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Narrative review

Candidate anti-tuberculosis medicines and regimens under clinical evaluation

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ABSTRACT

Background: Tuberculosis (TB) is the leading cause of mortality by an infectious disease worldwide. Despite national and international efforts, the world is not on track to end TB by 2030. Antibiotic treatment of TB is longer than for most infectious diseases and is complicated by frequent adverse events. To counter emerging *Mycobacterium tuberculosis* drug resistance and provide effective, safe drug treatments of shorter duration, novel anti-TB medicines, and treatment regimens are needed. Through a joint global effort, more candidate medicines are in the clinical phases of drug development than ever before.
Objectives: To review anti-TB medicines and treatment regimens under clinical evaluation for the future treatment of drug-susceptible and drug-resistant TB.
Sources: Pre-clinical and clinical studies on novel anti-TB drugs.
Content: Description of novel protein synthesis inhibitors (oxazolidinones and oxaboroles), respiratory chain inhibitors (diarylquinolines and cytochrome bc1 complex inhibitor), cell wall inhibitors (decaprenylphosphoryl-β-d-ribose 2′-epimerase, inhibitors, thioamides, and carbapenems), and cholesterol metabolism inhibitor currently evaluated in clinical trials and novel clinical trial platforms for the evaluation of treatment regimens, rather than single entities.
Implications: A large number of potential anti-TB candidate medicines and innovations in clinical trial design for the evaluation of regimens, rather than single medicines, provide hope for improvements in the treatment of TB. **Michael Hoelscher, Clin Microbiol Infect 2024;30:1131**

Introduction

After years of sluggish decline, the estimated incidence of tuberculosis (TB) rose to 10.6 million cases and deaths increased to 1.3 million in 2022 because of the COVID-19 pandemic [1]. Among the estimated 10.6 million incident cases, 3.1 million cases are not notified or given appropriate treatment, further contributing to the on-going transmission of *Mycobacterium tuberculosis* [1].

Most pulmonary TB cases are “drug-susceptible” (DS-TB) and treatable with the 6-month rifampicin-based standard regimen developed 50 years ago. The World Health Organization (WHO) also now recommends a 4-month-rifapentine-based regimen for the treatment of pulmonary TB under certain conditions [2]. Overall successful outcomes in TB have remained in the range of 83% to 86%

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for several years [1]. More recently it has been demonstrated that high treatment success can be achieved for DS-TB patients by a treatment strategy, including bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol over 8 weeks and retreatment in case of relapse [3].

The duration, complexity, and toxicities of the standard regimen frequently result in nonadherence, leading to suboptimal outcomes and the emergence of resistance.

In 2022, the incidence of TB caused by strains of *M. tuberculosis* resistant to rifampicin and isoniazid [multidrug-resistant (MDR)] or just to rifampicin [rifampicin resistant (RR)] was estimated to be 410 000 [1]. Successful treatment outcomes for MDR/RR-TB are reported in 63% of individuals, substantially lower than for DS-TB. More than 70% of MDR/RR-TB cases worldwide are the result of primary transmission of drug-resistant *M. tuberculosis* [4].

During the 2010s, important breakthroughs were made in MDR-TB and extensively drug-resistant (XDR)-TB treatment, first with demonstrating the potency of oxazolidinones (linezolid) essentially as monotherapy among highly resistant patients in a Korea-based clinical trial [5,6], then with registration of the first diarylquinoline (bedaquiline) and the nitroimidazoles (delamanid and pretomanid [PA]) for MDR/RR-TB treatment [7–9]. Though the reduction in median time to sputum culture conversion over 6 months was not significant in the primary analysis of the Phase 3 trial of delamanid (51 days vs. 57 days), overall sputum culture conversion at 2 months (58.4% and 53.5%) and 6 months (87.6% and 86.1%) was higher than previous reports from controlled trials assessing MDR-TB treatment, suggesting broader improvements in MDR-TB diagnosis and treatment over time [10].

The subsequent bedaquiline, PA, and linezolid regimen resulted in a substantial reduction of MDR/RR-TB treatment durations to 6 months of therapy with ~90% of treatment success [9,11].

The WHO has recommended combination regimens with bedaquiline, PA, and linezolid with or without moxifloxacin (BPaLM) as front-line treatment [10]. Though greatly improving outcomes and reducing treatment duration, these regimens are still fraught with toxicities requiring close clinical monitoring, challenging many treatment programs [7].

