



Proposal for a standardised treatment regimen to manage pre- and extensively drug-resistant tuberculosis cases

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A potential standardised regimen to manage extensively drug-resistant tuberculosis (XDR-TB) and pre-XDR cases <http://ow.ly/LucH30bUjjH>

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Introduction

Drug-resistant tuberculosis (TB) has become one of the main obstacles to controlling (and eventually eliminating) this disease [1–4]. The World Health Organization (WHO) reports that the number of patients suffering from TB with resistance to rifampicin (RR-TB) or multidrug-resistant TB (MDR-TB, resistance to at least isoniazid and rifampicin) is increasing alarmingly each year. Furthermore, the treatment success rates achieved globally are suboptimal, barely exceeding 50% [1, 2, 5]. The proportion decreases to 25% in patients with extensively drug-resistant tuberculosis (XDR-TB) (MDR-TB plus resistance to at least one fluoroquinolone (FQ) and a second-line injectable (SLI) drug) and to <20% when the drug resistance profile is beyond XDR [1, 2, 5].

The outcomes observed as of today suggest that specific patients achieve treatment success, but the impact on the RR-/MDR-TB epidemic is rather limited [6, 7].

Therefore, the need to improve our capacity to render permanently noninfectious and cure the vast majority of M/XDR-TB patients is obvious [8]. To achieve this goal, the WHO has recently recommended the so-called "shorter regimens" (9–12 months) for patients with RR-/MDR-TB who are susceptible to FQs and SLIs, or who have not previously received these two groups of drugs [2, 9–13].

These "shorter regimens" have achieved relapse-free success rates in 85–90% of the MDR-TB patients treated [14–17].

While an impact on the MDR-TB epidemic is forecast by scaling-up the use of these regimens, this does not work automatically for XDR- or pre-XDR-TB cases. The success rate in these cases depends on several factors (*e.g.* challenges to confirm the resistance patterns, availability of new drugs, clinical training, programmatic conditions, *etc.*).

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The aim of this article is to discuss the possibility of designing a standardised regimen which, ideally supported by the use of rapid diagnostic methods to identify eligible patients [9], would be potentially effective in the majority of cases affected by pre-XDR- and XDR-TB.

However, even without access to these rapid diagnostic methods, or waiting for their results, this regimen could work in patients failing the shorter or conventional standardised MDR-TB regimens. Therefore, the target of this regimen would be most of the patients with pre-XDR- and XDR-TB.

This regimen would complement the existing set of available standard regimens for new cases and MDR-TB cases (the WHO-recommended “shorter” regimen).

Rationale for a standardised regimen to manage pre-XDR-TB and XDR-TB cases

The first and most important justification to look for a potential standard regimen is represented by the low success and high failure/death rates presently achieved in treating pre-XDR and XDR-TB cases [1, 2, 9, 14].

Moreover, currently many of the XDR-TB cases are patients failing the MDR-TB standardised regimen, or new TB patients who are in contact with these cases. Therefore, *Mycobacterium tuberculosis* strains in these patients often carry a very similar pattern of extended resistance, including the drugs previously prescribed (ethionamide/prothionamide, cycloserine/terizidone among others) [18–21].

Basic regimen requirements

This regimen should satisfy four basic requirements, common to all anti-TB regimens [18–20]:

- 1) at least four new drugs (never used before), likely to be effective, need to be present;
- 2) two of them should be “core” drugs, at least one having a good bactericidal activity and one a good sterilising activity. Ideally, both (or at least the sterilising drug) should be given for the entire duration of treatment;
- 3) the other two drugs are the so-called “companion” drugs, whose function is to protect the action of the core drugs;
- 4) the treatment should be administered for sufficient time to cure patients while preventing relapse. Compounds with higher sterilising activity (rifampicin, pyrazinamide and, probably, moxifloxacin, levofloxacin, linezolid, bedaquiline and delamanid) [19] are potentially useful to reduce the treatment duration, although some of them will not be eligible for this regimen [19, 20].

