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Future Directions in Treating Multidrug- and Extensively Drug-Resistant Tuberculosis: New and Breakthrough Regimens

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Abstract

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis represent escalating global health threats, driven by ongoing transmission, diagnostic limitations, and historically inadequate treatment options. Conventional treatment approaches required prolonged courses spanning 6-24 months, characterized by substantial toxicity and poor treatment outcomes.The therapeutic landscape has undergone a significant transformation over the past decade with the introduction of novel antimycobacterial agents, including bedaquiline, delamanid, and pretomanid, alongside repurposed companion drugs such as linezolid, moxifloxacin, and clofazimine. These advances have enabled the development of shorter, all-oral regimens that substantially reduce patient burden while improving cure rates. The BPaL regimen (bedaquiline, pretomanid, linezolid) and its modification BPaLM (incorporating moxifloxacin) represents landmark achievements, offering effective treatment within shortened timeframes. Complementary approaches, including host-directed therapies, aim to enhance immune responses and minimize tissue pathology to prevent treatment failure and relapse.Despite these therapeutic advances, significant implementation challenges persist. Key concerns include drug safety profiles, equitable access in resource-limited settings, integration with HIV care, comprehensive resistance monitoring, and

addressing systemic health inequities that perpetuate disease transmission.This review examines the pathogenesis and epidemiology of drug-resistant tuberculosis within programmatic contexts, evaluates current treatment paradigms and emerging innovations, discusses supportive care strategies, and synthesizes evidence regarding novel regimens and adjunctive therapeutic approaches.

INTRODUCTION

Tuberculosis remains among the leading infectious causes of mortality worldwide (Mohajan et al., 2014). While drug-susceptible tuberculosis typically responds to standard six-month treatment regimens, the emergence of drug resistance has created substantial therapeutic challenges. Multidrug-resistant tuberculosis (MDR-TB) is characterized by resistance to rifampicin and isoniazid, the cornerstone first-line anti-tuberculosis agents. Further resistance patterns include pre-extensively drug-resistant tuberculosis (pre-XDR-TB), involving additional resistance to fluoroquinolones, and extensively drug-resistant tuberculosis (XDR-TB), which encompasses resistance to fluoroquinolones and second-line injectable agents.The clinical and economic burden of drug-resistant tuberculosis is profound, characterized by increased treatment costs, elevated mortality rates, and sustained transmission within vulnerable populations. These factors collectively contribute to perpetuating cycles of disease transmission and socioeconomic disadvantage.Historically, MDR-TB and XDR-TB treatment required prolonged regimens lasting 9-24 months, incorporating toxic injectable agents with limited efficacy and substantial adverse effects. These lengthy, complex protocols frequently resulted in treatment discontinuation, treatment failure, and the development of additional resistance patterns.Recent therapeutic innovations have fundamentally transformed the treatment landscape. Novel antimycobacterial agents and evidence-based regimen optimization have enabled the development of shorter, all-oral

treatment approaches (Dover et al., 2011). The introduction of regimens combining bedaquiline, pretomanid, and linezolid, with or without moxifloxacin, represents a paradigm shift from injectable-based protocols previously recommended by the World Health Organization and national regulatory bodies.These contemporary regimens demonstrate superior treatment outcomes, including higher cure rates and reduced treatment duration for patients with MDR-TB and XDR-TB. However, optimal implementation requires careful patient selection, comprehensive monitoring protocols, and systematic evaluation of treatment response and adverse effects

BACKGROUND

Epidemiology And Public-Health Impact

Global burden: Every year hundreds of thousands of people develop MDR/RR-TB (rifampicin-resistant), with treatment outcomes historically poorer than drug-sensitive TB. MDR/XDR-TB disproportionately affects low- and middle-income countries, people with HIV, and socially marginalized populations (Daneshi et al., 2025). The persistent global burden of drug-resistant TB also contributes significantly to the broader antimicrobial resistance (AMR) crisis.

