Treatment-shortening regimens for tuberculosis: updates and future priorities

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Revolutionary new TB treatments are shortening treatment time and saving lives. This article highlights the latest breakthroughs and discusses what is next on the horizon. https://bit.ly/3rc7dDB

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Abstract

In the past 2 years, remarkable advances have been made in shortening tuberculosis (TB) treatment. In particular, four clinical trials (Study 31/A5349, Nix-TB, ZeNix and TB-PRACTECAL) have provided evidence of the efficacy of regimens based on new and repurposed drugs: the 4-month regimen for drug-susceptible TB, and the 6-month bedaquiline–pretomanid–linezolid regimen with or without moxifloxacin for multidrug-resistant/rifampicin-resistant TB. Even if the evidence at the basis of these new regimens is compelling, several questions remain open, particularly concerning linezolid dose finding, the upsurging threat of bedaquiline-resistant *Mycobacterium tuberculosis* and the feasibility of applying these results to the paediatric population. Several ongoing trials may fill the remaining gaps and produce further reliable evidence to address the outstanding questions in TB treatment shortening.

Introduction

Tuberculosis (TB) represents one of the major global health concerns, with 10.6 million estimated new cases in 2021 and 1.6 million attributed deaths during that year [1]. In this context, multidrug-resistant (MDR)/rifampicin-resistant (RR) TB represents an epidemic within the epidemic, with 450 000–470 000 estimated cases in 2021 and 191 000 attributed deaths [1].

MDR/RR-TB treatment success rates, even if they have steadily increased in the past 10 years, still remain well below the World Health Organization (WHO) target of 90% [1]. Among the several underlying causes of this slow improvement, the length of the recommended treatment (up to 18–24 months) and the complexity of the daily prescription schedule (>20 pills per day), as well as the use of injectable drugs and the not infrequent occurrence of adverse reactions to medications, play an important role in leading to lack of adherence to the prescribed treatment course [2, 3]. Moreover, the costs associated with MDR/RR-TB treatment, sometimes catastrophic for both affected people and healthcare systems, frequently represent an important barrier to guaranteeing that the resources needed to ensure treatment adherence (*e.g.* directly observed therapy services and transportation to health centres) are available [4].

Furthermore, the disruption of TB care services worldwide due to the coronavirus disease 2019 (COVID-19) pandemic dealt a heavy blow to MDR/RR-TB treatment and diagnostic capacity, finally leading, for the first time in decades, to an upsurge in MDR/RR-TB incidence and mortality in 2020–2021 [1, 5].

Nonetheless, the research on the development of new TB drugs and innovative TB regimens has never been more active and vibrant than in the past 2 years. After three decades of quiescence, we now have more than 25 compounds at different stages of development, including 17 new chemical entities, and at least 22 trials currently evaluating different TB regimens [1, 3]. These innovative studies and clinical trials are particularly needed to develop shorter, all-oral regimens for the treatment of drug-resistant (DR) TB, to guarantee the best possible care to the people affected, and to tackle resistance upsurge and spreading. Therefore, several clinical trials have been performed and are currently evaluating possible shorter treatment for drug-susceptible (DS) TB and DR-TB (table 1).

Among these trials, the data obtained from four key studies (Study 31/A5349 [6], Nix-TB [7], ZeNix [8] and TB-PRACTECAL [9]) have informed a recent breakthrough in TB treatment. WHO has published a rapid update on the programmatic use of the 4-month rifapentine–moxifloxacin regimen (given with isoniazid and pyrazinamide) for DS-TB and the 6-month bedaquiline–pretomanid–linezolid (BPaL) regimen, without or with moxifloxacin (BPaLM), for MDR/RR-TB [10].

As the evidence provided by Study 31/A5349, Nix-TB, ZeNix and TB-PRACTECAL has noticeably contributed to inform the WHO recommendation, we aim to provide an overview of the key findings of these four clinical trials, highlighting their strengths but also their limitations, and informing about actions for the immediate future.

Overview of studies supporting all-oral shorter regimens for DR-TB

To provide a full overview of the trial results, the number and percentage of grade 3 or higher adverse events for each of the four trials are described in table 2.

