Recent advances in the treatment of tuberculosis

Title page

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Abstract:

Background

Tuberculosis is a global health challenge and one of the leading causes of death worldwide. In the last decade, the tuberculosis treatment landscape has dramatically changed. After long years of stagnation, new compounds entered the market (bedaquiline, delamanid and pretomanid) and phase III clinical trials have shown promising results towards shortening duration of treatment for both drug-susceptible (Study 31/A5349, TRUNCATE-TB, SHINE) and drug-resistant tuberculosis (STREAM, NiX-TB, ZeNix, TB-PRACTECAL). Dose optimization of rifamycins and repurposed drugs have also brought hopes of further development of safe and effective regimens. Consequently, international and World Health Organization clinical guidelines have been updated multiple times in the last years to keep pace with these advances.

Objectives

This narrative review aims to summarize the state-of-the-art on treatment of drug-susceptible and drug-resistant tuberculosis, as well as recent trials results and an overview of ongoing clinical trials.

Sources

A non-systematic literature review was conducted in PubMed and MEDLINE, focusing on the treatment of tuberculosis. Ongoing clinical trials were listed according to the authors' knowledge, and completed consulting clinicaltrials.gov and other publicly available websites (www.resisttb.org/clinical-trials-progress-report, www.newtbdrugs.org/pipeline/trials).

Content

This review summarizes the recent, major changes in the landscape for drug-susceptible and drug-resistant treatment, with a specific focus on their potential impact on patient outcomes and programmatic TB management. Moreover, insights in host-directed therapies, and advances in pharmacokinetic and pharmacogenomics are discussed. A thorough outline of ongoing therapeutic clinical trials is presented, highlighting different approaches and goals in current TB clinical research.

Implications

Future research should be directed to individualize regimens and protect these recent breakthroughs by preventing and identifying the selection of drug resistance and providing widespread, affordable, patient-centered access to new treatment options for all people affected by tuberculosis.

Main article

Introduction

Tuberculosis (TB) remains a global health challenge, with an estimated incidence of 10.6 million new cases occurring in 2021, according to the 2022 World Health Organization (WHO) Global TB Report.[1] The incidence of multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) is increasing, with an estimated 450,000 new cases in 2021.

Existing treatments for drug-susceptible (DS) and drug-resistant (DR) TB for adult and children have saved millions of lives. However, TB is still a leading infectious cause of death with 1.6 million deaths (including 187,000 people living with HIV) occurring in 2021 and in the near future could replace again COVID-19 as the leading cause of death by a single infectious agent.[1]

Recent therapeutic advances have dramatically renewed the landscape for DS- and DR-TB treatment. This review aims to highlight these major changes and their potential impact on patient outcomes and programmatic TB management.

Treatment of drug-susceptible TB

For much of the last 50 years, DS-TB has been treated with the so-called 'short-course chemotherapy' regimen. Administered over six months, the regimen was the result of a series of clinical trials conducted between 1946 and 1986 by the British Medical Research Council.[2] These trials demonstrated that an 'intensive' phase of two months of rifampicin, isoniazid, and pyrazinamide, followed by a 'continuation' phase of four months of rifampicin and isoniazid, could cure most patients. Pyrazinamide was added to the regimen in the intensive phase to permit treatment shortening from nine to six months.[2] This 'one-size-fits-all' regimen subsequently became the global standard, recommended for treating all forms of DS-TB.

Short-course chemotherapy has saved millions of lives, but six months of pill-taking challenges patients and TB treatment programmes alike. There has, therefore, been much interest in shortening the regimen. There were early signals that the addition of fluoroquinolones might shorten treatment, with trials suggesting that these drugs reduced the time-to-sterilisation of sputum when added to the standard therapy.[3, 4] However, three independent phase III trials published in 2014 showed that four-month regimens containing moxifloxacin or gatifloxacin did not meet the pre-defined non-inferiority margins when compared to the standard six-month regimen.[5–7] Nonetheless, subsequent analyses of the results of these trials have shown that specific subgroups of patients may benefit from less than six months of treatment.[8, 9]