Microbiology and Mechanisms of Resistance

Mycobacterium tuberculosis (Mtb) is an obligate human pathogen with a lipid-rich cell wall that impedes drug permeability and contributes to the necessity for specific antimycobacterial agents. Resistance arises through chromosomal mutations (rarely horizontal gene transfer), such as rpoB mutations for rifampicin resistance, katG/inhA mutations for isoniazid resistance, gyrA/gyrB for fluoroquinolone resistance, and mutations in ATP synthase or other targets for newer drugs. Combination therapy

reduces the likelihood of selecting for resistant mutants; therefore regimen design matters.

Pathophysiology Relevant To Therapy

Mtb exists in multiple metabolic states (actively replicating, slowly replicating, non-replicating / persistent) and resides in varied tissue environments (intracellular in macrophages, caseating necrotic lesions, and cavities). The success of a regimen is largely determined by the drug's ability to penetrate lesions and its activity against non-replicating bacilli (Kaur et al., 2024). Because pathogenesis and treatment results are shaped by host immune responses (cellular immunity, granuloma formation), supplementary host-directed treatments are appealing.

Diagnostic Considerations Before Initiating Therapy

Selecting an effective regimen and preventing the resistance amplification require accurate and timely drug-susceptibility testing (DST). Phenotypic DST remain essential for certain medications, while modern molecular platforms (such as Xpert MTB/RIF and its variations, targeted sequencing) offer quick identification of rifampicin resistance and specific second-line resistance indicators. To minimize resistance selection, programs should ideally confirm the absence of resistance to bedaquiline, pretomanid, and linezolid before initiating regimens containing these drugs (where feasible) or, at the very least, ensure that prior exposure has not been prolonged. Standard-of-care and established therapies (pre-recent breakthrough era)

Historically, MDR-TB regimens comprised complex combinations of second-line agents, including injectable aminoglycosides (amikacin and kanamycin), fluoroquinolones, and various oral agents such as cycloserine, ethionamide, and clofaziminers. These regimens were lengthy and frequently associated with severe

toxicities (ototoxicity from injectables, hepatotoxicity and neuropsychiatric effects). With the advent of novel oral agents, programmatic guidelines shifted toward all-oral regimens.

Breakthrough Regimens: BPaL and BPaLM (Short, All-Oral Regimens)

The BPaL and BPaLM regimens mark a transformative step forward in the management of multidrug-resistant and extensively drug-resistant tuberculosis (Sah et al., 2025). These regimens are designed as short, potent, all-oral treatment options that combine drugs with complementary mechanisms of action.

Bedaquiline (B) is a diarylquinoline antimycobacterial agent, exerts its therapeutic effect by selectively targeting mycobacterial ATP synthase, resulting in cellular energy depletion and demonstrating potent bactericidal properties when administered orally. **Pretomanid (Pa)**, classified as a nitroimidazooxazine compound, demonstrates dual mechanisms of action dependent on oxygen availability: under aerobic conditions, it disrupts mycolic acid synthesis, while in hypoxic environments, it generates reactive nitrogen species, enabling efficacy against mycobacteria across diverse tissue microenvironments. **Linezolid (L)**, an oxazolidinone antibiotic, provides robust antimycobacterial activity through protein synthesis inhibition and demonstrates particular utility against drug-resistant isolates, though treatment requires careful monitoring due to associated hematological and peripheral neuropathy risks. In the **BPaLM** regimen, **moxifloxacin (M)**, a combination incorporates **moxifloxacin**, a fourth-generation fluoroquinolone that enhances the regimen's bactericidal capacity through synergistic interactions while expanding the spectrum of antimycobacterial activity.

Collectively, these drugs provide complementary mechanisms that target multiple metabolic states of *Mycobacterium tuberculosis* and penetrate diverse lesion

environments (Mehta et al., 2024). Their combination enables shortened treatment durations, with trials and emerging WHO recommendations supporting regimens as brief as six months—an unprecedented improvement compared to traditional lengthy and toxic therapies.