Emerging resistance to bedaquiline [11–13], threatens the TB medicine most integral to MDR/RR-TB treatment. The need to develop new transformative regimens of shorter duration, more favourable safety profiles, with limited to no pre-existing resistance has never been greater.

In response to these challenges and building from the success of several initiatives linking activities of academia, industry, government agencies, non-governmental organizations, and donors including the Cape Town Declaration of the Working Alliance for TB Drug Development [14] in 2000, the TB Drug Accelerator [15] (established in 2012 as a TB drug discovery and development mechanism), and recent successes in treatment shortening for drug-susceptible TB [3,16], two large TB regimen development partnerships—UNITE4TB [17], and the Project to Accelerate New Treatments for Tuberculosis [18], have been launched to further advance regimen development. Both are closely coordinated and share the aim to develop transformative regimens of shorter duration (<4 months) with limited to no pre-existing *M. tuberculosis* drug resistance.

TB drug pipeline

The TB pipeline with recently approved drugs and a robust pipeline of new agents and classes present an unprecedented opportunity to identify transformative new TB regimens (see Fig. 1 [19], for a description and Fig. 2 for mechanisms of action).

The following summary highlights a list of promising agents based on target and class according to stage of clinical development.

Protein synthesis inhibitors

Oxazolidinones inhibit protein synthesis; linezolid has been very effective in treating highly drug-resistant tuberculosis [5,6].

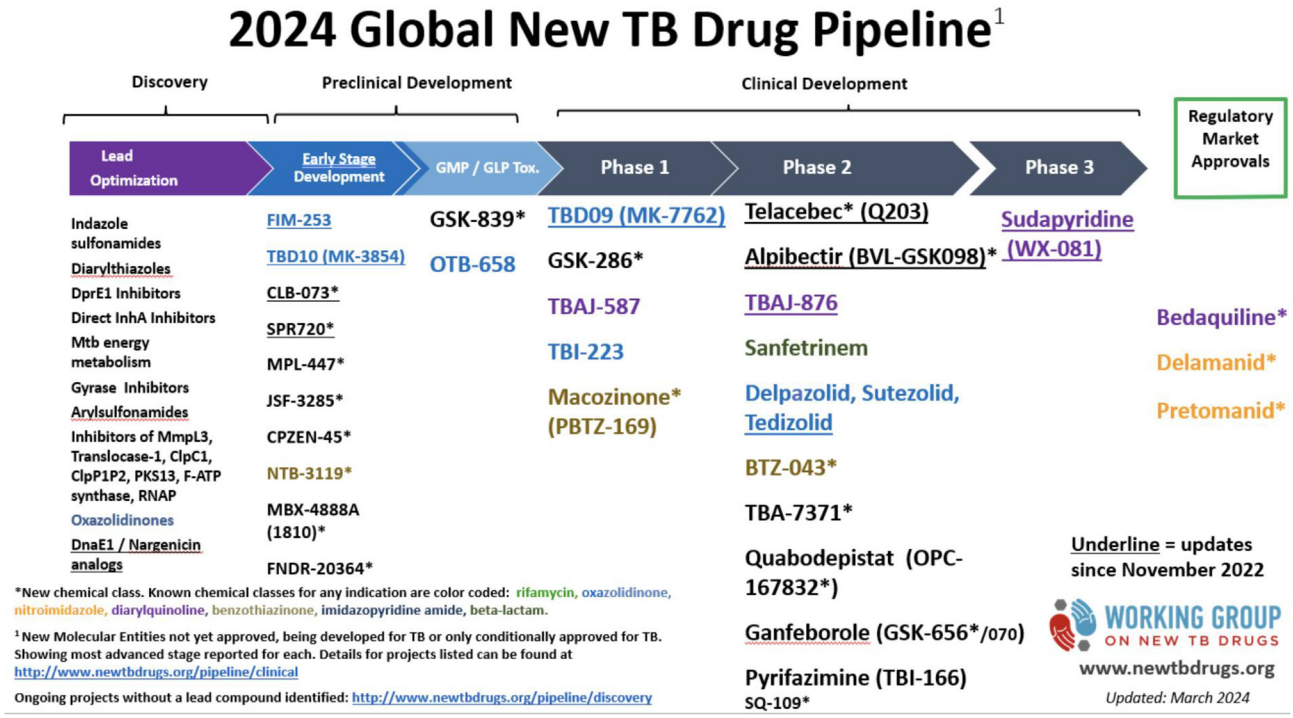

Fig. 1. 2023 Global TB drug pipeline [19]. TB, tuberculosis.