Investigators turned to shorten treatment by optimising the pharmacokinetics of the drugs used, especially the rifamycins (rifampicin, rifabutin, rifapentine). Clinical studies have confirmed that rifampicin doses up to 40mg/kg/day were well-tolerated and increased early bactericidal activity,[10] but whether high rifampicin doses can safely shorten therapy, or improve outcomes from TB meningitis, remains the subject of ongoing trials (**Table 1**). Recent data from a large

phase III trial (Study 31/A5349) showed that rifapentine – a rifamycin with a longer half-life – used in combination with isoniazid, pyrazinamide and moxifloxacin, can shorten therapy to four months.[11] In May 2022, the WHO conditionally recommended that eligible persons aged ≥12 years with pulmonary DS-TB may receive this four-month regimen.[12]

A reinvigorated anti-TB drug pipeline has enabled new approaches to treatment (**Table 1**). A recent phase II trial compared pretomanid - a new nitroimidazole - with either rifampicin or rifabutin, in combination with isoniazid and pyrazinamide, against the standard 6-month regimen.[13] The pretomanid-rifabutin regimen induced faster bacterial killing in sputum than the other regimens, but with more frequent hepatic adverse events, probably due to the pretomanid/pyrazinamide combination, which may temper the use of this combination for future DS-TB treatment.[14]

It has long been recognised that there is a subset of patients, often with less severe TB, that may be cured with less than six months of therapy.[15] The SHINE trial showed that sixteen weeks was non-inferior to six months of treatment in children with DS, non-severe, smear-negative TB.[16] The TRUNCATE-TB trial investigated a strategy of giving eight-week treatment regimens to adults with mild or moderately severe pulmonary TB, with the possibility to extend treatment in those with poor response and retreatment for relapses. [17] One strategy arm using an initial eight-week combination of bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol met the 12% non-inferiority margin, with marked reduction in total time on treatment, and without major safety concerns. Overall, 3 (2%) participants out of 189 in the successful strategy arm extended regimen and 24 (13%) started a second treatment course. Two participants in the bedaquiline-, linezolid-containing arm relapsed with confirmed acquired phenotypic drug resistance to bedaquiline (and clofazimine). Implementation research is needed to evaluate the outcome of such strategy in

diverse populations. Of note, the definition of TB severity is heterogeneous among the aforementioned studies and would greatly benefit from consensus on validated criteria.[8, 9]

Treatment of isoniazid-resistant, rifampicin-susceptible TB

Isoniazid resistance without concurrent rifampicin resistance is the most common type of *M. tuberculosis* resistance worldwide, present among an estimated 10.6% of all TB cases in 2019.[18] In 2018, WHO recommended a regimen consisting of six months of rifampicin, ethambutol, pyrazinamide, and levofloxacin to treat isoniazid-resistant TB, following an individual patient data (IPD) meta-analysis containing 3,923 patients with isoniazid-resistant, rifampicin-susceptible TB which indicated that the addition of a fluoroquinolone, compared to six months of standard treatment with or without isoniazid, increased the likelihood of treatment success (adjusted odds ratio: 2,8 [95% confidence interval: 1,1-7,3]).[12, 19] This recommendation was, however, conditional, based on a very low certainty of evidence. In instances of noncavitary disease, low bacillary burden, or pyrazinamide toxicity, European-American guidelines have suggested that pyrazinamide may be given only during the first two months of treatment, provided the fluoroquinolone used is later-generation.[20] Patients with fluoroquinolone resistance or contraindications are generally recommended to be treated with rifampicin, ethambutol and pyrazinamide only for six months. However, these two latter recommendations lack clinical trial evidence and are based on expert opinion. When additional drug resistance is detected or highly likely, individualised regimens are needed.

At the time of the WHO guidelines, there was no clear evidence if using high-dose isoniazid within such regimens was beneficial. This is likely to be influenced by the resistance mutation(s) present

(for example, mutations in *inhA* and its promoter are usually associated with lower-level resistance than *katG* mutations) and the patient's acetylator status.[21] There is recognition that isoniazid may be included in regimens simply due to the use of fixed-dose combination pills. As the majority of the evidence for the treatment of isoniazid-resistant TB derives from secondary observational data, bespoke clinical trials (potentially drawing from emulated target trials) would be needed to strengthen the evidence base.[22]