Regimen composition and possible alternatives

To be consistent with the regimen requirements discussed above, and with the available drugs’ characteristics [9], the following antibiotics are candidates for the proposed standardised regimen:

- 1) *Linezolid*. Core drug with bactericidal and sterilising capacity [19, 22–25]. It needs to be prescribed at a dose of 600 mg·day⁻¹, which might be lowered to 300 mg·day⁻¹ (or 600 mg every 2 days) if adverse events occur.
- 2) *Bedaquiline*. This is also a potentially core drug with bactericidal and sterilising characteristics [18, 19, 26–30]. Some countries may value the use of delamanid instead of bedaquiline, as it also has the features of a core drug [19, 28, 31, 32].
In very selected cases with high level FQ resistance (*e.g.* mutation in *gyaA94Gly*) and complete SLI resistance (mutation in *rrs1410* or 1484) the possibility of a future combined use of *bedaquiline* and *delamanid* might be considered given special criteria are met [33]. This might be the only alternative in those low resource settings where the use of carbapenems is not possible.
- 3) Clofazimine. It may be considered core because of its possible sterilising capacity [14–17, 19, 34–39], although it can at least play the role of a companion drug. If the patient has previously received clofazimine in a failing regimen (“shorter RR/MDR-TB regimen”), this drug should be replaced by cycloserine (that just plays the role of a companion drug).
- 4) A carbapenem class antibiotic, which needs to be administered with amoxicillin/clavulanic acid to protect its action. Although it is now a candidate to be a companion drug, there is increasing evidence that it may play a future core drug role [19, 40], especially because of its possible good bactericidal activity. Based on the existing evidence, the best carbapenem would probably be meropenem [41, 42], although imipenem/cilastatin (often more easily available) [42, 43] or ertapenem (given the possibility to administer it once a day intramuscularly, it can act as switch therapy useful for ambulatory/home care) might also have a role [44–46]. However, given the need for parenteral administration with carbapenems, delamanid is also a potential choice (needing electrocardiogram monitoring), as discussed previously.
Para-amino salicylic acid (PAS), which is a weaker alternative, can be considered only in resource-limited settings under the conditions that LPA (line probe assay) for second-line drugs (SLDs) is available and susceptibility to any FQ and/or any SLI is documented (a combination not often available in real life).

- 5) Furthermore, there is need to reinforce and protect the four drugs mentioned above with more “supporting” drugs (important for XDR- and even more for pre-XDR-TB):
- a. An FQ, different from that used in the MDR-TB regimen, (*e.g.* high doses levofloxacin if moxifloxacin has been used previously, and vice versa). In case of pre-XDR-TB because of SLI resistance, this FQ would play a key role in the regimen [19]. But even in cases of XDR-TB, the FQ might still play a role, especially considering that there is no complete cross-resistance among all new FQs [47–50]. If the result of conventional drug susceptibility testing (DST) demonstrates resistance to all FQs, including high concentrations of moxifloxacin, this FQ could be discontinued. If moxifloxacin is used, it is necessary to closely monitor the QTc interval (corrected QT) in the electrocardiogram, because the regimen includes already two other QT-prolonging drugs (bedaquiline and clofazimine), plus the possibility to use delamanid.
 - b. A SLI different from that used in the MDR-TB regimen. For instance, amikacin can be considered if kanamycin has been used before. However, ideally all these patients should undergo LPA for SLDs to identify correctly the eligible patients based on the mutations identified. The SLI plays an essential role in pre-XDR-TB because of FQ resistance, although its use is still important in cases of XDR-TB, because of the nontotal cross-resistance among FQs described above. However, following demonstration that the mutations *rrs1410* and *rrs1484* do indeed carry cross-resistance between all SLIs, when these mutations are present the use of streptomycin could be considered in the absence of *rpSL* mutations [51, 52]. Moreover, if DST shows resistance to all SLIs, they need to be stopped and streptomycin can be considered (given DST susceptibility exists). In cases of complete resistance to all the SLIs and to streptomycin, this drug should be removed from the regimen.
 - c. High-dose isoniazid may have a role in cases with low-level resistance [53, 54]. It might also be used to treat failures in the shorter MDR-TB regimen, where isoniazid is prescribed at the dose of 10 mg·kg⁻¹ body weight [2]. However, in this XDR-TB regimen, isoniazid would be recommended at daily doses of 15–20 mg·kg⁻¹ body weight. According to the available evidence, isoniazid should be discontinued when high-level resistance is confirmed *in vitro* and when the LPA demonstrates double mutation in *katG* and *inhA*.

