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REVIEW

The Changing Paradigm of Drug-Resistant Tuberculosis Treatment: Successes, Pitfalls, and Future Perspectives

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SUMMARY Drug-resistant tuberculosis (DR-TB) remains a global crisis due to the increasing incidence of drug-resistant forms of the disease, gaps in detection and prevention, models of care, and limited treatment options. The DR-TB treatment landscape has evolved over the last 10 years. Recent developments include the remarkable activity demonstrated by the newly approved anti-TB drugs bedaquiline and pretomanid against *Mycobacterium tuberculosis*. Hence, treatment of DR-TB has drastically evolved with the introduction of the short-course regimen for multidrug-resistant TB (MDR-TB), transitioning to injection-free regimens and the approval of the 6-month short regimens for rifampin-resistant TB and

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MDR-TB. Moreover, numerous clinical trials are under way with the aim to reduce pill burden and shorten the DR-TB treatment duration. While there have been apparent successes in the field, some challenges remain. These include the ongoing inclusion of high-dose isoniazid in DR-TB regimens despite a lack of evidence for its efficacy and the inclusion of ethambutol and pyrazinamide in the standard short regimen despite known high levels of background resistance to both drugs. Furthermore, antimicrobial heteroresistance, extensive cavitary disease and intracavitary gradients, the emergence of bedaquiline resistance, and the lack of biomarkers to monitor DR-TB treatment response remain serious challenges to the sustained successes. In this review, we outline the impact of the new drugs and regimens on patient treatment outcomes, explore evidence underpinning current practices on regimen selection and duration, reflect on the disappointments and pitfalls in the field, and highlight key areas that require continued efforts toward improving treatment approaches and rapid biomarkers for monitoring treatment response.

KEYWORDS tuberculosis, drug resistance, antimicrobial drugs, treatment regimens, short-course treatment, drug-resistant tuberculosis, emerging resistance, individualized treatment, microbial heteroresistance, standardized treatment

Tuberculosis (TB) is a formidable infectious disease and a leading cause of morbidity and mortality (1). In 2020, the World Health Organization (WHO) estimated that 1.3 million people died of TB and approximately 10 million people developed active TB. Of the latter, approximately 132,222 cases were rifampin (RIF)-resistant or multidrug-resistant tuberculosis (RR/MDR-TB) (2). Treatment for drug-resistant cases is expensive, protracted, and toxic, with an average treatment success of approximately 56%, compared to 85% for drug-sensitive TB (DS-TB) (3). Suboptimal treatment options, slow progress in the development of new drugs, poor treatment adherence support, and the public health approach to drug-resistant TB (DR-TB) treatment provision may all be contributing factors to amplifying drug resistance in *Mycobacterium tuberculosis* (4).

DR-TB results when *M. tuberculosis* develops resistance to any anti-TB drug. The most frequently reported form of DR-TB is RR-TB, which refers to an *M. tuberculosis* strain that is resistant only to RIF or has additional resistance to isoniazid (INH) (RR/MDR-TB) or is resistant to other first-line or second-line anti-TB drugs (5). Isoniazid-resistant TB (Hr-TB), i.e., *M. tuberculosis* strains that are only resistant to INH (5), has become more common in recent years. Among the 1.4 million cases of INH-resistant TB reported in 2019, 79% presented as Hr-TB (6). An MDR-TB strain with additional resistance to fluoroquinolones (FQs) is known as pre-extensively DR-TB (pre-XDR-TB), while MDR-TB strains resistant to bedaquiline (BDQ) and linezolid (LZD) are known as XDR-TB (7). Pre-XDR-TB and XDR-TB remain the most severe forms of DR-TB.

The continuous spread of DR-TB remains a significant challenge and threatens global TB control. DR-TB transmission remains a primary mechanism, whereby an individual gets infected by a resistant strain (8). Alternatively, drug resistance can emerge during the course of treatment (acquired) (8). Approximately half of new MDR-TB cases are reported among patients who have never been previously exposed to TB treatment, which points to transmission (9). Additionally, most of previously treated patients contract DR-TB through transmission rather than acquired resistance (10). Delays in treatment response and treatment failure increase the risk of transmission within communities (11, 12). Furthermore, DR-TB may be largely transmitted outside a household (13).

Increasing levels of DR-TB have warranted the development of novel drugs and the repurposing of alternate drugs to treat DR-TB. Recent years have seen notable advances in the development of shorter and more efficacious regimens for treatment of RR-TB. After years of DR-TB patients being subjected to long and toxic injectable-based regimens of 18 to 20 months, introduction of a short-course regimen of 9 to 12 months was a major advancement. The continuous improvement was observed through introduction of new drugs, such as BDQ, and all-oral short regimens (14). The recent approval of additional

shorter RR/MDR-TB and XDR-TB regimens (6 to 9 months) and of BDQ with pretomanid (PTM) and LZD (BPaL) and BDQ, PTM, LZD, and moxifloxacin (MFX) (BPaLM) have been major shifts in the history of DR-TB treatment (15).

However, DR-TB treatment needs to be delivered in an optimal health care system. The characteristics of health care systems are likely to impact the new advancements. Timely diagnosis, financial systems to offer a full course of treatment and support to patients with DR-TB, and dedicated and well-trained health care professionals remain some of the important aspects of an optimized health care system (16). Rapid front-line diagnostic tests, such as Gene Xpert MTB/RIF Ultra, are now used by most countries and have improved RR-TB diagnosis (17). In addition, decentralized care has been implemented in countries such as South Africa to increase access to DR-TB treatment (18). However, patient risk factors, such as HIV coinfection, alcohol abuse, and treatment adherence, contribute to a stagnation seen in improving treatment outcomes (19).

Health care systems still require assessment to identify factors that could undermine or enhance the quality of DR-TB care. Determinations of whether patients with DR-TB have access to proper and quality care, whether DR-TB infections are transmitted, and whether patients receiving DR-TB treatment have successful outcomes or not, are crucial.

HISTORY OF DR-TB GUIDANCE

DR-TB treatment has evolved over the last 2 decades with notable continuous improvements (Table 1). The treatment of MDR-TB was formally endorsed in 2000, with a recommendation to use standardized or individualized long-course injectable-based regimens of 18 months (20). The former was referred to as a standard regimen given to all patients with MDR-TB in the absence of drug susceptibility testing (DST), while the latter was given based on DST results. In 2006, revised DR-TB treatment guidelines by the WHO (21) concurred with reports on outbreak of XDR-TB (then defined as MDR-TB with additional resistance to FQs and injectables) in KwaZulu Natal (22). Further revised DR-TB treatment guidelines were published in 2008, and they emphasized the use of a standardized regimen (23). The strategy to decentralize MDR-TB treatment was included in the 2011 guidelines (18, 24). In 2012, after 4 decades of stagnation in the TB drug development pipeline, BDQ was introduced into TB treatment regimens (25). The drug demonstrated remarkable bactericidal activity and improved treatment success in DR-TB patients (26–28). This was followed shortly by the introduction of delamanid (DLM) and PTM (29). In 2016, the WHO endorsed an injectable-based 9- to 12-month short-course regimen for the treatment of MDR-TB, which marked a major shift in the treatment of TB, following the success of the regimen in a cohort study in Bangladesh (30, 31). Data from the STREAM (Standardized Treatment Regimen of Antituberculosis Drugs for Patients with MDR-TB) trial demonstrated high rates of cure (78.1%) with this novel 9-month regimen compared to conventional long-course regimens (32). In 2018, the WHO, which had previously endorsed the use of a shorter injectable-containing regimen based on observational studies, reaffirmed its recommendation following release of the STREAM trial data (33). The next breakthrough came with transition to an all-oral BDQ-containing long-course regimen, in which BDQ replaced the injectable drug (31, 33). Furthermore, in 2019, the shorter all-oral BDQ-containing regimen was introduced, initially for operational research but later for wider clinical application (5, 14). A recent ground-breaking innovation was the novel, 6-month all-oral BPaL and BPaLM regimens, which are recommended for RR/MDR-TB and XDR-TB (15).

The WHO hierarchical reclassification of anti-TB drugs has prioritized FQs, BDQ, and LZD, which are placed in group A, as they are considered highly effective and strongly recommended for inclusion in all regimens unless contraindicated (34). In line with this recommendation, the definition of XDR-TB, which is based on resistance to second-line injectables, became less clinically relevant, leading to the 2021 revised definitions for DR-TB (7). Although DR-TB remains a significant public health challenge, encouraging novel drugs, diagnostic advances, and highly effective therapeutic regimens are emerging. In this review, we explore the evidence base underpinning the key changes to DR-TB treatment, outline the

TABLE 1 Summary of 2 decades of changes to DR-TB treatment regimens[a]

