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The pipeline of new molecules and regimens against drug-resistant tuberculosis

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ABSTRACT

The clinical development and regulatory approval of bedaquiline, delamanid and pretomanid over the last decade brought about significant progress in the management of drug-resistant tuberculosis, providing all-oral regimens with favorable safety profiles. The Nix-TB and ZeNix trials of a bedaquiline – pretomanid – linezolid regimen demonstrated for the first time that certain forms of drug-resistant tuberculosis can be cured in the majority of patients within 6 months. Ongoing Phase 3 studies containing these drugs may further advance optimized regimen compositions. Investigational drugs in clinical development that target clinically validated mechanisms, such as second generation oxazolidinones (sutezolid, delpazolid, TBI-223) and diarylquinolines (TBAJ-876 and TBAJ-587) promise improved potency and/or safety compared to the first-in-class drugs. Compounds with novel targets involved in diverse bacterial functions such as cell wall synthesis (DrpE1, MmpL3), electron transport, DNA synthesis (GyrB), cholesterol metabolism and transcriptional regulation of ethionamide bioactivation pathways have advanced to early clinical studies with the potential to enhance antibacterial activity when added to new or established anti-TB drug regimens. Clinical validation of preclinical *in vitro* and animal model predictions of new anti-TB regimens may further improve the translational value of these models to identify optimal anti-TB therapies.

1. Introduction

After a hiatus of more than 40 years, the approvals of bedaquiline, delamanid and pretomanid over the past decade have been major steps forward for the management of drug-resistant tuberculosis (DR TB), enabling all-oral treatment regimens, including some of significantly shorter duration and improved treatment success [1–5]. Due to bolstered research and development efforts across academia, pharmaceutical companies and public–private partnerships, the pipeline of investigational drugs is larger than it has ever been with 16 compounds of 12 drug classes (9 novel classes; 7 novel targets) in clinical development [6,7]. Ineligibility for short course DR regimens, remaining complexities and toxicities of all current regimens affecting treatment adherence as well as the threat of resistance development to new and repurposed drugs [4,8–10], underscore the need for continuous efforts in drug and regimen development against DR TB, including extensively drug-resistant (XDR) TB under the new 2021 classification [11].

This article provides an update of new clinical data of the recently approved drugs and an overview of ongoing evaluations in clinical regimen trials including a snapshot of new compounds in early clinical development. This brief overview will introduce new regimens, new drugs, and new approaches that could aid to shorten and simplify the management of DR TB.

Recently approved drugs & regimens evaluating these Given the large unmet need associated with TB and especially with multidrug resistant (MDR) TB, bedaquiline, delamanid and pretomanid had each received orphan drug designation status. Approvals of all these compounds were based on limited data from pivotal clinical trials. However, while bedaquiline and delamanid were approved as add-ons to current, complex MDR regimens, pretomanid was approved in the specific context of a 3-drug novel regimen, exemplifying a new approach to antituberculous treatment development [12]. Several ongoing clinical studies aim to further evaluate efficacy and safety of these 3 drugs in regimens of shortened duration (Table 1); these regimens often also include off-label use of antibiotics licensed for other indications, such as fluoroquinolones (FQ) and linezolid as well as clofazimine, an antimicrobial compound with potent anti-inflammatory activity used for the treatment of leprosy (these drugs are often referred to as

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Table 1
Approved drugs in Phase 2/3 development for drug-resistant tuberculosis and investigational drugs in Phase 2 for drug-sensitive and drug-resistant tuberculosis [78,81].