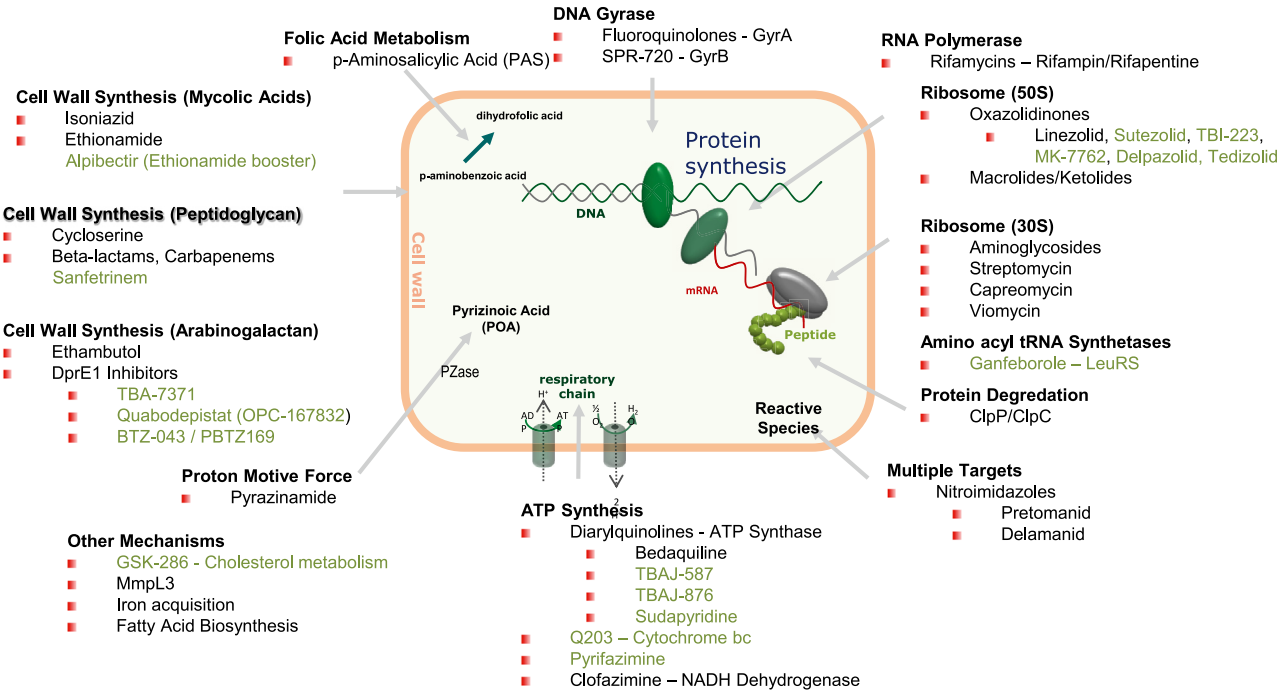

Fig. 2. TB drug targets and agents/class. TB, tuberculosis.

In the first controlled clinical trial assessing linezolid's use in the treatment of refractory MDR-TB and XDR-TB, a high proportion of patients [27/38 (71%)] achieved cure, while 'only' 4/38 (11%) acquired resistance [6], consistent with the infrequent emergence of resistance observed *in vitro* [5,6,20]. However, longer-term treatment with linezolid results in substantial side effects, including myelosuppression and neuropathy requiring dose reduction or treatment interruption in a high proportion of patients [7]. Toxicity is mediated through the inhibition of host mitochondrial protein synthesis and is associated with higher drug levels at the end of the dosing interval [6]. Two clinical trials—ZeNiX and PRACTECAL—demonstrated that the use of 600 mg (1200 mg was used previously), given for 9 or 26 weeks, led to reduced toxicity, sustained high cure rate, and subsequently recommended in the recent WHO treatment guidelines [21]. Now candidate agents from the class with anticipated similar efficacy but possibly improved safety have been identified, including sutezolid, depazolid, TBI-223, and tedizolid (Table 1). Oxaboroles are a new class of protein synthesis inhibitors showing promising safety and efficacy results in an early bactericidal efficacy trial with the component Ganfeborole (GSK3036656) (Table 1).