TABLE 1 Global clinical development pipeline for new drug regimens to shorten treatment of tuberculosis (TB) disease

Trial name	Study details	Condition/disease	Phase	Recruitment status
SimpliciTB	Bedaquiline–pretomanid–moxifloxacin–pyrazinamide (BPaMZ)	DS-TB and DR-TB	3	Completed
endTB	Bedaquiline and delamanid with various existing regimens for MDR-TB and XDR-TB	MDR-TB	3	Completed
endTB-Q	Bedaquiline–delamanid–linezolid–clofazimine for fluoroquinolone-resistant MDR-TB	Pre-XDR-TB	3	Completed
TRUNCATE-TB	Several 2-month regimens for DS-TB	DS-TB	3	Completed
RIFASHORT	High-dose rifampicin with standard regimen for DS-TB treatment	DS-TB	3	Completed
ZeNix	Safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in participants with pulmonary, XDR-TB, pre-XDR-TB or non-responsive/intolerant MDR-TB	XDR-TB, pre-XDR-TB, or treatment-intolerant or non-responsive MDR-TB	3	Completed
Study 31/A5349	Rifapentine-containing TB treatment-shortening regimens	DS-TB	3	Completed
Nix-TB	Safety and efficacy of bedaquiline plus pretomanid plus linezolid in subjects with DR pulmonary TB	XDR-TB and MDR-TB	3	Completed
TB-PRACTECAL	Bedaquiline and pretomanid with existing and repurposed anti-TB drugs for MDR-TB	RR-TB	2–3	Completed
MDR-END	Treatment shortening of MDR-TB using existing and new drugs	MDR-TB	2	Completed
BEAT-TB	Bedaquiline–delamanid–linezolid–levofloxacin–clofazimine (6-month oral regimen for RR-TB) or bedaquiline–delamanid–linezolid–clofazimine (6–9-month oral regimen for pre-XDR-TB and XDR-TB)	Pre-XDR-TB, XDR-TB, MDR-TB and RR-TB	3	Active, not recruiting
TB-TRUST	Ultra-short treatment for fluoroquinolone-sensitive MDR-TB	RR/MDR-TB	3	Active, not recruiting
DRAMATIC	Efficacy and tolerability of bedaquiline, delamanid, levofloxacin, linezolid and clofazimine	MDR-TB	2	Recruiting
Hi-DoRi-3	High-dose rifampicin to shorten DS-TB treatment	DS-TB	3	Not yet recruiting
CLO-FAST/ A5362	Shorter regimens including clofazimine and rifapentine for DS-TB	DS-TB	2	Suspended (temporarily closed (paused) to accrual)

DS: drug-susceptible; DR: drug-resistant; MDR: multidrug-resistant; XDR: extensively drug-resistant; RR: rifampicin-resistant. Updated and adapted from [1].

TABLE 2 Occurrence of adverse events of grade ⩾3 in the Study 31/A5349, Nix-TB, ZeNix and TB-PRACTECAL trials

Trial and regimen	Patients n	Grade ⩾3 adverse events n (%)[#]	Percentage-point difference from control/standard care (CI)[¶]
Study 31/A5349 [6]			
Control	825	159 (19.3)	NA
Rifapentine–moxifloxacin	846	159 (18.8)	−0.6 (−4.3 to 3.2)
Rifapentine	835	119 (14.3)	−5.1 (−8.7 to −1.5)
Nix-TB [7]			
BPaL, linezolid 600 mg twice daily	44	27 (61)	NA
BPaL, linezolid 1200 mg once daily	65	35 (54)	NA
ZeNix [8]			
BPaL, linezolid 1200 mg, 26 weeks	45	14 (31)	NA
BPaL, linezolid 1200 mg, 9 weeks	46	11 (24)	NA
BPaL, linezolid 600 mg, 26 weeks	45	9 (20)	NA
BPaL, linezolid 600 mg, 9 weeks	45	11 (24)	NA
TB-PRACTECAL [9]			
Standard care	43	26 (60)	NA
BPaLM	40	10 (25)	−36 (−57 to −14)
BPaLC	43	18 (42)	−19 (−39 to 2)
BPaL	43	11 (26)	−35 (−54 to −15)

