An update on repurposed medications for the treatment of drug-resistant tuberculosis

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1. Introduction

In spite of recent advances in science to improve the diagnosis and treatment of tuberculosis (TB), drug-resistant (DR) forms of the disease continue to pose a serious challenge for the medical community. DR-TB is a growing global public health problem, with more than 480,000 new multidrug-resistant TB (MDR-TB, i.e. TB disease caused by Mycobacterium tuberculosis (MTb) strains resistant, to at least isoniazid (INH) and rifampicin (RFP) cases and 190,000 deaths estimated to have occurred in 2014 [1]. Globally, only about one in three cases of MDR-TB is diagnosed and only one in four offered treatment for their disease. The limited therapeutic arsenal results in frequent treatment failures and high mortality rates. The unfavorable treatment success rates have contributed to ongoing community transmission of highly resistant forms of MTb, and have fueled epidemic proportions of MDR-TB and extensively drug-resistant TB (XDR-TB, i.e. TB disease caused by MDR-TB strains with additional in vitro resistance to at least one fluoroquinolone and one second-line injectable drug, amikacin, capreomycin, or kanamycin) in large areas around the globe [2].

When designing an effective background regimen for the treatment of MDR-TB and XDR-TB, the World Health Organization (WHO) recommends a stepwise approach of including at least four active drugs in order of priority based on presumed efficacy and safety. Of note, most of the drugs used in the current MDR-TB treatment regimen – and in fact the entire regimen itself – have never been tested in formal clinical trials. One core issue faced by many clinicians is difficulty in identifying at least four active agents necessary to design an effective multidrug regimen that the patient can also tolerate. This is even more challenging when managing cases with additional resistance patterns ‘beyond just INH and rifampicin resistance’. During the past half century of great antibiotic revolution for the treatment of all infectious diseases, not much has been added to the anti-TB armamentarium. There is some reason for optimism, as new drugs – including bedaquiline (BDQ) and delamanid (DLM) – have shown promise in the treatment of MDR-TB [3]. Such drugs, however, must be used in combination with additional effective agents in order to achieve the best possible treatment outcomes. Given the dearth of new agents in the TB pipeline, providers and programs have turned to the use of medications that are indicated for the treatment of other infections but have shown promise in the treatment of DR-TB – defined as TB disease caused by infection with MTb strains that are resistant to any of the known anti-TB medications [4]. These include the beta-lactams (β-lactams), clarithromycin (CLR), clofazimine (CFZ), the fluoroquinolones (FQs), and linezolid (LZD). This paper will review the evidence on efficacy, safety, and tolerability of these ‘re-purposed’ agents for the treatment of DR-TB.

This is a non-systematic review of clinical cases, non-randomized clinical studies, and randomized clinical studies published between 1998 and 2015, as well as pharmacological studies published as far back as 1957. The authors used the...
key words, such as tuberculosis, MDR, repurposed drugs, and pharmacology to extract relevant literature from Cochrane Library, EMBASE, and PubMed databases. It is not the intention of this review to describe the weight of evidence, but rather to discuss past and ongoing trials, and future directions for the use of these repurposed anti-TB drugs, which are presented in alphabetical order below.

2. β-Lactams

Initially developed for the treatment of gram-positive infections, β-lactams have been used for TB treatment. β-lactams inhibit cell-wall synthesis by binding to the transpeptidases, which catalyze peptidoglycan cross-linking. *MTb* contains the gene *blaC*, which encodes an extended spectrum β-lactamase [5], rendering *MTb* inherently resistant to most β-lactam antibiotics *in vitro*. While most β-lactamase inhibitors (i.e. sulbactam and tazobactam) only transiently inhibit *blaC* β-lactamase, clavulanic acid irreversibly inhibits it [6]. Co-administration of clavulanate (CLV) reduces the minimum inhibitory concentration (MIC) of amoxicillin against *MTb* from ≥16 µg/ml to 2–8 µg/ml [7]. Carbapenems are also hydrolyzed by *blaC* but at a slower rate than amoxicillin. *In vitro* studies have shown that the combination of CLV improves the MIC of meropenem from 8 to 1 µg/ml, and that this combination sterilizes aerobic and anaerobic, nonreplicating, and persistent *MTb* cultures, and was active against drug-susceptible and XDR strains of *MTb* [8].

2.1. Pharmacokinetic and pharmacodynamic data

The bactericidal activity of β-lactams against other bacteria is correlated to the time above MIC (*T_{MIC}*) of amoxicillin–clastatin dose of 100 mg/kg twice daily reduced sputum and lung colony forming units (CFU) counts by approximately 1.5 and 0.75 log_{10} CFUs/g, respectively, and reduced mortality despite achieving only 12% *T_{MIC}*. Murine studies have been mixed with respect to meropenem–clavulanate–CLV’s effect on mouse mortality and *MTb* CFU’s in lung and spleen, although in some studies meropenem–CLV seems to be superior to imipenem–CLV [6].