Study Name/ Registration#/ Sponsor	Phase	Study Design	Pulmonary TB Category/ Age	Regimens	Treatment Duration	N	Countries	Study Status/ Estimated Completion‡	Comments/Results of Evaluating safety and effectiveness of bedquiline plus MBT..
Approved Drugs in Phase 2/3 Regimen Studies: DR TB									
Pretomanid-Bedaquiline based: 6 months*									
Nix-TB NCT02333799 TB Alliance	3	Single arm OL	MDR (TI/NR) XDR ≥ 14 years	$BPaL_{1200}$	6 months	109	South Africa	Completed 8/2020	High efficacy (6 months after end of treatment: ITT Population: 90%; 95% CI: 83-95) of BPaL regimen in patients with highly drug-resistant TB; 2 patients treated for 9 months based on positive cultures (Month 4 and 5); 2 patients experienced relapse. Linezolid toxicity: 81% peripheral neuropathy and 48% myelosuppression [26]
ZeNix NCT03086486 TB Alliance	3	R, Double blinded for L dose	MDR (TI/NR) (Pre-) XDR ≥ 14 years	BPaL 1200 x 26 weeks BPaL 1200 x 9 weeks BPaL 600 x 26 weeks BPaL 600 x 9 weeks	26 weeks	180	South Africa, Georgia, Russia, Moldova	Active, not recruiting, 12/2021	Linezolid dose optimization for BPaL regimen. High success rate 6 months after completion of treatment with reduced rates of peripheral neuropathy and myelosuppression [55]: **MITT population** / **Efficacy** / **Neuro-pathy** / **Myelosuppression** BPaL 1200 x 26 weeks / 93% / 38% / 29% BPAL 1200 x 9 weeks / 89% / 24% / 15% BPAL 600 x 26 weeks / 91% / 24% / 13% BPAL 600 x 9 weeks / 84% / 13% / 16%
SimpliciTB NCT03338621 TB Alliance	2c	Partially randomized, C OL	RR HR MDR DS ≥ 18 years	BPaMZ x 26 weeks (DR TB) BPaMZ x 17 weeks (DS TB) HRZE/HR x 26 weeks (DS TB)	26 weeks	455	South Africa, Tanzania, Uganda, Philippines, Malaysia, Georgia, Russia, Brazil	Active, not recruiting, 2/2022	Evaluating safety, tolerability, and efficacy of BPaMZ regimen in DS TB (4 months treatment) and DR TB (6 months treatment); primary endpoint: time to culture conversion over 8 weeks; secondary endpoint: bacteriological or clinical failure, relapse at 52 weeks
TB-PRACTECAL NCT02589782 Medecins Sans Frontiers (MSF)	2/3	R, C, OL Seamless two-stage	At least RR ≥15 years	**Stage 2:** BPaML 600x16 weeks; 300 x 8 weeks SOC	24 weeks	552	South Africa Belarus, Uzbekistan	Active, not recruiting, 12/2022	Evaluating BPaL regimen alone and in combination with other drugs **Stage 1 with 3 interventional regimens:** $BPaML_{600x16\ weeks;\ 300\ x\ 8\ weeks}$ $BPaCfzL_{600x16\ weeks;\ 300\ x\ 8\ weeks}$ $BPaL_{600x16\ weeks;\ 300\ x\ 8\ weeks}$

(*continued on next page*)

Table 1 (*continued*)

									SOC Decisions on regimens for Stage 2 based on interim analysis for 8-week efficacy/safety; enrollment in Stage 2 ended early [57].
Bedaquiline based: 6 - 9 months*									
Stream Stage 2 NCT02409290 International Union against Tuberculosis and Lung Disease	3	R, C, OL	RR ≥15 years	BLfxCfzEZ 40 weeks + Hh/Pto 16 weeks "Bangladesh Regimen": M (or L) CfzEZx 40 weeks + K/Hh/Pto 16 weeks	40 weeks	588	South Africa, Ethiopia, Uganda, India, Georgia, Moldova, Mongolia,	Active, not recruiting 7/2022	Evaluating safety and effectiveness bedaquiline plus MBT in 9- month regimen. Non-inferiority design; secondary objective to evaluate superiority of bedaquiline-based regimen. 2 arms were stopped early: 1) long regimen, including injectable; 2) 28-week regimen including bedaquiline and injectable [20].
NExT NCT02454205 University of Cape Town	2/3	R, C, OL	RR ≥18 years	LBLfxZ+Eto/Hh/Tzd SOC (9-12 months)	6-9 months	154	South Africa	Active, not recruiting; 6/2021	Evaluating safety, tolerability and efficacy of all oral regimen compared to SOC including injectable (Kanamycin). Gene-directed diagnostic approach to individualize use of high-dose INH versus ethionamide. Enrollment was terminated early in 2019.
Delamanid based: ≥ 9 months*									
MDR-END NCT02619994 Seoul National Hospital	2/3	R, C, OL	RR MDR ≥ 19 years	$DLfxZL_{600\ x\ 8\ weeks,\ 300\ x7\text{-}10\ months}$ SOC (including injectables) 20 months	9-12 months	238	South Korea	Unknown 6/2021	Evaluating safety and efficacy of shorter all oral regimen containing linezolid and delamanid. Non-inferiority design for success rate at 24 months after start of treatment[78].
Bedaquiline-Delamanid based: 6-9 months*									
Beat TB NCT04062201 Wits Health Consortium (Pty) Lyd	3	R, C, OL	At least RR ≥ 12 years	BDLLfxCfz x 24 weeks SOC (B-based; 9 months)	24 weeks	400 (T)	South Africa	Active, recruiting, 3/2023	Evaluating safety and efficacy of 5 drug regimen including bedaquiline, delamanid and linezolid in South Africa.
ACTG 5343 DELIBERATE study NCT02583048 National Institute of Allergy and Infectious Diseases (NIAID)	2	R, OL	MDR ≥18 years	B + MBT D + MBT B + D + MBT	24 weeks (MBT for longer)	84	South Africa, Peru	Completed	Combining bedaquiline and delamanid has a modest, not more than additive effect on QTc interval; encouraging microbiology data [28].