Guideline	Recommended regimen composition	Treatment duration	New recommendations
Guidelines for establishing DOTS-PLUS pilot projects for management of MDR-TB (20)	MDR-TB standard regimen 6 mo EMB-OFX-PZA-CM-ETO/PAS/CS 12 mo EMB-OFX-ETO/PAS/CS	18 mo	• Recommendations for standardized and individualized treatment approaches • Regimens to contain at least 3 effective drugs including an injectable agent • DST to be performed at baseline and every 3 mo thereafter until patient converts to consecutive negative sputum
	MDR-TB standard regimen (Peru), 3 mo KAN-CFX-ETO-PZA-EMB 15 mo KAN-ETO-Z-EMB	18 mo	
	MDR-TB regimen when waiting for DST 6 mo HREZ + CM + OFX ± PAS	6 mo	
	INH monoresistant or INH- and STR-resistant regimen 2 mo HREZ 7 mo RE	9 mo	
	INH, EMB, streptomycin resistance regimen 2 mo RIF-OFX-PZA-CM 7 mo RIF-OFX-PZA	9 mo	
	DS-TB regimen, 2–3 mo HREZ 2–3 mo HREZ/4HR	4–6 mo	
Guidelines for programmatic management of drug-resistant TB, 2006 (21)	RR/MDR-TB standardized regimen, 8 mo KAN-OFX-PTO-CS 12 mo OFX-PTO-CS	20 mo	• Implementation of standardized and individualized DR-TB regimens
Guidelines for programmatic management of DR-TB, emergency update, 2008 (23)	Standardized MDR-TB regimen, 6 mo Z-KAN (CM)-OFX-ETO-CS 12 mo PZA-OFX-ETO-CS	18 mo	• CFX removed from DR-TB regimen due to weak efficacy, especially compared to other FQs
WHO guidelines for programmatic management of DR-TB, 2011 update (24)	RR/MDR-TB regimen, 8 mo PZA-MFX-KAN-ETO/PTO-CS/PAS 12 mo PZA-MFX-ETO/PTO-CS/PAS	20 mo	• Recommended 8-mo intensive phase • EMB removed from standard DR-TB regimen, with option for use • Early antiretroviral treatment for HIV-DR TB coinfected patients
WHO treatment guidelines for DR-TB, 2016 update (31)	INH resistance, 6–9 mo HRZE or 6–9 mo RZE	6–9 mo	• First standardized short regimen for specific indications[c] • Shorter MDR-TB regimen recommended under specific conditions[c]
	Shorter RR/MDR-TB regimen, 4–6 mo KAN-MFX-PTO-CFZ-INHhd-EMB 5 mo MFX-CFZ-PZA-EMB	9–11 mo	• Use of high-dose INH and/or E for regimen strengthening • DR-TB drugs regrouped based on effectiveness and safety; • CFZ and LZD recommended as core second-line drugs; • PAS grouped as add-on agent • BDQ and DLM also assigned to specific add-on agent subgroup
	Longer MDR-TB regimen, 8 mo PZA-MFX-KAN-CFZ-EMB 12 mo MFX-CFZ-EMB-PZA	20 mo	
Key changes to treatment of MDR/RR-TB, 2018 rapid communication (33)	Longer standardized regimen,[b] 6–8 mo LZD-BDQ-LFX-CFZ-TZD 12 mo LFX-CFZ-TZD	18–20 mo	• Revised grouping of anti-TB drugs for longer regimens • All-oral long regimen for RR/MDR-TB • Group A (LFX/MFX, BDQ, and LZD), group B (CFZ, CS, and TRD), and group C (EMB, PZA, imipenem-cilastatin, AMK (STR), ETO/PTO, PAS, DLM) • KAN and CM no longer recommended
	Shorter MDR-TB regimen, mainly standardized, injection based 4–6 mo AM-MFX-PTO/ETO-CFZ-PZA-INHhd-EMB 5 mo MFX-CFZ-PZA-EMB	9–11 mo	

(Continued on next page)

TABLE 1 (Continued)

Guideline	Recommended regimen composition	Treatment duration	New recommendations
Key changes to treatment of DR-TB, 2019 rapid communication (14)	All-oral shorter regimen, 4–6 mo BDQ-LFX (or MXF)-LZD, INHhd-CFZ-EMB-PZA 5 mo LFX-CFZ-EMB-PZA	9–11 mo	• Transitioning to short-course injection-free regimen • Injectable agent replacement by BDQ • The first-ever short, 6-mo, all-oral regimen for XDR and unresponsive MDR-TB treatment (under research conditions)
	Novel treatment regimen, BPaL	6–9 mo	
WHO consolidated guidelines on DR-TB treatment, 2019 (34)	INH-monoresistant standardized regimen, 6 mo RZE + LFX	6 mo	• Use of an FQ in INH-monoresistant TB regimen • Use of LFX instead of MFX
	RR/MDR-TB, Shorter-course, all-oral for eligible MDR/RR-TB patients, standard regimen composition of 4–6 mo BDQ-LFX-LZD, INHhd-CFZ-EMB- 5 mo LFX-CFZ-EMB-PZA	9–11 mo	• Grouping of anti-TB drugs remains the same
	RR/MDR-TB, Injection-containing shorter-course regimen, 4 mo AMK-MFX-CFZ-INHhd-PTO-EMB-PZA 5 mo MFX-CFZ-EMB-PZA	9 mo	
	RR/MDR-TB, Long-course all-oral regimen,[b] RR-TB, MDR-TB, and pre-XDR-TB (second-line resistance) 6 mo BDQ-LFX-CFZ-LZD 12 mo LFX-CFZ-LZD	18 mo	
	RR/MDR-TB, Long-course individualized regimen,[b] pre-XDR-TB (FQ resistance) and XDR-TB, 6–8 mo BDQ-CFZ-LZD-DLM-TRD-PZA-INHhd 12 mo CFZ-LZD-TRD-PZA-INHhd	18–20 mo	
WHO consolidated guidelines on DR-TB treatment, 2020 (5)	Short all-oral RR/MDR-TB regimen, 6 mo BDQ 4–6 mo LFX/MFX-CFZ-PZA-EMB-INHhd-ETO 5 mo LFX/MFX-CFZ-PZA-EMB	9–11 mo	• Safety on extended use of BDQ beyond 6 mo • Guidance on BDQ use during pregnancy
	BPaL, 6–9 mo BDQ-PTM-LZD	6–9 mo	
Key changes to the treatment of DR-TB, 2022 rapid communication (15)	BPaL regimen, BDQ-PTM-LZD BPaLM regiman, BDQ-PTM-LZD-MFX	6–9 mo	• Programmatic use of BPaL and BPaLM for RR/MDR-TB and pre-XDR-TB

[a]DST, drug susceptibility testing; DR-TB, drug-resistant TB; HR-TB, isoniazid monoresistant TB; RR-TB, rifampin-resistant TB; MDR-TB, multidrug-resistant TB; XDR, extensively drug-resistant TB; HREZ, isoniazid, rifampin, ethambutol, pyrazinamide; RIF, rifampin; STR, streptomycin; AM, amikacin; PAS, *p*-amino salicyclic acid; KAN, kanamycin; CM, capreomycin; OFX, ofloxacin; CFX, ciprofloxacin; ETO, ethionamide; CS, cycloserine; LFX, levofloxacin; BDQ, bedaquiline; MXF, moxifloaxcain; LZD, linezolid; INHhd, high-dose isoniazid; CFZ, clofazimine; EMB, ethambutol; PZA, pyrazinamide; PTO, prothionamide; ETO, ethionamide; DLM, delamanid; TRD, teridizone; BPaL, bedaquline-pretomanid-linezolid; BPaLM, bedaquiline-pretomanid-linezolid-moxifloxacin.

[b]Longer regimens are recommended when construction of MDR/RR-TB regimen with three group A and two group B drugs is not possible due to intolerance to the medicines, acquired additional resistance, etc.

[c]Standardized short regimen is recommended for patients who have not been previously treated for >1 month with second-line drugs used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded; a shorter MDR-TB regimen of 9 to 12 months may be used instead of the longer regimens.

impact of the new drugs and regimens on patient treatment outcomes, explore evidence on current practices on regimen selection and duration, analyze the effectiveness of a new generation of antimicrobial treatments, and explore recent innovations in DR-TB treatment. We also discuss innovative trials under evaluation and reflect on the disappointments and pitfalls in the field and highlight key areas that require continued efforts toward improving diagnostics, treatment approaches, and rapid biomarkers for monitoring treatment response.

THE NEW GENERATION OF ANTIMICROBIAL TREATMENT

Bedaquiline

BDQ, the first new anti-TB drug to be approved in the last 4 decades, has become a front-line drug recommended by WHO for the treatment of RR/MDR-TB due to its substantial contribution in improving DR-TB treatment success rates (34). BDQ is a diarylquinoline drug which acts by binding to the ATP synthase of *M. tuberculosis*, which in turn inhibits the metabolism of mycobacterial energy (35, 36). This unique mechanism of action, its efficacy against both replicating and nonreplicating *M. tuberculosis* organisms, and its narrow spectrum of action limited to mycobacteria species are among the desirable properties of the drug that have contributed to its success (35).

Early *in vitro* studies demonstrated BDQ's exceptional bactericidal activity against *M. tuberculosis* in phase II and IIb studies (37). A phase II clinical study (C208) aimed at investigating the effectiveness of BDQ in combination with the background regimen for MDR-TB was conducted with a cohort of treatment-naive MDR-TB patients from seven countries (Brazil, India, Latvia, Peru, Philippines, Russian Federation, Thailand, and South Africa) (37). The study was designed in two stages: BDQ was administered for 2 months in stage one ($n = 47$) and for 6 months in stage two ($n = 160$). The study reported significantly higher rates of sputum culture conversion in the BDQ group compared to the placebo-controlled group (78.8% versus 57.6%) (37). However, an increased rate of mortality was reported in the BDQ group (11.4% [9/79] versus 2.5% [2/81]). High mortality rates in early studies may have resulted from BDQ having a long half-life and its association with QT prolongation, potentially leading to arrhythmia and sudden death (28). The follow-on study (C209) was an open-label single-arm trial ($n = 233$; 63.5% with MDR-TB, 18.9% with FQ resistance, and 16.3% with FQ and injectable resistance) that evaluated the safety, efficacy, and tolerability of BDQ in a larger cohort. The study reported that BDQ was generally well tolerated. The mortality rate was significantly lower, at 6.9% (38). The proportions of patients with culture conversion at week 24 was 79.5% and at week 120 was 72.2%, comparable to the C208 study.

Despite the improvement in treatment outcomes, the unexplained higher mortality risk associated with BDQ in clinical trials retarded access and rapid scale-up of the drug's implementation (37). Cost was also a challenge, and early use of BDQ relied on a donation program that was intended to accelerate access to BDQ (39).

More recent data from cohorts worldwide and an individual-patient data meta-analysis demonstrated a significant reduction in time of culture conversion, improved treatment success, and decreased mortality in patients who received BDQ-based regimens, while allaying previous safety concerns (26, 40–42). The use of BDQ in programmatic settings in South Africa demonstrated improved treatment success rates (49% in 2015 versus 19% in 2012) and reduced the risk of all-cause mortality (41). In a cohort of DR-TB patients receiving a BDQ-based regimen ($n = 200$) and with a high prevalence of HIV coinfection (67%), favorable outcomes were reported in 73% (146/200), with a mortality rate of 12.5% (25/200) (26). Similarly, a significantly lower mortality rate of 12.6% (128 deaths) was reported among the 1,016 patients who received BDQ-based treatment, compared to 24.8% (4,612 deaths) among 18,601 patients who received the standard regimen for 18 to 24 months (41). Encouragingly, long-term outcomes (24 months posttreatment) were substantially improved in patients receiving BDQ (66.2% [45/68 patients] versus 13.2% [27/204]; $P < 0.001$) (43). In addition, a significantly lower rate of treatment failure was observed in the group of patients who received BDQ-containing treatment (5.9% versus 26%) (43). Similar results have been reported in other settings (28, 42, 44–46). More recently, a treatment success rate of 90% when using BDQ in combination with LZD and PTM for the treatment of XDR-TB and nonresponsive MDR-TB was

reported in the NiX-TB study (47). There are numerous clinical trials under way evaluating BDQ-based short-course regimens for DR-TB.