Evidence-Based And Outcomes

Clinical trials and programmatic data (Nix-TB, ZeNix, TB Alliance studies, operational research) have shown high rates of culture conversion and favorable outcomes with BPaL/BPaLM regimens in MDR/XDR contexts, with many cohorts reporting success rates markedly higher than historical controls and with shorter durations (e.g., 6 months). Several observational and trial reports show favorable outcomes across diverse settings, though careful monitoring for linezolid toxicity and other adverse events is required. The WHO consolidated guidelines recommend consideration of regimens such as the 6-month BPaLM for eligible patients (Auer et al., 2024).

Safety and Monitoring

Ensuring patient safety is central to the successful implementation of BPaL and BPaLM regimens, as each drug carries specific risks requiring careful monitoring. Linezolid remains one of the most effective components but is associated with dose-dependent toxicities, including hematologic suppression such as anemia and thrombocytopenia, as well as peripheral and optic neuropathy. To mitigate these risks, dose reduction strategies—such as administering 600 mg once daily or using intermittent dosing—are increasingly adopted, alongside close monitoring with complete blood counts and neurological assessments. Emerging evidence also suggests that front-loaded or intermittent dosing schedules may preserve efficacy while reducing cumulative toxicity. Bedaquiline, while highly effective, raises concerns about QT interval prolongation,

making baseline and periodic electrocardiogram (ECG) monitoring essential, particularly when used with other QT-prolonging agents. Pretomanid is generally well tolerated, but its use in pregnancy is not recommended due to limited safety data, and routine liver function monitoring is necessary to prevent hepatotoxicity (Occhineriet al., 2022). On a broader scale, programmatic implementation requires health systems to ensure the availability of ECGs, laboratory testing, adverse event management, and regular clinical follow-up to maximize both safety and therapeutic success.

Adjunctive Strategies And Novel Approaches

Host-Directed Therapies (HDTS)

Rationale: Enhance host immune mechanisms, reduce pathological inflammation, accelerate bacillary clearance, reduce lung damage and relapse (Kelly, et al 2020). HDTs include repurposed drugs (e.g., metformin, statins, NSAIDs, azithromycin), immune modulators (cytokines, interferons), cell therapies and experimental immunotherapies. Several trials and reviews have identified promising candidates and mechanisms (autophagy induction, modulation of macrophage responses, limiting damaging neutrophilic inflammation). However, rigorous randomized data for HDTs in MDR/XDR-TB are still emerging and require careful patient selection to avoid harm (e.g., immune overactivation). Recent randomized trials and programmatic projects aim to define which HDTs add clinically meaningful benefit.

Immunotherapy And Biologics

Therapeutic vaccines and monoclonal antibodies are under investigation to boost protective immunity or modulate harmful inflammation. Early-phase trials explore safety and immunogenicity. CAR-T or adoptive cell therapies for Mtb are conceptual and face

major technical barriers, but appear in review literature as future possibilities (Chamorro et al., 2023).

Precision Pharmacology And Regimen Optimization

Pharmacokinetic/pharmacodynamic modeling, therapeutic drug monitoring (TDM), and lesion-penetration studies inform individualized dosing (e.g., linezolid dosing strategies to balance efficacy and toxicity). Drug–drug interactions (e.g., with antiretrovirals) must be accounted for. Ongoing research seeks to define optimal durations and combinations to minimize toxicity and resistance emergence.

Diagnostics To Support Therapy

Rapid molecular tests with expanded resistance detection (including gyrA/gyrB, rpoB, and potentially novel drug targets) permit faster selection of effective regimens. Whole-genome sequencing (WGS) and targeted sequencing are increasingly used in high-resource settings for comprehensive DST and epidemiologic surveillance (Lim et al., 2023). Point-of-care tests to monitor treatment response are in development.

Programmatic And Implementation Issues

Eligibility And Rollout Of New Regimens

WHO guidance suggests BPaLM/BPaL use for many patients with MDR/RR-TB who have limited prior exposure to these medicines, but programmatic scale-up requires training, supply chains for new drugs, monitoring infrastructure (ECG, labs), pharmacovigilance, and community engagement. The guidance also provides conditional recommendations with recognition of evidence certainty limits, emphasizing programmatic research.