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Table 1 (*continued*)

endTB NCT02754765 MSF	3	R, C, OL	RR ≥ 15 years	BLMZ BLCfzLfxZ BDLLfxZ DLCfzLfxZ DCfzMZ SOC	39 weeks	750 (T)	South Africa, Lesotho, India, Pakistan, Kazakhstan, Georgia, Peru	Active recruiting 4/2021	The endTB project includes an observational study and 2 clinical trials to evaluate shorter, less toxic, and more effective treatments for MDR TB. Regimens aim to improve understanding of the role of B and D alone and in combination in MDR treatment. Non-inferiority design.
endTB-Q NCT03896685 MSF	3	R, C, OL 2:1 randomization	RR plus FQ-R ≥ 15 years	$BDCfzL_{600}$ x 16 weeks; 300 x 8-23 weeks SOC	24-39 weeks	324 (T)	Lesotho, India, Pakistan Vietnam, Kazakhstan, Peru	Active recruiting 12/2022	Evaluating a bedaquiline and delamanid based regimen in FQ-resistant TB. Non-inferiority design.
Investigational Drugs in Phase 2 Regimen Studies – DS and DR TB									
Ethylenediamine: SQ109									
NCT01785186 PanACEA/LMU – Dr. Hoelscher	2	R, C, OL Multi-arm Multi-stage	Rifampicin sensitive	$R_{20mg/kg}$ QHZ $R_{10mg/kg}$ QHZ $R_{35mg/kg}$ EHZ $R_{20mg/kg}$ MHZ $R_{10mg/kg}$ HZE	12 weeks, followed by 14 weeks of HR	365	South Africa, Tanzania	Completed 3/2015	Recruitment to SQ109 arms terminated after 1st interim analysis as criteria for Week 12 culture conversion compared to RHZE control not met. 35 mg/kg rifampicin was safe and shortened the time to stable culture conversion from 62 to 48 days [79].
Infectex Ltd Sequella Inc.	2b/3	R, DB, placebo controlled	MDR	Q + SOC Placebo + SOC	unknown	140	Russia	Completed 2016	SQ109 was well tolerated and increased sputum culture conversion (SCC) at Month 6 [80]. **SCC Month 6** | Q + SOC | Placebo + SOC | p- value Per Protocol | 79.7% | 61.4% | 0.0486 Intention to Treat | 61% | 42.9% | 0.0412
Oxazilidinone: Sutezolid									
SUDOCU NCT03959566 PanACEA/LMU – Dr. Hoelscher	2b	R, C, OL	DS	$BDMStz_{600}$ $BDMStz_{1200}$ $BDMStz_{600bid}$ $BDMStz_{800bid}$ BDM	12 weeks	75 (T)	South Africa, Tanzania	Active, recruiting, 12/2021	All study regimens given for 3 months, followed by 3 months of standard treatment in NTP program. Primary endpoint: change in bacterial load over time. Exposure response and toxicity modelling for dose finding.
Oxazilidinone: Delpazolid									
DECODE NCT04550832	2b	R, OL	DS	$BDMDzd_{400}$ $BDMDzd_{800}$ $BDMDzd_{1200}$	16 weeks	75 (T)	South Africa, Tanzania	Active, not yet recruiting	For patients with sustained SCC at Week 8: no further treatment after week 16. For patients without

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Table 1 (*continued*)

LegoChem Biosciences, Inc				BDMDzd$_{800bid}$ BDM				1/2023	sustained SCC at Week8: HR continuation treatment in NTP. Primary endpoint: change in bacterial load over time. Secondary endpoint: observation for relapse to Week 52 for those who discontinue treatment at Week 16. Exposure response and exposure toxicity modelling for dose finding.
Carbostyril (DprE1 inhibitor): OPC-167832									
OPC-167832 NCT03678688 Otsuka Pharmaceutical Co, Ltd.	2	R, C, OL	DS	Stage 2: BOPC DOPC BDOPC RHZE	14 days EBA	118 (T)	South Africa	Active, recruiting, 11/2021	Stage 1: Dose-ranging OPC mono-EBA Stage 2: EBA with drug combinations that have shown potent activity in animal regimen studies [81].