Treatment of MDR/RR-TB

In 2018, the results of an IPD analysis with more than 12,000 patients with MDR/RR-TB, and an observational cohort about the impact of bedaquiline on TB mortality in South Africa, led to substantial changes in the recommendations for management of patients with MDR/RR-TB.[20,21] The recommendation to change from 18-20 months of treatment to an all-oral, shorter, 9-12 month regimen, as well as the recommendation against the use of injectables (namely capreomycin and kanamycin), marked a drastic shift in the management of patients with MDR/RR-TB.[25, 26] STREAM Stage 2 trial was a phase III trial that compared a nine-month injectable containing regimen (four months of kanamycin, isoniazid, prothionamide, and nine months of moxifloxacin, clofazimine, ethambutol, pyrazinamide) with a nine-month all-oral regimen where bedaquiline replaced kanamycin. The primary endpoint, favourable treatment outcome, was reached with the injectable-containing regimen in 71% of participants and with the all-oral regimen in 83%.[27] Most importantly, grade 3/4 hearing loss was documented in only 2% of participants receiving the all-oral regimen vs. 9% in the injectable-containing regimen. The WHO recommended the nine- to twelve-month regimen with bedaquiline (and the option of replacing ethionamide with linezolid given for two months) in 2022 for the treatment of MDR/RR-TB

without fluoroquinolone resistance as second option.[28] The TB-PRACTECAL trial consolidated the evidence that MDR/RR-TB can be treated successfully with a six-month regimen.[29] A regimen with bedaquiline, linezolid, pretomanid and moxifloxacin (BPaLM) was documented in the modified intention to treat analysis to be superior to the standard of care (89% favourable outcomes in BPaLM group versus 51% in standard of care). At least as important as the efficacy of the regimen were the safety results: only 25% patients on BPaLM, compared to 60% on standard of care suffered a grade 3/4 adverse event within 108 weeks after randomization.[30] The trial was stopped early due to the superiority of the BPaLM regimen and the WHO recommended it (very low certainty of evidence) as the preferred treatment option for fluoroquinolone-susceptible MDR/RR-TB in 2022 guidelines, even if the trial included also participants with fluoroquinolone-resistant TB.[28] The NExT trial supports the potential of bedaquiline, linezolid (600 mg daily) and fluoroquinolones to shorten MDR/RR-TB treatment to six months.[31] An interim analysis of the BEAT-Tuberculosis trial with bedaquiline, linezolid and delamanid for 6 months showed also high efficacy with 87% obtaining a favourable outcome.[32] The MDR-END trial, using a non-bedaquiline based regimen with delamanid, linezolid, levofloxacin and pyrazinamide for 9-12 months, showed 75% success and the regimen was non-inferior to a 20-24 month regimen based on WHO 2014 MDR-TB guidelines.[33, 34] **Table 2** shows completed and ongoing trials not yet published concerning treatment of MDR/RR-TB.

Unfortunately, despite all progress with new regimens, the scarcity of drug resistance testing against bedaquiline, linezolid, pretomanid, delamanid, and other key drugs is a substantial threat to all the progress made in the treatment of MDR/RR-TB.[35] The lack of user-friendly, standardized phenotypic drug susceptibility testing limits not only the scale-up of diagnostics, but also undermines the trust of treating physicians in their implementation in clinical practice. It is

crucial to implement widespread routine surveillance systems for drug resistance.[36] Moreover, drugs included in these regimens are not accessible everywhere and their availability is jeopardized by unacceptably high costs in many countries.[37]

