




Regimens to treat multidrug-resistant tuberculosis: past, present and future perspectives

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The article reviews the evolution of the strategies and regimens to manage drug-resistant tuberculosis, opening a window on future perspectives. <http://bit.ly/2Q1RhX0>

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ABSTRACT Over the past few decades, treatment of multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB) has been challenging because of its prolonged duration (up to 20–24 months), toxicity, costs and sub-optimal outcomes. After over 40 years of neglect, two new drugs (bedaquiline and delamanid) have been made available to manage difficult-to-treat MDR-/XDR-TB cases. World Health Organization (WHO) guidelines published in March 2019 endorsed the possibility of treating MDR-TB patients with a full oral regimen, following previous guidelines published in 2016 which launched a shorter regimen lasting 9–10 months.

The objectives of this article are to review the main achievements in MDR-TB treatment through the description of the existing WHO strategies, to discuss the main ongoing trials and to shed light on potential future scenarios and revised definitions necessary to manage drug-resistant TB.

Introduction

Over the past few decades, treatment of multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB) has been challenging because of its prolonged duration (up to 20–24 months), toxicity, costs and unsatisfactory outcomes [1, 2].

Until recently the recommended regimen for MDR-TB included, among other drugs, a fluoroquinolone (FLQ) and a second-line injectable (amikacin, capreomycin or kanamycin) [3]. The importance of these two classes of drugs in obtaining a successful outcome is reflected in the definition of a sub-category of MDR-TB, named pre-XDR (extensively drug-resistant)-TB, *i.e.* MDR-TB strains also resistant to either any FLQ or any second-line injectable [3]. In fact, this latter group, pre-XDR-TB patients, presented favourable outcomes at a frequency intermediate between simple MDR (*i.e.* resistance to isoniazid and rifampicin only) and XDR-TB [4].

Methods

A non-systematic review of relevant scientific documents published in English (in Google Scholar and other grey literature sources) was performed using the Google search engine without time limit. The

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TABLE 1 Historical list of recommended regimens for multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB)

Name	Year	Main features/regimens	Length of treatment	[Ref.]
DOTS-PLUS	2000	Rational use of second-line drugs in resource-limited settings GLC to facilitate access to proven quality second-line anti-TB drugs to overcome difficulties in procurement and cost		[6, 7]
Guidelines for the programmatic management of drug-resistant TB	2006	Management of MDR-TB to be integrated into comprehensive national TB control plans First “modern” categorisation of drugs used to treat MDR-TB into five groups Options for tailoring diagnosis and care to different epidemiological and programmatic conditions worldwide	18 months after culture conversion	[9]
Guidelines for the programmatic management of drug-resistant TB: emergency update	2008	Definition of XDR and acknowledgement of this threat Recommendations on drug resistant management Introduction of rapid DST		[10]
WHO guidelines for the programmatic management of drug-resistant TB: 2011 update	2011	Importance of rapid DST stressed Regimens including at least four, and ideally five, drugs likely to be effective Drugs to be included are a FLQ, an injectable agent, ethionamide or prothionamide, PZA and either cycloserine or para-aminosalicylic acid. Other drugs such as EMB or group 5 drugs could be added, but they should not be counted among the four effective drugs	20 months (with an 8-month intensive phase)	[11]
WHO consolidated guidelines on drug-resistant TB treatment	2019	Continued recommendation of using shorter regimen whenever possible If using injectables use amikacin Drugs reclassified into three groups (A, B and C) for the purpose of composing the longer regimen: Group A includes three drugs to be prioritised and used, if possible, in all regimens: levofloxacin/moxifloxacin, BDQ and LZD Group B includes two drugs to be possibly added to all regimens (CFZ and cycloserine/terizidone) Group C includes “other” agents (including injectables) to be used as a substitute to complete a regimen of at least four drugs when agents from groups A and B cannot be used	Longer regimen: may be standardised or individualised; duration 18–20 months, modified depending upon patient response Shorter regimen: 9–12 months	[32]

WHO: World Health Organization; RR: rifampicin-resistant; GLC: Green Light Committee; DST: drug susceptibility testing; FLQ: fluoroquinolone; PZA: pyrazinamide; EMB: ethambutol; CFZ: clofazimine; BDQ: bedaquiline; LZD: linezolid.

following keywords were used: “tuberculosis”, “treatment regimens” and “World Health Organization treatment guidelines”. All retrieved documents were evaluated by the authors and those considered relevant for the purpose of the mini-review were included.