The Abbreviations:

Drugs: B: Bedaquiline; Cfz: Clofazimine; D: Delamanid; Dzd: Delpazolid; E: Ethambutol; Eto: Ethionamide; H: INH; Hh: INH high-dose; K: Kanamycin; L: Linezolid; Lfx: Levofloxacin; M: Moxifloxacin; OPC: OPC-167832; Pa: Pretomanid; Pto: Prothionamide; Q: SQ109; R: Rifampicin; Stz: Sutezolid; Tzd: Terizidone Z: Pyrazinamide.

Subscript text indicates drug dose (mg), dosing frequency (bid: twice per day) or duration of treatment.

Other: DR: Drug-resistant; DS: Drug-susceptible; EBA: Early Bactericidal Activity; FQ-R: Fluoroquinolone resistant; HR: Isoniazid-resistant; ITT: Intention-to-treat; MBT: multidrug background therapy; MDR: Multidrug resistant; mITT: Modified intention-to-treat; NTP: National TB Programme; OL: Open label; R: Randomized; RR: Rifampicin-resistant; SCC: Sputum culture conversion; SOC: Standard of Care (generally based on local guidelines and respective WHO recommendations); T: Target; TR: Treatment-resistant, TI: Treatment-intolerant; XDR: Extensively drug resistant (pre-2021 classification).

ǂ Study status as per Clinicaltrials.gov, accessed 8/20/2021.

*Bedaquiline is approved for 400 mg once daily × 2 weeks followed by 200 mg three times per week for 22 weeks; delamanid is approved for 100 mg twice per day for 24 weeks; some regimens listed evaluate different dosing or duration.

Table 2
New anti-TB compounds in early clinical development.

Mechanism of Action	Class	Licensed Compound for Class	Investigational Compound	Phase	Comments/Advantage
Protein Synthesis Inhibition					
23S rRNA binding	Oxazolidinone	Linezolid	Sutezolid (PNU-100480)	2b See Table 1	Potentially more efficacious than linezolid with better therapeutic index for MPS-associated toxicity. In a Phase 2a EBA study, sutezolid at 600 mg twice daily and 1,200 mg daily was safe, well tolerated, and readily showed significant bactericidal activity in sputum and blood [66].
			Delpazolid (LCB01-0371)	2b See Table 1	Potentially improved safety profile vs. linezolid. In a Phase 2a EBA study, the bactericidal activity of delpazolid was comparable to linezolid [68].
			TBI-223	1	Low MPS activity and potentially improved safety profile vs. linezolid [82] .
Leucyl-tRNA synthetase inhibition	Oxaborole		GSK 3,036,656 (GSK-656)	1	Novel mechanism of protein synthesis inhibition. May be able to replace an oxazolidinone without MPS-associated toxicity [83].
Cell Wall Synthesis Inhibition					
DprE1 inhibition	Azaindole (non-covalent)		TBA-7371	2a (EBA) NCT04176250	Highly potent, novel cell wall inhibitor. Ascending dose mono EBA active, recruiting.
	Benzothiazone (covalent)		BTZ-043	2a (EBA) NCT04044001	Highly potent, novel cell wall inhibitor. Ascending dose mono EBA active, recruiting.
			Macozinone (PBTZ-169)	1	Highly potent, novel cell wall inhibitor
	Carbostyril (non-covalent)		OPC-167832	2a (EBA) NCT03678688	Highly potent, novel cell wall inhibitor. Mono and combo EBA active, recruiting.
MmpL3 inhibition (and electron transport?)	1,2-ethylene diamine		SQ109	2b See Table 1	EBA was relatively poor in combination with rifampicin, but Phase 2b study suggested improved activity when added to MDR regimens [79,80,84]. Potential multi-targeting effects.
Electron Transport Chain Inhibition					
ATP synthase inhibitor	Diarylquinoline	Bedaquiline	TBAJ-876	1	Potentially active against bedaquiline resistant strains [40]; improved safety profile.
ATP synthase inhibitor	Diarylquinoline	Bedaquiline	TBAJ-587	1	Potentially active against bedaquiline resistant strains [41]; improved safety profile.
Cytochrome bcc complex	Imidazopyridine amide		Telacebec (Q203)	2a (EBA) NCT03563599	EBA study showed good dose-dependent bactericidal activity over 14 days good [85]. Possible synergy with AtpE inhibitors (bedaquiline).
Electron transport and reactive oxygen production	Riminophenazine	Clofazimine	TBI-166	1	Improved safety and activity profile vs clofazimine [86].
DNA Synthesis Inhibition					
GyrB	Benzimidazole		SPR720	1	Maintains activity against fluoroquinolone resistant strains; also in development for nontuberculous mycobacteria [87].
Cholesterol Catabolism Inhibition					
Unknown target			GSK2556286 (GSK-286)	1	Ability to penetrate TB lesions and to reduce relapse rates in mice.
Transcriptonal Regulators Inhibition					
EthR transcriptional repressor			BVL-GSK098	1	Novel bacterial transcriptional regulators stimulating bioactivation pathways for ethionamide (Eto) resulting in an increase of Eto efficacy and reduced resistance to Eto. The combination of BVL-GSK098 could allow for lower dose of ethionamide or prothionamide improving safety and tolerability [88].