2.2. Clinical studies

The use of amoxicillin–CLV (amox–clav) alone against *MTb* has had generally poor results. An early bactericidal activity (EBA) study from South Africa showed no benefit of amox–clav over the control [9], and a study from Pakistan examining the MIC of drug-resistant clinical isolates of *MTb* found that 98% of the isolates were resistant to amox–clav [10]. Another EBA study showed some success with amox–clav, over 7 days amox/clav reduced the sputum CFU by an average of 0.1 log_{10} CFUs/ml per day (in comparison, INH reduced CFU by 0.27 log_{10} CFUs/ml per day) [11]. Low cost, good tolerability, and low toxicity profile work in favor of its use, but only in combination with a carbapenem, in situations where treatment options are very limited.

Similar to amox–clav, the carbapenems meropenem, imipenem–clastatin, and ertapenem are β-lactam antibiotics with cell-wall activity. Human data is sparse [12] but meropenem–CLV as part of regimens (usually also containing LZD) for patients with MDR and XDR-TB has shown successful treatment outcomes with respect to culture conversion and mortality [13–15]. Between 2005 and 2016, seven studies have managed to provide scientific evidence on the efficacy, safety, and tolerability of carbapenem-containing regimens in patients with MDR- and XDR-TB. The therapeutic contribution and efficacy/effectiveness profile of meropenem, imipenem, and ertapenem when added to a background regimen in the treatment of MDR- and XDR-TB cases has generally been positive, with treatment success rates higher than 50% in all the studies included in the systematic review [16], and up to 80% in patients receiving ertapenem-containing regimens [17,18]. Of note, carbapenems should always be used in combination with CLV, and amoxi-CLV is currently the only source of CLV. Dauby and colleagues reported the successful use of a combination of meropenem/CLV and LZD in the management of an adolescent with advanced XDR-TB, in which clinical improvement and culture sterilization were observed within 11 weeks of introduction of this combination [15]. There is optimism on the potential role of carbapenems in the TB treatment arena, and the NCT02349841 and NCT02381470 phase – two trials, evaluating the individual bactericidal contribution of the carbapenems will elucidate the real therapeutic contribution of the carbapenems in TB treatment success. Clinical evaluation of the efficacy of carbapenems could be significantly affected by their stability and pharmacokinetics following long-term administration [19].

2.3. Dosing and safety

The carbapenems must be given with CLV in order to be effective against TB. The WHO recommends an amox–clav dose of 500/125 to 1000/250 mg orally given three times per day, and an imipenem dose of 500–1000 mg intravenously every 6 h. A *T_{MIC}*, of 50% for isolates for which amox–clav MICs are 4 or 8 µg/ml can be achieved safely using the new formulations of amox–clav (2000/125 mg) administered twice or thrice daily, respectively. However, it is important to note that CLV is not commercially available in combination with carbapenems. To this end, many treatment programs using carbapenems combine with amox–clav, for the purpose of accessing the CLV component. Overall, β-lactams are well-tolerated, although anaphylactic reactions can occur in about 0.01% of patients. Sotgiu et al. also found that the safety and tolerability profile of carbapenems was very good, with the proportion of adverse events attributable to carbapenems being less than 15% [16]. However, carbapenems can only be given intravenously, which makes long-term administration difficult, although the drug ertapenem can be given once daily and intramuscularly [17].

3. CLR

CLR is a macrolide, and acts by irreversibly binding to the 50S subunit of the bacterial ribosome, inhibiting transpeptidation during protein synthesis. It is considered bacteriostatic. *MTb* displays intrinsic, rapidly inducible resistance due to methylation of 23S rRNA by the ermB gene product, which prevents macrolide binding to the ribosome [20]. Although *in vitro* and mouse studies have shown some limited activity against MTB, the clinical significance of these findings is unknown [21,22].
There are no clinical studies that have been conducted to evaluate the efficacy of CLR for the treatment of TB, and data on CLR use for TB treatment in humans is scarce. The presence of inducible resistance to CLR in M. tuberculosis has rendered this drug nearly obsolete in the treatment of TB. CLR is also hepatotoxic and has been found to induce severe, reversible hepatic dysfunction, associated with QT prolongation and ventricular arrhythmias, including ventricular tachycardia and Torsades de pointes [23]. Given its severely limited efficacy and its toxicity, CLR is no longer recommended by the WHO for treatment of tuberculosis [24].

