Classification of antituberculosis drugs: a new proposal based on the most recent evidence

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The classification of the anti-TB drugs should probably be modified to optimise the use old and new compounds http://ow.ly/QbDSP

Multidrug-resistant (MDR) tuberculosis (TB) (resistance to at least isoniazid and rifampicin), with >480 000 cases in 2013, 10% of them being affected by extensively drug-resistant (XDR)-TB (MDR-TB with additional resistance to any fluoroquinolone, and to injectable second-line drugs (SLDs) (capreomycin, kanamycin or amikacin)), continues to represent a real threat to TB control [1–4]. In some high MDR-TB burden countries, the prevalence of MDR-TB among new cases exceeds 20% and among retreatment cases, reaches almost 50% [1, 5].

Prevention and quality diagnosis and treatment of MDR- and XDR-TB are part of the crucial interventions included in Pillar 1 of the new World Health Organization (WHO) End TB Strategy, which is focussed on the goal of TB elimination [6–8]. Unfortunately, the outcomes of these cases are suboptimal, with 60% success among MDR-TB cases [2], 40% among XDR-TB cases [3] and <20% among the cases with resistance patterns beyond XDR-TB [4]. This means not only high mortality but also significant human suffering and transmission of the *Mycobacterium tuberculosis* strains within the community [9]. Unfortunately, at present, the treatment of MDR/XDR-TB is still very long, toxic and expensive [10, 11].

The original WHO guidance on the management of MDR-TB was issued in 1996 [12] and since then, several updated guidelines have been published. The fundamentals on MDR/XDR-TB treatment were published in the 2006 and 2008 WHO guidelines [13, 14], where the basic rationale to design therapeutic regimens for these cases was described. According to these recommendations, which are currently followed worldwide, the anti-TB drugs are classified into five main groups indirectly considering the evidence available, the safety and/or the effectiveness of the different drugs. These groups start from the most effective drugs (group 1), grouping the other drugs progressively according to decreasing order of efficacy [15].

In the 2011 revision of the WHO MDR/XDR-TB guidelines [16], the composition of different groups of anti-TB drugs was not modified. Therefore, since 2006, the rationale of the classification of the anti-TB drugs has not been changed but several studies have examined the effectiveness, efficacy and safety of the group 5 drugs, and some of these drugs appear to be more effective and well tolerated than others that currently have "higher" ranking in the classification. Furthermore, promising new drugs active against *M. tuberculosis* have been discovered in the last couple of years [17–20] and have become progressively available in many parts of the world to treat MDR/XDR-TB.

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Rationale of anti-TB treatment

During the two decades that span the discovery of streptomycin in 1943 and that of rifampicin in 1963, practically all the active drugs against *M. tuberculosis* were discovered, making it very easy to cure TB [21]. Furthermore, during those years, the fundamental basis of TB treatment was defined based on the analysis of multiple randomised clinical trials (RCTs), the fundaments of which are still entirely valid today [21–23]: 1) combining different effective drugs to avoid the selection of resistant *M. tuberculosis* strains; and 2) ensuring that treatment is long enough to sterilise the tissues infected with *M. tuberculosis* and, therefore, prevent relapse [22, 23].

It is currently accepted that any anti-TB treatment should include at least four drugs that are likely to be effective [16, 22], of which at least two are essential or core drugs and two are companion drugs. The core drugs are those with the capacity to kill *M. tuberculosis* in any of its metabolic phases. In contrast, the role of the companion drugs is to accompany the essential core ones, protecting their action and avoiding resistance selection [22]. Among the core drugs, one should have good bactericidal activity and the other should present good sterilising activity. These two drugs should ideally be maintained for the whole treatment duration [22]. The bactericidal drugs quickly reduce the bulk of the rapid multiplying bacilli, decreasing infectiousness and avoiding the disease's progression. The sterilising drugs attack the dormant and semidormant bacillus populations, allowing cure while preventing relapse [21, 22]. The drugs with the best sterilising activity are those that may reduce the duration of the treatment. The two companion drugs are no longer necessary after bacteriological conversion [22, 23].

Importantly, if a core drug cannot be used because of documented resistance or toxicity, it should be replaced by another with a similar efficacy (bactericidal and sterilising). Similarly, an accompanying drug should be replaced by another with a similar action.

Classification of anti-TB drugs and potential for an update

To build an appropriate anti-TB regimen for MDR/XDR-TB, WHO recommends a stepwise process based on five groups of anti-TB drugs [13, 14, 15, 24]. The stepwise process leading to the adequate design of a regimen suitable to cure MDR/XDR-TB patients is summarised in table 1 [22, 25].