Safety Systems And Pharmacovigilance

As new regimens move into broad use, collecting real-world safety and effectiveness data is essential. Pharmacovigilance systems should capture adverse drug reactions,

monitor for the emergence of resistance to new agents, and enable rapid policy updates (Anestina et al., 2025).

Equity, Access, And Cost Considerations

Although shorter regimens reduce some costs, the price and availability of novel drugs remain issues in many settings. International procurement mechanisms, tiered pricing, and inclusion in national essential medicines lists are critical to equitable access.

Hiv Coinfection And Special Populations

TB treatment regimens must be harmonized with antiretroviral therapy (ART). Careful control is necessary for drug interactions and overlapping toxicities (such as those between linezolid and certain antiretrovirals). Pregnant and breastfeeding women, children, and those with severe comorbidities often have limited trial data and deserve focused research and tailored guidance (Illamola, et al., 2018).

CLINICAL CASE VIGNETTES (ILLUSTRATIVE)

Case 1: Short, Effective Therapy In XDR-TB

An evaluation is conducted on a 34-year-old man who has been diagnosed with pulmonary XDR-TB and has failed previous treatment. He is resistant to isoniazid, rifampicin, moxifloxacin, and an injectable. The patient is placed on a BPaL regimen (under programmatic direction with careful monitoring) following baseline ECG and labs and evaluation for prior exposure to bedaquiline, linezolid, or pretomanid. By week eight, the sputum culture converts and stays negative for the full six months, improving both clinically and radiographically. Peripheral neuropathy is caused by linezolid in the third month; recovery is possible with a neuropathy management plan and dose decrease. This scenario reflects many reported outcomes showing high culture conversion but underscores the need for toxicity surveillance.

Case 2: Programmatic scale-up challenge

A district TB program in a low-resource setting introduces BPaLM for eligible MDR/RR-TB patients (Long et al., 2025). Challenges encountered include intermittent ECG availability, stockouts of moxifloxacin, limited lab capacity for CBC monitoring for linezolid toxicity, and patient travel barriers for monthly clinic visits. The program progressively establishes decentralized monitoring with point-of-care ECG devices, partnerships for drug procurement, and community-based nurses trained to assess neuropathy and draw CBCs, improving retention and outcomes. This highlights the systems changes required to achieve regimen benefits in routine care.

CHALLENGES AND LIMITATIONS

Resistance To New Drugs

Emergent resistance is a worry as bedaquiline, pretomanid, and linezolid are used more frequently. To reduce selective pressure, proper regimen selection, stewardship, and surveillance are necessary. Scale-up should be accompanied by phenotypic and genetic surveillance for resistance markers.

Toxicity Management And Drug Interactions

Utility may be limited by linezolid-related haematologic and neurologic toxicity; studies are ongoing to determine dosage, duration, and safer alternatives (Cattaneo, et al., 2023). When taking bedaquiline with other medications that extend QT, it is necessary to monitor QT prolongation.

Evidence Gaps

For some populations, such as pregnant women, children under 15, and people with severe liver or kidney damage, many trials have small sample sizes. More thorough

characterization is still required for long-term results, relapse rates after two years in programmatic use, and head-to-head regimen comparisons.

Programmatic Capacity

Safe adoption may be hampered by a lack of resources (labs, ECGs, and qualified clinicians). While sentinel surveillance techniques and phased rollouts are realistic, building infrastructure requires time and money.

RESEARCH PRIORITIES AND FUTURE DIRECTIONS

Addressing important research goals that can improve current treatments and increase their worldwide impact is essential for future advancements in tuberculosis management (Dartois, et al., 2022). With multiple trials and modelling studies now in progress, a primary focus is optimizing the use of linezolid by determining the minimal effective dose and evaluating intermittent techniques to lower the risk of neuropathy and cytopenias while preserving efficacy. Equally critical is the establishment of robust molecular surveillance systems, such as whole-genome sequencing or targeted resistance panels, to detect emerging resistance to bedaquiline, pretomanid, and linezolid at an early stage. Host-directed therapies (HDTs) also represent a promising frontier, and rigorous randomized controlled trials are needed to identify interventions that can shorten treatment duration, protect against lung damage, and improve outcomes for patients with co-morbidities, including HIV. Vaccine development remains an indispensable global priority, with both prophylactic and therapeutic candidates urgently required to reduce TB incidence and curb the evolution of drug resistance. To ensure that innovative regimens like BPaL and BPaLM can be safely and fairly implemented in settings with limited resources through decentralized monitoring, community-based care, and cost-reduction tactics, access and implementation science

must be developed. These research avenues collectively provide a road map for TB control that is safer, more efficient, and available everywhere.