Delamanid and Pretomanid

DLM and PTM belong to the nitroimidazole drug group and are both prodrugs requiring nitro-reductive activation. Drug activation generates toxic nitrogen species, which inhibit mycolic acid biosynthesis and cellular respiration (36, 48). Given the similar mechanisms of action, cross-resistance between both drugs has been reported (49).

Early bactericidal activity (EBA) studies of DLM and PTM demonstrated safety and antimycobacterial activity in smear-positive patients with pulmonary TB (50, 51). In a 14-day dose-ranging DLM monotherapy study of 48 patients with MDR-TB, drug activity was observed despite administration of DLM in various doses. The reported bacterial clearance was similar to that of second-line injectable agents, higher than pyrazinamide (PZA) but lower than FQ, INH, ethambutol (EMB), LZD, and rifamycin (50, 52). This antimycobacterial activity translated into significantly improved clinical outcomes at 6 months after DLM treatment initiation in a randomized phase IIb study with 481 MDR-TB patients. This phase IIb study assessed efficacy of DLM (at 100 mg or 200 mg twice daily) versus placebo given for 2 months with an optimized background regimen for MDR-TB in nine countries and showed significantly higher sputum culture conversion rates at month 2 (41% versus 29.6% in the placebo group) among patients receiving 200 mg of DLM (53). In a substudy conducted among 213 patients that received an additional 6 months of DLM, significantly higher rates of favorable treatment outcomes were observed (74.5% versus 55% in the 2-month DLM group) (54). Unfortunately, these findings could not be replicated in a larger phase III trial. In the Otsuka 21 randomized study, involving more than 500 participants, DLM administered for 6 months in combination with a background regimen for MDR-TB yielded no differences in time to culture conversion (DLM group, 87.6%, versus placebo group, 86.1%), cure at 30 months follow-up (DLM group, 77.1%, versus placebo group, 77.6%) or mortality rate (DLM group, 5.3%, versus placebo group, 4.7%) (55, 56).

While data describing performance of DLM under programmatic settings are limited, all reports point to improved outcomes in recipients of a DLM-containing regimen. In a retrospective South African study, sputum culture conversion at month 2 and 6 was reported in 52% (16/31) and 81% (25/31) of patients who received a DLM-containing regimen, respectively (57). Furthermore, the endTB study (NCT02754765) reported an 80% culture conversion rate at month 6 among 325 patients, where all patients were culture positive at baseline, with 20% HIV coinfected and >60% with FQ and/or injectable resistance (58). In a separate cohort from Latvia, a DLM-containing regimen was associated with a cure rate of 84.2% (16/19) at 6 months follow-up (59).

The combination of DLM and BDQ has also been explored to increase therapeutic options and regimen efficacy for MDR-TB patients. Programmatic use of DLM and BDQ has demonstrated remarkable effects in reducing times to sputum and culture conversion and improving treatment success (60). More than 70% of patients receiving regimens with DLM-BDQ achieve sputum culture conversion by 6 months and treatment success (61–63). Despite a high rate of HIV coinfection and a high burden of resistance to FQs and injectables among South African DR-TB patients, most patients experienced treatment success (62). Furthermore, the effect of DLM-BDQ has been reported to be similar to that of BDQ use alone (n = 122; 52.5% HIV coinfected), in terms of sputum culture conversion rates at month 6 (BDQ group, 95.2%, versus combined group, 81.8%) and at month 18 (BDQ group, 63.4% versus combined group, 67.5%) (64), despite the DLM-BDQ group having more extensive drug resistance profiles and higher rates of previous treatment failure. There is an ongoing clinical trial assessing the safety and tolerability of combined use of DLM and BDQ (AIDS Clinical Trial Group study; NCT02583048).

While early studies demonstrated insufficient bactericidal activity with PTM monotherapy use, efficacy of optimal drug combinations containing PTM evaluated in murine models demonstrated a dose-dependent PTM bactericidal activity. This observed bactericidal activity was similar to that obtained with INH and RIF, highlighting the

significant potential of the addition of PTM to shorten TB therapy (51). A phase IIb study assessing the use of PTM in combination with MFX and PZA (PaMZ) for patients with DS-TB or MDR-TB demonstrated superior bactericidal activity in the DS-TB group compared to the MDR-TB group. PTM tested in combination with BDQ displayed faster mycobacterial clearance when used in a BDQ-PTM-MFX-PZA (BPaMz) group compared to a BDQ-PTM-PZA (BPaZ) group (65). Subsequent phase III studies utilizing BPaZ had to be suspended, while BPaMZ is currently under evaluation in a phase III study (SIMPLICITB Study, NCT03338621). The addition of PTM in the BPaL and BPaLM regimens has increased the overall bactericidal activities of the combinations and has significantly decreased the duration of treatment required for relapse-free cure (47).

REPURPOSED DRUGS TO POTENTIATE NEW REGIMENS

Clofazimine

Clofazimine (CFZ) belongs to the riminophenazine group and was originally used for the treatment of leprosy; however, due to its bactericidal activity against *M. tuberculosis*, it now plays an integral role in TB treatment (66). Its putative mechanism of action is believed to be linked to redox cycling. The drug undergoes enzymatic reduction, thereby creating toxic reactive oxygen species (67). Renewed interest in the drug stems from its role in the short-course treatment regimen that achieved substantial cure rates in a cohort of Bangladesh patients (68). The Damien Foundation trials suggested that CFZ was a critical companion drug in the short-course regimen, as it replaced the more toxic thioamide in the continuation phase and efficiently compensated for its lost efficacy (68). A large-scale individual-patient meta-analysis that included 12,030 patients and assessed the safety and effectiveness of CFZ found that it significantly improved treatment success rates (40). CFZ is currently listed as a priority drug (group B) for the longer RR/MDR-TB regimen. As with BDQ, resistance to the drug is linked to mutations in the *Rv0678* gene (linked to drug efflux); therefore, cross-resistance between the two drugs is a major concern (69).

Linezolid

LZD is an oxazolidinone that acts by inhibiting the 50S ribosomal subunit during protein synthesis. It has demonstrated high activity against *M. tuberculosis* and currently forms a part of many investigational regimens in phase III clinical trials. LZD is currently classified as a group A anti-TB drug and is a core second-line agent associated with the potential to improve survival when used as part of a well-constructed multidrug regimen (34). Concerns of LZD-associated peripheral neuropathy and myelotoxicity have previously limited its use (70). The optimal dose that provides maximum bactericidal activity while counterbalancing toxicity became an important area of research. In the absence of a comprehensive understanding of LZD pharmacokinetics and pharmacodynamics, LZD toxicity has been managed through LZD dose reduction (47). *In vitro* preclinical evaluation of an optimal LZD dose in a hollow fiber infection model demonstrated that a 300-mg dose of LZD administered at 12-h intervals was associated with high bactericidal activity against *M. tuberculosis*; however, it was more toxic than a 600-mg dose administered once daily (71). In further hollow fiber model work, LZD at a dose of 300 mg/day did not reach or exceed pharmacokinetic-pharmacodynamic targets for toxicity, while it maintained high levels of microbial killing activity. A dose of 600 mg/day, or 1,200 mg on alternate days, produced marginally higher microbial killing but at the cost of breaching the pharmacokinetic-pharmacodynamic thresholds for mitochondrial toxicity in just under 20% of simulated patients (72). Clinical trials have shown that LZD doses of 600 mg and 1,200 mg/day in a clinical setting produce similar clinical effects as predicted by the hollow fiber model (47, 73). The recent results from the ZeNix trial confirmed that a 600-mg dose of LZD per day is sufficient and associated with improved safety compared with 1,200 mg/day (73). Hence, the WHO now recommends the use of 600 mg of LZD in the recently approved regimens with BPaL and BPaLM, while further clinical studies are needed on the efficacy of 300 mg/day (15).

RECENT INNOVATIONS IN THE DR-TB TREATMENT LANDSCAPE: SHORT-COURSE TREATMENT FOR DR-TB

The introduction of short-course treatment for DR-TB heralded a new era for the treatment of DR-TB (30). These novel regimens are described in detail in the sections below, and a landscape analysis of the changes to DR-TB treatment is presented in Table 1.

Short-Course Regimen for RR-TB and MDR-TB

The first major innovation in the treatment of DR-TB was demonstrated with the introduction of a short-course regimen for MDR-TB, reducing the treatment duration from >18 months to 9 to 12 months (31). The initial observational study reporting the effectiveness of this short-course regimen was conducted in Bangladesh, thus attracting the colloquial name, "the 9-month Bangladesh regimen." The regimen consisted of 9 to 12 months of treatment, comprising a 4- to 6-month intensive phase of treatment with kanamycin (KAN), gatifloxacin (GFX), prothionamide (PTO), CFZ, and high-dose INH, followed by a 5-month continuation phase of GFX, CFZ, PZA, and EMB (30). GFX was the core drug of the regimen and was administered at high doses to ensure relapse-free cure and suppression of resistant mutants (74, 75). The complex multidrug regimen was based on preclinical data on individual drug characteristics and real-world iterative regimen modification until the final regimen was constructed. Injectable KAN was added to ensure early bactericidal activity and protect against the development of resistance to FQs (21), CFZ and PZA were active against organisms with low metabolic activity, preventing relapse of infection (76, 77), and high-dose INH and PTO were added to protect core drugs (78). The initial evaluation included patients with proven or suspected MDR-TB (n = 206). Patients received in-hospital observation for the duration of the intensive phase of the treatment and were followed for a duration of 24 months; the regimen resulted in an 87.9% cure rate (68). An updated report on this cohort revealed the continued efficacy of the regimen in 515 patients, 84.5% of whom achieved relapse-free treatment success (30).

Following the positive preliminary results of the Bangladesh study, five subsequent prospective cohort studies were conducted in Benin, Niger, Cameroon, and West and Central Africa. The studies noted minor modifications to the initial regimen (predominantly in the dosage of FQ or the replacement of GFX with MFX) and in the duration of the intensive phase of the regimen (30, 79–81). This was followed by a phase III randomized controlled study, the STREAM study, which evaluated a modified short-course regimen (high-dose MFX [400 to 800 mg/day, depending on patient's weight] replacing GFX) compared to the standard 18- to 24-month WHO regimen (82). Following the initial recommendation of the standard short "Bangladesh" regimen by the WHO, the affirmative results of the STREAM study led to the widespread adoption of the regimen (33).