As described, this proposed standardised six or seven drug regimen meets the minimum accepted requirements for all TB treatments [18–20]. It includes four new drugs (linezolid, bedaquiline, clofazimine/cycloserine and carbapenem/delamanid) and two or three possible supporting drugs. Of the four new drugs, at least two are bactericidal (linezolid and bedaquiline). Additionally, bactericidal activity may also be ensured by the carbapenem (or delamanid) and by the three supporting drugs (FQ, SLI and high-dose isoniazid) if these drugs are effective on the given strain.

The regimen includes also at least two or three sterilising drugs (linezolid, bedaquiline and clofazimine, if used in the regimen). Furthermore, the sterilising activity of the regimen could be also enhanced by a FQ. Finally, as the regimen includes two or three sterilising drugs, it is possible that in the future (if controlled clinical trials will support) the regimen might be shortened (*e.g.* 12 months after bacteriological conversion).

A summary of the possibilities to design a standardised regimen for patients with pre-XDR-TB or XDR-TB is presented in table 1. Each country will fine-tune it according to the drugs being used in the RR/MDR-TB regimen and their availability.

The doses recommended for each of these drugs are summarised in table 2.

What patients would be eligible to receive this standardised regimen

As discussed above, this standardised regimen could target the majority of confirmed pre-XDR-TB or XDR-TB patients in the world. Potentially, the regimen has the characteristics to manage also patients failing a standardised MDR-TB regimen (conventional 21 months or shorter 9–12 months regimens) while waiting for the DST results to SLD. Although LPA and DST testing is strongly recommended, the regimen might be effective also in settings where LPA and DST are eventually not available. However, the patients who have already received more than one of the four new drugs included in the regimen, or those for whom resistances to the core drugs of this regimen has been confirmed with rapid testing, will not be eligible.

Duration of the proposed regimen

Because of the composition of the proposed regimen (which includes two or three sterilising core drugs), the total duration of the regimen would possibly be 13–15 months, with at least up to 12 months treatment following culture conversion. All drugs are necessary throughout the treatment (particularly

TABLE 1 Summary of the possibilities to design a standardised regimen for patients with pre-XDR-TB or XDR-TB

Regimen composition	Drug	Activity	Proposed recommendations
1. Two core drugs (always in the regimen)	Linezolid	Bactericidal and sterilising	Delamanid could replace linezolid or bedaquiline if: one of these drugs has been used previously proven resistance to one of these drugs severe toxicity.
	Bedaquiline	Bactericidal and sterilising	
2.a One companion drug (one of the following)	Clofazimine (first choice)	Sterilising	Bedaquiline: potentially QT-prolonging drug To be given if never administered before, especially useful in MDR-TB patients failing a conventional 21–24 months MDR-TB regimen. Potentially QT-prolonging drug
	Cycloserine	No bactericidal and sterilising	To be given if never administered before, and when clofazimine was administered in a previous failing regimen (shorter 9–12 months RR/MDR-TB regimen)
2.b One companion drug (one of the following)	One carbapenem+amoxicillin/clavulanate	Bactericidal	3 options: meropenem (first choice) imipenem/cilastatin ertapenem
	Delamanid	Bactericidal and sterilising	ECG monitoring needed
	PAS (para-aminosalicylic acid)	Bacteriostatic	Justified in low income countries under the following conditions: carbapenems and delamanid cannot be used LPA to SLD showing possible susceptibility to Amk or Mfx
3. Three supporting drugs One FQ One SLI High-dose isoniazid	One FQ (moxifloxacin)	Bactericidal and sterilising	Depending on the patient's previous treatment history In pre-XDR or XDR-TB patients not previously treated for TB with a FQ QTc interval close monitoring if used with bedaquiline and clofazimine
	One FQ (high dose moxifloxacin)	Bactericidal and sterilising	If levofloxacin has been used previously to treat TB
	One FQ (high dose levofloxacin)	Bactericidal and sterilising	If moxifloxacin has been used previously to treat TB
	If a DST shows resistance to levofloxacin and moxifloxacin, the FQ will be discontinued from the regimen		
	One second line injectable (amikacin)	Bactericidal	In pre-XDR or XDR-TB patient not previously treated for TB with a SLI If kanamycin or capreomycin have been used previously to treat TB
	If a DST shows resistance to all the second line injectables, this drug will be discontinued from the regimen		
	High dose isoniazid	Bactericidal	Dose: 15–20 mg·kg ⁻¹ Isoniazid is discontinued when: high level of resistance is confirmed <i>in vitro</i> when the LPA demonstrates double mutation in <i>katG</i> and <i>inhA</i>