The Abbreviations: EBA: Early Bactericidal Activity; MDR: Multidrug resistant; MPS: Mitochondrial Protein Synthesis; NTM: Nontuberculous mycobacteria.

"repurposed" and not discussed in detail here) [13–17].

1.1. Bedaquiline

1.1.1. Clinical data

Bedaquiline, a first-in-class diarylquinoline that inhibits the proton pump of mycobacterial ATP synthase, received initial conditional approval in the United States in 2012 based on a randomized Phase 2b study in MDR and pre-XDR patients. The bedaquiline-containing arm demonstrated significantly shorter time to sputum culture conversion in liquid culture through 24 weeks compared to placebo, when added to a World Health Organization (WHO) Standard of Care (SOC) and significantly higher proportions of patients achieving culture conversions at 120 weeks [18]; these findings were supported by a small open label study which also included XDR-TB patients (pre-2021 classification) [18,19]. The confirmatory Phase 3 STREAM (Stage 2) trial is still ongoing comparing two bedaquiline-containing regimens against SOC (Table 1) [20]. Since approval, experience with bedaquiline in operational research and programmatic settings has resulted in the WHO recommendation to include it in all oral regimens and has established its clinical utility as a cornerstone of MDR TB treatment regimens [2,4,21–25]. Ongoing clinical trials are evaluating bedaquiline in combination with other approved and investigational drugs in regimens of 6 to 9 months duration (Table 1) [26,27].

Safety concerns related to QT prolongation require ECG monitoring during therapy [27,28]. Clinical experience has demonstrated that the drug is generally well tolerated with severe QT prolongation being uncommon and adverse events leading to discontinuations being rare, also in the combination with delamanid [29–31]. Bedaquiline analogs that are in early clinical development will hopefully have less cardio-

dysrhythmic side effects (Table 2).

1.1.2. Anti-tubercular activity and resistance

Bedaquiline is bactericidal for replicating and non-replicating *M. tuberculosis* (MTB), demonstrated synergy with some first-line drugs and potent sterilizing activity in murine TB with shortened treatment durations [32,33]. In Phase 2 early bactericidal activity (EBA) studies over 7 and 14 days, onset of bactericidal activity was delayed relative to most other antituberculous drugs, which could be due to the need to deplete a significant amount of existing intracellular ATP stores before bedaquiline can exert its bactericidal effect; in addition, due to the large volume of distribution of multiple compartments and long terminal half-life, effective or/and steady state concentrations for the parent and main metabolite M2 may have not been reached during the EBA dosing period [34,35] [TB Alliance, unpublished data]. The 14-day EBA study evaluated 4 dose levels ranging from 100 mg to 400 mg with cumulative loading over the first two days of 300 mg (100 mg cohort), 700 mg (200 mg cohort), 900 mg (300 mg cohort) and 1200 mg (400 mg cohort). In this study, dose-dependent bactericidal activity was observed by Day 14 (TB Alliance, unpublished data).