4. Clofazimine

CFZ is a riminophenazine initially synthesized for the treatment of TB, but the development of which was hindered by inconsistent results in animal models [25]. It has been used for the treatment of leprosy since 1969. Its mode of action remains undefined, but studies have implicated membrane perturbation in Staphylococcus aureus [26], inhibition of phospholipase A2, and effects on potassium transportation [26]. CFZ was also found to cluster with known respiratory modulators on transcriptional analysis, indicating that it may inhibit bacterial cell growth by interfering with electron transporters [27]. In addition to its antibacterial activity, CFZ has other desirable pharmacological characteristics that work in favor of its use, including anti-inflammatory effects, prooxidative activity, and immunopharmacological properties [28].

4.1. Pharmacokinetic and pharmacodynamic data

CFZ has substantial antituberculosis activity in mouse models, achieving mean plasma concentrations of 0.55 µg/ml at steady state from a 20-mg/kg daily dose. At this dose, CFZ mono-therapy is bactericidal [29]. The most significant concern with CFZ is cross-resistance with BDQ, which has been documented from some laboratory studies. Although this cross-resistance may have important clinical implications when using the new anti-TB agents, its mediation through an efflux-pump mechanism does not appear to be correlated to prior CFZ use [30]. CFZ has a prolonged lag time for absorption, high variability in bioavailability, and a terminal half-life of 70 days [31]. With prolonged use, it also accumulates in the liver, lungs, fat, bone, skin, and macrophages. The remarkable tissue accumulation of CFZ – especially in the macrophages – with repeated dosing yields high enough concentrations to inhibit the growth of viable bacilli even after organ homogenates are transferred onto culture. The co-administration of CFZ with INH has been found to alter its PK properties, with reduced tissue accumulation and rising serum and urine concentrations [32]. Despite this tissue accumulation, CFZ is relatively well tolerated. CFZ achieves a mean steady-state serum concentration of about 0.24 µg/ml after 1 month of 50 mg/day, giving it a potentially low EBA quotient. In a 14-day bacterial activity evaluation study, CFZ mono-therapy as well as in combinations with pretonamid and BDQ, does not appear to have measurable activity in the first 14 days of treatment [33]. In animal studies, the use of CFZ did not prevent death in heavily infected animals, but its potent activity against hypoxic, nonreplicating M. tuberculosis suggests CFZ may have potential as a sterilizing drug [34]. However, the activity of CFZ may be attenuated in hypoxic pulmonary granulomas with caseous necrosis, suggesting varying sterilizing potential in different pathological loci [35].

4.2. Clinical studies

Until recently, CFZ has almost exclusively been restricted to the treatment of leprosy. However, CFZ is recommended as a second-line agent for use in combination with other drugs where it has clearly been shown to improve the effectiveness of DR-TB treatment regimens, by acting as a facilitator compound [36]. Interest in the use of CFZ was sparked by Van Deun and colleagues who demonstrated cure of MDR-TB in nearly 90% of patients receiving a 9-month regimen including high-dose gatifloxacin, high-dose INH, and CFZ in addition to standard second-line drugs [37]. Another group achieved treatment success rates of >60% when 98% of XDR-TB patients received CFZ as part of the treatment backbone [38]. In a prospective, multicenter, randomized control study in China, the use of CFZ for the treatment of MDR-TB was associated with accelerated sputum culture conversion, and radiological resolution of cavitary disease. Although there were some methodologic concerns with this study – most notably the continued administration of treatment regimens that were ineffective – the treatment success rate was 74% in the CFZ group, compared to 54% in the control group [39].

4.3. Dosing and safety

CFZ is used at a dose of 50–100 mg daily for the treatment of MDR-TB or XDR-TB [4]. It is no longer recommended for the treatment of AIDS-associated Mycobacterium avium complex (MAC) infection because of its association with excess mortality in this patient population. However, among leprosy patients taking the same dose (100 mg daily) that was reported with AIDS-associated MAC infection, CFZ has little serious toxicity [40]. Slowly reversible red-black skin discoloration occurs in virtually all patients treated with CFZ for a few months. Tang and colleagues reported rates of skin discoloration and itching of 94% and 47%, respectively [39].

5. FQs

The FQs have long been a mainstay in the treatment of MDR-TB, and, in fact, levofloxacin (LFX) and moxifloxacin (MFX) are considered to be among of the most effective categories of antituberculous agents. The FQs work by T′ binding a DNA-drug–enzyme complex and specifically inhibiting bacterial ATP-dependent topoisomerase II (DNA gyrase) enzyme and interfering with DNA transcription. FQs have acceptable bactericidal and sterilizing actions in combination with other antituberculous agents. Good tolerance, general availability and affordability make FQs a preferred choice among the ‘repurposed’ agents. Although the FQs have not been demonstrated to shorten the treatment duration drug-susceptible [41], the central role played by gatifloxacin in the 9-month MDR-TB regimen suggests an important role in shortening the treatment of MDR-TB [37].
5.1. Pharmacokinetic and pharmacodynamic data