XDR-TB: extensively drug-resistant tuberculosis; QT: measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; MDR-TB: multidrug-resistant tuberculosis; RR: rifampicin-resistance; ECG: electrocardiogram; LPA: Line Probe Assay; Amk: amikacin; Mfx: moxifloxacin; SLD: second-line drug; FQ: fluoroquinolone; QTc: corrected QT; SLI: second-line injectables.

those which are new and core, such as linezolid and bedaquiline), with the exception of SLI and high-dose isoniazid, which could be discontinued after 4 months of treatment. However, these drugs could be extended to 6 months if sputum smear microscopy is positive at the end of the fourth month of treatment. If sputum smear microscopy and culture remain positive at the end of the sixth month of treatment, a regimen failure should be accepted and the case should be re-evaluated to undergo an individualised regimen. If a carbapenem is included in the regimen, it might be discontinued after 6 months following bacteriological conversion. As bedaquiline is a core drug in this regimen, it should be administered for the whole treatment duration (not only for 6 months) [2], as it already happens in some settings [30, 55, 56].

Possible severe adverse effects and controls throughout treatment

The adverse events are likely to be similar to those occurring with the regimen currently recommended for the treatment of MDR-TB, including shorter regimens. A potential advantage (which of course needs to be confirmed by adequate studies) is that the potential new regimen contains fewer drugs of most of the anti-XDR regimens currently in use.

TABLE 2 Recommended doses for the drugs used in the proposed pre-XDR and XDR-TB regimen

Drug	Body weight kg				
	30–35	36–45	46–55	56–70	>70
Linezolid 600 mg	1 pill	1 pill	1 pill	1 pill	1 pill
Bedaquiline 100 mg	4 pills/24 h during 2 weeks, followed by 2 pills 3 times weekly until the end of the treatment				
Delamanid 50 mg	2 pills/12 h				
Clofazimine 100 mg	1 pill				
Meropenem/imipenem	500 mg/12 h	500 mg/12 h	1 gr/12 h	1 gr/12 h	1,5 gr/12 h
Amoxicillin/clavulanate	1000 mg/12 h				
Amikacin/kanamycin/capreomycin	0.5 g	0.750 g	0.750 g	1 g	1 g
Moxifloxacin	400 mg	600 mg	600 mg	800 mg	800 mg
Levofloxacin	500 mg	750 mg	1 gr	1 gr	1 gr
PAS 4 g	1+1 pill	1+1 pill	1+1 pill	1+1 pill	1+1+1 pill
Isoniazid 300 mg	2 pills	2.5 pills	3 pills	3.5 pills	4 pills

XDR-TB: extensively drug-resistant tuberculosis; PAS: para-aminosalicylic acid.

Close attention is necessary on possible electrocardiogram (ECG) alterations (QT interval), as several QTc-prolonging drugs are part of the possible new regimen (bedaquiline, sometimes delamanid, clofazimine and FQs, especially if moxifloxacin is used). A weekly ECG control will be necessary at least in the first month of treatment; it can eventually be reduced in frequency (*e.g.* monthly) in the absence of clinical disturbances or previous QTc increase over 500 ms.