ETHICAL, SOCIAL, AND POLICY CONSIDERATIONS

The introduction of BPaL and BPaLM antibiotics for tuberculosis has benefits that are somewhat overshadowed by ethical, social, and policy issues that, if ignored, could prevent any real evaluation of the benefits to humanity. This is true of many highly resource-intensive, innovative medications. The sale of drugs BPaL and BPaLM, which offer unprecedented advantages and costs, would exacerbate harm and social TB disparities, particularly affecting individuals most affected by drug-resistant TB and the sickest with TB. Advancements in maintaining their use in medicine would be wasted if they, like many antibiotics, were misused .In addition to addressing any adverse antibiotic side effects, consent and monitoring throughout treatment remain crucial. Global initiatives to combat stigma and the social determinants that contribute to the spread of tuberculosis, such as poverty, lack of access to food and shelter, and low social standing, which provide little TB care, are equally essential (Rasanathan, et al., 2011). These socioeconomic factors make TB treatment feedback cycles worse overall. These kinds of interventions are required to uphold the ethical, social, and policy current TB control steps that, by being innovative and focused on the future, direct the application of consistent dosages of attention. When combined with the new medication TB and a lot of thought, these suggested BX provide a practical, ethical, and future-proof answer.

PRACTICAL, CLINIC-LEVEL GUIDANCE

These actions must be taken for medication regimens and therapy as well because the safety and effectiveness of the BPaL and BPaLM regimens depend on careful clinical planning and ongoing monitoring. Before initiating treatment, the clinician must

conduct a medication susceptibility review and baseline evaluations, which include an ECG, CBC, LFT, and, if relevant, a pregnancy test (Padoan, et al., and 2020). Counselling of potential toxicities and the necessity of monitoring is necessary for patients. In addition to the prescribed CBC monitoring for linezolid-associated cytopenias, ECG monitoring for bedaquiline-associated clinical evaluations for neuropathy and eyesight, LFTs, and additional tests for bacteriological conversion, patients must get these tests monthly. Dose holds, symptomatic therapy, and dose shifts as small as 600 mg once daily are further potential adjustments.Intermittent dosing is a helpful way to lower toxicity while maintaining efficacy, according to new research. Nutrition and mental health services must be provided in addition to medication.

CONCLUSION

The management of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis has historically been characterized by prolonged treatment duration, significant toxicity, and suboptimal cure rates. However, recent therapeutic advances have introduced novel all-oral regimens that substantially improve treatment outcomes. Combination therapy incorporating bedaquiline, pretomanid, and linezolid, with optional moxifloxacin supplementation, has demonstrated the potential to reduce treatment duration to six months while maintaining high efficacy rates. This represents a fundamental shift in tuberculosis management, offering considerable benefits for both patients and healthcare systems through reduced treatment burden and improved adherence.Current international guidelines for MDR and XDR tuberculosis reflect this paradigmatic change, emphasizing these innovative therapeutic approaches. However, successful implementation requires careful consideration of safety monitoring protocols, equitable access strategies, and resistance surveillance mechanisms.Future directions in

MDR tuberculosis treatment should integrate host-directed therapies alongside existing antimicrobial interventions. Such approaches may enhance treatment efficacy by targeting host immune responses in addition to the pathogen itself.The optimal management of MDR and XDR tuberculosis necessitates a comprehensive framework encompassing evidence-based regimens, rigorous safety monitoring, systematic patient surveillance, continued research initiatives, and strengthened health system capacity. This integrated approach offers the greatest potential for reducing tuberculosis-related mortality and transmission rates.

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