Pharmacodynamic data shows that the effectiveness of FQs has increased with the later generation agents. A comparison of FQs using an in vitro model designed to predict sterilizing activities show that MFX has the greatest bactericidal activity against slow growing bacteria, and the best activity against persistors. The EBA activity was similar on days 2–7, but LFX (at 1000 mg/day) had the highest area under curve24 (AUC24/MIC ratio, and demonstrated the best EBA. Generally, later generation FQs have more favorable Cmax/MIC ratios. Evidence of LFX activity against ofloxacin (Ofx)-resistant strains suggests that there is not complete cross-resistance among the FQs. Of note, recent studies of the FQs in children suggest that higher doses of these drugs may be needed in children than are currently recommended due to a higher rate of metabolism in children [42].

5.2. Clinical studies

A complete review of the clinical studies of the FQs in the treatment of MDR-TB is beyond the scope of this paper, but there has been recent interest in identifying the ideal FQ for the treatment of MDR-TB and the ideal dosing. Although both ciprofloxacin and ofloxacin were used early in the course of management of MDR-TB, there is now a general agreement that the later generation FQs, especially high dose LFX and MFX, are the most useful drugs in this category [43]. In a recent study of 151 patients with FQ-susceptible TB, there were no differences in short- or long-term outcomes found when comparing MFX and LFX [44]. Although MFX has demonstrated in vitro activity against a subpopulation of MTb that persists in specific niches under drug pressure, achieving treatment shortening in mice, MFX does not diffuse well in caseum and may be the reason behind its failure to shorten therapy in recent clinical trials [45]. MFX appears to be especially effective in individuals with ofloxacin resistance, although its QTc prolonging potential limit its use in combination with CFZ, BDQ and DLM, in favor of LFX [46]. There has been widespread interest in the ‘9-month Bangladesh regimen’. An observational study on treatment outcomes among 515 patients treated with such a regimen, based on the GFX as a core drug, demonstrated an 82% relapse-free treatment success rate after the patients were followed up for 24 months [47].

5.3. Dosing and safety

In general, the FQs are safe and well-tolerated medications. The main adverse event seen with the FQs (especially moxifloxacin) is QTc prolongation, and careful monitoring of the QTc is indicated in individuals on moxifloxacin and other QTc prolonging medications (especially with respect to TB treatment, BDQ, CFZ, and DLM). The FQs have also been associated with central nervous system adverse events, but these adverse events are rare [48].

In terms of dosing, the ideal dose of LFX has not been established although doses of 750–1500 mg per day are commonly given in adults. Levofloxacin dosing for MDR-TB is currently being studied in the OPTI-Q trial (NCT01918397), which will look at four different doses of levofloxacin. Currently, an MFX dose of 400 mg per day for adults (and 7.5–10 mg/kg day for children) is considered a standard dose of MFX but multiple studies if 9–12 month regimens have used a dose of 800 mg per day [49], and this is the dose that is being assessed in the STREAM trials (NCT02409290).

6. LZD

LZD is an oxazolidinone antibiotic, with a mode of action not shared by other antibiotics. LZD inhibits bacterial protein synthesis by binding to the 23S rRNA. It also inhibits mammalian mitochondrial protein synthesis, giving rise to dose- and duration-dependent myelopoietic and neuropathic toxicity. It has a low EBA, but has been shown to be effective in treating MTb infections [50].

6.1. Pharmacokinetic and pharmacodynamic data

The activity of LZD against gram-positive bacteria is mostly linked to the AUC and MIC. Pharmacokinetic and susceptibility data indicates that LZD should prove useful in the treatment of TB. The drug has good lung penetration and has been used chiefly for the treatment of infections caused by highly resistant forms of S. aureus. A pharmacokinetic study comparing the serum LZD concentrations of patients with MDR (and one XDR) TB taking 600 or 1200 mg daily dose of LZD, found that 600-mg daily dose of LZD achieved an adequate AUC24/MIC ratio [51]. LZD is a reversible, nonselective inhibitor of monoamine oxidase and has the potential for interaction with adrenergic and serotonergic agents. Patients on selective serotonin reuptake inhibitors for the treatment of depression, have a risk of developing serotonin syndrome with co-administration of LZD.

6.2. Clinical studies

A meta-analysis and systemic review published in 2012 by Cox et al. compared the efficacy and safety of LZD at >600 versus ≤600 mg daily, in combination with an optimized background regimen (OBR). HIV infection was reported in 5% of total patients and in 28% of patients with XDR-TB. Overall treatment success was 68%, with no significant differences between patients receiving >600-mg daily dose (62%; 95% confidence interval [CI]: 37–87%) or ≤600-mg daily dose (67%; 95% CI: 54–80%, respectively). Although there was also no difference in successful outcomes between patients who received any dose of LZD for >7 months or ≤7 months, the authors speculated that the high proportion of sputum conversion (98%) compared to the lower treatment success rate (68%) may mean that stopping treatment early has negative consequences [52].

