The future of drug-resistant tuberculosis treatment: learning from the past and the 2019 World Health Organization consolidated guidelines

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The World Health Organization (WHO) recently launched the consolidated guidelines on drug-resistant tuberculosis (DR-TB) treatment [1]. They include a new drug classification to manage rifampicin-resistant (RR) and multidrug-resistant (MDR)-TB, while proposing either a shorter regimen (including injectable drugs) or a longer all-oral one as the recommended treatment options. Efficient diagnostic tools are presently available to diagnose resistance to second-line drugs within a few hours (instead of the weeks previously needed) [2]. Therefore, the challenge for National TB Programmes is now to capture these new recommendations in their national guidelines. The aim of this article is to contribute to the ongoing discussion on RR-/MDR-TB treatment considering the lessons learnt over the past 70 years of anti-TB chemotherapy. Other important topics raised in the 2019 WHO drug-resistant treatment guidelines, such as the treatment of isoniazid-resistant TB or the comparison between the two WHO-approved regimens for MDR-TB, have not been addressed within the constraints of this short editorial.

Anti-TB chemotherapy has dramatically improved TB patients' outcomes. From 1946 to 1976, several anti-TB drugs were discovered, including the two most effective ones, *e.g.* isoniazid (H) and rifampicin (R). In parallel, randomised controlled trials using several drugs in combination raised the evidence supporting the two core principles of anti-TB chemotherapy: 1) combining at least two drugs (to avoid selection of naturally resistant mutants) for 2) a sufficient duration to cure and prevent relapses (to effectively sterilise the infected tissues) [3, 4].

Randomised controlled trials proved that a two-drug regimen was effective in all TB forms if there was no resistance to any of those drugs [3–5]. Based on these findings, since the 1980s a 9-month regimen with

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TABLE 1 Treatment approaches to drug-susceptible (DS) and drug-resistant tuberculosis (TB): number and type of drugs, and treatment duration

Reference	DS-/MDR-/XDR-TB	Minimum number of drugs in the regimen	Duration of the regimen	Drugs in the regimen	Reason for changing (increasing or decreasing) the number of drugs in the regimen	Reason for changing (increasing or decreasing) the regimen duration
Fox *et al.* [3] (1999) ATS [6] (1986)	DS-TB	2	9 months	H+R		
Fox *et al.* [3] (1999) ATS [6] (1986) WHO [7] (1991)	DS-TB	3	6 months	H+R+Z or 2HRZ/4HR	Increase: adding Z to reduce duration of the treatment course	Decrease: two drugs with major sterilising activity
WHO [9] (2003)	DS-TB	4	6 months	2HRZE/4HR	Increase: prevent failure in the era of increasing H resistance	Decrease: two drugs with major sterilising activity
Caminero *et al.* [4] (2018)	DS-TB	3/4	6 months	2HRZE/4HR or 2HRZ/4HR if susceptibility is known before starting treatment	Increase: prevent failure in the era of increasing H resistance	Decrease: two drugs with major sterilising activity
WHO [12] (1996)	MDR-TB	4	21 months	AG, Eto, Z, Ofx	Increase: quite a lot of drugs with very reduced efficacy	Increase: lack of drugs with strong sterilising activity
WHO [13] (2006) WHO [14] (2008) WHO [15] (2011)	MDR-/XDR-TB	At least 4–5	18–24 months	Fluoroquinolones (Ofx/Lfx, moderately sterilising)+others	Increase: several drugs with limited efficacy	Increase: lack of drugs with strong sterilising activity
WHO [16] (2016) Ahmad Khan *et al.* [18] (2017) Nunn *et al.* [20] (2019)	MDR-TB	7	9–11 months	Km, Mfx, Pto, Cfz, Z, high-dose H, E	Increase: to assure bactericidal activity in the intensive phase	Decrease: two drugs with major sterilising activity plus the possible action of Z if susceptible
Ahmad *et al.* [21] (2018)	MDR-TB	5	19–22 months	All anti-TB drugs, excluding H and R	Increase: several drug with limited efficacy	Increase: lack of drugs with strong sterilising activity
WHO [1] (2019)	MDR-TB	4	Two options: 18–20 months (including a 15 to 17-month continuation phase) or 9–11 months	At least four active drugs: always Lfx/Mfx, Bdq and Lzd+Cfz or cycloserine/terizidone (other group C drugs to be employed when first choices cannot be used) Km, high-dose H, Pto, high-dose Mfx, Cfz, E, Z	Decrease: very active core drugs Increase: to assure bactericidal activity in the intensive phase	Increase: not justified because four sterilising drugs are included Decrease: two drugs with major sterilising activity, plus the possible action of Z if susceptible
Current paper 2019	MDR-TB	3	6	Lfx/Mfx (Cfz), Bdq and Lzd	Decrease: very active drugs; unlikely resistance due to previous exposure	Decrease: three drugs with major sterilising activity