Another major breakthrough, marking a turning point in the fight against DR-TB, was the recommendation of the first all-oral (injection-free) long-course regimen (33). With the overwhelming success of BDQ, the drug was incorporated into the standard long regimen, replacing the second-line injectable drug. Shortly thereafter, an all-oral BDQ-containing shortened regimen, based on high levels of efficacy demonstrated in the South African TB Program, was recommended. This change has significantly improved treatment outcomes and has improved the retention of RR/MDR-TB patients in care (83). Furthermore, the continuation of the STREAM trial to stage 2, aimed to assess whether the 9-month all-oral BDQ regimen is superior to the injectable-based "Bangladesh" regimen assessed in stage 1 and the WHO-recommended MDR-TB regimen in accordance with 2011 MDR-TB treatment guidelines.

The 6-Month BPaL Regimen

Another novel combination advancing the treatment of DR-TB patients is the BPaL regimen. The Nix-TB study was an open-label, single-group study that evaluated the safety and efficacy of the novel combination of BDQ, PTM, and LZD for 6 to 9 months in patients with nonresponsive MDR-TB or XDR-TB (n = 109). Despite extensive drug resistance, high rates of previous treatment, and a high burden of cavitary disease, 90% of the patients enrolled in the study had favorable treatment outcomes. Among the 109 patients enrolled,

63/71 (89%) of XDR-TB and 35/38 (92%) of nonresponsive MDR-TB patients who displayed poor responses to prior treatment, achieved favorable outcomes on the BPaL regimen at 6 months follow-up (47). Adverse events related to LZD toxicity, documented in 81% of the participants, was manageable following dose reduction of LZD (47). A follow-up phase III study evaluated safety and efficacy of various doses and treatment durations of LZD plus BDQ and PTM in participants with pulmonary TB, XDR-TB, pre-XDR-TB, or nonresponsive or intolerant MDR-TB (ZeNix study; NCT 03086486). The results of that study were recently presented, and among 181 patients that were enrolled, the success rate achieved among patients who received the highest dose of LZD (1,200 mg) for 6 months was 93%, similar to results observed among those who received 1,200 mg for 2 months and achieved 89% success (73). In addition, 91% and 84% success rates were achieved for those receiving 600 mg LZD for 6 months and 2 months, respectively. There was a clinical efficacy reduction of 2 to 9% in patients who received LZD at a lower dose and/or for a shorter duration; however, these results demonstrated that LZD dose reduction and duration do not significantly impact the clinical efficacy of the BPaL regimen. Thus, a dose of 600 mg for 2 months may be sufficient to achieve adequate efficacy while counterbalancing safety.

INNOVATIVE TRIALS UNDER EVALUATION

There are several DR-TB studies assessing novel regimens for the treatment of DR-TB with the overall aim of reducing treatment duration, pill burden, and drug toxicity and improving treatment outcomes. Among the ongoing studies, there are significant overlaps and striking similarities, including various combinations of four to five group A or repurposed drugs and treatment durations ranging from 6 to 12 months, and BDQ and LZD are the most common drugs in all regimens. The studies are grouped according to their treatment duration in Table 2.

The WHO recently considered the results of two major clinical trials, TB PRACTECAL and ZeNIX, to strengthen the evidence on the use of 6-month regimens for RR/MDR-TB. The TB-PRACTECAL and ZeNIX trials evaluated similar regimens, except that ZeNIX did not evaluate BPaLM and its primary objective was to evaluate various doses and durations of LZD exposure within the BPaL regimen. The results from the ZeNIX study showed that a 600-mg dose of LZD offered the best balance of safety and efficacy (73). Furthermore, data from the TB PRACTECAL trial revealed improved safety and efficacy of the BPaLM regimen compared to the standard-of-care RR/MDR-TB regimen (15). In addition, the BPaL (600-mg) regimen retained excellent efficacy without addition of MFX in the presence of FQ resistance (pre-XDR-TB patients).

The NExT trial, which evaluated the efficacy of an all-oral 6- to 9-month regimen against an injectable-containing long regimen (24 months), demonstrated that a 6-month injectable-free MDR-TB regimen (containing BDQ, LZD, and levofloxacin [LFX]) significantly improved treatment outcomes (84). The endTB clinical trial, which is presently evaluating five different short MDR-TB regimens, completed enrollment in 2021; results are anticipated soon (NCT02754765).

All of the described new regimens for DR-TB are expected to improve the treatment outcomes for DR-TB. However, the future concern may be implementation of these regimens on a larger scale, especially in countries with high TB burden and limited resources. Further, emergence of drug resistance to drugs such as BDQ, which represents a backbone in most of these new regimens, may compromise the overall efficacy provided by the regimens.

CLINICAL MANAGEMENT OF DR-TB IN CHILDREN AND ADOLESCENTS, PREGNANT WOMEN, AND PEOPLE LIVING WITH HIV

Children and Adolescents

Children and adolescents have suffered neglect in DR-TB research for years. However, recent steps have been taken to improve care in this population. Though the majority of children do not suffer from severe forms of TB, many still get infected with DR-TB. Research in improved diagnostics, shorter regimens, practical formulations, and palatable medication

TABLE 2 Emerging DR TB regimens: anticipated evidence pipeline from innovative clinical trials under way

Type and name of trial (registry no.)	Drug regimen assessed and duration of treatment	Arm(s)	Phase(s)	Status	Timelines
6-mo DR-TB regimens					
SimpliciTB trial (NCT03338621)	Safety and efficacy of BDQ, PTM, MFX, and PZA (BPaMZ) in DR-TB patients for 6 mo	Arm 1: drug-sensitive BPaMZ; Arm 2: drug-sensitive TB standard regimen; Arm 3: drug-resistant BPaMZ	II and III	Fully enrolled; in follow-up stage	
TB PRACTECAL (NCT02589782)	Short-course regimen containing BDQ, PTM, and LZD ± MFX-CFZ for MDR-TB (6 mo)	Arm 1: regimen 1 (BDQ, PTM, MFX, and LZD); Arm 2: regimen 2 (BDQ, PTM, LZD, and CFZ); Arm 3: regimen 3 (BDQ, PTM, and LZD); Arm 4: control regimen (standard-of-care regimen for MDR/XDR-TB consistent with WHO guidelines)	II and III	Recruitment terminated; analysis under way	2017–2022
ACTG A5312 (NCT01936831)	Different doses of INH and generic variants of INH-resistant *M. tuberculosis* (6 mo)	Arm 1: exptl arm, participants with *inhA* mutations receiving 5, 10, or 15 mg/kg of INH; Arm 2: exptl arm, participants with DS-TB receiving 5 mg/kg dose of INH; Arm 3: no-intervention arm, participants with *katG* mutation did not receive study drug	II	Stage 1 completed; completed results available; stage 2 under way	2014–2021
6- to 9-mo DR-TB regimens					
STREAM trial stage 2 (NCT02409290)	Comparing all-oral with BDQ or OBR[a] with BDQ and injectable (6–9 mo)	Arm 1: WHO-approved MDR-TB regimen in accordance with 2011 WHO MDR-TB treatment guidelines; Arm 2: regimen described by Van Deun (68), MFX replaced with LFX; Arm 3: all-oral regimen (BDQ, CFZ, EMB, LFX, and PZA) for 40 wks supplemented with INH and PTO for first 16 wks	III	Fully enrolled; in follow-up stage	2016–2022
NExT (NCT02454205)	Injection-free regimen of BDQ, ethionamide, or high-dose INH, LZD, LFX, and PZA for 6–9 mo	Arm 1: active comparator, conventional treatment for 21–24 mo consisting of injectable agent; Arm 2: exptl, interventional treatment for 6–9 mo of all-oral regimen	III	Completed	2015–2021
BEAT-TB, India (CTRI/2019/01/017310)	Short-course regimen (6–9 mo) for MDR-TB and resistance to FQ vs injectable of BDQ, DLM, LZD, LFX, and CFZ	Arm 1: intervention regimen (BDQ, DLM, LZD, CFZ)	IV	Open for enrollment (India)	2019–2023
ZeNix (NCT03086486)	Various doses and durations of LZD plus BDQ and PTM for XDR-TB, pre-XDR-TB, or complicated MDR-TB (>6 mo)	Arm 1: exptl regimen, 1,200 mg LZD for 26 wks, placebo LZD for 26 wks + PTM, BDQ; Arm 2: exptl regimen, 1,200 mg LZD for 9 wks, placebo LZD for 9 wks, PTM and BDQ; Arm 3: exptl regimen, 600 mg LZD for 26 wks, placebo LZD for 26 wks + PTM and BDQ; Arm 4: exptl regimen, 600 mg LZD for 9 wks, placebo LZD, PTM and LZD	III	Results presented	2017–2021
9-mo DR-TB regimens					
endTB (NCT02754765)	Shorter regimens containing BDQ and/or DLM, MFX-LFX and PZA, and LZD-CFZ for MDR/XDR-TB (9 mo)	Arm 1: endTB regimen 1 (BDQ, LZD, MFX and PZA); Arm 2: endTB regimen 2 (BDQ, LZD, CFZ, LFX, and PZA); Arm 3: endTB regimen 3 (BDQ, DLM, LZD, LFX, and PZA); Arm 4: endTB regimen 4 (DLM, LZD, CFZ, LFX, and PZA); Arm 5: endTB regimen 5 (DLM, CFZ, MFX, and PZA); Arm 6: endTB regimen 6 (control regimen; MDR-TB standard regimen consistent with WHO guidelines)	III	Fully enrolled; in follow-up stage	2016–2021
BEAT-Tuberculosis, South Africa (NCT04062201)	Short-course regimen (6 mo) for MDR-TB consisting of BDQ, DLM, LZD, LFX, and CFZ vs standard of care (9-mo regimen)	Arm 1: exptl regimen, study strategy (BDQ, DLM, LZD, LFX, and CFZ); Arm 2: active comparator regimen, control strategy (MDR-TB standard-of-care regimen)	III	Recruiting (South Africa)	2019–2023
9- to 12-mo DR-TB regimens					
DELIBERATE ACTG 5343 (NCT02583048)	Drug-drug interactions and QT effect of BDQ and/or DLM regimens (9–12 mo)	Arm 1: BDQ + MDR-TB background regimen; Arm 2: DLM + MDR-TB background regimen; Arm 3: BDQ and DLM + MDR-TB background regimen	II	Completed	2016–2021
EndTB-Q (NCT03896685)	BDQ, DLM, LZD, and CFZ for FQ-resistant MDR-TB (9–12 mo)	Arm 1: endTB-Q regimen (BDQ, DLM, CFZ, and LZD for 24 or 39 wks);	III	Open for enrollment (Pakistan, India,	2020–2023