The choice of the drugs is based on their efficacy and toxicity, where group 1 includes first-line drugs and group 2–5 include SLDs. Group 5 includes the drugs with potentially limited efficacy or limited clinical evidence [13, 14, 24].

Here, we briefly describe the main characteristics of the anti-TB drugs, based on the most recent publications and experience on the safety and efficacy of each drug. Based on this, we propose either to keep or to change the ranking of each compound in the classification of anti-TB drugs.

Group 1

All potentially effective group 1 drugs should be included in the regimen, considering that isoniazid, rifampicin and pyrazinamide are core drugs, and ethambutol is a companion drug. High-dose isoniazid should be added to an MDR/XDR-TB regimen when the *katG* mutation is not documented by the GenoType line probe assay (Quest Diagnostics, Madison, NJ, USA) but it should not be counted as one of the four active drugs [13, 14, 24]. Pyrazinamide should always be used, although its drug susceptibility test is unreliable, but it also should not be considered as one of the four active drugs [13, 14, 24].

Group 2

According to the current WHO classification [13, 14, 26], group 2 includes the injectable SLDs and group 3 includes the fluoroquinolones. The fluoroquinolones (particularly the later-generation fluoroquinolones, like high-dose levofloxacin or moxifloxacin [24]) are core drugs, with bactericidal and sterilising activity, as well as a good safety profile [22–24], and their use predicts a favourable outcome in MDR-TB treatment [2–4, 26, 27]. Conversely, the injectable SLDs have only bactericidal activity (not sterilising) and their safety profile is clearly worse. For these reasons, a future revision of the present classification might include fluoroquinolones in group 2 (table 2).

Group 3

If we include the fluoroquinolones in group 2, the question is what drugs should comprise group 3. Theoretically, they should be the injectable SLDs (the other currently used core drugs with bactericidal activity) [22, 23]. However, considering future scenarios, to be confirmed by stronger evidence on efficacy and safety, group 3 should include three core oral drugs, linezolid, bedaquiline and delamanid, instead of the injectables. These three drugs might be able to change the bleak prognosis of MDR-TB patients with resistance to fluoroquinolones (some clinicians call these cases pre-XDR, using a non-approved definition) (table 2).

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TABLE 1 Principles in designing treatment for a patient with multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB)

Steps	Considerations
1) Diagnosis	Analyse the following information Medication history: ≥1 month monotherapy or adding one drug to a failing regimen is a strong predictor of resistance DST: most reliable for R and H; little less reliable for second-line injectables and FQs; unreliable for E, Z; do not perform for group 4 drugs Perform HIV test: if positive, initiate CPT immediately and ART to all TB patients within the first 8 weeks after initiation of anti-TB treatment
2) Number of drugs	At least four effective drugs never used in the past and/or susceptible by DST, taking into account DST reliability and cross-resistance
3) Drug selection	Use Z and evaluate the use of E but neither should be considered as one of the four main effective drugs; E should be considered, especially in patients treated only with category 1 regimen in the past Always include one group 2 drug: one newer-generation FQ, preferably high-dose Lfx (1 g) or Mfx. To be counted among the 4 main effective drugs in MDR-TB, but not in the XDR-TB because possible cross-resistance Include one group 3 drug: one second-line injectable (Km, Am or Cm); to be counted among the four main effective drugs in MDR-TB but not in XDR-TB because of possible cross-resistance Include as many group 4 drugs as needed (Eto/Pto, Cs/Trd, PAS) until completing a regimen with at least four effective drugs; always consider Eto/Pto the first choice among group 4 drugs If necessary, use group 5 drugs to strengthen the regimen or when a regimen with four effective drugs has not been attained with the previous groups; if available, Lzd should be the first choice of group 5 drug
4) Length of TB treatment	Minimum length of treatment is 21 months, divided as follows Intensive phase: 6 months and ≥4 months after culture conversion; longer if three effective drugs are not available during the continuation phase Continuation phase: ≥14 months
5) Surgery	Consider only if few effective drugs are available, localised pulmonary lesions are present and the person has sufficient respiratory reserve
6) Ideal regimen	Standardised: if there has been no use of SLDs in the past Individualised: if there has been use of SLDs in the past or there is a history of contact with an MDR patient who had used them (treat with the effective regimen of the index case)

DST: drug susceptibility testing; R: rifampicin; H: isoniazid; FQ: fluoroquinolone; E: ethambutol; Z: pyrazinamide; CPT: co-trimoxazole preventive therapy; ART: antiretroviral therapy; Lfx: levofloxacin; Mfx: moxifloxacin; Km: kanamycin; Am: amikacin; Cm: capreomycin; Eto: ethionamide; Pto: prothionamide; Cs: cycloserine; Trd: terizidone; PAS: *p*-aminosalicylic acid; Lzd: linezolid; SLD: second-line drug.