ATS: American Thoracic Society; WHO: World Health Organization; MDR: multidrug resistant; XDR: extensively drug resistant; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; AG: aminoglycoside; Eto: ethionamide; Ofx: ofloxacin; Lfx: levofloxacin; Km: kanamycin; Mfx: moxifloxacin; Pto: prothionamide; Cfz: clofazimine; Lzd: linezolid; Bdq: bedaquiline.

two drugs (isoniazid and rifampicin) or a 6-month regimen with three drugs (HR plus pyrazinamide (Z)) were recommended by WHO and other major scientific societies (table 1) [3–7]. Rifampicin and pyrazinamide both have high sterilising activity [3–6]; the use of rifampicin allowed decrease of the 18–24 month regimens to 9 months, while pyrazinamide further shortened treatment duration to just 6 months [3, 4, 6, 7].

The concept that by using sterilising drugs it is possible to shorten treatment duration was demonstrated in several randomised controlled trials [3–8]. The effectiveness of HR and HRZ regimens became jeopardised when the prevalence of primary isoniazid resistance increased globally, boosting the risk of making HR-based regimens ineffective and creating additional resistances (*e.g.* transforming an isoniazid-resistant case into a MDR-TB one) [4, 8]. In order to prevent this possibility, WHO recommended addition of a fourth drug, ethambutol [4, 9]. Its contribution was therefore not necessary if isoniazid resistance was not present [4]. In summary, pyrazinamide and ethambutol were not important for increasing regimen effectiveness, their role being to shorten the regimen (in the case pyrazinamide) and to protect rifampicin in case isoniazid resistance was present (for ethambutol).

Therefore, two highly effective drugs administered for an adequate period of time are sufficient to cure practically all of drug-susceptible cases [3–8, 10]. However, acquisition of drug resistance is often more complex, especially because it has been proven that drug resistance can develop even if the treatment regimen is correctly prescribed/taken and no resistance is present, due to individual pharmacokinetic variability [11]. In addition, variable drug penetration capacity in lung lesions and variability in strain characteristics of *M. tuberculosis* (*i.e.* lineage) also play a role in the risk of developing drug resistance.

Since no other drugs with sterilising activity other than rifampicin and pyrazinamide were available for decades, cases of RR- and MDR-TB (or when adverse events to rifampicin occurred) were treated for 18–24 months with less effective drugs, and WHO recommended this from 1996 to 2016 [12–16]. Ofloxacin and levofloxacin (Lfx) were the only fluoroquinolones recommended to treat DR-TB at the time, both with moderate sterilising activity and limited capacity to shorten regimens. Although pyrazinamide was routinely used in MDR-TB cases, it was not considered as a core effective drug because its previous use in almost all cases increased the risk of pyrazinamide resistance.

As new evidence supported a shorter regimen for RR-/MDR-TB [16], WHO recommended its use in 2016 under specific conditions including susceptibility to fluoroquinolones and injectable drugs [16]. This regimen was shortened to 9–11 months [17] because high-dose moxifloxacin (Mfx) and clofazimine (Cfz) have high sterilising activity [4]. The regimen also included pyrazinamide, which could play an important role in treatment shortening in the absence of resistance. A 2017 meta-analysis of studies of this shorter regimen confirmed its effectiveness [18], and which was further demonstrated in nine African countries [19]. In 2019 a non-inferiority randomised controlled trial (the STREAM trial) showed the shorter regimen had similar outcomes to the longer one [20]. It is important to point out that the longer regimen used in the STREAM trial included the "classic" old oral drugs and an injectable agent, very different from the all-oral longer regimen currently recommended by the WHO (which includes new and re-purposed drugs).