Treatment of MDR/RR and fluoroquinolone-resistant TB

Challenges that clinicians face when managing patients with pre extensively drug-resistant (pre-XDR) TB, defined as RR/MDR-TB with additional fluoroquinolone resistance, include limited efficacy with current regimens, a high adverse event profile, unaffordable costs for most settings, and the potential to amplify drug resistance given the limited availability of registered novel drugs.[38] The only ongoing trial is reported in **Table 3**. The BEAT-India trial specifically recruited persons with pre-XDR-TB and used a six to nine-month four-drug regimen (bedaquiline, linezolid at 600 mg daily, clofazimine, and delamanid), 139/153 participants (91%) had a favourable outcome, though linezolid-associated toxicity was considerable.[39] Over half of the participants developed myelosuppression (85, 52%) or neurotoxicity (69, 42%) of any grade, although 34 patients were able to take a lower (300 mg) dose of linezolid. NiX-TB and ZeNix trials used a three-drug 6 months BPaL regimen in pre-XDR-TB or MDR-TB with previous failure (linezolid was dosed 1200 mg daily for 6 months in NiX-TB and 600 mg or 1200 mg daily for 2 or 6 months in ZeNix). Neither study had a control arm and the number of participants included was relatively small. Nix-TB showed ~90% favourable outcome rate in 109 participants, with 81% experiencing peripheral neuropathy and 48% myelosuppression. ZeNix confirmed the efficacy results (favourable outcome ranged between 84% and 93% across different linezolid doses groups) and the risk-benefit ratio seemed in favour of the group that received linezolid at 600mg daily for six months. Nine participants had baseline phenotypic bedaquiline resistance, of whom six had a

favourable outcome.[40, 41] The BPaL regimen can be prescribed in case of proven fluoroquinolone resistance, according to WHO recommendations (very low certainty of evidence).[42] The optimal linezolid dosing posology remains to be established, as current WHO recommended dosing (600 mg daily throughout the treatment) is based on very low certainty of evidence; ongoing efforts may inform policies on reduced/intermittent linezolid administration[43, 44]. In patients with more extensive disease and with unfavourable linezolid pharmacokinetics (sub-optimal linezolid levels relative to minimal inhibitory concentration (MIC)),[45] there are concerns about the amplification of resistance, even if evidence is still lacking. Moreover, monitoring linezolid side effects outside clinical trial settings in high-endemic, low-resource areas may be challenging.

In summary, the available findings seem to indicate that a six to nine-month, three- to four-drug regimen to treat fluoroquinolone-resistant MDR/rifampicin-resistant disease is feasible. Although there is no solid evidence base, where appropriate (multiple poor prognostic features), it would be reasonable for clinicians to opt for a four-drug regimen (i.e. bedaquiline-linezolid-delamanid-clofazimine as in the BEAT-India regimen) or to extend the duration of the regimen in case of culture positivity at the four-month time point when using a six-month regimen. Overall, it is imperative that capacity for drug-susceptibility testing of Group A drugs (fluoroquinolones, bedaquiline and linezolid), and pretomanid, is urgently developed and rolled out. Concerningly, emerging bedaquiline resistance acquisition has been reported in programmatic setting in South Africa, Moldova and other countries.[46–49]

Host-directed therapy

Host-directed therapy (HDT) for TB may either boost host defence ('antimicrobial') or control an exuberant inflammatory phenotype ('anti-inflammatory'). Determining the correct timing of HDT is a challenge. It is equally complicated to identify underlying TB endotypes, defined as distinct immune, epigenetic, metabolic, molecular and transcriptional profiles. In addition, recognised immune risk factors include Mendelian susceptibility to mycobacteria, untreated HIV-1 infection, or TNF inhibitors use. In HIV-1 infection, provision of antiretroviral therapy reduces individual risk for developing TB by 60-80% and reduces mortality, and is thus the most effective HDT widely in use. Conversely, excessive dysregulated immune responses may contribute to tissue damage and even death, such as in tuberculous meningitis, or HIV-tuberculosis immune reconstitution inflammatory syndrome (TB-IRIS).

Whilst there has been considerable activity recently on preclinical evaluation of HDT, clinical trial evidence is lacking. Interferon-gamma modestly increased bacterial clearance and resolution of fever in patients with cavitary TB in a single randomized-controlled trial,[50] and TNF- and interleukin-1 antagonists have shown to be effective in steroid-refractory paradoxical reactions.[51, 52] Vitamin D3 potentially has both antimicrobial and anti-inflammatory actions through promotion of autophagy and the induction of antimicrobial cathelicidin:[53] however, clinical trial evidence of the benefit of systematic addition of vitamin D3 has been modest or non-existent. Metformin therapy of diabetes mellitus associates epidemiologically with benefit, but did not lead to earlier sputum conversion in a recent trial.[54] A type 4 phosphodiesterase inhibitor and everolimus, a mTOR inhibitor, both modestly enhanced recovery of lung function at end of therapy in a recent trial in South Africa.[55] The clearest evidence of anti-inflammatory benefit exists for corticosteroids, which are associated with 30% lower mortality of HIV-1 uninfected TB meningitis,[56] and reduce constriction and hospitalization in TB pericarditis,[57] and both

prevent and improve outcome of TB-IRIS.[58, 59] However, this benefit may vary according to different patient genotypes (i.e. leukotriene A(4) hydrolase) and pro-inflammatory cytokine concentrations (i.e. in cerebrospinal fluid of TB meningitis patients).[60, 61]