Respiratory chain inhibitors

As *M. tuberculosis* cannot utilize substrate-level phosphorylation, oxidative phosphorylation represents their only source of energy. Inhibition of the mycobacterial respiratory chain, generating adenosine 5′-triphosphate, represents targets divergent from most currently used TB drugs. This dependency applies to non-replicating organisms as well, highlighting the potential for treatment-shortening.

Bedaquiline specifically inhibits mycobacterial adenosine 5′-triphosphate synthase by binding to subunit c of the enzyme essential for energy generation in *M. tuberculosis*. First approved by the US Food and Drug Administration and the European Medicines Agency in 2012 and 2014, respectively, is indicated as part of combination therapy for the treatment of pulmonary MDR-TB in adults and, children (5 years and older and weighing ≥15 kg). Bedaquiline is listed by WHO as a group A drug for inclusion in all MDR/RR-TB regimens, making it integral to new regimens. Novel respiratory chain inhibitors are the diarylquinolines TBAJ-876 and TBAJ-587 and sudapyridine, and the cytochrom bc1 complex inhibitor telacebec (Q203) (Table 2).

Mycobacterial cell wall synthesis disruption

Delamanid, a dihydro-nitroimidazooxazole derivative, acts by inhibiting the synthesis of mycobacterial cell wall components, methoxy mycolic acid, and ketomycolic acid [22]. It is currently included as a group C drug in WHO guidelines. In a systematic review and meta-analysis, Nasiri et al. [23] concluded the overall pooled treatment success of delamanid containing regimen was 80.9% and 72.5% in observational and experimental studies, respectively. In its 2022 guidelines, WHO has conditionally recommended including delamanid in the treatment of MDR/RR-TB in children of any age on the longer regimen. PA-824 was first identified in 2000, in a series of nitroimidazopyran derivatives synthesized and tested for anti-TB activity. It has activity against static *M. tuberculosis* isolates that survive under anaerobic conditions. It was developed by the TB alliance for the treatment of tuberculosis in combination with bedaquiline and linezolid (BPaL) and was first approved in 2019. Whether pretomanid can be substituted with delamanid as results from preclinical studies [24] needs to be evaluated in clinical studies.

DprE1 is a critical enzyme in the production of lipoarabinomannan and arabinogalactan, both essential components of the mycobacterium cell wall [25]. Inhibition of DprE1 leads to cell lysis and bacterial death [26]. Currently, four DprE1 inhibitors, in three chemical classes are in clinical development. The two benzothiazinones (BTZ-043 and PBTZ-169), a carbostyril derivative (quabodepistat previously known as OPC-167832), and an

Table 1
Protein synthesis inhibitors

Compounds	Description
Oxazolidinones	
Sutezolid (PNU-100480)	Compared with linezolid: • Thiomorpholine analogue with the potential to avert toxicity through better specificity for bacterial ribosomes. • Showed higher potency in the mouse model, with similar potential to shorten treatment [31]. In clinical evaluation • Demonstrated early bactericidal activity (EBA) of 0.088 log10 CFU/ml*d (95% CI: −0.112 to −0.065) when 600 mg twice daily was administered as 14-d monotherapy [32]. • In a 12-wk 75-participant PanACEA-SUDOCU trial (in combination with bedaquiline, delamanid, and moxifloxacin), no neuropathy or myelosuppression demonstrated; nor added efficacy on the primary endpoint of quantitative bacterial load [33]. • Despite one case of drug-induced hepatotoxicity, no further hepatic safety signals stemming from the phase 2A trial were observed. • Additional Phase 2 investigation planned in EDCTP-funded PanTB-—HM trial, by PAN–TB collaboration, and by ACTG.
Delpazolid (LCB01-037)	• Depazolid appears to have lower C_{min} mainly through a more rapid elimination and therefore may have less toxicity [34]. • In 13 clinical isolates of linezolid-resistant TB from China, 7 were delpazolid-susceptible, raising the possibility for incomplete cross-resistance [35]. • Currently under evaluation in a 16-wk dose-finding study; results are expected in the second half of 2024 [36].
TBI-223	Compared to linezolid: • In mitochondrial protein synthesis, inhibition is 14-fold lower [37]. • In murine studies, efficacy appears equivalent. • In development by TB Alliance; currently in phase I human trials. • Further testing is planned by ACTG.
Tedizolid	Tedizolid is another repurposed oxazolidinone currently evaluated in a phase 2A study.
Oxaboroles	
Ganfeborole (GSK3036656)	• First in class oxaborole boron-containing Leucyl-*t*RNA synthetase inhibitor; interferes with protein synthesis/translation and is shown to target *M. tuberculosis in vitro* and *in vivo* [38]. • Low dose compound recently completed 14-d phase 2a EBA trial in rifampicin-susceptible pulmonary TB patients: ◦ Daily treatment with Ganfeborole at 5, 15, and 30 mg was associated with EBA, measured by the rate of change in $\log_{10}$ colony forming units and time to positivity of *M. tuberculosis* cultures over 14 d; 30 mg dose displayed the highest EBA [39]. ◦ Further phase 2a trial with Ganfeborole in combination with bedaquiline, delamanid, or BTZ-043 is currently underway.

