

The treatment of rifampin-resistant (RR) and MDR TB (resistance to both isoniazid and rifampin) is an area of active investigation and is evolving rapidly. Historically, RR/MDR TB has been treated with individualized regimens taking into account the results of drug resistance testing and prior treatment exposure. In 2019, ATS, CDC, IDSA, and the European Respiratory Society (ERS) issued MDR TB treatment guidelines recommending a fully oral regimen consisting of at least 5 active drugs for most patients with drug-resistant TB, including people with HIV.⁹³

Since the publication of the 2019 guidelines, however, several clinical trials have examined the efficacy and safety of a 6-month, all-oral regimen comprised of bedaquiline, pretomanid, and linezolid (“BPaL”). Pretomanid is a novel oral antimycobacterial agent that was approved by the FDA in 2019 exclusively as part of the BPaL regimen. The initial study (“Nix-TB”) on which approval was based, was a single-arm study in 109 patients, of whom 51% were people with HIV.²⁶⁵ Although the study had no control arm, 90% of participants had a favorable outcome. High rates of peripheral neuropathy were seen in Nix-TB study participants, and this was attributed to the high dose of linezolid used (1200 mg daily). The follow-up ZeNix study (n=181) compared outcomes of patients receiving the BPaL regimen at different linezolid doses and showed similarly favorable outcomes with a lower dose of 600 mg daily.²⁶⁶ The TB-PRACTECAL study compared a regimen in which moxifloxacin was added to BPaL (aka “BPaLM”) to longer injectable-based regimens, which were the standard of care at the time.^{267,268} In modified intention-to-treat analyses, 121 of 138 (88%) participants in the BPaLM arm achieved treatment success compared with 81 of 137 (59%) of those receiving standard of care. Disease recurrence occurred in one participant in the BPaLM group (n=151) and four in the BPaL group (n=123); new resistance to bedaquiline was observed in the BPaL group in isolates from three of four recurrences, with no new resistance to other drugs in the regimens.²⁶⁷

The BPaL and BPaLM regimens have been used in the United States, and treatment outcomes thus far have been very successful among 152 patients with culture-positive pulmonary TB, most of whom received the 600 mg daily dose of linezolid.^{269,270} Three recurrences after treatment completion were reported among 116 who received BPaL and none among 36 patients who received BPaLM.

Based on these data, **BPaLM is recommended as the preferred therapy for people with HIV with pulmonary RR-TB and without known resistance to the component medications (AI).**²⁷¹

Patients with RR-TB with fluoroquinolone resistance should receive BPaL without moxifloxacin (**AI**). This recommendation is similar to that of WHO, which conditionally recommends both the BPaL and BPaLM regimens to patients ≥15 years of age with RR-TB who have not had previous exposure or resistance to the drugs in the regimen.²⁷² BPaLM and BPaL regimens should be given for a total of 26 weeks (6 months) (**AI**). Treatment should be extended up to a total of 39 weeks (9 months) if sputum cultures are positive between months 4 and 6 (**AI**).

For patients who have not been included in BPaL or BPaLM studies—such as those with extrapulmonary TB or those with known or suspected resistance to bedaquiline, pretomanid, or linezolid—we recommend an individualized regimen consisting of at least 5 active drugs, based on the results of resistance testing and prior treatment exposure (**AI**). Component medications should be selected using the ranking outlined in the ATS/CDC/IDSA/ERS guidelines.⁹³ When possible, an initial individualized regimen should contain bedaquiline, linezolid, a fluoroquinolone (levofloxacin or moxifloxacin), clofazimine, and a D-alanine analog (cycloserine or terizidone). All remaining drugs should be used to complete the regimen only when the recommended drugs cannot be used. Kanamycin and capreomycin are no longer recommended due to the increased risk of treatment