Pharmacokinetics and pharmacogenomics

Advances in pharmacokinetics have accelerated the pace of TB drug development. In a salient example, pharmacometric analyses of two clinical trials optimized rifapentine dosing from an initial posology of 10 mg/kg daily to a fixed 1200 mg daily dose of rifapentine as part of the newly-approved four-month regimen.[11, 12, 62] While pharmacokinetic studies have demonstrated that rifampicin exposure increases at least dose-proportionally,[63, 64] and that higher rifampicin doses exhibit dose- and exposure-response relationships,[65, 66] clinical trials have yet to confirm whether treatment shortening is possible with high-dose rifampicin (**Table 1**). [16] The pharmacokinetic analysis of SHINE and results from a separate cohort study indicated substantially reduced drug exposures in children in lower weight bands and in those who transition onto adult doses (≥25 kg), underlining the need for doses to account for the higher mg/kg requirement of smaller individuals.[67, 68] Despite significant gains in treatment shortening for adults, adolescents, and children with DS-TB, pharmacokinetic studies suggest that treatment approaches tailored to patient characteristics may be achievable.

Pharmacogenetic evaluations have not yet gained guideline endorsements in the treatment for TB. The best described pharmacogenetic signal to date, for isoniazid acetylator status, has been considered—but not recommended—by the WHO to inform the use of high-dose isoniazid for the treatment of DR-TB for rapid acetylators.[69, 70] The recent development of a cartridge-based

multiplex quantitative PCR assay on the GeneXpert platform that differentiates NAT2 acetylator genotype signals raises hope that the personalization of treatment, based on host genetic polymorphisms, may be within grasp.[71]

Future research priorities

There remains a pressing need to find well-tolerated, safe, short regimens for both DS and DR-TB,[11, 29] including in particular a better-tolerated alternative for linezolid. Cure of most non-severely affected patients with a two-month duration of treatment may be achievable. Long-acting injectable drugs also have transformative potential, for both prevention and treatment of TB. In parallel with the quest for new regimens, it is important to evaluate strategic, more individualised, treatment approaches, or individual risk-based strategy such as those tested in the TRUNCATE-TB trial.[17] Efficient testing of multiple new regimens requires identification of a biomarker that is a reliable surrogate for relapse-free cure.[72] This would accelerate the identification and advancement of promising regimens to testing in definitive trials, as well as guide physicians decisions to individualise treatments.[73] Testing adjunctive host-directed therapies, with the goals of enhancing bacterial clearance and minimising post-tuberculosis lung damage, is an important but neglected research direction. Understanding TB endotypes may enable a stratified approach to use such host-directed agents.[74, 75]

Implementation research remains critically important to evaluate and optimise outcomes in programmatic settings. There is a need to improve treatment outcome definitions based on long-term outcome benchmarks.[76] Research on the optimal approaches to roll out molecular diagnostic drug susceptibility tests accompanying the availability of new regimens is important to

ensure that affected patients receive appropriate therapy.[35] Barriers accessing new drugs (including rifapentine) and regimens are significant, [77, 78] and there is a need for research into how these can be overcome to ensure rapid translation of new findings into practice. This particularly applies to special populations, such as children of all ages and pregnant women: inclusion of these groups in future clinical trials should be prioritized. **Table 4** summarizes research priorities.

Conclusions

The last two decades have seen major changes in the management of TB. The availability of new compounds, coupled with renewed interest in TB regimen development, has led to impressive achievements which will have to be sustained in the coming years. While the focus in recent years has been in treatment shortening with new drug combinations, future aims may include improving current regimens by increasing the quality of supporting evidence (including operational and programmatic data), reducing toxicity and optimizing efficacy, for instance by enhancing pharmacokinetic properties, identifying optimal HDT, and further individualizing regimens. In parallel, future efforts should be directed to protect these recent advances by preventing and identifying the selection of drug resistance and providing widespread, affordable, patient-centred access to new treatment options for all people affected by TB.