(Continued on next page)

TABLE 2 (Continued)

Type and name of trial (registry no.)	Drug regimen assessed and duration of treatment	Arm(s)	Phase(s)	Status	Timelines
		Arm 2: endTB-Q control regimen (MDR-TB standard regimen consistent with WHO guidelines)		Lesotho, Peru, and Vietnam)	
MDR-END (NCT02619994)	Combination of DLM, LZD, LFX, and PZA for MDR-TB patients without FQ resistance (9–12 mo) vs 20–24 mo with injectables	Arm 1: control regimen (locally used WHO-approved MDR-TB regimen in Korea); Arm 2: exptl regimen (DLM, LZD, LFX, and PZA)	II	Fully enrolled; in follow-up stage	2016–2021
Opti-Q (NCT01918397)	High-dose LFX (9–12 mo)	Arm 1: active comparator regimen, LFX 11 mg/kg daily and OBR Arm 2: exptl regimen, LFX 14 mg/kg daily and OBR; Arm 3: exptl regimen, LFX 17 mg/kg daily and OBR; Arm 4: exptl regimen, LFX 20 mg/kg daily and OBR	II	Follow-up completed; currently analyzing results	2015–2021
DRAMATIC[b] (NCT03828201)	Evaluating the safety and efficacy of all-oral regimen containing LFX, BDQ, LZD, DLM, and CFZ; patients to be randomized for different durations of treatment (study duration uncertain)	Arm 1: exptl regimen, DRAMATIC-16 wks (DLM, LFX, BDQ, CFZ, and LZD) Arm 2: exptl regimen, DRAMATIC-24 wks (DLM, LFX, BDQ, CFZ, and LZD) Arm 3: exptl regimen, DRAMATIC-32 wks (DLM, LFX, BDQ, CFZ, and LZD) Arm 4: exptl regimen; DRAMATIC-40 wks (DLM, LFX, BDQ, CFZ, and LZD)	II	Recruiting	2021–2025

[a]OBR, optimized background regimen. Abbreviations for drug names are provided in Table 1, footnote a.
[b]DRAMATIC, Duration-Randomized Study of Treatment of Patients with MDR-TB.

for children has gained momentum (85). Regimens shorter than those used to treat adults may be effective in children and can solve problems such as costs to families and health care systems, reduced toxicity, and lower risk of drug-drug interactions among HIV-coinfected children and also improve adherence (86). Steps have been taken toward conducting clinical trials in children and adolescents. Though the SHINE (Shorter Treatment for Minimal Tuberculosis in Children) trial focused on DS-TB, it achieved a milestone as a TB clinical trial in children and paved a way for DR-TB clinical trials in the future (87). In the latest WHO DR-TB guidelines (2021), BDQ is recommended as part of an all-oral short regimen in children <6 years of age (6). Additionally, BDQ may be included in longer RR/MDR-TB regimens in patients aged 6 to 17 years. Furthermore, DLM is also recommended to be included in the treatment of children and adolescents with RR/MDR-TB (6). These new drugs have shown outstanding activities for adults and are expected to offer the same benefit for children and adolescents.

Pregnant Women

DR-TB treatment in pregnant women has always been challenging, because anti-TB drugs used for treatment are potentially harmful to the fetus and these patients are often excluded from clinical trials (88). Anti-TB drugs used in previous regimens, i.e., aminoglycosides and ethionamide, are known to be teratogenic to the fetus (88). Hence, the previous guidelines often excluded the use of these drugs in short and long RR/MDR-TB regimens in pregnant women (34, 89). The WHO has downgraded the use of injectable drugs and recommends the use of all-oral regimens in pregnant women. However, the data on safety of drugs such as BDQ and DLM during pregnancy or breastfeeding are limited. It will be some time before there is evidence on the outcomes from the use of these new regimens in pregnant women, given the low incidence of pregnancy during RR/MDR-TB treatment (90). Individualized regimens consisting of drugs with known safety profiles are often recommended (34).

People Living with HIV

Timely diagnosis of DR-TB and treatment initiation among people living with HIV (PLHIV) remains the first step toward improving treatment outcomes. Even though DR-TB and HIV coinfected patients receive the same treatment as non-HIV-coinfected patients, HIV-coinfected patients may frequently experience serious adverse events and require treatment observation for any DR-TB and HIV treatment complications (91).

PLHIV have often been excluded in clinical research studies; however, progress in recent years has been made, and this population has increasingly been included in major trials, e.g., the STREAM and NiX TB trials. In the STREAM trial, one-third of the enrolled patients were PLHIV; even though the analysis based on HIV status was not done, this study achieved treatment success of 78.8% and 79.8% for short and long regimens, respectively (32). Similarly, the NiX-TB study experienced successful treatment outcomes (90%), despite 51% of patients having HIV coinfection (47). HIV status did not impact treatment outcomes, as results were consistent regardless of HIV status. It has been reported that an MDR-TB short-course regimen is generally tolerated among PLHIV, even though adverse events such as hearing loss are more frequently reported in this population (81).

There has been increasing interest in using new and repurposed drugs in PLHIV with DR-TB, with promising treatment outcomes. The NExT-TB study reported that 55% of patients were HIV coinfected, and the use of a new drug (BDQ) and a repurposed drug (LZD) in the regimen was associated with improved outcomes (84).

THE GRAY AREAS

The Composition of DR-TB Regimens: Drug Selection and Treatment Duration

A hallmark feature of *M. tuberculosis* infection is its long periods of latency, which is linked to the ability of the organism to persist in the host tissues. TB disease therefore requires an extended duration of combination antibiotic treatment to achieve complete sterilization of both actively multiplying and dormant bacilli. Thus, the main objectives of combination drug therapy for TB are the following: (i) to rapidly reduce the mycobacterial burden, thereby reducing disease transmission; (ii) to eradicate persistent mycobacterial populations and prevent

TABLE 3 Core and companion drugs and their bactericidal and sterilizing activities in the treatment of MDR-TB (long-course regimen)[a]

	Characteristics			Use in MDR/XDR-TB treatment regimens		
Drugs (grouping according to WHO)	Bactericidal activity	Sterilizing activity	Resistance prevention	Core drug	Companion drug used for its bactericidal or sterilizing effect	Other companion drugs
Group A						
FQs (LFX and MFX)	High	High	High	X		
BDQ	High	High	High?	X		
LZD	High	Low	High	X		
Group B						
CFZ	Low	High	High		Sterilizing	
Cycloserine or terizidone	Moderate	Low	Moderate			Bacteriostatic
Group C						
EMB	Low	Low	Moderate			Bacteriostatic
DLM	High	High	High	X		
PZA	Low	High	Low		Sterilizing	
Imipenem-cilastatin OR meropenem	High	High	Moderate?			Bactericidal
Second-line injectables						
Ethionamide or PTO	High	Low	High			Bacteriostatic and bactericidal
PAS	Moderate or high	Low	Moderate			Bacteriostatic
INH high-dose	Low or moderate	Low	High			Bactericidal

[a]Updated from Van Deuen et al. 2018 [74]. Abbreviations of drug names are defined in Table 1, footnote a.

relapse infection; and (iii) to prevent the acquisition of drug resistance (92). In order to meet these objectives, TB treatment regimens are comprised of core drugs, which drive the efficacy of the regimen, complemented by companion drugs that support the activity of the core drugs. Core drugs have both bactericidal and sterilizing effects, essential for relapse-free cure, and are ideally administered throughout the treatment period (74). In the absence of a core drug, a regimen is substantially ineffective or almost entirely loses its efficacy (81). Companion drugs are used to ensure the core drug is protected by preventing the selection of resistant mutants and preventing relapse after treatment completion (74). In Table 3, we present an update on microbiological characteristics of drugs according to the recent WHO classification and outline their roles in long-course RR/MDR-TB treatment (updated from Van Deun et al. summary in 2018 [74]). Individual-patient meta-analyses and published efficacy data have been used by WHO as the basis to grade anti-TB drugs (93). Given that relatively few new anti-TB drugs are available amid the increasing severity of drug-resistant strains, the diverse microbiological activity of individual drugs is often not taken into consideration when constructing a regimen. Instead, grouping is prioritized on the most effective drugs currently available. As opposed to the prior classification, there is a breadth of data available on the new and repurposed drugs to support their prioritized grading in group A. Drug combinations using group A drugs have treatment success rates as high as 90% for the most severe forms of TB (47).

Despite decades of TB treatment research, the optimal number of drugs required to construct an effective regimen remains an area of uncertainty. The Preserving Effective TB Treatment study (PETTS) and an earlier individual-patient meta-analysis demonstrated the inclusion of at least four effective drugs improved treatment success and decreased mortality rates (40, 93). The latest meta-analysis suggested that the inclusion of new drugs and a later-generation FQ contributed to the overall treatment success rate observed in that analysis (93). On the basis of these findings, WHO recently reclassified anti-TB drugs into three main groups according to the available evidence on effectiveness and safety of the drugs (34). To design an appropriate regimen, WHO recommends a stepwise process to construct a regimen of at least four drugs likely to be effective. DR-TB drugs are ranked into three main groups (Table 1) (34). Regimens are

selected in a stepwise process prioritizing the inclusion of all three group A drugs (BDQ, LZD, and MFX or LFX) drugs. If all three group A drugs cannot be included in the regimen, selection is made from the group B list. Group C drugs are included in the regimen when an effective regimen cannot be derived from the former groups.

Innovations in DR-TB treatment have resulted in a substantial reduction in treatment duration in programmatic regimens. However, the optimal duration following culture conversion and the lack of effective biomarkers to guide treatment duration contribute to this area of uncertainty. An increasing number of new studies aim to reduce treatment duration (described in the previous section and in Table 2).

Role of High-Dose INH in Treatment of MDR-TB

INH has been the cornerstone of TB treatment and remains an essential component in the treatment of DS-TB. However, the utility of the drug has been severely compromised with the emergence of *M. tuberculosis* variants displaying resistance to INH. INH displays potent EBA against *M. tuberculosis*, allowing for rapid clearance of ~95% of the bacterial load within 2 days of treatment using standard doses of the drug (4 to 6 mg/kg) (94). Resistance to INH is mediated by mutations in the *inhA* gene and its promoter region, which lead to a minimal increase in the MIC, ranging between 0.25 and 2 mg/L (95). Additionally, mutations in *katG* confer higher levels of INH resistance, with MICs ranging between 1 and 16 mg/L (95). Given that INH displays a dose-dependent EBA, higher doses of the drug (up to 20 mg/kg) may result in exposures likely to overcome resistance mediated by *inhA* and *katG* mutations.