Other adverse events are likely to occur, including optic neuritis, or haematological alterations (usually due to linezolid). The reduction of the linezolid dose from 600 to 300 mg·day⁻¹ or 600 mg three times weekly is generally sufficient to manage them [19, 57, 58]. The possibility to use TDM (treatment drug monitoring) to adjust the dose and minimise adverse events has been recently recommended [59, 60].

Therefore, it will be important to monitor these potential adverse effects, *e.g.* performing a clinical control, blood analysis (including haemogram and biochemistry with liver, renal and pancreatic function tests) and a sputum examination (for bacilloscopy and culture) on a monthly basis. It would also be necessary to perform a monthly audiometry while prescribing SLIs. Finally, a chest radiograph every 3–6 months and, eventually, pregnancy and HIV tests at the start of treatment should be performed.

Potential limitations and risks related to the use of the proposed regimen for pre-XDR- and XDR-TB cases

As discussed above, the ideal approach is to prescribe the regimen based on GenoType for SLD. However, this regimen has characteristic making it potentially effective in patients failing the standardised MDR-TB regimens, or waiting for the conventional DST result (or, as the extreme scenario, in patients living where these tests are not available). As the potential efficacy of this regimen is based on drugs like linezolid and bedaquiline, the capacity of monitoring their possible toxicity needs to be ensured (especially QTc, haemogram auditory and visual acuity).

Last, but not least, it is imperative that all the drugs composing the regimen are available in the country, that active drug safety monitoring and management (aDSM) is in place, as well as patient-centred and supportive models of care to ensure proper follow-up and care of patients undergoing treatment.

Need for further research to validate this proposal for pre-XDR and XDR-TB cases

To validate this proposal further clinical and operational research are necessary, including:

- 1) randomised clinical trial(s) testing this regimen under operational conditions, although designing and conducting them will be challenging. The trial(s) should ideally be able to study the efficacy of the regimen even in patients with TB resistant to FQs and SLIs, and evaluate its ideal duration;

TABLE 3 The three standardised regimens potentially able to manage the different categories of TB cases

TB patients categories	Standardised treatment regimen	Recommendations
1. Standardised treatment regimen for patients with rifampicin-susceptible TB	2 HRZE [#] /4 HR	[#] : In case of a positive sputum smear microscopy at the end of the second month of treatment, consider to check susceptibility to isoniazid before switching to the continuation phase (isoniazid, rifampicin)
2. Standardised treatment regimen for RR/MDR-TB patients, susceptible to FQs and SLIs	4 Km-hMfx [¶] -Cfz-Eto/ Pto-Z-E-hH ⁺ /5 hMfx [¶] -Cfz-E-Z	Standardised shortened treatment with SLD The intensive phase should be extended to 6 months when at the end of the fourth month of treatment, sputum smear microscopy is still positive [¶] : HMfx (600–800 mg·day ⁻¹) ⁺ : hH (15 mg·kg ⁻¹ body weight)
3. Standardised treatment regimen for patients with pre-XDR-TB and XDR-TB	Lzd-Bdq-Mrp/Clav (or Dlm)-Cfz-Amk [§] -hLfx [§] -hH [§]	[§] : With the considerations on duration and possible change of drugs exposed in the text

TB: tuberculosis; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; RR: rifampicin-resistant; MDR: multidrug-resistant; Km: kanamycin; hMfx: high-dose moxifloxacin; Cfz: clofazimine; Eto: ethionamide; Pto: prothionamide; hH: high-dose isoniazid; SLD: second-line drug; XDR: extensively drug-resistant; Lzd: linezolid; Bdq: bedaquiline; Mrp/Clav: meropenem/clavulanate; Dlm: delamanid; Amk: amikacin; hLfx: high-dose levofloxacin.