Target based mutations in the *atp*E gene affecting the membrane spanning domain region of the ATP synthase are associated with bedaquiline exposure and cause relatively high increases (8–133-fold) in the minimum inhibitory concentration (MIC) but may be associated with a fitness cost [36,37]. Mutations in *Rv0678* which derepress the MmpS5-MmpL5 efflux pump are more common; they cause a 2 to 8- fold MIC increase, have been observed with and without bedaquiline exposure and can be associated with cross-resistance to other classes of drugs, such as clofazimine [38]. Resistance development under treatment has been associated with clinical failure or relapse, including in the Phase 2 clinical studies [18,19,27,36,39]. Investigational diarylquinolines aim to overcome bedaquiline resistance and have demonstrated efficacy against bedaquiline resistant *Rv0678* mutants in mouse models [40,41]. (Table 2).

1.2. Delamanid

1.2.1. Clinical data

Delamanid is a prodrug of the nitroimidazole class that undergoes reductive metabolism by MTB to produce an active free radical which inhibits the synthesis of mycolic acid. It received conditional approval by the EMA in 2014 based on a Phase 2 study demonstrating that a statistically significantly higher proportion of MDR/XDR TB patients receiving delamanid plus optimized background regimen (OBR) compared to placebo plus OBR achieved sputum culture conversion (SCC) at 8 weeks[42]. In a subsequent Phase 3 study a delamanid-containing regimen did not meet the pre-specified non-inferiority criteria with regard to the median time to SCC over 6 months compared to OBR alone; however, a significant shorter time to SCC was demonstrated in sensitivity analyses and in subgroup analyses in patients without cavitation and/or fluoroquinolone resistance [43]. While global experience with delamanid remains limited, some data support its effectiveness in a multidrug background regimen [21,44–46]. Ongoing clinical trials evaluate delamanid in various oral regimens of 6–12 months duration in rifampicin-resistant (RR), MDR and FQ-resistant TB, some also in combination with bedaquiline (endTB – Table 1) and will provide a better understanding of its role in current MDR TB management. A randomized controlled trial demonstrated that delamanid given alone adds approximately 6–8 ms to the QTc interval in a combination regimen and that combining delamanid with bedaquiline has a modest, not more than additive effect with no grade 3 or 4 QTc prolongation observed [28] (Table 1).

1.2.2. Anti-tubercular activity and resistance

Delamanid is active against replicating, hypoxia induced dormant and intracellular MTB with low MIC values; it had potent sterilizing activity in murine and guinea pig models of TB when given alone. When given with rifampicin and pyrazinamide, sterilizing activity was superior to a standard regimen of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E; HRZE) [47,48].

In vitro frequency of spontaneous resistance development is high and comparable to isoniazid, as the enzymes involved in activation of the prodrug are not essential [49,50]. Resistance mutations are associated with genes involved the bioreductive activation of the drug within MTB (ddn (*Rv3547*), fgd1) or the cofactor F420 biosynthesis (fbiA, fbiB, fbiC, fbiD) and most confer cross-resistance to pretomanid [50].

1.3. Pretomanid

1.3.1. Clinical data

Pretomanid is also a nitroimidazole prodrug that undergoes nitroreduction within the mycobacterial cell, although the chemical structure is distinct from delamanid, which imparts distinct pharmacological properties, including lower protein binding and higher tissue penetration. In actively replicating MTB, inhibition of mycolic acid biosynthesis is the primary mechanism of activity, like delamanid. Under hypoxic condition, the formation of des-nitro metabolites of pretomanid generates reactive nitrogen intermediates, including nitric oxide, which may be the primary mechanism of killing against latent bacteria, although more recent metabolomic data also indicate that inhibition of the pentose phosphate pathway may also cause accumulation of toxic intermediates lethal to both replicating and non-replicating bacteria [51]. [52]. Pretomanid (Pa) was approved in 2019 by the FDA (under the Limited Population Pathway for Antibacterial and Antifungal Drugs) and in 2020 by the EMA, both as part of a 6-month regimen containing bedaquiline (B) and linezolid (L; BPaL regimen) for treatment of XDR TB (pre-2021 classification) and treatment intolerant or non-responsive MDR TB. For the first time, there is now evidence that effective treatment for at least subsets of MDR TB can be accomplished with the same duration as for DS TB [53]. The pivotal trial for pretomanid approval was the Phase 3 Nix-TB trial, a single arm open label study in 109 patients with treatment intolerant or non-responsive MDR TB or XDR TB. Ninety percent (95% CI: 83–95%) of patients in the intention-to-treat (ITT) population achieved a favorable outcome 6 months after treatment completion and favorable outcomes were sustained 24 months post treatment completion (88% in ITT) [26,54]. A comparison between the cohort receiving the BPaL regimen in the Nix-TB study and a contemporaneous cohort treated with longer bedaquiline and linezolid-containing regimens showed significantly more patients achieving a favorable outcome with BPaL [5]. However, in the Nix-TB study, linezolid associated toxicity frequently necessitated dose interruption or reductions, but with no apparent impact on efficacy [26]. The ongoing ZeNix trial compares 4 different dosing strategies for linezolid (Table 1): Results of the primary analysis 6 months post treatment completion confirm the high relapse-free cure rate of the BPaL regimen in all study arms but improved tolerability with reduced linezolid dosing and/or duration [55]. Pretomanid in combination with drugs that prolong the QT interval (such as bedaquiline) may cause additive QT prolongation and ECG monitoring is indicated [53].