Tables

Table 1: Registered, unpublished clinical trials for the treatment of drug-susceptible tuberculosis (as of July 6th, 2023).

Therapeutic approach	Trial (adult TB patients)	Experimental regimen(s)	Clinical trials registration	Phase	Status
Optimizing rifampicin	IMAGINE-TBM	High-dose R and H for TB meningitis	NCT05382742	II	In preparation
	INTENSE-TBM	High-dose R and high-dose Lzd for TB meningitis	NCT04145258	III	In preparation
	ReDEFINe	High-dose R for TB meningitis	NCT02169882	II	Enrolling
	STEP2C	High-dose R and Mfx for 3 or 4 months	NCT05807399	IIC	Enrolling
	HARVEST	High-dose R for TB meningitis	ISRCTN15668391	III	Enrolling
	SURE	High-dose R, H, Z + Lfx (+/- aspirin) for children with TB meningitis	ISRCTN40829906	III	Enrolling
	RIFASHORT	Higher dose R (to 1800 mg/d) – 4 months	NCT0258152	III	Completed
	CRUSH-TB	Bdq+Mfx+Z+Rbt or Dlm – 4 months	NCT05766267	IIC	Final preparation

Regimens including new drugs	DECODE	16 weeks of experimental of Delpazolid at different doses associated with Bdq+Dlm+Mfx	NCT04550832	II	Enrolling
	Safety and Efficacy of 4-month Regimen of OPC-167832+Dlm+Bdq		NCT05221502	II	Enrolling
	CLO-FAST (ACTG A5362)	Cfz+Rpt+HZE – 13-17 weeks	NCT04311502	IIC	Enrolling
	SUDOCU	Bdq+Dlm+Mfx vs. Bdq+Dlm+Mfx+Sutezolid (3 dosages)	NCT03959566	II	Completed
	SimpliciTB	Bdq+Ptm+Mfx+Z – 4 months	NCT03338621	III	Completed

R = rifampicin, H = isoniazid, Lzd = linezolid, TB = tuberculosis, Z = pyrazinamide, Lfx = levofloxacin, Mfx = moxifloxacin, Bdq = bedaquiline, Pa = pretomanid, Dlm = delamanid, Rbt = rifabutin, Cfz = clofazimine.

372 **Table 2. Recently completed and ongoing, unpublished trials on rifampicin-resistant tuberculosis treatment (excluding**
373 **fluoroquinolone-resistant tuberculosis) (as of July 6th, 2023).**

Trial	Phase	Control Arm	Country	Experimental treatment regimen(s)	Treatment duration (months)	Notes	Clinicaltrials.gov identifier
Recently completed trials							
OptiQ	II	No	Peru, South Africa	Lfx 11, 14, 17 or 20 mg/Kg plus background regimen	6	750-1000 mg Lfx qd achieved target AUC/MIC	NCT01918397
SimpliciTB	II	Yes (only for DS-TB)	8 countries	Bdq, Pa, Z, Mfx	4	Not non-inferior to HRZE; no comparator for MDR-TB arm	NCT03338621
SUDOCU	II	No	South Africa, Tanzania	Sutezolid, Bdq, Dlm, Mfx	3	regimen well tolerated	NCT03959566
TREAT-TB (India)	III	No	India	Bdq, Dlm, Lzd and Cfz	6-9 months	91% favourable outcomes	CTRI/2019/01/017310