The average rate of adverse events was 62%, with most due to peripheral and optic neuropathy (36%) and bone marrow suppression, particularly anemia (28%). There was a nonsignificant trend toward fewer adverse events in patients receiving ≤600-mg daily dose (34% vs. 50%). However, the proportion of patients requiring LZD to be discontinued due to adverse events was significantly lower in the ≤600 versus the >600 mg daily dose (29% vs. 61%, overall pooled proportion was 36%). Although data is limited, among studies reporting the outcome of adverse events, hematological events largely resolved with reduction or
cessation of LZD[53–55]. The outcome of peripheral neuropathy was much more varied, with symptoms resolving/improving in some patients, while remaining unchanged in others [56,57]. In some patients LZD was continued despite peripheral neuropathy, while in others LZD was discontinued. Optic neuropathy led to immediate discontinuation of LZD in nine reported cases, and in all patients symptoms resolved, although in a few cases that took several weeks [58]. Individual studies and another meta-analysis published since the meta-analysis by Cox et al., also evaluating >600 and ≤600 mg daily dose of LZD, support this findings [59].

Despite the improvement in side effects with 600-mg daily dose of LZD, it was thought that 300-mg daily dose may still be effective, and have even fewer adverse effects. A study by Koh et al. looked that the efficacy and safety of 300-mg daily dose of LZD given to 51 MDR/XDR-TB patients. All patients were HIV negative and 51% had XDR-TB. Favorable outcomes occurred in 78% of patients, including 53% of the patients with XDR-TB. There was no difference in the rate of sputum culture conversion between MDR-TB and XDR-TB patients (76% vs. 81%, respectively). Twenty-seven percent of patients experienced one major adverse event, all of them neuropathies (with one optic neuropathy), none of whom restarted LZD. Twenty percent of patients had minor hematological events, none of which required stopping LZD. This supports some observations that the hematological toxicities of LZD may be more easily overcome with dose reduction [60]. Another study, that treated exclusively XDR-TB patients, found significantly fewer adverse events in patients who were treated for the majority of the time with 300 versus 600 mg daily dose of LZD[61]. Despite the dose of LZD, adverse effects (especially anemia, thrombocytopenia, lactic acidosis, and optic neuropathy) need to be carefully monitored as they can be severe and life threatening. In a prospective, randomized controlled trial, it was described that the risk of mitochondrial toxicity increases with increasing LZD trough concentrations, regardless of the dose patients were receiving. However, patients on 600-mg dose had a significantly higher risk of adverse events than those on 300-mg dose [61].

Importantly, in the study by Koh et al., even though 27% of patients had to have LZD discontinued due to adverse events, these patients tolerated, and were therefore able to be treated with, LZD for a median of 278 days (IQR: 174–412 days) [60]. A meta-analysis by Sotgiu et al. comparing >600 to ≤600 mg daily dose of LZD found that patients taking ≤600 mg tolerate LZD for longer periods [median 590 days (IQR 155–750 days) versus 252 days (IQR 120–540)] with no difference in successful outcomes [59].

Although the efficacy of 300-mg daily dose of LZD appears to be comparable to higher doses, concerns do remain about MTb developing resistance at these lower doses. In the study by Lee et al., serum trough levels were found lower than the MIC in nine patients receiving 300- mg daily dose of LZD, but never in the group receiving 600-mg daily dose. This, however, was not associated with time to culture conversion. Four subjects who had unfavorable outcomes had MTB isolates whose MICs increased by a factor of 8–32, however, these were evenly distributed across the two treatment groups [62]. Certainly, the possibility of resistance to LZD with lower treatment doses requires continued vigilance and caution.

### 6.3. Dosing and safety

A barrier to using LZD to treat MDR-TB is the development of serious side effects. The mitochondrial toxicity of LZD means that tissues that are most dependent on oxidative metabolism are at the greatest risk for toxic side effects [63]. LZD is associated with reversible myelosuppression (including anemia, leucopenia, pancytopenia, and thrombocytopenia), especially when administered for prolonged periods of time. Peripheral neuropathy and optic neuropathy have been reported in patients receiving LZD. However, the initial high dose of LZD used (1200 mg daily) to treat MDR-TB was based on the treatment of gram-positive bacterial infections [53]. There is evidence that lower doses of LZD are effective and better tolerated. Since MDR-TB requires prolonged treatment, and the adverse effects of 1200-mg daily dose of LZD preclude treatment for a long period of time. The possibility of reducing the dose of LZD, while maintaining its efficacy, has been investigated [53]. Most studies have examined three doses of LZD: 1200, 600, or 300 mg daily. All of the studies used LZD in combination with an OBR. Although earlier studies using 1200-mg daily dose of LZD showed treatment success (75–90% of patients either cured or converted sputum cultures to negative, including XDR-TB patients), there were significant adverse effects [64]. In one study, 70% of the patients had to stop LZD due to serious side effects, mostly due to bone marrow suppression or peripheral neuropathy [65].