BPaL: bedaquiline, pretomanid, linezolid; BPaLM: bedaquiline, pretomanid, linezolid, moxifloxacin; BPaLC: bedaquiline, pretomanid, linezolid, clofazimine; NA: not applicable. [#]: TB-PRACTECAL data are reported as the number (%) of patients with ⩾1 event of grade ⩾3; [¶]:TB-PRACTECAL BPaLM group are two-sided 96.6% confidence intervals; confidence intervals for all other groups in the table are two-sided 95% confidence intervals.

Study 31/A5349

Study 31/A5349 [6] was an international, multicentre, randomised, open-label, phase 3, noninferiority trial aiming to determine whether 4-month treatment regimens including rifapentine, with or without moxifloxacin, can be used to treat participants with pulmonary DS-TB. The intervention was compared with the standard 6-month regimen. The trial included 2343 participants (768 were in the control group, 791 in the rifapentine–moxifloxacin group, and 784 in the rifapentine group), aged ⩾12 years. People living with HIV were enrolled into the study (194 out of the 2343 participants) to evaluate possible drug–drug interactions between high-dose rifapentine and efavirenz. A $CD4^+$T-cell count of ⩾100 cells·mm^{-3} was required among the enrolment criteria. The primary efficacy outcome was survival free of TB at 12 months after randomisation. In comparison with the control group, noninferiority of the rifapentine–moxifloxacin arm was demonstrated. In particular, 15.5% of the rifapentine–moxifloxacin group *versus* 14.6% of the control group (adjusted absolute difference of 1.0 percentage points, 95% CI −2.6–4.5) had an unfavourable outcome.

Unfavourable outcome was defined as any participant with positive cultures from two sputum samples collected at 17 weeks or after 17 weeks without an intervening negative culture, as well as any participants who died, withdrew from the study or were lost to follow-up during the treatment period, or who died from TB during the post-treatment follow-up, or received additional TB treatment.

The total duration of follow-up was 18 months. A main limitation of the study was that the participants and the trial site staff were aware of the treatment-group assignment.

Nix-TB

Nix-TB [7] was a single-arm non-randomised BPaL evaluation. The trial included 109 people with extensively drug-resistant (XDR) TB or non-responsive MDR/RR-TB. The data gathered demonstrated a favourable outcome in 98 out of 109 participants (90%; 95% CI 83–95) after 6 months of BPaL treatment and 6 months of post-treatment follow-up.

In the trial, an unfavourable outcome was defined as bacteriological failure, relapse or clinical failure or death through follow-up until 6 months after the end of treatment, whereas a favourable outcome was defined as resolution of participant clinical TB disease, negative culture status at 6 months from end of therapy, and not meeting any of the parameters of an unfavourable outcome according to the provided definition.

Follow-up continued for 24 months after the completion of the treatment and a secondary end-point of treatment failure was measured at this time. The study enrolled individuals co-infected with HIV (56 out of

109 participants) with a $CD4^+$ T-cell count of ⩾50 cells·mm^{-3} and participants were aged ⩾14 years. The two main limitations of this study were the lack of a randomised control group and of a defined standard regimen for the treatment of XDR-TB at the time of trial initiation. Another limitation is that this study has been conducted in only one country, potentially limiting the possibility of generalising the obtained findings.

ZeNix

ZeNix [8] was a randomised trial, following Nix-TB, to investigate the efficacy of a BPaL regimen with a lower dose and shorter duration of linezolid, reducing the overall toxicity of the treatment. ZeNix enrolled 181 participants, aged ⩾14 years (⩾18 years in Russia and Moldova), with MDR/RR-TB plus resistance to a fluoroquinolone and/or a second-line injectable drug, or patients with MDR/RR-TB intolerant to or non-responsive to treatment. Patients were enrolled in Africa and Eastern Europe. People living with HIV and a $CD4^+$ cell count of <100 cells·mm^{-3} were ineligible and a total of 36 HIV-positive participants were enrolled in the trial.