Linezolid

Linezolid is a core oral drug with bactericidal and sterilising action. Evidence on good efficacy is accumulating, including meta-analyses [28, 29] and two RCTs [30, 31], in addition to observational studies [28, 32–37]. Unfortunately, the current cost and the documented toxicity [28–37] can be a barrier to its wider use. Nonetheless, the price of generic, quality-assured linezolid has reduced significantly in the last year and further cost reduction globally is expected soon [38]. With regard to toxicity, a reduced initial linezolid dose or a dose adjustment during treatment (*e.g.* using the therapeutic drug monitoring (TDM) approach) has shown to improve tolerance without affecting efficacy [30, 36, 39–42]. In fact, adverse events are lower when a linezolid dose of 300 mg·day^{-1} is used [40]. TDM is a useful and simple tool that is easy to perform: blood samples are collected on paper strips, packed in plastic bags and sent to the laboratory [35, 43].

TABLE 2 A proposal for a future grouping of antituberculosis drugs

Group name	Anti-tuberculosis drugs
Group 1	First-line oral drugs: isoniazid, rifampicin, ethambutol, pyrazinamide
Group 2	Quinolones: high-dose levofloxacin, moxifloxacin
Group 3	Linezolid, bedaquiline (?), delamanid (?)
Group 4	Injectable second-line drugs: kanamycin, amikacin, capreomycin
Group 5	Ethionamide/prothionamide, clofazimine, carbapenems (?)
Group 6	Cycloserine, *p*-aminosalicylic acid, amoxicillin/clavulanate

Bedaquiline and delamanid

Bedaquiline and delamanid might have the characteristics needed to be part of this hypothetical group 3 if the promising (but still incomplete) data available are confirmed and the two drugs can be safely prescribed for the whole treatment duration, not only for 6 months.

Bedaquiline targets both actively replicating and dormant bacilli [44–46], and therefore has the characteristics required of a core drug. The available evidence on efficacy and safety includes RCTs [17, 18] and observational studies, including experience derived from compassionate use programmes [47–49]. With regard to its efficacy, the first randomised phase II controlled trial on bedaquiline reported faster sputum-culture conversion in the patients receiving bedaquiline than in the control group (hazard ratio 11.8, 95% CI 2.3–61.3; p=0.003). Furthermore, the proportion of patients who converted was 48%, compared with the 9% for the placebo group, at 2 months, and it was 77.6% *versus* 57.6% at 6 months [17]. The results of the final analysis (phase IIb clinical trial) [18] at the end of 30 months of follow-up showed a 58% cure rate for the patients who had received bedaquiline, compared with 32% for the controls (p=0.003).

The main concern regarding safety of bedaquiline is the unexplained higher number of deaths in the bedaquiline group [17]. However, the most common adverse reaction associated with this drug was a QTc interval increase on ECG [17, 18, 47]. For instance, in the small French cohort described by Guglielmetti *et al.* [47], this event occurred in seven (20%) patients and two (6%) cases required bedaquiline discontinuation.

These adverse events are crucial for the WHO recommendations on bedaquiline use [50] and, for this reason, monitoring, active pharmacovigilance and proper management of adverse events are critical among the five criteria that should be in place for the implementation of this drug. Finally, an additional potential issue is the cross-resistance with clofazimine [51].

Delamanid can also be considered a core drug because of its bactericidal and sterilising activity [19, 20]. Unlike bedaquiline, so far, it does not show cross-resistance with the other anti-TB drugs [19, 20, 52, 53]. Some RCTs and observational studies have addressed its efficacy [19, 20], and there are also some positive experiences from its compassionate use [54, 55]. In the first clinical trial published on delamanid [19], culture conversion at 2 months was more likely to occur in the group that received this drug than in the placebo group. The more recent study by Skripconoka *et al.* [20] showed that patients who received delamanid for ≥6 months achieved more favourable outcomes (74.5%) than those who received it for ≤2 months (55%). Additionally, the group that received a longer drug course reported less mortality (1%), compared with the short-term or no-delamanid groups (8.3%). With regards to adverse events, the QTc prolongation was more common in the delamanid group, while the other side-effects were similarly distributed in the three groups [24]. For this reason, the WHO recommendations on delamanid use [56] include the same five implementation criteria as in the case of bedaquiline [50].

As mentioned above, an important limitation of bedaquiline and delamanid use is that, so far, they can be used only during the first 6 months of treatment. When treating XDR-TB patients, these drugs should be added to an optimised background regimen that often includes weak and/or poorly tolerated drugs (from the limited drug options remaining), with adverse events requiring the interruption of either the whole treatment or just one compound. When this happens, the regimen becomes even weaker and, once bedaquiline or delamanid are stopped after 6 months, the regimen is prone to fail**.** The possibility of maintaining bedaquiline and/or delamanid for the entire length of treatment will be an important step forward, also for their use for patients with MDR patterns of resistance other than XDR-TB, or the so-called pre-XDR-TB.

