly rifapentine and isoniazid has been shown to be equally effective for HIV-seronegative patients with noncavitary pulmonary TB who have negative sputum cultures at 2 months. Patients with cavitary pulmonary TB and delayed sputum-culture conversion (i.e., those who remain culture-positive at 2 months) should be tested immediately for drug-resistant TB, and a change of regimen should be considered. To prevent isoniazid-related neuropathy, pyridoxine (10–25 mg/d) should be added to the regimen given to persons at high risk of vitamin B_6 deficiency (e.g., alcoholics; malnourished persons; pregnant and lactating women; and patients with conditions such as chronic renal failure, diabetes, and HIV infection, which are also associated with neuropathy). A full course of therapy (completion of treatment) is defined more accurately by the total number of doses taken than by the duration of treatment, although the course should not include interruptions of longer than 4 weeks. Specific recommendations on the required number of doses for each of the various treatment regimens have been published jointly by the American Thoracic Society, the Infectious Diseases Society of America, and the CDC. In some developing countries where the ability to ensure adherence to treatment is limited, a continuation-phase regimen of daily isoniazid and ethambutol for 6 months was used in the past. However, this regimen is associated with a higher rate of relapse, failure, and death, especially among HIV-infected patients, and is no longer recommended by the WHO.

Lack of adherence to treatment is recognized worldwide as the most important impediment to cure. Moreover, the tubercle bacilli infecting patients who do not fully adhere to the prescribed regimen are likely to become drug resistant. Both patient- and provider-related factors may affect adherence. Patient-related factors include a lack of belief that the illness is significant and/or that treatment will have a beneficial effect; the existence of concomitant medical conditions (notably alcohol or substance abuse); lack of social support; fear of stigma and discrimination associated with TB; and poverty, with attendant joblessness and homelessness. Provider-related factors that may promote adherence include the support, education, and encouragement of patients and the offering of convenient clinic hours. In addition to specific measures promoting adherence, two other strategic approaches are used: direct supervision of treatment with support to the patient, consisting of incentives and enablers such as meals, travel vouchers, cash transfers, and grants to replace income loss; and provision of fixed-drug-combination products that reduce the number of tablets the patient needs to swallow. Because it is difficult to predict which patients will adhere to the recommended treatment for a disease that has important public as well as individual health implications, all patients should have their therapy directly supervised, especially during the initial phase, with

TABLE 202-3 RECOMMENDED ANTITUBERCULOSIS TREATMENT REGIMENS

	Initial Phase		Continuation Phase	
Indication	**Duration, Months**	**Drugs**	**Duration, Months**	**Drugs**
New smear- or culture-positive cases	2	HRZE[a,b]	4	HR[a,c,d]
New culture-negative cases	2	HRZE[a]	4	HR[a]
Pregnancy	2	HRE[e]	7	HR
Relapses and treatment default (pending susceptibility testing)	3	HRZES[f]	5	HRE
Failures[g]	← Tailored according to drug susceptibility testing →			
Resistance (or intolerance) to H	Throughout (6–9)	RZE[h]		
Resistance (or intolerance) to R	←	Same as for MDR-TB; see below[i]	→	
MDR-TB (resistance to at least H + R)	Throughout (20 months in most cases)	Q, Inj[j], Eto/Pto, Z, Cs/PAS		
XDR-TB	← See Table 202-4 →			
Intolerance to Z	2	HRE	7	HR

[a]All drugs can be given daily or intermittently (three times weekly throughout). A twice-weekly regimen after 2–8 weeks of daily therapy during the initial phase is sometimes used, although it is not recommended by the WHO. [b]Streptomycin can be used in place of ethambutol but is no longer considered a first-line drug. [c]Some experts suggest extending the continuation phase to 7 months for patients with cavitary pulmonary tuberculosis who remain sputum culture–positive after the initial phase of treatment. However, treatment in such patients must be guided by drug susceptibility testing to rule out drug-resistant TB. [d]A clinical trial showed that HIV-negative patients with noncavitary pulmonary tuberculosis who have negative sputum AFB smears after the initial phase of treatment can be given once-weekly rifapentine/isoniazid in the continuation phase. [e]The 6-month regimen with pyrazinamide can probably be used safely during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease. If pyrazinamide is not included in the initial treatment regimen, the minimal duration of therapy is 9 months. [f]Streptomycin should be discontinued after 2 months. Drug susceptibility results will determine the best regimen option. [g]The availability of rapid molecular methods to identify drug resistance allows initiation of a proper regimen at the start of treatment. [h]Although normally not recommended, a fluoroquinolone may strengthen the regimen for patients with extensive disease. A later-generation agent (such as levofloxacin, moxifloxacin, or possibly gatifloxacin; see text) is preferred. [i]Isoniazid is added if susceptibility to this agent is confirmed or presumed. [j]Amikacin and kanamycin (aminoglycosides) or capreomycin (polypeptide). Any of these injectable agents is recommended for the first 8 months in most patients, but the duration may be modified according to the clinical response to therapy. Continuation of treatment with the injectable drug for at least 4 months after culture conversion is advised.

Abbreviations: Cs/PAS, cycloserine or para-aminosalicylic acid; E, ethambutol; Eto/Pto, ethionamide or prothionamide; H, isoniazid; Inj, an injectable agent (the aminoglycosides amikacin and kanamycin or the polypeptide capreomycin); MDR-TB, multidrug-resistant tuberculosis; Q, a quinolone antibiotic; R, rifampin; S, streptomycin; WHO, World Health Organization; XDR-TB, extensively drug-resistant tuberculosis; Z, pyrazinamide.