Table 1 summarizes key information on the repurposed drugs for treating TB.

### 7. Discussion

The historical development of drug resistance in a step-wise manner, as new drugs were being developed and introduced as single agents for the treatment of TB served as the basis for multidrug therapy as recommended for decades. The principles of treating MDR-TB thus stipulate the use of at least four drugs to which the MTb strain is susceptible. Unfortunately, there are limited therapeutic options for designing these regimens and the pace of new drug development has been slow. In this setting, clinicians have had to rely on some drugs developed for other bacterial infections that do seem to have some activity against MTb.

While awaiting the development and approval of new agents, the criteria for selecting among the various ‘repurposed’ agents for multidrug therapy in patients with DR-TB is challenging, the efficacy, safety and cost must be considered. There are randomized clinical trials supporting the use of CZF and LZD, although the ideal dosing for LZD has not yet been established and toxicity remains a concern. The FQs have a clear role in the treatment of MDR-TB, with both moxifloxacin and levofloxacin showing efficacy in FQ-susceptible strains. The ideal dosing of these two drugs is being established, and in settings of ofloxacin resistance, it is unclear which – if any – FQ might still be effective. The carbapenems when given in combination with CLV appear to have some role to play in the management of MDR-TB, although currently the need for intravenous administration limits their use. CLR is no longer recommended for the treatment of MDR-TB. Although additional work needs to be done with these agents,
**Table 1. Summary information on repurposed drugs.**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Specific agents</th>
<th>Type of data supporting use in TB</th>
<th>Dosing</th>
<th>Adverse events</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>Amoxicillin–clavulanic</td>
<td>Case report</td>
<td>500–1000 mg twice daily</td>
<td>Rash</td>
<td>Likely only effective with carbapenems</td>
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<tr>
<td></td>
<td>acid</td>
<td>Observational studies</td>
<td>1000 mg twice daily</td>
<td>Seizures</td>
<td>Must be given intravenously or intramuscularly</td>
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<tr>
<td></td>
<td>Imipenem</td>
<td>Observational studies</td>
<td>2000 mg twice daily</td>
<td></td>
<td>Must be given with clavulanic acid</td>
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<tr>
<td></td>
<td>Meropenem</td>
<td>Observational studies</td>
<td>1000 mg once daily</td>
<td></td>
<td>Must be given intravenously</td>
</tr>
<tr>
<td></td>
<td>Ertapenem</td>
<td>Observational studies</td>
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**Macrolides [22]**

<table>
<thead>
<tr>
<th>Clarithromycin</th>
<th>Case report</th>
<th>100 mg daily</th>
<th>Skin pigmentation changes, QTc prolongation with cardiac arrhythmias, liver toxicity</th>
<th>Component of short course 9–12 months regimens</th>
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</table>

**Riminoephenezines [29,40]**

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<th>Cefazolin</th>
<th>Nonplacebo controlled randomized trial, observational studies</th>
<th>750–1500 mg daily</th>
<th>Well tolerated</th>
<th>Key component of multdrug-resistant TB (MDR-TB) treatment</th>
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**Fluoroquinolones (FQs) [43,44,48]**

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**Oxazolidonones [51,52,65]**

<table>
<thead>
<tr>
<th>Linezolid</th>
<th>Nonplacebo controlled randomized trial, observational studies</th>
<th>300–600 mg daily</th>
<th>Peripheral neuropathy, bone marrow suppression, optic neuritis</th>
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**Table 2. WHO grouping of repurposed agents in bold.**