Ongoing trials

ACTG A5356	II	No	Multicountry	Bdq, Cfz, Dlm, and Lzd (different posologies)	6	TIW dosing of Lzd	NCT05007821
DECODE	II	No	South Africa, Tanzania	Delpazolid, Bdq, Dlm, Mfx	3 months	Dose-ranging and tolerability	NCT04550832
DRAMATIC	II	No	Multicountry	Lfx, Bdq, Lzd, Dlm, and Cfz	4 to 9	Duration-randomized clinical trial	NCT03828201
BEAT Tuberculosis	III	Yes	South Africa	Bdq, Dlm, and Lzd, plus Lfx or Cfz	6	Experimental regimen adapted according to rapid molecular testing	NCT04062201
endTB**[43]**	III	Yes	Multicountry	Bdq, Mfx, Lzd, and Z; or Bdq, Cfz, Lfx, Lzd, and Z; or Bdq, Dlm, Lfx, Lzd, and Z; or Dlm, Cfz, Lfx, Lzd, and Z; or Dlm, Cfz, Mfx, and Z	9	Trial implementing Bayesian adaptive randomization	NCT02754765
TB-TRUST	III	Yes	China	Lfx, Lzd, Cs, and Z (or Cfz if resistant to Z)	6 to 9	No follow-up available	NCT03867136
TB TRUST Plus	III	No	China	Bdq, Z, Lzd, Cs, Cfz	6-9 months	Regimen guided by Z susceptibility testing	NCT04717908

InDEX	IV	Yes	South Africa	Individualized regimens	NS	WGS-derived individualized regimen	NCT03237182
PROSPECT	IV	No	China	Cfz, Cs, Lfx, Lzd, and Pto; or Bdq, Cfz, Cs, Lfx, and Lzd	6 (first regimen), 9 (second regimen)	No follow-up available	NCT05306223
GRACE-TB	NA	Yes	China	Individualized regimens	NS	Individualized regimen guided by rapid molecular tests	NCT03604848
SMARTT	NA	Yes	South Africa	WGS-guided regimen	NS	Individualized regimen guided by rapid molecular tests	NCT05017324

374 DS-TB = drug-susceptible tuberculosis, Lfx = levofloxacin, Bdq = bedaquiline, Pa = pretomanid, Z = pyrazinamide, Mfx = moxifloxacin, HRZE =
375 isoniazid + rifampicin + pyrazinamide + ethambutol, MDR-TB = multidrug-resistant tuberculosis, Dlm = delamanid, Lzd = linezolid, Cfz =
376 clofazimine, Cs = cycloserine, Pto = prothionamide, NS = not specified, NA = not applicable, TIW = three times weekly, WGS = whole genome
377 sequencing.

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Table 3. Recently completed and ongoing, unpublished trials on rifampicin-resistant, fluoroquinolone-resistant tuberculosis treatment (as of July 6th, 2023).

Name of trial	Regimen	Duration of trial regimen	Site	Inclusion criteria	Status	Participants enrolled
endTB-Q [44] (NCT03896685)	Bdq-Lzd-Dlm-Cfz	24-39 weeks	India, Kazakhstan, Lesotho, Pakistan, Peru and Vietnam	Pre-XDR TB (FQ-resistant TB) in ≥15 year-old with pulmonary tuberculosis according to a validated rapid molecular test	ongoing	Enrolment completed in March 2023

Bdq = bedaquiline, Lzd = linezolid, Dlm = delamanid, Cfz = clofazimine, Pre-XDR TB = pre-extensively drug resistant tuberculosis, FQ = fluoroquinolone.

384 **Table 4. Research priorities**

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New drugs and regimens • Shorter, well-tolerated and safer regimens for drug-susceptible and drug-resistant tuberculosis • Sustained early development pipeline of new anti-TB compounds, including long-acting injectable drugs
Tailored treatment approach • Treatment strategies based on more individualised treatment, including the identification of criteria to define TB severity • Surrogate biomarker of relapse-free cure
Host-directed therapies • Improved understanding of TB endotypes • Host-directed therapies to accelerate bacterial clearance or reduce post-TB morbidity
Implementation research • Identify barriers to access to new drugs (including special populations, for instance children) • Optimise rollout of drug-susceptibility testing for new drugs (including rapid molecular tests and evidence on relationship between phenotypic-genotypic resistance profiles)

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Author contributions:

IM and **LG** conceptualized and supervised the review process, wrote part of the initial draft, revised the full draft, and approved the final manuscript; all other authors wrote part of the initial draft, revised the full draft, and approved the final manuscript.

Transparency declaration:

Conflict of interest disclosure:

IM, MB, DC, KD, GG, CRH, YK, CLa, CLi, HM, GT, ZU, RvC, GEV, RJW, and LG have nothing to declare

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