Participants were considered to have a favourable outcome if they had negative culture status during treatment to the end of follow-up (26 weeks after the end of treatment) and if they had not already been classified as having had an unfavourable outcome. An unfavourable outcome was defined as treatment failure or disease relapse (clinical or bacteriological) at 26 weeks after completion of treatment.

A favourable outcome was observed, ranging between 84% and 93% in different treatment groups. The authors concluded that the risk–benefit ratio supported the use of BPaL with a linezolid dose of 600 mg for 26 weeks. This group was characterised by a lower incidence of adverse events and fewer linezolid dose modifications.

TB-PRACTECAL

TB-PRACTECAL [9] was an open-label, randomised, controlled, two-stage, phase 2–3, noninferiority trial. The trial was articulated in two stages. The stage 1 primary objective was to evaluate safety and efficacy of 24-week BPaL regimens with the addition of moxifloxacin or clofazimine, identifying the regimen to select for analysis in stage 2.

The primary efficacy outcome used in stage 1 was culture conversion in liquid cultures at 8 weeks after randomisation, whereas the primary safety outcome was the incidence of death or discontinuation of treatment by week 8. The primary objective in stage 2 was to evaluate the safety and efficacy of a 24-week BPaLM regimen in MDR/RR-TB. In this stage, the main efficacy outcome was an unfavourable status (defined as a composite of death, treatment failure, treatment discontinuation, loss to follow-up, or recurrence of TB) at the end of the follow-up period, 72 weeks after randomisation.

The study was conducted in seven sites and participants aged ⩾15 years with MDR/RR-TB were eligible for inclusion regardless of HIV status or $CD4^+$ count. Out of a total of 532 participants who underwent randomisation, 153 were HIV positive.

Interim trial results demonstrated that BPaLM treatment is safer and noninferior in treating MDR/RR-TB in comparison to the standard of care, and recruitment was stopped early by the Data and Safety Monitoring Board. In stage 2, the BPaLM regimen was shown to be both noninferior and superior to the standard regimen with respect to the primary composite outcome described.

Unanswered questions and gaps in the available evidence

Although the compelling evidence produced in these trials has contributed to shortening the treatment of DS-TB and MDR/RR-TB, gaps persist and unanswered questions remain. Among them, those that need urgent answers are as follows. What should be the dose and duration of linezolid? Can delamanid replace pretomanid if needed? How do we address threats posed by bedaquiline-resistant TB? How do these results apply to the TB paediatric population?

Linezolid dose finding

Based on the ZeNix trial results, it was concluded that the overall risk–benefit ratio favoured the group that received the three-drug regimen with linezolid at a dose of 600 mg for 26 weeks [8]. Nonetheless, peripheral neuropathy occurred in nearly one quarter of participants allocated to this regimen group. This represents a major concern for patients and providers, warranting further investigation into alternative treatment options that will balance high efficacy with a reasonable safety profile. In this regard, new evidence may be generated by the endTB [11, 12] and endTB-Q [13] phase 3, adaptive, randomised clinical trials evaluating the efficacy and safety of shorter treatment regimens in, respectively,

fluoroquinolone-susceptible and fluoroquinolone-resistant MDR/RR-TB. Another randomised phase 2 study, ACTG A5356, is also currently ongoing to evaluate the activity, safety and tolerability of two possible linezolid dosing strategies for treatment of MDR/RR-TB, pre-XDR-TB and XDR-TB, combined with bedaquiline, delamanid and clofazimine (ClinicalTrials.gov identifier NCT05007821).

Moreover, studies such as PanACEA Sutezolid Dose-finding and Combination Evaluation (SUDOCU) (ClinicalTrials.gov identifier NCT03959566) and PanACEA DElpazolid Dose-finding and COmbination DEvelopment (DECODE) (ClinicalTrials.gov identifier NCT04550832) are currently evaluating other oxazolidinones for safety, efficacy and tolerability. If proved safe and tolerable, sutezolid or delpazolid may be considered as a substitute for linezolid in regimens in future phase 2 and 3 trials.