ACTG, Adult Clinical Trials Group; EDCTP, European and Developing Countries Clinical Trials Partnership; PanTB-HM, A Novel pan-TB Regimen Targeting Both Host and Microbe; PAN-TB, Project to Accelerate New Treatments for tuberculosis.

Table 2
Respiratory chain inhibitors

Compounds	Description
Diarylquinolines	
TBAJ-876 and TBAJ-587	• TBAJ-876 and TBAJ-587 are dialkoxypyridine analogues of bedaquiline resulting from next-generation diarylquinoline lead optimization efforts. • Compared with bedaquiline (and its metabolites): ◦ Both compounds were selected based on improved potency and reduced potential for QT-intervall prolongation as demonstrated by *in vitro* cardiac ion channel current inhibition screening studies and dog studies [40]. ◦ Minimal inhibitory concentrations (MIC) of TBAJ-876 and TBAJ-587 ~8- to 10-fold lower against laboratory and clinical strains. ◦ Similarly, N-des-methyl metabolites of TBAJ-876 and TBAJ-587 have lower MIC. ◦ *In vivo*, lower doses of TBAJ-876 and TBAJ-587 produced similar efficacy. ◦ At similar doses, more rapid bactericidal and sterilizing activity was observed, including against rv0678 strains. ◦ Although the shared mechanism of action (vulnerable to the same resistance mutations), greater potency could provide efficacy against rv0678 while maintaining a higher barrier to resistance. ◦ Mutations in *Rv0678*, as the most common mechanism leading to resistance by activation of transcription of an efflux transporter (MmpL5-MmpS5); clofazimine resistance is also associated with mutations in *Rv0678* through the same mechanism [13]. • Phase 1 trials were completed for both compounds, demonstrating a generally well-tolerated safety profile. • Phase 2 trial of TBAJ-876 is underway in patients with drug-susceptible TB, with a range of doses being evaluated in combination with pretomanid and linezolid.
Sudapyridine	• Sudapyridine—bedaquiline derivative developed in China; currently undergoing phase 3 evaluation there.
Cytochrom bc1 complex inhibition	
Telacebec (Q203)	• First-in-class, orally active imidazopyridine carboxamide inhibitor of the QcrB subunit of the cytochrome bc1 complex, causing depletion of ATP synthesis [41]. • MIC_{50} of 2.7 nM in broth culture medium and MIC_{50} of 0.28 nM against *M. tuberculosis* H37Rv, infected macrophages. • Following single- and multiple-dose Phase 1 studies, a 14-d monotherapy trial in drug-sensitive TB patients demonstrated dose-dependent EBA [42]. • Highly active against two other mycobacterial species, *M. leprae* and *M. ulcerans*—causative agents of leprosy and Buruli ulcer, respectively.

ATP, adenosine 5′-triphosphate; bc1, respiratory complex III; EBA early bactericidal.

azaindole (TBA-7371). Phase 2a trials for all four compounds have been completed and both quabodepistat and BTZ-043 have advanced to phase 2b/c trials (Fig. 3 and Table 3).

Novel compounds with alternative activities to those mentioned above are the ethionamide/prothionamide booster alpibectir (BVL-GSK098), a new ß-lactam named sanfetrinem cilexetil and GSK2556286, an inhibitor of the mycobacterial cholesterol mechanism (Table 4).