<table>
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<th>Group B</th>
<th>Group C</th>
<th>Group D1</th>
<th>Group D2</th>
<th>Group D3</th>
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<tbody>
<tr>
<td>Beta-lactams</td>
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<td>Imipenem</td>
<td>Meropenem</td>
<td>Ertapenem</td>
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<td>Moxifloxacin</td>
<td>Gatifloxacin</td>
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<td>Cefazolin</td>
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The WHO recommends that persons with MDR-TB be treated with an initial regimen containing at least four drugs plus pyrazinamide. They recommend adding additional agents from groups A, B, and C if a regimen containing at least four drugs plus pyrazinamide, ethambutol, kanamycin, amikacin, capreomycin, ethionamide, cycloserine, and rifampin is not effective. They recommend using one agent from group A, one from group B, and one from group C if a regimen containing at least four drugs plus pyrazinamide is not effective. If only three agents from these groups are available, they recommend using two agents from group A, one from group B, and one from group C. These recommendations are intended to provide a framework for evaluating new agents for MDR-TB treatment, and to guide clinicians in selecting the most appropriate regimen for each patient. The WHO recognizes that repurposing agents for the treatment of MDR-TB is an important step in the development of new treatments for this disease.
<table>
<thead>
<tr>
<th>Study</th>
<th>Trial registry number</th>
<th>Study description</th>
<th>Repurposed agents used</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>STREAM: The Evaluation of a Standard Treatment Regimen of Anti-TB Drugs for Patients With MDR-TB (STREAM II)</td>
<td>NCT02409290</td>
<td>Comparison of a 6- and 9 month bedaquiline (BDQ)-containing regimen against the WHO and Bangladesh regimen</td>
<td>Clofazimine (CFZ), moxifloxacin (MFX)</td>
<td>Enrollment started 2016</td>
</tr>
<tr>
<td>Evaluating a New Treatment Regimen for Patients With MDR-TB – a Prospective Open-label Randomized Controlled Trial (NEXT trial)</td>
<td>NCT02454205</td>
<td>Open label randomized controlled trial of a 6–9 month injection-free regimen containing BDQ, LZD, LFX, ethionamide/high dose isoniazid, and pyrazinamide</td>
<td>Levofloxacin (LFX), linezolid (LZD)</td>
<td>Enrollment 2015</td>
</tr>
<tr>
<td>A Phase 2 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of Combinations of Bedaquiline, Moxifloxacin, PA-824 and Pyrazinamide During 8 Weeks of Treatment in Adult Subjects With Newly Diagnosed DS-TB or MDR-TB, Smear-Positive Pulmonary TB (GATB NC-005)</td>
<td>NCT02193776</td>
<td>Study of combinations of BDQ, MFX, PA-824, and pyrazinamide for 8 weeks for DS-TB and MDR-TB patients, with one arm for MDR-TB patients adding MFX to BDQ, PA-824 and pyrazinamide</td>
<td>MFX</td>
<td>Ongoing but not recruiting</td>
</tr>
<tr>
<td>A Phase 3 Open-Label Partially Randomized Trial to Evaluate the Efficacy, Safety and Tolerability of the Combination of Moxifloxacin Plus PA-824 Plus Pyrazinamide After 4 and 6 Months of Treatment in Adult Subjects With Smear-Positive Pulmonary DS-TB and After 6 Months of Treatment in Adult Subjects With Smear-Positive Pulmonary MDR-TB (STAND, GATB NC-006)</td>
<td>NCT02342886</td>
<td>Efficacy, safety and tolerability of a combination of MFX, PA-824, and pyrazinamide treatments after 6 months of treatment in subjects with MDR-TB compared to a combination of MFX, PA-824, and pyrazinamide treatments in DS-TB subjects; there will be a comparator arm for MDR-TB</td>
<td>MFX</td>
<td>On hold</td>
</tr>
<tr>
<td>Prospective, Randomized, Blinded Phase 2 Pharmacokinetic/Pharmacodynamic Study of the Efficacy and Tolerability of Levofloxacin in Combination With Optimized Background Regimen for the Treatment of MDR-TB (Opti-Q)</td>
<td>NCT01918397</td>
<td>Efficacy and safety study of increased doses of LFX in combination with optimized background therapy</td>
<td>LFX</td>
<td>Enrollment started 2015</td>
</tr>
<tr>
<td>Treatment Shortening of MDR-TB Using Existing and New Drugs (MDR-END)</td>
<td>NCT02193776</td>
<td>Comparing efficacy of a treatment regimen including delamanid, LZD, LFX, and pyrazinamide for 9–12 months, with a control arm of the standard treatment regimen including injectables for 20–24 months for the treatment of quinolone sensitive MDR-TB</td>
<td>LZD, LFX</td>
<td>Not yet enrolling</td>
</tr>
<tr>
<td>endTB</td>
<td>Not yet registered</td>
<td>Adaptive trial of multiple all oral 9–12 month treatment regimens for MDR-TB</td>
<td>MFX, LFX, LZD, CFZ</td>
<td>Enrollment expected in 2016</td>
</tr>
<tr>
<td>TB PRACTICAL</td>
<td>Not yet registered</td>
<td>Comparing efficacy of an all oral, 9–12 month regimen containing PA-824, PZA, LFX, LZD, and CFZ with standard of care</td>
<td>LFX, CFZ, LZD</td>
<td>Enrollment expected in 2016</td>
</tr>
</tbody>
</table>
a long way in elucidating the role of repurposed drugs in the programmatic introduction of new anti-TB agents, especially during this time of increasing antibiotic resistance [66].