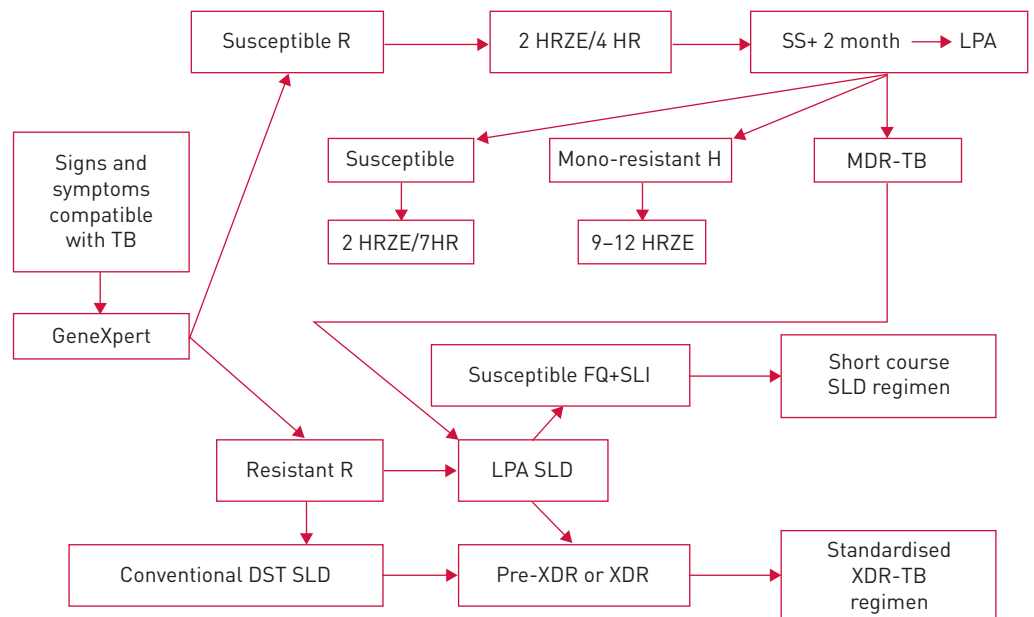


FIGURE 1 Proposed algorithm ensuring early detection of tuberculosis and prevention of possible amplification of the resistance pattern in programmatic conditions. R: Rifampicin; H: isoniazid; Z: pyrazinamide; E: ethambutol; SS+: sputum smear positive; LPA: line probe assay; MDR-TB: multidrug-resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis; FQ: fluorquinolones; SLI: second-line injectables; SLD: second-line drugs; DST: drug susceptibility testing.

- 2) more evidence on bedaquiline and delamanid safety when used for >6 months and programmatically [61] is necessary, as these two drugs are core pillars of the proposed regimen;
- 3) evidence on safety and efficacy of bedaquiline and delamanid combination is also necessary;
- 4) finally, the different programmatic and operational aspects of using a similar regimen need to be properly studied.

Proposal to manage most TB patients programmatically using just three standardised regimens

This article provides the rationale to treat most of the existing TB cases using just three standardised regimens. A summary of the three standardised regimens is available in table 3.

This proposal implies a molecular test performed at the beginning of the treatment to ensure susceptibility to rifampicin (GeneXpert and/or GenoType). If the strain is susceptible to rifampicin, the standardised first-line drug regimen (2HRZE/4HR, 2 months with isoniazid, rifampicin, pyrazinamide and ethambutol followed by 2 months with isoniazid and rifampicin) can be administered. On the contrary, if RR/MDR-TB is detected, a GenoType for FQs and SLIs (second-line injectables) needs to be performed. If this RR/MDR-TB strain is susceptible to FQs and SLIs, the standardised shorter 9–12 months RR/MDR-TB regimen should be offered to the patient. But if GenoType shows resistance to FQs and/or SLIs, the standardised regimen proposed in this article can be potentially considered.

Figure 1 shows the possible decision tree supporting this proposal.

Conclusions

In this manuscript we have proposed and discussed the rationale for proposing a standardised regimen to manage most of the patients with pre-XDR- and XDR-TB. We have also discussed the potential advantages and threats, which need to be confirmed by adequate studies.

If future studies will demonstrate that this approach is effective and safe, three standardised regimens will be potentially able to manage an important proportion of the existing TB patients (susceptible, MDR- and pre-XDR/XDR-TB ones) under programmatic conditions (table 3 and figure 1).

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