Regimens in clinical development

Bedaquiline received accelerated (US)/conditional (EU) approval in 2012 and 2014, respectively, and delamanid received conditional (EU) approval in 2014, based on trials that showed benefit on sputum culture conversion when added to an optimized background regimen for MDR-TB treatment. These agents were licensed without specific combination agents. The paucity of agents for

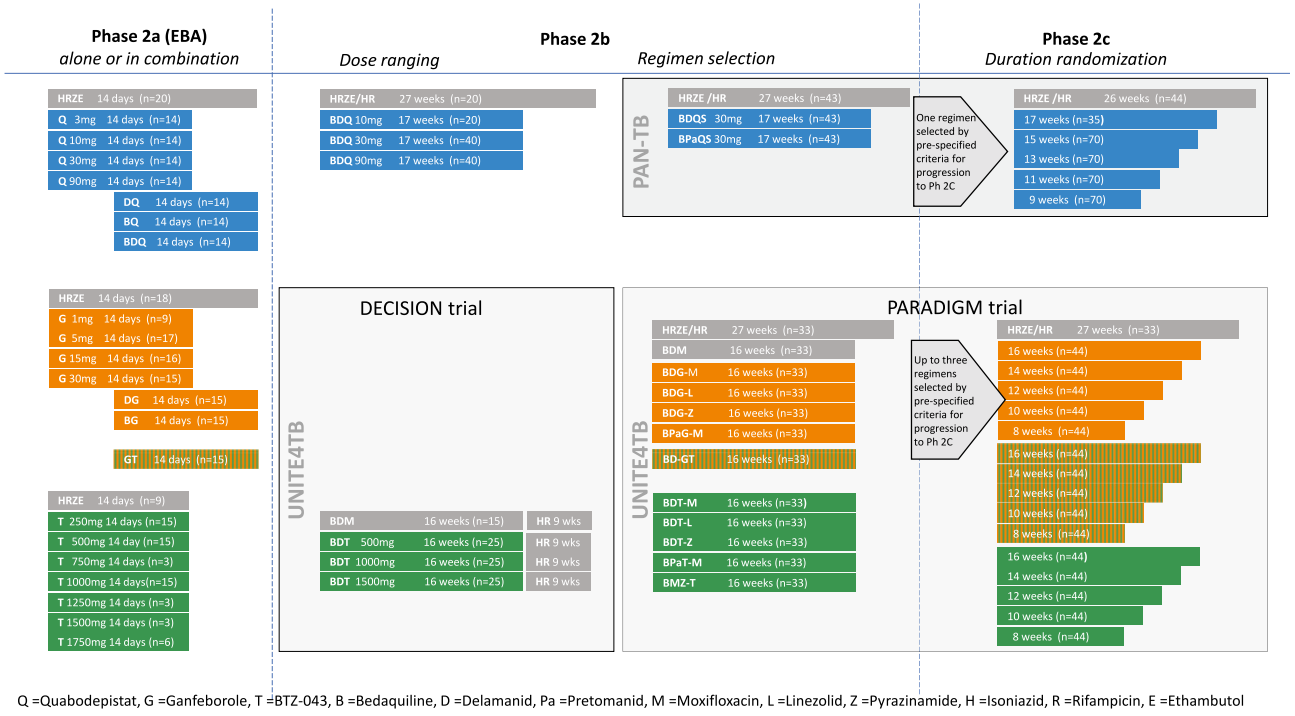

Fig. 3. Graphical display of the drug development plan for quabodepistat, ganfeborole, BTZ-043, and sutezolid.