The repurposed agents discussed here may have an especially important role in the treatment of MDR-TB in which there is additional resistance to other second-line drugs. Patients with these types of resistance – most notably those with resistance to the FQs and injectable agents – have outcomes that are markedly worse than those with MDR-TB [67,68]. Treatment with the novel agents BDQ and/or DLM have been recommended in such cases, but these drugs must be used in combination with other agents in order to achieve optimal outcomes. In most cases, the backbone of such treatment regimens includes at least LZD and CFZ, and in cases where there is high-level resistance, the carbapenems are often added as well.

For this first time in history, the global TB community is committed to TB elimination, and this is an exciting time in the field. At the same time, there are dire predictions about the rising rates of antimicrobial resistance worldwide, and unless radical action is taken, TB will be one of three drug-resistant pathogens that kills more people than cancer and costs the global economy more than 100 trillion USD [69]. Because of this, the WHO has identified controlling and preventing MDR-TB as one of eight priority actions in TB elimination [70]. Repurposed agents are key components of potent regimens that can be effective against most strains of TB, and their use in these regimens and in shorter regimens will not only improve treatment outcomes but also facilitate the work of health care and public health providers.

8. Expert commentary

There is growing evidence on the efficacy and safety of repurposed drugs for the treatment of DR-TB, supporting their program-wide inclusion in treatment regimens as recommended in revised WHO guidelines. However, additional work is needed to define optimum dosing as well as describe their role in regimen optimization.

9. Five-year view

The repurposed antituberculous agents will play a growing and significant role in the successful treatment of MDR-TB. These agents – especially CFZ and LZD – are being used and studied in potent and shortened regimens and will be game-changing agents in successful elimination of all forms of TB.

Key issues

- Despite the excitement brought by the development of bedaquiline (BDQ) and delamanid (DEL), and their potential in changing the landscape of drug-resistant TB (DR-TB) management, the anti-TB arsenal remains very limited in face of emerging antimicrobial resistance.
- There is an array of antimicrobial agents originally developed for the treatment of other infections but have conjured interest in the treatment of DR-TB, especially when resistance is beyond just against ‘rifampicin and isoniazid’.
- The authors present a non-systematic review of pharmacological studies, clinical cases, non-randomized clinical studies and randomized clinical studies, to describe the efficacy, safety and tolerability antimicrobials ‘re-purposed’ for the treatment of DR-TB.
- Although amoxicillin-CLV does not seem to offer much in improving outcomes alone, its low cost and favorable safety profile has popularized its use in background regimens for the treatment of extensively drug-resistant TB (XDR-TB).
- There is optimism around the potential therapeutic contribution of the carbapenems, meropenem, imipenem and ertapenem in the treatment of DR-TB, whose roles are being evaluated in two on-going phase two trials.
- Clofazimine (CFZ) has substantial anti-TB activity and unique pharmacokinetic properties which potentiates sterilizing activity. CFZ has been demonstrated to improve DR-TB treatment outcomes and is a core drug in the ‘9-month Bangladesh regimen’.
- The flouroquinolones are very effective anti-TB agents with a very favorable safety profile. Generally, later generation agents are more effective with gatifloxacin being a core backbone agent in the ‘9-month Bangladesh regimen’. Concerns have been raised on potential synergistic cardio-toxicity, especially when used in combination with CFZ, BDQ and DEL, all of which prolong the QT interval.
- There are mixed feelings around the use of Linezolid (LZD) in the treatment of MDR-TB and XDR-TB. Although it appears to be a very effective anti-TB agent, with reportedly high culture conversion rates, it has the worst safety profile of all the repurposed agents.
- Inducible resistance to clarithromycin (CLR) has resulted in its relegation from the list of recommended anti-TB agents. This review does not find any place for CLR in the future of DR-TB therapy.
- There is need to better understand the pharmacokinetic and pharmacodynamics properties of these repurposed agents in order to optimize their use, in combination with new agents, to improve treatment outcomes for DR-TB.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (+) or of considerable interest (++) to readers.

3. Zumla Al, Gillespie SH, Hoelscher M, et al. New antituberculosis drugs, regimens, and adjacent therapies: needs, advances, and

- An excellent and comprehensive review of key diagnostic and policy advances in the field of MDR-TB.


- A systematic review on the repurposed medications and their role in MDR-TB treatment from a research point of view.


- One of the most comprehensive reviews on the role of the carbapenems in the treatment of MDR-TB.


- The seminal paper describing the first experience with the shortened “9 month” regimen.


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• A comprehensive review of the fluoroquinolones in children, with discussion on the issues facing children with MDR-TB in general.
• The largest and most comprehensive meta-analysis on the use of linezolid in the treatment of MDR-TB.
• The randomized controlled trial of linezolid for the treatment of MDR-TB.
• An excellent pooled analysis of outcomes among patients with MDR-TB and second-line drug resistance.