In the latest consolidated 2019 MDR-TB guidelines, the all-oral (injectable-free) longer regimen is recommended, while the shorter regimen is still considered a valid option [1]. To design the longer regimen, WHO recommends to combine all three group A drugs (Lfx/Mfx, bedaquiline (Bdq) and linezolid (Lzd)) plus at least one from group B (clofazimine or cycloserine/terizidone (Cs/Tzd)). The total duration of this regimen, which includes at least four drugs, is 18–20 months; 15–17 months of treatment are recommended after achieving bacteriological conversion [1].

The duration of this longer regimen is based on the results of a large individual data meta-analysis [21], which represents the best evidence available to date. In this meta-analysis, a five-drug regimen in the intensive phase and four-drug regimen in the continuation phase was associated with higher treatment success rates (and lower mortality), as compared to 0–2 drug regimens (adjusted odds ratio (aOR) 2.6, 95% CI 2.1–3.2; and aOR 2.8, 95% CI 2.2–3.5, respectively). Likewise, better treatment success rates were achieved with regimens lasting 19–22 months [21]. It is noteworthy that this study was based on cohorts treated using several drugs with limited efficacy [21] and poor sterilising activity (ethambutol, prothionamide/ethionamide (Pto/Eto), para-aminosalicylic acid (PAS), Cs/Tzd and injectables) [3, 4, 22, 23]. They were likely to provide a limited contribution to achieve treatment success, as the authors of the study recognise in their conclusions [21]. And, for cycloserine a difference in both mortality and treatment success was found when susceptible and resistant isolates where analysed independently, but not for the remaining drugs (including for ethambutol and pyrazinamide). Fortunately, most of the cohorts included in the meta-analysis included Mfx/Lfx. Table 1 shows the most relevant changes in the number of drugs and treatment duration along with the history of TB and RR-/MDR-TB treatment.

Considering the principles of anti-TB treatment discussed above, we can argue that a RR-/MDR-TB case sensitive to all the group A drugs could be cured using those three drugs only [10]. And, as all group A drugs have bactericidal and sterilising activity [4, 22–26], a shorter regimen (6–9 months) could possibly cure and prevent relapses [10]. Sensitivity to all group A drugs is a pre-condition to design an effective regimen. Ideally, resistance should be ruled out in all cases. Rapid detection of fluoroquinolone resistance is now available [2], and, as bedaquiline and linezolid have only recently been introduced in anti-TB regimens, primary resistance to them is unlikely (although it is appearing in some settings) [27]. In regions where bedaquiline and linezolid have been introduced recently, ruling out resistance to fluoroquinolones is probably sufficient to use a 6–9 months regimen based on the three group A drugs only. However, although background resistance levels to these compounds (bedaquiline, linezolid and clofazimine) are generally low, this might not be true in all settings and might change rapidly in the future. For this reason, when drug susceptibility testing for bedaquiline and linezolid becomes routinely available, it would ideally be necessary to rule out resistance to these three drugs before starting a regimen which includes them.

On the other hand, if resistance to fluoroquinolones is proven or likely, clofazimine (a bactericidal and sterilising drug from group B) [4, 18, 19, 22], could be a valid alternative. This is clearly not possible for cycloserine, as its bactericidal and sterilising activity is poor [3, 4, 22]. Interestingly, the currently ongoing open-label NIX-TB trial (F. Conradie; unpublished results presented at The Union World Conference on Lung Health, 2018), is based on the same arguments discussed above. It is testing a 6-month, three-drug regimen including linezolid, bedaquiline and pretomanid (which recently started its approval track of the US regulatory authorities) [28]. The NIX-TB trial results will inform future guidelines and clinical practice on all-oral shorter regimens for DR-TB.