Antimicrobial resistance: bedaquiline and pretomanid

The optimal use of new and repurposed all-oral bedaquiline-based regimens is threatened by the rapid emergence and spread of resistant strains. Primary resistance to bedaquiline was first documented in 2016, and South Africa and Moldova, two high MDR/RR-TB burden countries, reported bedaquiline resistance of 3% and 15%, respectively, in patients with previous exposure to bedaquiline or clofazimine [14, 15]. Therefore, a global plan to scale-up surveillance for bedaquiline resistance is urgently needed and new, fast, resistance diagnosis approaches should be investigated.

Even if it is still unknown if lineage-dependent differences in minimal inhibitory concentration distribution are clinically relevant, these have been observed for pretomanid for *Mycobacterium tuberculosis* lineage 1 strains [16]. Pretomanid is one of the key drugs in the BPaL regimen, belonging to the same nitroimidazole family as delamanid. Given the weight of evidence from pre-clinical and clinical studies showing the possibility of resistance to either delamanid or pretomanid alone while preserving susceptibility to the other [17–19], a clinical trial replacing pretomanid with delamanid within specific regimens may produce interesting data regarding the efficacy and/or safety profile of these regimens in comparison with the Nix-TB, ZeNix or TB-PRACTECAL regimens.

Whereas it is clear that the research for replacement drugs that could serve as the backbone for shorter regimens should be urgently prioritised, the limited availability of infrastructure for resistance testing and coverage of molecular techniques needed for the detection and prediction of *M. tuberculosis* resistant strains represent a barrier. Next-generation sequencing (NGS) testing technologies could mitigate some of these challenges, since they have the potential to improve access and coverage [20]. For instance, in South Africa, whole genome sequencing derived drug susceptibility testing could have enabled placement of 24% of patients with second-line MDR/RR-TB resistance on effective individualised regimens, if available [21]. Therefore, the rapid scale-up and utilisation of NGS resistance prediction through advances in culture-free sequencing should go hand in hand with roll-out of novel shorter regimens.

Children and TB trials

Although several adult treatment-shortening trials have been conducted or are currently ongoing, studies evaluating shorter regimens for children are scarce. Trials have often excluded children and pregnant women and more evidence is needed on optimal dose and regimen combinations with high efficacy and safety profiles in these populations.

Efforts to fill the gaps in childhood DR-TB shorter drug regimens include a quest for a palatable and dispersible formulation and optimal regimen for children with DR-TB strains. We do hope that the BEAT-TB [22] and BENEFIT Kids [23] trials will be able to address these issues, once the results are available. In the meantime, the SHINE trial has recently produced interesting evidence on DS-TB shorter treatment in children [24]. This open-label, randomised, controlled, noninferiority trial enrolled >1000 children aged <16 years with non-severe DS-TB in Uganda, Zambia, South Africa and India. Children were randomly assigned to 16 weeks or 24 weeks of standard first-line anti-TB treatment as recommended by WHO. The trial showed the noninferiority of the 16-week regimen in comparison to the 24-week one (unadjusted difference of −0.3 percentage points, 95% CI −2.3–1.6) and this regimen has been adopted into WHO guidelines for the treatment of TB among children.

Conclusions

To support clinical and policy decision making, we need strong evidence resulting in sound guidelines, as Patrick Phillips underlined during the third UNITE4TB webinar (7 July 2022) supported by the European Respiratory Society, which was about progress made to date in shortening TB treatment [25]. To obtain strong evidence and sound guidelines, we need to include vulnerable populations and children safely and

routinely in trials, we have to develop highly tolerable regimens to favour trial participant retention and adherence and, finally, we must protect the available new drugs from the development of resistance.

Nonetheless, it is important to remember that these changes have to be implemented in the current scenario of TB clinical trials, with its constraints and limits. TB researchers are actively working to harmonise international actions to overcome the limits of the traditional lengthy and expensive TB trials pathway, as well as the limited accuracy of the end-points currently used in phase 2 trials to predict relapse-free cure [26–28].

In conclusion, even if the current studies have led to important advances in TB care, we have to be mindful of the still existing gaps. This awareness will lead researchers to develop innovative approaches to gather strong evidence for results that will give effective and timely support to the approval of new shorter TB regimens.

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