Results

In previous years, major efforts have been made towards establishing a standardised, scalable approach for the treatment of MDR-/XDR-TB. The first effort began in the late 1990s when drug-resistant TB emerged as a major problem threatening TB control (table 1) [5]. In response, in 1999, the World Health Organization (WHO) and partners launched the programmatic approach named “DOTS-Plus” with the first pilot projects beginning the following year [6]. DOTS-Plus was built upon the five elements of DOTS: 1) sustained political and financial commitment; 2) diagnosis of TB by quality ensured sputum smear microscopy; 3) standardised short-course anti-TB treatment given under direct and supportive observation (DOTS); 4) regular uninterrupted supply of high-quality anti-TB drugs; and 5) standardised recording and reporting. DOTS-Plus introduced a rational use of second-line anti-TB drugs in resource-limited settings with a high MDR-TB burden. In addition, the Green Light Committee facilitated access to second-line drugs of proven quality and their proper use [7]. After collecting evidence of favourable results emerging from Green Light Committee-approved field projects, the WHO issued the “Guidelines for the programmatic management of drug-resistant tuberculosis” in 2006 [8]. One of the key recommendations was that management of MDR-TB should be integrated into comprehensive national TB control plans as suggested within the new Stop TB Strategy [9]. They also included the first “modern” categorisation of

drugs used to treat MDR-TB into five groups, recommending an 18 months of treatment after culture conversion [8].

The 2008 “emergency update” of these guidelines introduced the new definition of XDR-TB, which had meanwhile emerged in major outbreaks, and specific recommendations for its management, including the use of rapid drug-susceptibility testing (DST), were included [10].

The following version of the WHO guidelines issued in 2011 stressed the importance of rapid DST and updated the categories and types of drugs to be used [11]. Notwithstanding the low quantity and quality of evidence, the recommended treatment of MDR-TB included at least four, and possibly five, drugs likely to be effective for a recommended duration of 20 months (with an 8-month intensive phase) [11].

The first addition to these recommendations was based on new observational evidence of successful outcomes obtained from a standardised 9–12-month regimen developed and tested by the International Union Against Tuberculosis and Lung Diseases, the so-called “Bangladesh regimen” [12]. This regimen includes a 4–6 month intensive phase with a seven-drug regimen (kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol) followed by a 5-month course with moxifloxacin, clofazimine, pyrazinamide and ethambutol. The exclusion criteria are: 1) confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance); 2) exposure to >1 second-line medicine in the shorter MDR-TB regimen for >1 month; 3) intolerance to >1 medicine in the shorter MDR-TB regimen or risk of toxicity (*e.g.* drug–drug interactions); 4) extrapulmonary disease; 5) pregnancy; and 6) at least one medicine in the shorter MDR-TB regimen not available in the programme. This regimen, originally used in Bangladesh, was tested in other countries with similar favourable outcomes [13–15]. This led the WHO to recommend its use by national TB programmes under strict conditions in 2016 (if no listed exclusion criteria applicable to the patient) [3]. In settings with high prevalence of “simple” MDR strains this regimen was expected to work well. However, it seemed to have limitations in settings where a “mixture” of MDR strains was present, for instance where there was additional resistance, especially to pyrazinamide, or where it is difficult to obtain a complete resistance profile of isolated strains [16–19]. Pyrazinamide resistance, however, can often be associated with rifampicin resistance [20].

In a recent study, SUN *et al.* [21] present interesting data from China in a prospective cohort of MDR-TB cases where pyrazinamide resistance was or was not tested. The study results show that optimisation of treatment regimens based on pyrazinamide DST significantly improves treatment outcomes [21].

The Bangladesh regimen was later tested in an international, randomised controlled trial (STREAM 1). The final report has been published very recently, showing good results in the shorter regimen arm with 78.8% of patients achieving a favourable outcome [15]. Thus, this regimen constitutes a true innovation in shortening MDR treatment proving that, under specific conditions, it is an alternative option to the longer WHO regimen in simple MDR cases [14, 15]. Unfortunately, this regimen still includes an injectable agent during the intensive phase thus exposing patients to the risk of ototoxicity and nephrotoxicity and the unpleasant effects of its route of administration [13].

Over the past 2 years, a series of reports showed that treatment outcomes in patients with drug-resistant TB could be improved using new combinations of drugs given for shorter periods of time, better selecting the “old” drugs to include in the treatment regimen or introducing new drugs for prolonged periods of time [15, 22–27].

