Bedaquiline should be used with caution in people >65 years of age and in HIV-infected patients; its use is not advised in children and pregnant women. In early 2014, the European Medical Agency granted accelerated approval of another new agent, the nitroimidazole compound delamanid. Data from a phase 2B clinical trial in which delamanid was added to the WHO-recommended standard MDR-TB regimen have shown increased culture conversion at 2 months. Pending phase 3 trial results and in view of potential side effects of both new drugs (including QT interval prolongation in both cases and hepatotoxicity in the case of bedaquiline), the WHO recommends limiting the use of bedaquiline and delamanid to cases of MDR-TB when an effective WHO-recommended standard MDR-TB regimen cannot be designed because of known resistance, intolerance, or nonavailability of any second-line drugs in the regimen. Patients treated with bedaquiline or delamanid should be counseled, should give informed consent, and should be closely monitored during treatment. In particular, patients with cardiac anomalies such as prolonged QT interval or a history of ventricular arrhythmias should not be given these drugs. Currently, there is no information about simultaneous use of these two agents; therefore, combining them is not recommended.

Finally, a shorter (9-month) regimen consisting of gatifloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide given throughout the treatment period and supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of at least 4 months is reportedly effective for MDR-TB in certain settings. Further investigations are necessary to elucidate the role of this shorter regimen in MDR-TB treatment.

Patients with XDR-TB have fewer treatment options and a much poorer prognosis. However, observational studies have shown that aggressive management of cases comprising early drug-susceptibility testing, rational combination of at least five drugs, readjustment of the regimen, strict directly observed therapy, monthly bacteriologic monitoring, and intensive patient support may result in cure and avert death. **Table 202-4** summarizes the management of patients with XDR-TB. Some recently published studies regarding the use of linezolid in patients with XDR-TB suggest that, although it carries a high level of toxicity, this drug increases culture conversion.

For patients with localized disease and sufficient pulmonary reserve, lobectomy or pneumonectomy may be considered. Because the management of patients with MDR- and XDR-TB is complicated by both social and medical factors, care of these patients is ideally provided in specialized centers or, in their absence, in the context of programs with adequate resources and capacity, including community support.

TABLE 202-4 MANAGEMENT GUIDELINES FOR PATIENTS WITH DOCUMENTED OR STRONGLY SUSPECTED EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS (XDR-TB)

1. Use pyrazinamide and any first-line oral agents that may be effective.
2. Use an injectable agent to which the strain is susceptible, and consider an extended duration of use (12 months or possibly the whole treatment period). If the strain is resistant to all injectable agents, use of one that the patient has not previously received is recommended.[a]
3. Use a later-generation fluoroquinolone, such as moxifloxacin, high-dose levofloxacin, or possibly gatifloxacin.[b]
4. Use all second-line oral bacteriostatic agents (para-aminosalicylic acid, cycloserine, and ethionamide or prothionamide) that have not been used extensively in a previous regimen or any such agents that are likely to be effective.
5. Add bedaquiline or delamanid and one or more of the following drugs[c]: clofazimine, linezolid, amoxicillin/clavulanic acid, clarithromycin, and carbapenems such as imipenem/cilastatin and meropenem.
6. The simultaneous use of bedaquiline and delamanid is not recommended at the moment in view of the current lack of information on the potential of adverse reactions when these drugs are administered together.
7. Consider treatment with high-dose isoniazid if low-level resistance to this drug is documented.
8. Consider adjuvant surgery if there is localized disease.
9. Enforce strong infection-control measures.
10. Implement strict directly observed therapy and full adherence support as well as comprehensive bacteriologic and clinical monitoring.

[a]This recommendation is made because, although the reproducibility and reliability of susceptibility testing with injectable agents are good, few data are available on the correlation of clinical efficacy with test results. Options with XDR-TB are very limited, and some strains may be affected in vivo by an injectable agent even though they test resistant in vitro. [b]Gatifloxacin (no longer marketed in several countries, including the United States, because of previously observed dysglycemia) has recently been tested in a 4-month regimen that produced no detectable major side effects; thus, this drug could be reconsidered as a good alternative. [c]The number of drugs added is based on how many oral bacteriostatic drugs (see point 4 above) are believed to be effective: the advice is to add one drug if there is confidence in all three bacteriostatic drugs; two if there is confidence in only two bacteriostatic drugs; and three or more if there is confidence in only one bacteriostatic drug or none.

HIV-ASSOCIATED TB

Several observational studies and randomized controlled trials have shown that treatment of HIV-associated TB with anti-TB drugs and simultaneous use of ART are associated with significant reductions in mortality risk and AIDS-related events. Evidence from randomized controlled trials shows that early initiation of ART during anti-TB treatment is associated with a 34–68% reduction in mortality rates, with especially good results in patients with CD4+ T cell counts of <50/μL. Therefore, the main aim in the management of HIV-associated TB is to initiate anti-TB treatment and to immediately consider initiating or continuing ART. All HIV-infected TB patients, regardless of CD4+ T cell count, are candidates for ART, which optimally is initiated as soon as possible after the diagnosis of TB and within the first 8 weeks of anti-TB therapy. However, ART should be started within the first 2 weeks of TB treatment for patients with CD4+ T cell counts of <50/μL. In general, the standard 6-month daily regimen is equally efficacious in HIV-negative and HIV-positive patients for treatment of drug-susceptible TB. As for any other adult living with HIV **(Chap. 226)**, first-line ART for TB patients should consist of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI). Although TB treatment modalities are similar to those in HIV-negative patients, adverse drug effects may be more pronounced in HIV-infected patients. In this regard, three important considerations are relevant: an increased frequency of paradoxical reactions, interactions between ART components and rifamycins, and development of rifampin monoresistance with intermittent treatment. IRIS—i.e., the exacerbation of symptoms and signs of TB—has been described above. Rifampin, a potent inducer of enzymes of the cytochrome P450 system, lowers serum levels of many HIV protease inhibitors and some NNRTIs—essential drugs used in ART. In such cases, rifabutin, which has much less enzyme-inducing activity, has been used in place of rifampin. However, dosage adjustments for rifabutin and protease inhibitors are still being assessed. Several clinical trials have found that patients with HIV-associated TB whose degree of immunosuppression is advanced (e.g., CD4+ T cell counts of <100/μL) are prone to treatment failure and relapse with rifampin-resistant organisms when treated with "highly intermittent" (i.e., once- or twice-weekly) rifamycin-containing regimens. Consequently, it is recommended that all TB patients who are infected with HIV receive a rifampin-containing regimen on a daily basis. Because recommendations are frequently updated, consultation of the following websites is advised: *www.who.int/hiv*, *www.who.int/tb*, *www.cdc.gov/hiv,* and *www.cdc.gov/tb.*

SPECIAL CLINICAL SITUATIONS

Although comparative clinical trials of treatment for extrapulmonary TB are limited, the available evidence indicates that most forms of disease can be treated with the 6-month regimen recommended for patients with pulmonary disease. The WHO and the American Academy of Pediatrics recommend that children with bone and joint TB, tuberculous meningitis, or miliary TB receive up to 12 months of treatment. Treatment for TB may be complicated by underlying medical problems that require special consideration. As a rule, patients with chronic renal failure should not receive aminoglycosides and should receive ethambutol only if serum drug levels