The Phase 3 SimpliciTB study evaluates a 4 and 6 month regimen of bedaquiline, pretomanid, moxifloxacin (M) and pyrazinamide (BPaMZ) in patients with drug-susceptible (DS) (4 months) and MDR TB (6 months); in a Phase 2 study, BPaMZ given for 8 weeks demonstrated greater bactericidal activity against rifampicin-resistant TB than standard HRZE against DS TB [56]. TB PRACTECAL is a multistage Phase 2/3 randomized, controlled trial evaluating BPaL-based regimens for rifampicin resistant (RR) TB. TB PRACTECAL is based on an adaptive, two stage study design with progression of regimens dependent on 2-month sputum conversion results; in stage 2, BPaL combined with moxifloxacin given for 6 months was advanced (Table 1). Randomization was stopped prior to completion of enrollment based on a Drug Safety Monitoring Committee recommendation given superior

performance of the experimental BPaLM arm compared to the SOC arm [57]. In male rats, pretomanid exposure was associated with testicular toxicity and impaired fertility. In clinical trials of pretomanid-containing regimens, human male sex hormone levels have been within normal ranges. A clinical study in men with DR TB evaluates the impact of a pretomanid-containing regimen on sperm count and reproductive hormone levels [58].

1.3.2. Anti-tubercular activity and resistance

Pretomanid is bactericidal and regimens combining pretomanid and bedaquiline with either linezolid (BPaL) or moxifloxacin and pyrazinamide (BPaMZ) demonstrated significantly greater bactericidal and sterilizing activity compared to first-line regimens in animal models [59,60]. This experience supported the design of pretomanid-based regimens of shortened treatment duration in Nix-TB and SimpliciTB [35,56,59,60]. Resistance mutations are associated with genes involved in the bioreductive activation of the drug as described for delamanid [50].

2. New drugs in clinical development

With the recognition of the need for improved therapies for MDR TB, there have been enhanced efforts to identify novel anti-TB therapies. Over 100 novel compounds or screening efforts are listed on the Working Group on New TB Drugs website (https://www.newtbdrugs.org/pipeline/compounds) and approximately 16 compounds are in early clinical development (Table 2). New genetics-based approaches have enabled the identification of essential gene functions in MTB as potential drug targets as well as the ability to more readily assign a target to empirically identified anti-TB molecules [61], which has helped to expand the target-space for new TB drugs. Many of most advanced leads target clinically validated mechanisms. Examples are the new oxazolidinones, inhibiting protein synthesis and the new diarylquinolines, inhibiting the ATP synthase, that have potentially improved potency and/or safety compared with the first-in-class drugs (Table 1 and Table 2).

The oxazolidinone class is illustrative of efforts to further optimize clinically validated mechanisms: sutezolid (PNU-100480) was discovered contemporaneously with linezolid but was never developed clinically. It has very potent activity against intracellular MTB, whereas its main sulfoxide metabolite reaches high plasma concentrations and primarily acts against extracellular bacteria [62]. In murine models, sutezolid alone, as well as in first-line and isoniazid/rifampicin-free regimens, demonstrated more potent bactericidal and sterilizing activity than linezolid, with significant potential for treatment shortening [63–66]. Delpazolid (LCB01-0371) and TBI-223 are novel oxazolidinones with good antimycobacterial activity, lower potency against mitochondrial protein synthesis, and a shorter half-life than linezolid, which may improve mitochondrial toxicity associated with trough concentrations of linezolid and other oxazolidinones [67,68]. Both sutezolid and delpazolid are entering Phase 2b regimen studies in DS TB patients that aim for treatment shortening and if successfully developed may also be used for MDR TB management (Table 1). TBI-223 is being evaluated in an ascending dose Phase 1 study (Table 2). These trials will help to further our understanding on the potential for treatment shortening contributions of oxazolidinones observed in mouse models and may enable more rapid selection and development of even newer and safer oxazolidinones.