Group C drugs should be used when it is not possible to design an adequate regimen with group A and B drugs. According to WHO, group C drugs are "ranked by decreasing order of usual preference for use", placing ethambutol and pyrazinamide in first and third position, respectively (table 2). It seems the available evidence does not support such order [4, 21, 22]. Actually, in the most recent meta-analysis, ethambutol and pyrazinamide did not show benefits towards treatment success, independently from the susceptible/resistant result of the isolate (aOR 0.9, 95% CI 0.7–1.1; and 0.7, 95% CI 0.5–0.9, respectively), while carbapenems (imipenem and meropenem) did (aOR 4.0, 95% CI 1.7–9.1) [21]. We fear that most clinicians will favour ethambutol or pyrazinamide (more likely to be ineffective for previous use) over better, newer drugs, such as imipenem/meropenem and delamanid, which may be more effective and with a good safety profile [4, 17, 29, 30]. Amikacin, although rather toxic, can still be a resource drug in selected cases [1, 21–23].

The need for using group C drugs is justified by the extended resistance pattern of the *M. tuberculosis* strain. Thus, ideally, we need to prioritise the drugs based on efficacy, in particular looking to their bactericidal and sterilising activity [4, 23, 24].

Based on 1) the evidence available (from the meta-analysis and other observational studies) [4, 21–24, 29, 30] and 2) the bactericidal/sterilising activity of these drugs, we suggest the following order: imipenem/

TABLE 2 Proposed priority order of the World Health Organization group C drugs

2019 World Health Organization order, group C	Activity		Proposed order	Activity	
	Bactericidal	Sterilising		Bactericidal	Sterilising
Ethambutol (E)#	+/-	-	Imp/Mpm	+++	+/++?
Delamanid (Dlm)	++	++	Dlm	++	++
Pyrazinamide (Z)#	+/-	++/+++	Am/S	+++	-
Imipenem-Cilastatin (Ipm-Cln) or Meropenem (Mpm)	+++	+/++	Eto/Pto	+/++	-
Amikacin (Am) (or streptomycin (S))	+++	-	Z	+/-	++/+++
Ethionamide (Eto) or Prothionamide (Pto)	+/++	-	E	+/-	-
p-aminosalicylic acid (PAS)	-	-	PAS	-	-

Based on efficacy, considering both the bactericidal and sterilising activity of the drugs [4, 22]. #: risk of resistance to ethambutol and pyrazinamide is high in patients who have already received them and treatment failed; drug susceptibility testing currently available is not completely reliable for either of these drugs.

meropenem (despite the relatively small number of patients included in the meta-analysis; the single small "early bactericidal activity" study available and the high operational complexity of administering carbapenems in resource-limited settings), followed by delamanid, amikacin, Eto/Pto, pyrazinamide and ethambutol (table 2).

Moreover, the available evidence does not favour the use of PAS, as the patients exposed to PAS had lower success rate and higher mortality than those not receiving it (aOR 0.8, 95% CI 0.7–1.0; and 1.2, 95% CI 1.1–1.4 for treatment success and death, respectively) [21].

Furthermore, Cs/Tzd, currently ranked in group B, could be downgraded in future revisions if we consider their modest bactericidal and sterilising activity [3, 4, 8, 22] and the results of the recent meta-analysis [21]. Lastly, the use of injectables kanamycin and capreomycin is no longer recommended by WHO [1] based on the results of the above-mentioned meta-analysis [21]. However, because of their bactericidal activity [3–5, 22, 23] they might still represent an option in selected cases when no other drug is available and susceptibility to them has been confirmed.

In conclusion, we believe the recently published WHO guidelines for RR-/MDR-TB treatment represent an important step towards better management of patients with DR-TB.

In this article we provide elements to feed future discussions on the minimum number of drugs and on the duration of regimens to manage RR-/MDR-TB using new drugs. Evidence on the use of new drugs and regimens is rapidly growing [31] and the current concepts and practices will evolve in real time. Quality operational research assessing the benefits of different drug combinations and treatment durations is needed, including shorter regimens (6–9 months) based on Mfx-Bdq-Lzd for RR-/MDR-TB patients with proven fluoroquinolone susceptibility and on Bdq-Lzd-Cfz for those who are resistant to them. While waiting for the results of randomised controlled trials, well-designed operational research projects can provide rapid, and important, answers to improve the quality of MDR-TB care [32].

As far as we know, no trial has been planned yet to study the regimen we are proposing.

The WHO is supportive of testing all-oral regimens, but under operational research conditions only. Additional guidance was recently provided by the Global Drug Initiative document [33], where "modified" shorter regimens are encouraged for fluoroquinolone-susceptible strains only, under operational research conditions and within regimens including four drugs or more.

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