The perceived clinical benefit of high-dose INH is supported by many lines of evidence. A randomized placebo-controlled trial among MDR-TB patients conducted in India reported reduced time to culture conversion and improved treatment outcomes in patients treated with high-dose INH (16 to 18 mg/kg) compared to patients who received the standard dose of INH or placebo (96). Similar results of reduced time to culture conversion in a high-dose INH group versus a standard dose INH group were reported in a retrospective cohort study in Haiti (7 weeks versus 9.1 weeks) (97). The inclusion of high-dose INH in treatment-shortening studies for MDR-TB have demonstrated treatment success rates of ~55% to 70%. These studies led to the WHO endorsement of high-dose INH in the standard short-course regimen for MDR-TB (68, 79, 80). An individual-patient meta-analysis on 975 children supported the role of high-dose INH in achieving treatment success (98). A more recent meta-analysis on 12,030 patients lacked sufficient data to support the role of high-dose INH (40). It has been demonstrated that an INH dose of 10 to 15 mg/kg displayed similar EBA among *M. tuberculosis* strains with *inhA* mutations compared to the standard dose efficacy against DS-TB strains (99). However, there is a delayed drug activity in patients infected with *M. tuberculosis* strains bearing *inhA* mutations. In contrast to the rapid clearance observed between days 0 and 2 in patients infected with drug-susceptible strains, the average daily killing of mutant strains was higher on days 2 to 7 (99). Further work is under way to assess the activity against *katG* mutants, which confer higher levels of resistance than *inhA* mutants.

In addition to the underlying mycobacterial resistance, host genetics also impact the availability of INH. In the host, INH metabolism is mediated by the by N-terminal acetyltransferase 2 (NAT2). The presence of a mutation in the NAT2 gene leads to substantial differences in INH clearance, thereby classifying individuals into either "slow" or "fast" acetylators (100). The prevalence of NAT2 mutations differs geographically, with slow-acetylator status being prevalent in over two-thirds of individuals in Egypt and the United States but rare in northern Asia (101). Nonetheless, NAT2 genetic diversity has a complex evolutionary history, and significant heterogeneity is seen between people of different ancestries within geographic locations such as the United States (102, 103). Slow acetylators with *inhA* mutations may still benefit from the normal dose of INH; however, fast acetylators may require higher doses of 15 mg/kg (101). In the case of *katG* mutations, it has been postulated that even at high doses, effective levels of the drug cannot be achieved, even in individuals with slow-acetylator status. Optimal dosing of INH therefore requires consideration of the host genetics and pathogen mutation profiles. In a South African study, fast acetylators were less common than intermediate and slow acetylators, presenting at rates of 18, 43, and 34%,

respectively (104). Further, that study demonstrated that fast acetylators had faster INH clearance (2.3 times faster) than slow acetylators, suggesting that INH dosage should depend on the acetylator status of an individual (104). Thus, the impact of resistance-conferring mutations could potentially compromise treatment success rates and long-term outcomes in such patient populations. Importantly, further research is required to identify those patients likely to benefit from an INH high dose in the presence of INH resistance-conferring mutations and also on the potential role of the drug in new regimens.

Roles of Ethambutol and Pyrazinamide

EMB and PZA form a part of group C agents in the recent guidelines of DR-TB treatment (5), playing a supporting role to core drugs such as BDQ. PZA is used for its relapse-preventing properties, as it displays excellent sterilizing effect, assists in treatment shortening (74), and demonstrates excellent TB lung tissue penetration (105). EMB has low bactericidal and sterilizing effects but demonstrates moderate resistance prevention, thereby helping to complete the DR-TB regimen and prevent selection of mutant strains. High rates of resistance to both drugs have been reported among MDR-TB isolates, ranging from 44.1% to 80% for EMB (106, 107) and 36% to 85% for PZA (106, 108, 109). Notwithstanding this high background burden of resistance among MDR-TB isolates and the technical difficulties associated with phenotypic DST of EMB and PZA, these drugs have been part of the standard short regimen for a long time. Thus, they may have had less than the desired effect in protecting the core drugs and could potentially compromise long-term outcomes. In a retrospective study where PZA resistance correlated with RIF resistance, treatment success for the cohort ranged from 19 to 63% (110). This implies the importance of susceptibility testing to these drugs, as mandated by the WHO guidelines. Contrary to the previous guidelines, which precluded the use of the standard short-course regimen in patients with preexisting resistance to EMB and PZA, the results from the Bangladesh cohort showed 93.3% treatment success among participants (n = 242) with preexisting resistance to PZA and EMB (111). The success rate was similar (93.8%) to that in participants who were susceptible to both drugs (n = 81). The individual-patient data meta-analysis showed that the patients with resistance to PZA and EMB were at higher risk of treatment failure and relapse than were susceptible patients (40). However, the negative effects of PZA and EMB resistance on treatment outcomes were wholly mitigated in patients with FQ susceptibility. Studies have shown that despite resistance to PZA and EMB being present and associated with adverse outcomes, if FQ susceptibility is preserved the effect on the clinical outcomes is not significant enough to justify systematic DST at baseline (111). Several studies have found that resistance to PZA and EMB in patients with FQ-susceptible TB did not negatively affect clinical outcomes (30, 79, 81). In contrast, the results from the STREAM trial showed that background PZA resistance was associated with unfavorable outcomes in the per-protocol analysis (112).

EMB and PZA resistance is challenging to identify in clinical practice, mostly because the front-line molecular diagnostic assays, Gene Xpert Ultra and the line probe assay, do not cover these drugs and phenotypic DST is insufficiently reliable (113). Potential sources of inaccuracy may arise from uncertainty around critical concentrations for these drugs and the lack of standardized methods for culture-based MIC determinations (114). More recently, next-generation sequencing (NGS) has been used to detect mutations in the *pncA* gene and *embCAB* operon for PZA and EMB, respectively; however, not all mutations detected in these genes conferred phenotypic resistance (115, 116). Instead, sequencing results of *embCAB* and phenotypic DST have shown significant discordance (113, 116). Similarly, isolates bearing mutations associated with PZA resistance have demonstrated susceptibility by phenotypic DST (117). Unreliable phenotypic DST from these drugs complicates the clinical determination of false-negative and false-positive results from genotyping (118). Greater standardization of laboratory methods for phenotypic DST is needed, and greater certainty around critical concentrations and clinical breakpoints needs to be achieved.

Antimicrobial Heteroresistance

Heteroresistance in *M. tuberculosis* infection is common, i.e., where the *M. tuberculosis* population contains a mix of both susceptible and resistant organisms (119). The prevalence of mixed-strain *M. tuberculosis* infections has been reported in the range of 10 to 20% in settings in which TB is endemic (120, 121). Heteroresistance, commonly referred to as mixed-strain infection, has been reported for a number of key anti-TB drugs, including FQs, RIF, INH, PZA, second-line injectable agents, and BDQ (122). This phenomenon arises from suboptimal drug treatment, i.e., it is acquired resistance, or from mixed infection by strains with different susceptibilities, e.g., superinfection with a resistant strain in a patient with DS-TB (123). Consequently, heteroresistance complicates therapeutic management of TB and poses a threat to TB treatment success. Until recently, each TB episode was assumed to be caused by a single *M. tuberculosis* strain that elicited an immune response, serving to protect the host against infection with a secondary strain (124). However, molecular technology has demonstrated multiple TB disease-causing strains co-occurring in the same patient.

Heteroresistance has been associated with poor treatment outcomes, such as persistent infection and treatment failure in MDR-TB patients (119). In a study evaluating the impact of heteroresistance on treatment outcomes, using 24-locus mycobacterial interspersed repetitive unit variable number tandem repeat analysis in 66 DR-TB patients, 35/66 (53%) displayed mixed infection after 6 months of treatment. Heteroresistance was observed among 16/35 (45.71%) with mixed infection, of which 8/35 (22%) experienced treatment failure (125). While individualized treatment tailored by utilizing deep sequencing could overcome the challenge of heteroresistance, this may not be feasible in low-income countries.

Micro-heteroresistance for BDQ has been demonstrated through targeted sequencing of the *Rv0678* gene (126). In that report, initial phenotypic DST demonstrated BDQ susceptibility, while targeted sequencing done later during treatment showed an insertion in the *Rv0678* gene. Importantly, the newly discovered insertion, which was not present in the isolate before BDQ treatment, occurred at a frequency of $>$90% among isolates obtained after BDQ exposure (126). Heteroresistance was reported in approximately 11/158 MDR-TB isolates obtained from four countries (Thailand, Bangladesh, Tanzania, and Russia) by using NGS to sequence 11 gene regions. Heteroresistance was most commonly detected in the *gyrA* gene (codon 94; linked to FQ resistance), the *rpoB* gene (codons 526 and 531; linked to RIF resistance), and the *EmbB* gene (linked to EMB resistance) in 11–26% of isolates (122).

Extensive Cavitary Disease and Intracavitary Gradients

Pulmonary cavitation is the classic hallmark of TB disease associated with an increased bacterial load (127). Cavitary disease is often associated with drug resistance and treatment failure (128). Cavitary disease is highly contagious, as it is associated with a high *M. tuberculosis* load of approximately 1,011 bacilli/g, contributing to ongoing *M. tuberculosis* transmission (127). Given the associated risk of relapse and treatment failure (128), the use of the standard short treatment regimen is contraindicated.

A significant challenge associated with cavitary disease is the development of intracavitary gradients, arising from uneven penetration of anti-TB drugs in the various lung cavity compartments and leading to one of two scenarios: (i) acquisition of drug resistance due to inadequate drug exposure (129), or (ii) increased MICs due to low intracavitary drug concentrations (130). It was demonstrated that the pretreatment sputum MIC had an accuracy of 49.4% in predicting cavitary MICs in that study, and there were large concentration-distance gradients for each antibiotic. The location-specific concentrations were inversely correlated with MICs ($P < 0.05$) and therefore with acquired resistance (130). Additionally, findings from a study conducted in Georgia found multiple *M. tuberculosis* strains with varied resistant profiles in lung specimens obtained during resection surgery compared to sputum samples (40% versus 0 to 5%) (131). That study further demonstrated that strains were genetically distinct and the DST profile across samples was fully reversed, i.e., the caseum DST profile and sputum sample (from pre-XDR-TB to pan-susceptible TB) (131).