Perhaps more exciting and promising are the number of novel targets and compound candidates that have been identified and advanced to early clinical studies. These new mechanisms should be active against DS and DR TB and may also provide enhanced antibacterial activity when added to new or established anti-TB drug regimens (Table 2). The derivation of multiple clinical leads targeting the DprE1 protein that is essential for cell wall synthesis highlights the impact that identification of new mechanisms of action can have on advancement of novel classes of anti-TB drugs. Almost all the leads for DprE1 were identified in empiric whole cell screens, including use of high-content screening platforms to identify intracellular activity [69]. The identification of DprE1 as the target of these potent antibacterial leads by Christophe and Makarov allowed for the further association of DprE1 inhibition for many other pharmacophores having highly potent activity against MTB, including both covalent and non-covalent based mechanisms [69,70]. The promiscuity of DprE1 may be associated with the enzyme's low specificity for the electron acceptor required for the oxidoreductase activity but may also be attributed to the extra-cytoplasmic localization of DprE1 to the periplasmic space, which may provide easier access to inhibitors and enhanced "druggability" [71]. Hopefully, with multiple chemotypes of DprE1 inhibitors in clinical development, at least one of these will demonstrate highly effective curative properties.

3. Preclinical models to inform regimen development

The challenge for the development of improved treatment of TB is not just the identification of new targets, but the establishment of new combinations of drugs (and drug targets) that will provide eradication of diverse populations of MTB with shorter duration of therapy and improved tolerability. New *in vitro* assay methodologies like DiaMOND have enhanced the ability to measure and model the quantitative impacts of fixed ratios of drugs in combinations on MTB grown in a variety of media conditions that may better represent the multiple niches and growth states present in the clinical setting [72,73]. The cross validation of this *in vitro* approach with assessment in various mouse models of relapsing TB are in the early stages but show the potential for more efficient and cost-effective identification of drug combination regimens with a promise to deliver superior outcomes. Currently, the most developed and applied approach for regimen selection has been the systematic use of relapsing mouse models of TB [63,64]. By using consistent infection metrics, dosing regimens to replicate human exposures, and comparisons to clinically established regimens, the relapsing mouse models are able to assess the impact on treatment duration required for complete eradication of MTB from the lungs for various regimens and can establish the relative contributions of new agents within established regimens [74]. With the advancement of many new compounds and regimens into early clinical trials, the validation of the results from the relapsing mouse models as a surrogate in terms of translation to clinical cure with shorter duration regimens may be forthcoming, notwithstanding, that the model does not appear to fully recapitulate human pathology or dissemination of bacterial burdens into varied compartments and growth states. A variety of additional preclinical animal models have been proposed to more faithfully mimic human pathology and may, in the end, provide a more accurate assessment of the curative properties of novel drug regimens [75]. Regardless, none of the animal models, including non-human primate infections, can perfectly recapitulate the diversity of disease history, host-response, or overall pathology that is observed in human populations and the additional costs, complexity, and variability in the "staging" of many of these models may hinder their applicability as routine preclinical studies. Many animal models for infectious diseases, whether acute/chronic or disseminated/localized are imperfect reproductions of human disease but have been valuable surrogates for identification and development of effective therapies. Ultimately, "reverse-translational" experience with novel regimens will be needed to clarify and improve the applicability of preclinical models to identify optimal anti-TB therapies. These approaches are likely to provide critical advancements over current development strategies, where monotherapy or combination EBA studies are often used, but may not provide insight or guidance on the potential for shorter duration regimens with effective sterilizing activity [76,77].

4. Conclusions

Recognition of the public health threat of DR TB and new research tools have helped to propel anti-tuberculous drug research and development into a new era, which has seen initial success with recent drug and regimen approvals. A rich pipeline of new compounds in preclinical and clinical development is poised to further bolster the armamentarium against DR and hopefully also against DS TB through regimens of shortened duration and reduced toxicity, especially with improved understanding of the predictive value of preclinical regimens models. However, the biological complexity of the TB combined with divergent immunological responses in individuals and lack of diagnostic parameters that can accurately predict early eradication and cure continues to present significant challenges in the clinical development of novel drugs and drug regimens. Further, despite the development of new preclinical models, these are not perfect replications of the human course of the disease and the potential for high attrition rates remains a concern.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Todd A. Black reports a relationship with Merck & Co Inc that includes: employment and equity or stocks. Ulrike K. Buchwald reports a relationship with Merck & Co Inc that includes: prior employment.

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