Table 3
Mycobacterial cell wall synthesis disruption

Compounds	Description
DprE1 inhibitors	
BTZ-043	• The first molecule was discovered in 2009 with inhibitory activity against DprE1 enzyme. • Very low *in vitro* inhibitory activity at nanomolar concentrations [43]. • Accumulates within the rim of necrotic lesions and within 8 h after administration, penetrates the whole granuloma of C3HeJ/FeB nine mice that display a human-like pathology [44]. • Shown 2.5 log reduction of $\log_{10}$ CFU/lung at 200 mg/kg after 8 wk of dosing in C3HeJ/FeB nine mice [45]. • To date, 96 individuals exposed to BTZ-043 doses between 250 and 1750 mg in three phase 1–2 studies [46,47]; when taken with food, bioavailability markedly increases. • In phase 2a EBA trial BTZ-043 (given as monotherapy), a strong bactericidal effect over 14 d, similar to rifampicin [48], and did not show any significant safety concern.
Macozinone PBTZ-169	• Derivative of BTZ-043 but incorporates piperazine component. • *In vitro*, has demonstrated efficacy against MDR/RR strains of *M. tuberculosis;* reduction in log10 CFU/Lung of around 0.5 over 8 wk of treatment in C3HHeJ mice [49]. • From 2018 to 2020, two phase 1 trials were conducted to investigate the effects of different formulations [50,51]. • In 2017, phase 2a EBA trial was conducted in Russia and Belarus assessing three doses [52].
Quabodepistat OPC-167832	• Novel carbostyril derivative proved to have low MICs against Mycobacterium *tuberculosis* (ranging from 0.24 ng/mL to 2 ng/mL), with bactericidal activity against both growing and intracellular bacilli. • Did not show antagonistic effects with other anti-TB medicines tested, both *in vitro* and *in vivo* studies. • Mouse models of chronic TB showed potent bactericidal activities with a 2-log reduction in $\log_{10}$ CFU/lung over 8 wk at 20 mg/kg OD. • Treatment regimens containing agents showed efficacy in preventing relapse compared with standard treatment regimens for drug-susceptible TB [53,54]. • In phase 1b/2a study, all tested doses (3, 10, 30, and 90 mg) appeared to have significant bactericidal activity and did not show any significant safety concerns [55].
TBA-7371	• Non-covalent azaindole inhibitor of DprE1. • Demonstrates potent *in vitro* bactericidal activity against M tuberculosis with a minimum bactericidal concentration similar to its MIC against replicating M. tuberculosis. • MIC_{90} of TBA-7371 is 0.64 μg/mL and the MIC range is 0.04 to 5.12 μg/mL. • Demonstrated dose-responsive bacteriostatic and bactericidal *in vivo* efficacy against acute and chronic murine (Kramnik) TB; with a 1-log reduction in $\log_{10}$ CFU/lung over 8 wk at 100 mg/kg BID [49]. • Single- and multiple-dose Phase 1 studies have been completed, and a phase 2 dose-ranging and dose fractionation study has been recently completed, showing the highest activity with thrice daily dosing regimen [56].

BID, bis in die = twice daily; DprE1, decaprenylphosphoryl-β-d-ribose 2′-epimerase; EBA, early bactericidal; MIC, minimal inhibitory concentrations; OD, once daily; TB, tuberculosis.

Table 4
Compounds with other modes of action

Compounds	Description
Thioamides	
Alpibectir	Alpibectir an amido-piperidine, acts as a booster by activating *mymA* allowing for >3-fold lower doses of ethionamide while re-establishing
BVL-GSK098	sensitivity in ethionamide-resistant TB strains and potentiating its activity [57]. It is currently in phase 2a development [58].
Penicillin-binding proteins and transpeptidases	
Sanfetrinem cilexetil	Sanfetrinem cilexetil is a first-in-class oral tricyclic carbapenem, previously developed to treat otitis media in children three decades ago. Recently repurposed for TB after being identified as the most active against intracellular TB in a screen of 2000 β-lactam compounds and is very stable against β-lactamases [59]. A phase 2a 14-d EBA study in pulmonary TB patients is ongoing [60].
Cholesterol metabolism	
GSK2556286	GSK2556286 is an Rv1625 agonist leading to increased cAMP and reduced cholesterol metabolism [61]. *In vivo*, it demonstrates intracellular activity, and possibly sterilizing and treatment-shortening qualities [62]. A phase 1 double-blind, randomized, sequential, parallel-dose cohort study in healthy adult participants is currently recruiting [63].

cAMP, cyclic adenosine monophosphate; EBA, early bactericidal; TB, tuberculosis.

constructing new effective regimens at the time of approval amplified the risk of the emergence of resistance to them.

Pretomanid was the first drug licensed for use as part of a specific regimen (2019 in the United States), building on the previous successful evaluation of linezolid [6] and bedaquiline [27]. As the available recommended treatment for highly drug-resistant TB had poor outcomes at the time, the US Food and Drug Administration approved the combination on the basis of robust efficacy (90% favourable outcome after 6 months) in a single arm clinical trial of 109 XDR-TB and treatment-intolerant or non-responsive MDR-TB patients. However frequent side effects including peripheral neuropathy (81%) and myelosuppression (48%), attributable to linezolid dosing at 1200 mg daily, made this treatment less feasible for a broader range of patients with less severe disease [7]. Subsequent studies [9,21] that included MDR/RR-TB patients, and that used a more tolerable 600 mg daily dose of linezolid, led the WHO [2] to recommend BPaLM for MDR/RR-TB and BPaL for MDR/RR and FQ-R TB (pre-XDR, 2021 definition). As WHO revised the definitions and provided novel treatment guidelines for drug-resistant TB a situation resulted where regulatory agency approvals of pretomanid as part of the BPaL regimen are restricted to patients with XDR-TB while WHO recommends the BPaLM regimen for the treatment of MDR/RR-TB and pre-XDR-TB but not for XDR-TB. This situation must be solved urgently.