Various anti-TB drugs demonstrate varied abilities to penetrate the lung cavity, thereby resulting in suboptimal drug concentrations within cavities (105, 129). The potential of the

anti-TB drugs LZD, MFX, CFZ, PZA, KAN, INH, and RIF to penetrate TB cavities and the resulting concentrations have been evaluated (132). These studies demonstrated that the standard doses of INH and RIF had poor penetration to the cavitary lesions, and the resulting concentration at the site of disease was inadequate. However, a combination of MFX and CFX or CFZ and LZD standard doses in multidrug-level simulations demonstrated optimal penetration into caseous lesions, with adequate concentrations achieved at the site of disease (132). A recent study used a combination of positron emission tomography and computed tomography scanning and hollow fiber time-kill simulations and demonstrated heterogeneity in RIF concentrations across pathologically distinct cavitary lesions (133). In contrast, LZD and FQs have been reported to have great tissue penetration, making them an excellent choice in the treatment of cavitary disease (134, 135). There is an urgent need for innovative strategies to overcome challenges resulting from intracavitary gradients and more studies focusing on factors such as drug dosing and novel modes of delivery.

Individualized versus Standardized Treatment Approaches

A significant challenge in low-income high-TB burden settings is that care for DR-TB is offered as part of a simplified standardized programmatic response aimed at achieving the best possible public health outcomes. Using this approach, all patients with DR-TB receive a standard DR-TB regimen upon diagnosis of RR-TB, constructed based on predominant resistance patterns in the community without phenotypic resistance test results and thereby enabling immediate access to treatment (20). While this approach improves programmatic provision of care, it does not account for patient genetics and variabilities in pathogen susceptibility and is associated with a number of disadvantages, such as treatment failure in those with preexisting drug resistance to the selected regimen and risk of drug resistance amplification, including development of resistance to new drugs (136–138).

On the contrary, individualized regimens are tailored to respond to individual patient needs, as the regimens are constructed based on patient-specific DST results and clinical information (34). Recent data indicate that individualized study approaches improve the probability of treatment success and long-term treatment outcomes (136, 139). NGS technology has been explored extensively for individualized care approaches for DR-TB and is fast becoming the standard-of-care practice in some settings (140–142). However, in resource-limited settings with the highest burden of TB disease, it may be a long way from becoming routine practice (143). Given the persistently low treatment success rates and increased risk of amplified drug resistance, the continued used of standardized regimens that adopt a one-size-fits-all approach to all DR-TB in an era of increasing drug resistance is a serious public health concern (136). Individualized treatment approaches in resource-limited settings will require substantial investment in research, including operational and implementation research to enhance capacity in such settings (138).

Isoniazid Monoresistance Detection and Treatment Regimens

In 2019, 1.4 million incident cases of INH-resistant TB, among which 1.1 million cases were INH monoresistant, were reported for the first time by the WHO (6). INH resistance, now the most common form of TB drug resistance, is a serious concern, given that genomic evolution studies have shown that INH resistance is the first resistance type to develop along the pathway to multiple drug resistance (144). Of further concern is that detection of resistance to INH is not currently available using front-line TB diagnostic assays, such as Gene Xpert Ultra (144). Current diagnostic pathways focus on the detection of RIF resistance as a surrogate marker of MDR-TB and test for INH in a reflex manner. Thus, in the absence of routine *M. tuberculosis* culture and phenotypic testing, patients with INH monoresistance are undiagnosed and receive standard DS-TB treatment; resistance is detected later when they demonstrate a poor treatment response (145). A systematic review analyzing treatment outcomes of patients with INH-resistant TB treated with the recommended first-line anti-TB drugs reported pooled rates of failure or relapse, or both, and acquired drug resistance at rates of 15% (95% confidence interval [CI], 12 to 18%) and 3.6% (95% CI, 2 to 5%), respectively, compared to 4% (95% CI, 3 to 5%) and 0.6% (95% CI, 0.3 to 0.9%) in those with DS-TB (146). The 3-fold increase in poor

TB treatment outcomes and 6-fold increase in acquired TB drug resistance associated with undetected INH resistance warrants urgent attention. Patients with confirmed INH-monoresistant tuberculosis require 6 months of treatment with RIF, EMB, PZA, and LFX (34), yielding improved treatment success rates, reduced mortality, and reduced acquisition of drug resistance compared to patients receiving the standard 6-month regimen (34, 147).

More recently, a multicountry analysis of aggregate TB drug resistance using data collected between 2003 and 2017 involving 156 countries and 211,753 patients reported a global prevalence of INH-resistant TB of 7.4% (95% CI, 6.5% to 8.4%) among new TB patients and 11.4% (95% CI, 9.4% to 13.4%) among previously treated TB patients (148). Data analysis describing the prevalence of LFX and PZA resistance in addition to INH resistance was conducted for Azerbaijan, Bangladesh, Belarus, Pakistan, the Philippines, and South Africa and revealed a resistance prevalence to both PZA and LFX of 1.8% (95% CI, 0.2 to 6.4%) in the Philippines and 5.3% (95% CI, 0.1 to 26.0%) in Belarus, with no reported cases of additional PZA and LFX resistance in the other four countries (148). The overall low prevalence of resistance to PZA and FQs among patients with INH-monoresistant TB supports the use of the WHO-recommended modified treatment regimen.

Host-Directed Therapy

Host-directed therapy (HDT), a new and promising additional strategy, improves the efficacy of anti-TB treatment by modulating the host immune response to the infecting *M. tuberculosis* pathogen (92). Our improved understanding of *M. tuberculosis* pathogenesis and immunological mediators has contributed to novel and innovative host-directed approaches for use as adjuncts to antibiotic-based anti-TB treatment. The term HDT is used to describe all treatment options that potentially provide an antimicrobial or additive benefit through (i) interplay with host mechanisms exploited by *M. tuberculosis* to persist and replicate in the host, (ii) boosting host immune defense mechanisms against *M. tuberculosis*, (iii) targeting pathways contributing to disease or immunopathology, and/or (iv) modulating host factors associated with pathogenic responses (149, 150). HDTs can be used to target specific pathways that play a causal role in *M. tuberculosis* pathogenesis or can be used to ease symptoms, such as targeting inflammation (149). Thus, several HDTs have emerged as candidates for adjunctive use with current anti-TB treatment without additional risk of developing drug resistance, as they target highly conserved host pathways (151).

Even though most HDT studies have focused on DS-TB, few studies have shown that adjunct HDT can have a similar effect on DR-TB. Metformin (MET) is one of the most promising adjunctive HDTs. In *M. tuberculosis*-infected mice, MET regulated the growth of drug-resistant *M. tuberculosis* strains by improving lung pathology, reducing chronic inflammation, and enhancing the specific immune response (152). Furthermore, in a retrospective cohort of patients, MET improved the rate of sputum culture conversion in diabetes mellitus patients with cavitary disease (odds ratio [OR], 10.8; 95% CI, 1.22 to 95.63) (153). Similarly, in a separate case-control study, the protective effect offered by MET against TB was 3.9-fold higher in patients with diabetes (OR, 0.256; 95% CI, 0.16 to 0.40) (154).

Ibuprofen, carprofen, and 3,5-dinitro-ibuprofen showed a similar effect against three MDR-TB clinical isolates and H37Rv, with MIC values ranging from 20 to 50 μg/mL (155). These results demonstrated a potential effect that could lead to new TB therapy. A phase II study assessing the safety and efficacy of using adjunctive ibuprofen for XDR-TB (NCT02781909) has been completed; however, the results of this study are still pending. The initiation of this prospective, randomized, pilot study was highly influenced by the results obtained by Vilaplana and coworkers, in which treatment of *M. tuberculosis*-infected mice with ibuprofen resulted in statistically significant decreases in the size and numbers of lung lesions ($P = 0.0003$), decreases in the bacillary load ($P < 0.0001$), and improved survival ($P = 0.0094$) (156).

There is growing evidence that statins play a role in containing *M. tuberculosis* infection. Statins are primarily cholesterol reducers; however, they have also shown immunomodulatory and anti-inflammatory activities (157). *In vitro* studies have shown that statins reduce *M. tuberculosis* growth in infected cells (158, 159). *M. tuberculosis*-infected peripheral blood mononuclear cells and monocyte-derived macrophages from hypercholesterolemic individuals on

statin therapy showed reduced *M. tuberculosis* load or were more resistant to *M. tuberculosis* infection than were healthy individuals (160). Simvastatin in particular has been shown to increase the bactericidal effects of INH, RIF, and PZA in *in vitro* and *in vivo* murine models (158, 161, 162). Additionally, treatment with simvastatin reduces the time to lung culture conversion in mice (163). HDTs in combination with anti-TB treatment could potentially shorten treatment duration, reduce the number of drugs required for combination treatment, and potentiate the efficacy of DR-TB regimens (151).

ELEMENTS OF THE HEALTH CARE SYSTEM

A well-optimized health care system is one of the key components required to deliver effective treatment and care and improve treatment outcomes. There are challenges with accessing TB diagnostics and treatment which have resulted in increased TB deaths (2). The adoption of rapid molecular diagnostics, such as use of GeneXpert Ultra, has allowed rapid diagnosis of TB and RIF resistance directly from sputum (164) and has been found to be suitable for implementation at lower levels of health care systems. The recently introduced GeneXpert MTB/XDR has eliminated the concerns of missed Hr-TB case detection, as it has additional probes for detection of INH, FQ, ethionamide, and injectables resistance (165). The current challenge with these diagnostic techniques is their inability to differentiate between dead and viable *M. tuberculosis* (166).

While the use of sputum culture conversion to monitor treatment response has remained the most effective way over the decades, its limitation is that it can only detect viable *M. tuberculosis* and is therefore unable to predict clinical outcomes. There are other methods currently being explored, such as the tuberculosis molecular bacterial load assay, which quantifies viable *M. tuberculosis*. This is advantageous over culture due to its rapid turnaround time, near-zero rates of contamination, reproducibility, and providing information on the rate of *M. tuberculosis* decline during treatment (167). Unfortunately, there is limited evidence on its use on a larger scale, and its use in place of culture in resource-constrained countries is likely to be limited by its high installation costs (166).

Patients receiving DR-TB treatment are often discouraged by the long treatment duration and the high burden of adverse events. Patient-centered and personalized counseling and support for treatment adherence are crucial (168). Reporting of clinical events is one of the major components of patient safety. Health care workers should be encouraged to report patients' adverse events, missed visits, and treatment response. Different barriers to in-hospital reporting have been reported, including the absence of feedback, fear of blame, and the lack of positive changes emanating from the reporting process (169). Health care systems require optimization to deliver better and improved care to patients with DR-TB.