A recent meta-analysis of individual patient data in MDR-TB treatment attempted to attribute a specific weight to each drug that has been used in MDR-/XDR-TB treatment regimens [28]. The study compared the association of each drug with failure or relapse *versus* treatment success. Treatment success was positively associated with the use of linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline and clofazimine. Mortality was significantly reduced with the use of linezolid, levofloxacin, moxifloxacin or bedaquiline. Surprisingly, compared with regimens without any injectable, amikacin provided only modest benefits, while kanamycin and capreomycin were associated with worse outcomes. The negative effect of the injectables on outcomes could be due to the decision by the treating clinicians to use them in the worst clinical cases, based on the resistance profile or despite it. Another possible bias could be due to changing drugs during the course of treatment or misclassification of treatment outcomes. Therefore, rather than concluding that the injectables should be avoided, the study emphasised the relevance of the use of later generation fluoroquinolones, bedaquiline, linezolid and clofazimine. What the study also showed is that treatment outcomes can be improved when bedaquiline is used as a substitute for second-line injectable agents [28].

As a result of all the information accumulated over the years, by 2017, at least 62 countries had introduced shorter regimens for treatment of MDR-/rifampicin resistant-TB and 68 countries had started using

bedaquiline [1]. In particular, bedaquiline has recently emerged as a key drug to be included in regimens despite the fact that it received temporary approval after only a phase 2B clinical trial and without full information on its efficacy and potential toxicity [1, 23]. Fortunately, despite initial concerns on possible cardiac toxicity (QT interval prolongation on electrocardiogram), recent data show that such toxicity is limited in severity and frequency, and is generally reversible [29, 30]. Nevertheless, particular attention in monitoring QT is necessary when bedaquiline is given with other drugs with a potential to prolong the QT interval, *i.e.* clofazimine, later-generation fluoroquinolones and delamanid [29].

Based on the evidence from the new studies and the meta-analysis cited above, in mid-2018 the WHO issued a rapid communication and in March 2019 the updated consolidated guidelines, substantially changing the approach to treatment of MDR-/XDR-TB [31, 32]. The updated guidelines address the role of both the longer and shorter treatment regimens and reclassify the drugs used to compose the longer (18–20 month) regimen into 3 groups (A, B and C) (table 1). Apart from the ranking by effectiveness or toxicity, the choice of drugs in a regimen is also determined by factors such as: preference for oral over injectable agents; results of DST; reliability of existing DST methods for second-line drugs; population drug-resistance patterns and levels; history of previous use of the drugs; drug tolerability; and potential drug–drug interactions. Finally, the WHO, while recommending the use of the shorter regimen whenever possible, emphasised: 1) the need to exclude kanamycin and capreomycin from all regimens; and 2) to replace them with amikacin if a second-line injectable is still necessary [32].

While this historical account summarises the past and present of MDR-/XDR-TB treatment, the question that arises is, what does the future hold?

From what has been explained so far, the first logical conclusion is that there is a continuous need to study new regimens, combining new and old drugs for different durations of time. There is also a need to revisit drug resistance definitions based on the challenges to be faced by the introduction of new regimens [33]. The trials that have been planned or are ongoing are listed in table 2.

Recently the Global TB Alliance presented promising preliminary data from the Nix-TB trial conducted in South Africa [34], the first clinical trial aiming to test a novel anti-TB regimen with the potential to be a shorter, all oral and affordable treatment for XDR-TB and complex forms of MDR-TB. The Nix-TB regimen consists of three drugs against which there is, currently, minimum potential resistance: bedaquiline, pretomanid and linezolid. This regimen (BPaL) achieved a cure rate of 85–90% after a 6-month course of treatment. The final results for the full patient cohort will be available in 2019 and it is expected that the new regimen could be approved for use by the second half of the year. For this regimen to succeed on a wide scale, it will be imperative to safely use its three components and minimise the risk of drug resistance to any of them. While minimum resistance to bedaquiline is expected for settings with no exposure to this drug, in those countries that have already decided to use bedaquiline widely, the risk of rapidly increasing resistance will need to be closely monitored to avoid treatment failures, deaths and onset of future additional resistance [35]. Other challenges to the implementation of this regimen can derive from linezolid toxicity and the occurrence of resistance to bedaquiline in those patients exposed to clofazimine (due to the partial cross-resistance between the two drugs) [36].

A second regimen under testing by the Global Alliance in the trial SimpliciTB is the BPamZ regimen composed of bedaquiline, pretomanid, moxifloxacin and pyrazinamide. In the initial phase 2B trial, culture negativity was obtained within 2 months of treatment, three times faster than among drug-susceptible TB patients on the standard 6-month short-course regimen. The BPamZ regimen is now being tested for all types of TB as a potential shorter “universal regimen” and results are expected in 2021. The potential wide use of the regimen will, as for BPaL, be conditional to minimisation of creation of resistance to its new components. Concerningly, the presence of resistance to the fluoroquinolones and pyrazinamide among rifampicin-resistant cases, although frequently low, is already well documented in certain settings [20, 21, 37].