The desired profile that new TB regimens could efficiently treat all forms of TB regardless of resistance patterns might be feasible. Treatment responses for MDR-TB and DS-TB were closely comparable in the NC005 and SimpliciTB trials [28,29] and now an all-oral 6-month regimen is available for MDR TB. Although WHO has developed updated target regimen profiles for TB treatment the rich pipeline of drugs in advanced stages of development, opens the possibility for a Project to Accelerate New Treatments for tuberculosis regimens that could treat both DS-TB and DR-TB.

As experience has shown, shorter, less toxic, and affordable regimens cannot be designed at the drawing table. Human safety and drug–drug interactions cannot be reliably predicted preclinically as the recent example of the BPaMZ (Bedaquiline-pretomanid-moxifloxacin-pyrazinamide) regimen demonstrates. Withdrawal because of adverse events (mostly hepatic) in 10% (28 of 277) of patients in both investigational arms showed the limitations of this combination [29].

Consequently, a new dawn of regimen development is emerging, as evidenced by the development pathways of the new drugs quabodepistat, ganfeborole, BTZ-043, and sutezolid (Fig. 3). In general, a candidate drug will usually be evaluated in a 14-day early bactericidal monotherapy trial to show its anti-TB effect and generate some information on PK-PD (pharmacokinetic/pharmacodynamic) and dose selection. With quabodepistat and BTZ-043, for efficiency in development, phase 1b multiple dosing was first evaluated in TB patients to generate efficacy information for phase 2 dose selection. Next, these agents are each undergoing evaluation in 4-month dose-finding combination studies. TBAJ-876, after completing phase 1 studies in healthy subjects, is being evaluated for anti-TB activity in a dose-ranging study in combination with pretomanid and linezolid, for an initial 8-week period, followed by HR continuation. These efforts aim to generate data for PK-PD modelling and will inform on efficacy over a longer treatment duration, but also on toxicities that occur late in treatment, and their relation to exposure, following the example of two oxazolidinone studies—PanACEA-SUDOCU and DECODE—planned for this purpose.

As outlined, selection of the most promising partner drugs for combination requires human trials, before a pivotal phase 3 trial is launched, since time, financial, and logistical challenges prohibit multiple regimens from being evaluated in parallel in phase 3 trials. Innovative regimen selection trials will perform an adaptive selection step to choose an effective and safe combination, currently using a sputum bacteriological endpoint for this interim decision (phase 2b). The final primary endpoint will then focus on sterilizing activity across a range of disease severity, specifically the power of a regimen to prevent relapse, for confirming regimen efficacy [30]; this will include an exploration of the optimal length of treatment with a duration-randomization assessment (phase 2c). Optionally, de-risking phase 2 designs, if successful, with exceptionally promising arms might not require any adaptation, potentially allowing for a seamless transition into a phase 3 trial. As such, a large platform trial like PARADIGM4TB may evolve into a phase 3 platform that may generate pivotal licensing data on more than one regimen, whilst simultaneously containing a phase 2b regimen selection phase.

Author contributions

MH and CW designed the structure of the review. MH, DB-A, MD, NH, MK, ES, ST, CW wrote the first draft. MH, DB-A, MD, NH, MK, ES, CL, CW, ST revised the manuscript. All authors approved the manuscript for submission and publication.

Transparency declaration

CL has received an honorarium for consultation service to INSMED, a company that produced liposomal amikacin as an inhalation suspension for the treatment of NTM-PD outside of the scope of this work. CL received speakers' honoraria from INSMED, GSK, Gilead, Astra Zeneca, MedUpdate, and MedUpdateEurope outside of the scope of this work. NHand MH have received funding from LigaChem (formerly LegoChem) Biosciences for the DECODE clinical trial at their institution. NHand MH are employees of LMU Klinikum, the university that develops BTZ-043. ST is an employee and shareholder in GSK. DBA is an employee of, and shareholder in, GSK, and reports patents planned, issued, or pending. MD is an

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