Group 4

Following the proposed reclassification of groups 2 and 3, the injectable SLDs might have the characteristics of a future group 4 (table 2). In fact, based on their bactericidal activity, they remain core SLDs but given their cumulative toxicity (more than 6–8 months of treatment increase the chance of deafness or kidney problems) and the need for parenteral administration, they would rank lower than the previously described compounds.

Group 5

A future hypothetical group 5 should include the thionamides (ethionamide or prothionamide) that currently belong to group 4, of which they represent the best drugs: the only ones with some bactericidal activity [27]. Among the limitations of the thionamides are poor gastric tolerance, possible cross-resistance with isoniazid and lack of clinical trials analysing their authentic role in the treatment of TB. The change

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from group 4 to 5 is not actually a downgrade of the thionamides but rather our proposed upgrade of other, possibly better drugs.

A new revised Group 5 might therefore include other SLDs that, although not very powerful, can offer support in the treatment regimens (table 2), such as clofazimine (gaining more and more evidence over time on its effectiveness and safety profile) and perhaps the carbapenems (imipenem/cilastatin and meropenem) combined with clavulanic acid. In fact, although the experience is still very limited, this carbapenem/clavulanate combination seems to be helpful in the treatment of XDR-TB patients [57–59]. In a study by De Lorenzo *et al.* [57], patients treated with meropenem/clavulanate in addition to a linezolid-containing MDR-TB regimen achieved a higher smear conversion rate at 3 months than controls (87.5% *versus* 56%, p=0.02). These drugs deserve proper evaluation, especially in terms of optimal dose and administration schedule [60, 61]. Until more evidence is available, these three antibiotics should be considered companion drugs and cannot rank higher in the classification.

Possible new group 6

Finally, a hypothetical new group 6 (table 2) might be considered in order to include the remaining drugs: *p*-aminosalicylic acid (PAS) (a drug with limited efficacy that is very poorly tolerated) and cycloserine (limited efficacy and major adverse psychiatric reactions), which belong to the current group 4; and amoxicillin/clavulanate (well tolerated but with limited activity against *M. tuberculosis*), which is part of the current group 5. The other drugs of the current group 5, such as clarithromycin and other macrolides, and thioacetazone, might not deserve to be included in the anti-TB drug arsenal.

Potential implications of this new classification

This hypothetical proposal may have some important implications. For instance, if the current evidence can be consolidated, some drugs, like linezolid, should also be considered also for MDR-TB cases and not only for XDR-TB. It should be noted, however, that many clinicians in developed countries are already using this drug to build effective MDR-TB regimens in their routine practice. The same would happen with bedaquiline and delamanid if they were upgraded to a higher anti-TB drug group. However, in their case, more evidence is probably needed to support a possible change in the current WHO recommendations regarding these two drugs, recommendations that currently allow their use only in XDR-TB or in MDR-TB cases when four drugs not previously used are not available to build and effective regimen [50, 56].

The need to monitoring patients closely in order to recognise and promptly manage possible adverse events related to some of the drugs that we propose to upgrade should not be different from the actual need for monitoring and properly managing patients receiving MDR-TB treatment. In fact, some currently used drugs, such the injectable SLDs, the thionamides, cycloserine and PAS, require close patient follow-up and efforts to prevent and manage the frequent side-effects.

Finally, other issues that should be considered are the cost, possibility of testing drug susceptibility and drugs availability. However, there is the optimistic expectation (and already some evidence) that the market progressively responds to public health needs and demands, especially when international institutions and communities feed this demand.

Conclusions

In spite of the limitations of the present proposal (it is based not on a systematic review but only on expert opinion and the analysis of the most relevant publications), the evidence accumulated in the last few years suggests that a new classification of the anti-TB drugs is necessary in the near future. However, a systematic review should be pursued in order to confirm or strengthen the basis of our call for a revision.

How the available evidence should be used for the reclassification process is a crucial issue because there are methodological difficulties in evaluating the effect of a single component of a multidrug regimen. The core difficulty in evaluating the role and contribution of a single drug is represented by the fact that DST-tailored regimens are put together as a cocktail of different drugs; however, this difficulty is the same faced some years ago, when the potential role of each anti-TB drug was evaluated in order to build the current recommendations for MDR-TB management. However, further studies, especially RCTs, are needed to establish the efficacy that drugs like linezolid, bedaquiline, delamanid, clofazimine and carbapenems/clavulanate will have in the anti-TB armamentarium.

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