The studies listed in table 2 aim to provide a proof-of-concept that treatment of MDR-/XDR-TB can be significantly shortened and fully oral through combinations of new and old anti-TB drugs. The likelihood that from any of these studies a single regimen will emerge as the best and only one to be recommended is, after all, low. Rather, one can expect that different options (in terms of type of drugs, dosages and treatment duration) will be available in the future in the quest for more precision in treatment. For instance, it is possible that more than one regimen will be adequate for simple MDR-TB while in the presence of additional resistance patterns, single or combined (*e.g.* pyrazinamide, fluoroquinolones and injectables), progressively fewer and fewer regimens will retain good performance and be recommended. The final regimen will critically depend on a full and rapid understanding of the drug-resistance pattern through the use of new technologies such as next-generation sequencing [38, 39].

TABLE 2 Innovative ongoing trials for an “all-oral” treatment of multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB)

Trial number/ name	Type of TB (MDR/XDR)	Study phase	Regimens studied	Promoter	Duration of new regimen	Status	Patients n	
1	Nix [#]	XDR	3	Pretomanid, bedaquiline and linezolid	TB Alliance	6 months	Ongoing	>75 [¶]
2	ZeNix	XDR	3	Pretomanid, bedaquiline and linezolid (linezolid treatment dose and duration are double-blinded)	TB Alliance	26 weeks	Enrolling	180 (estimated)
3	STREAM	MDR	3	A: local WHO standard B: clofazimine, ethambutol, moxifloxacin and pyrazinamide (40 weeks) + isoniazid, kanamycin and prothionamide (first 16 weeks) C: bedaquiline, clofazimine, ethambutol, levofloxacin and pyrazinamide (40 weeks) + isoniazid and prothionamide (first 16 weeks) D: bedaquiline, clofazimine, levofloxacin and pyrazinamide (28 weeks) + isoniazid and kanamycin (first 8 weeks)	IUATLD	36/56 weeks	Enrolling	Currently >300
4	NeXT	MDR	3	Linezolid, bedaquiline, levofloxacin, pyrazinamide + ethionamide or terizidone or high-dose INH	South African investigators	6–9 months	Not yet recruiting	300 (estimated)
5	TB PRACTECAL	MDR/XDR	2–3	A: local WHO standard B: bedaquiline and pretomanid + linezolid, moxifloxacin C: bedaquiline and pretomanid + linezolid, clofazimine D: bedaquiline and pretomanid + linezolid	MSF	6 months	Enrolling	Currently >100 (630 estimated)
6	End TB	MDR	3	A: bedaquiline, linezolid, moxifloxacin, pyrazinamide B: bedaquiline, linezolid, clofazimine, levofloxacin, pyrazinamide C: bedaquiline, delamanid, linezolid, levofloxacin, pyrazinamide D: delamanid, clofazimine, levofloxacin, linezolid, pyrazinamide E: delamanid, clofazimine, moxifloxacin, pyrazinamide F: local WHO standard, including the possible use of bedaquiline or delamanid	MSF and PIH	9 months	Enrolling	Currently >170 (750 estimated)
7	SimpliciTB	MDR (or single resistance to isoniazid or rifampicin)	2	Bedaquiline, pretomanid, moxifloxacin, pyrazinamide	TB Alliance	6 months	Enrolling	Currently >10 (150 estimated)
8	MDR-END	MDR	2	Delamanid, linezolid, levofloxacin and pyrazinamide <i>versus</i> local WHO standard	Seoul National University Hospital	9–12 months	Enrolling	(238 estimated)

IUATLD: International Union Against Tuberculosis and Lung Diseases; MSF: Médecins Sans Frontières; PIH: Partners In Health; WHO: World Health Organization; INH: isoniazid; [#]: definitive results pending; [¶]: information reported only for this number of patients.

Discussion

Therefore, the scale-up of regimens may also require new definitions of drug resistance that encompass all new and old drugs recommended as component of regimens [33] and are useful not only for surveillance purposes but also to inform treatment choices. In this scenario, specific resistance profiles (e.g. MDR, MDR + pyrazinamide, MDR + fluoroquinolone(s), XDR, XDR + bedaquiline and MDR + bedaquiline) will match appropriate regimens. At the same time, through the use of modern technology including sequencing, therapeutic drug monitoring, clinical decision support systems and digital solutions, even patients experiencing multiple failures and/or toxicities with unusual and/or more complex resistance profiles could be cured. In this regard, national and international bodies of experts (TB consilia) may be important in supporting personalised design of regimens for challenging resistance patterns [40].

After years of uncertainty in the search for optimal treatments for MDR-/XDR-TB, some of the mentioned recent breakthroughs are fostering progress. The ongoing and planned clinical trials will help care providers and national programmes to offer better, shorter, more effective and safer regimens to treat people affected by MDR-/XDR-TB while contributing to elimination of this disease.

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