DISAPPOINTMENTS AND PITFALLS

Emerging Resistance to BDQ

Despite the apparent success of BDQ, recent demonstrations of treatment-emergent BDQ resistance pose a significant threat that could potentially reverse recent and anticipated gains associated with novel BDQ-containing regimens. A retrospective analysis of a South African cohort evaluated five patients (5/92; 5.4%) with preexisting BDQ resistance and a further five patients (5/87; 5.7%) that acquired BDQ resistance over the course of BDQ treatment (170). All five patients had preexisting FQ-resistant/RR-TB at initiation of the BDQ-containing regimen, and 4/5 patients failed treatment. Despite inclusion of at least four likely effective drugs as per WHO recommendations, these patients acquired resistance to BDQ, confirming that the complementary activity of included drugs is relatively more important to prevent acquired drug resistance than the number of active drugs in a regimen. Similarly, development of acquired BDQ resistance in 7/124 (5.6%) of patients was reported in a cohort study, despite 4/7 patients receiving an individualized WGS- and DST-based regimen (171). Emergence of BDQ resistance despite individualized treatment administered within a highly controlled in-patient setting suggests that patient nonadherence is not the only contributor to acquired TB drug resistance. Suboptimal

protection provided by remaining companion drugs to a core drug(s), in this case BDQ/CFZ, warrants further exploration. More recently, a study in Pakistan reported BDQ resistance in 8/26 patients (30.8%) and the rates of acquired BDQ resistance were found to be significantly higher among patients who did not receive a second-line injectable drug compared to those that did (172).

There are currently no rapid molecular-based methods for detection of BDQ resistance, as mutations linked to this drug are scattered around the whole genome. WGS is currently used to identify mutations in the *RV0678*, *atpE*, *Rv1979c*, and *pepQ* genes, which have been reported to be associated with BDQ resistance (173). Although WGS utilization has increased in most countries, it is still not part of the standard of care except in high-income countries with a low TB burden (174–176). Hence, BDQ resistance detection relies mostly on phenotypic DST. The MGIT 960 system has been reported to have the most reproducible results for BDQ resistance detection (177).

While *RV0678* mutations in BDQ are associated with cross-resistance to CFZ, it has been shown that only one-third of CFZ-resistant strains are resistant to BDQ, while all strains resistant to BDQ are CFZ resistant (178). These findings lead to the suggestion that CFZ resistance cannot be confidently used as a marker for BDQ resistance. Additionally, DST is required to confirm susceptibility or resistance, and the role of *Rv0678* mutation needs better understanding (178). The wide adoption of all-oral regimens which contain both BDQ and CFZ emphasizes the need of routine phenotypic DST; the rollout of these drugs in settings with limited phenotypic DST could result in continuous spread of drug resistance (179).

Poor Performance of DLM and Emerging Drug Resistance

Initially, DLM use outside of clinical trials was limited; however, reports citing DLM's success made it an appealing choice for DR-TB treatment (180). The concerning high rates of acquired DLM resistance during treatment suggest a significantly lower threshold for development of acquired drug resistance (46, 181). Data from a single patient initiated on a DLM-containing regimen for TB relapse following previous treatment with a BDQ-containing regimen demonstrated a 125-fold increase in the MIC at treatment failure, corresponding to $\geq$2.0 μg/mL, compared to the pre-DLM treatment MIC of 0.016 mg/L (181). Furthermore, in a prospective observational study, there was a higher rate of acquired resistance in the DLM group than in the BDQ group (36% versus 10%) (46), highlighting its increasing propensity for the development of resistance.

A phase II global study (Trial 204) reported a very low MIC for DLM in 460 isolates from DLM-naive patients with TB. Various degrees of resistance to other anti-TB drugs did not affect the distribution of the MICs. Furthermore, there was no difference observed in MIC distributions in most regions or countries for patients with drug-resistant isolates. However, 2/460 isolates from Egypt and Korea (both of which have high TB prevalence) were reported to have high MICs of 1 mg/L and $>$8 mg/L, respectively (182). Baseline and naturally occurring resistance to DLM appeared to be rare ($<$1%), from geographically diverse populations, and against DS-TB, MDR-TB, and XDR-TB strains. Adherence to the recent WHO recommendation that DLM may only be added to a well-constructed MDR-TB treatment regimen is necessary to prevent the emergence of additional resistance.

Furthermore, in a randomized clinical trial 213 (NCT01424670), $>$90% of the population had previous TB treatment exposure before enrollment and randomization. DLM resistance was reported in 2/327 patients at baseline, and acquired resistance was detected in 4/327 patients in the group receiving DLM, compared to none in the control group receiving a standard-of-care regimen (183). All four patients with acquired resistance to DLM were hospitalized; this indicated that nonadherence may not be the only factor contributing to acquired drug resistance. Moreover, these four participants only received two anti-TB drugs that were likely to be effective, in addition to DLM (183). In a Korean study, DLM resistance was reported in 41/420 clinical isolates from patients with no previous exposure to DLM; the clinical breakpoint of 0.2 mg/L was used to determine the resistance (48). The same critical concentration was used in a similar study from China, and 7/220 MDR and XDR clinical isolates were found to be resistant to DLM (184).

Lack of Biomarkers To Assess DR-TB Treatment Response

TB biomarkers are a potentially useful tool to monitor the curative response to treatment and are crucial to assess if an *M. tuberculosis*-infected host is responding effectively to anti-TB treatment (185). Sputum culture conversion, described by at least two consecutive negative cultures or smears taken on different occasions at least 7 days apart, is the current measure for assessing bacteriological response (7). Several innovative approaches have been described as predictive markers in monitoring treatment response. Certain chemokines and inflammatory markers were identified as candidate predictive markers in delayed sputum culture conversion in MDR-TB patients ($n = 50$) (186). Furthermore, that study demonstrated that among culture-positive patients at baseline, some patients showed significant positive correlations between plasma levels of C-reactive protein (CRP), serum amyloid A (SAA), vascular endothelial growth factor A (VEGF-A), soluble interleukin-2 receptor alpha (sIL-2Rα [CD40]), and interferon gamma-induced protein 10 (IP-10) and delayed sputum culture conversion. In addition, a combination of monocyte chemoattractant protein (1MCP-1 [CCL2]), IP-10, sIL-2Rα, SAA, CRP and a positive acid-fast bacilli smear could differentiate fast from slow responders and was predictive of delayed sputum culture conversion with high sensitivity and specificity. However, this must be evaluated on a larger scale (186). Markers of bacterial burden can thus effectively measure bactericidal activity; however, they are at the margins of detectability during the crucial subsequent sterilizing phase (187).

Relapse is mediated by a small subset of subpopulations of residual *M. tuberculosis* that survive the sterilizing phase of the treatment. Thus, the prediction of relapse will likely require a biomarker that is capable of quantifying sterilizing drug activity and survival of very small subpopulations of residual *M. tuberculosis* (187). The identification of more accurate biomarkers predictive of TB outcomes is a key research priority (188).

CONCLUSION AND FUTURE PERSPECTIVES

Even though there have been significant developments made within the DR-TB treatment landscape, the disease remains a major concern in public health. The COVID-19 pandemic has resulted in disruptions across the TB care cascade. The diagnosis and appropriate treatment of patients with RR was already challenging prepandemic, with fewer than half of an estimated 500,000 patients benefitting from diagnostic and treatment advances. However, incredible advances in reducing DR-TB treatment-related toxicity and treatment duration with improvements in DR-TB treatment outcomes have been achieved with the introduction of new antimicrobial drugs and the widespread use of repurposed drugs to potentiate new regimens. These antimicrobials have proven to be highly active in DR-TB regimens and have achieved excellent treatment outcomes. Furthermore, another major advancement was the introduction of the Bangladesh short-course regimen for treatment of MDR-TB. This regimen was associated with improved treatment outcomes and offered patients a chance to complete their treatment in 9 months. The recent transitioning of this regimen to an all-oral regimen has significantly improved outcomes and retention of RR/MDR-TB patients in TB care (47, 73, 83, 84, 189). The BPaL and BPaLM regimens added to these already-existing developments by providing the first-ever 6-month regimen for the treatment of DR-TB (14). Other studies are under way and are aiming to reduce the treatment duration and pill burden. These regimens are expected to be more efficacious in eradicating *M. tuberculosis*, thereby reducing the potential of relapse (74). Notwithstanding the availability of several new treatment strategies, getting the right drugs to the right patients in time to positively impact outcomes is essential, requiring access to rapid and accurate diagnostics to meet emerging public health needs.

Regardless of the successes observed, areas of uncertainty remain. The specific number of drugs required to construct an effective regimen remains uncertain; though that may be the case, it is important to ensure that constructed regimens provide maximum protection against acquired resistance and efficiently sterilize dormant subpopulations. Failure to detect pretreatment resistance enhances the vulnerability of new drugs to acquired resistance, creating further setbacks for patients and programs. Further, the use of high-dose INH in the absence of evidence for its effectiveness requires urgent attention, as it may render this

drug useless in the future due to an increased burden of resistance. In addition, the use of drugs such as PZA and EMB, ignoring the burden of resistance reported on these drugs, is concerning, as patients may be subjected to suboptimal treatment. Other clinical aspects requiring attention, as they are associated with poor treatment outcomes, are antimicrobial heteroresistance and intracavitary disease. Better approaches in diagnostics and treatment are required to offer patients improved clinical outcomes. Individualized treatment approaches may offer better treatment outcomes; however, implementing them on a larger scale may be a challenge for resource-limited countries, and so the treatment remains standardized. A new approach of using adjunct HDT in combination with a background regimen has demonstrated a potential to reduce treatment duration and the number of drugs required to complete a regimen and further potentiates the efficacy of DR-TB regimens.

All the substantial development achieved may be reversed by the emergence of resistance to new drugs, especially BDQ. This suggests that new potential core drugs should be used only for defined recommendations and within defined regimens, to prevent further resistance acquisition (74). Furthermore, the lack of biomarkers to monitor treatment response, including prediction of treatment failure or relapse, may be a contributor in reversing the major advancements achieved (185).

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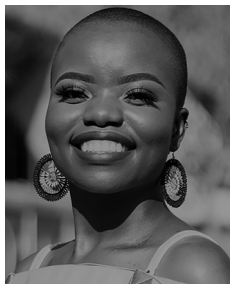

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