Review Article

Management of drug-resistant tuberculosis in special sub-populations including those with HIV co-infection, pregnancy, diabetes, organ-specific dysfunction, and in the critically ill

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Abstract: Tuberculosis (TB) remains a major problem globally, and is the leading cause of death from an infectious agent. Drug-resistant TB threatens to marginalise the substantial gains that have recently been made in the fight against TB. Drug-resistant TB has significant associated morbidity and a high mortality, with only half of all multidrug-resistant TB patients achieving a successful treatment outcome. Patients with drug-resistant TB in resource-poor settings are now gaining access to newer and repurposed anti-TB drugs such as bedaquiline, delamanid and linezolid. However, with ever increasing rates of co-morbidity, there is little guidance on how to manage complex patients with drug-resistant TB. We address that knowledge gap, and outline principles underpinning the management of drug-resistant TB in special situations including HIV co-infection, pregnancy, renal disease, liver disease, diabetes, and in the critically ill.

Keywords: Drug-resistant tuberculosis (drug-resistant TB); HIV co-infection; bedaquiline; linezolid; delamanid

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Introduction

Despite a slight decline in the global tuberculosis (TB) incidence over the last 13 years, there remains a substantial burden of disease with an estimated 10.4 million incident cases in 2015 (1). According to World Health Organization (WHO) estimates, ~1.8 million people died from TB in the same year making TB the world's leading infectious cause of death (2).

TB diagnosis and management is complicated by drug resistance, which continues to threaten efforts at TB control because of its increasing burden in many countries (3), contributing to approximately 20% of global TB mortality (1), prohibitively high treatment costs (4,5), and higher incidence rates in health care workers (6). Globally, there were an estimated 580,000 rifampicin resistant TB cases in 2015 (1). Approximately 10% of multi-drug resistant tuberculosis (MDR-TB) patients have extensively drug-resistant TB (XDR-TB), defined by resistance to rifampicin, isoniazid, fluoroquinolones and an injectable agent (7). While drug-sensitive new TB cases have a treatment success rate of >85%, drug-resistant TB patients fare poorly, with only ~50% of patients achieving

Table 1 Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

WHO class	Agent (abbreviation)		Key toxicity	Comments
A. fluoroquinolones[2]	Levofloxacin (Lfx); moxifloxacin (Mfx)		All: QTc prolongation (Mfx>Lfx), arthralgia; hepatotoxicity	Lfx: is the fluoroquinolone (FQ) of choice in bedaquiline (Bdq)-containing regimens
B. second-line injectable agents	Amikacin (Am); capreomycin (Cm); kanamycin (Km); (streptomycin)[3]		All: nephrotoxicity, ototoxicity, electrolyte derangement (K, Mg and Ca)	All: use with caution in patients with diabetes mellitus, renal disease or hearing impairment
C. other core second-line agents[2]	Ethionamide/prothionamide (Eto/Pto); cycloserine/terizidone (Cs/Trd); linezolid (Lzd); clofazimine (Cfz)		Eto/Pto: diarrhoea, nausea, vomiting and hypothyroidism; Trd/Cs: CNS effects including psychosis, confusion and depression; Lzd: peripheral neuropathy, myelosuppression and ocular toxicity; Cfz: QTc prolongation, skin and conjunctival pigmentation	Eto/Pto: with symptoms of nausea and vomiting also consider drug induced hepatitis or pancreatitis; monitor TSH. Lzd: pyridoxine may ameliorate hematological toxicity; if myelosuppression occurs, stop Lzd and transfuse as appropriate; Lzd may be re-introduced at a reduced dose in selected cases (9,10)
D. add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide (Z); ethambutol (E); high-dose isoniazid (H^h)	Z: hepatotoxicity, gout; E: ocular toxicity; H^h: hepatotoxicity, peripheral neuropathy	H^h: use with pyridoxine to prevent peripheral neuropathy; beware of drug-drug interaction, e.g., with antiepileptic agents
	D2	Bdq; delamanid (Dlm)	Bdq: QTc prolongation, arthralgia, hepatitis and headache; Dlm: Hypokalemia, nausea, vomiting, dizziness and QTc prolongation	Bdq/Dlm: close monitoring of QTc is recommended especially when using these agents in combination with other QTc prolonging drugs; Bdq: efavirenz (EFV) should be changed to nevirapine (NVP) or a protease inhibitor [may increase Bdq levels ≈2-fold with unclear significance (11)], alternatively, an integrase strand transfer inhibitor can be used. Dlm: no significant anticipated drug-drug interactions with ARVs (12)
	D3	p-aminosalicylic acid (PAS); imipenem-cilastatin[4] (Ipm); meropenem[4] (Mpm); amoxicillin-clavulanate[4] (Amx-Clv); (thioacetazone)[5] (T)	PAS: diarrhoea, hypothyroidism, nausea and vomiting; Ipm: seizures	PAS: with symptoms of nausea and vomiting also consider drug induced hepatitis or pancreatitis; monitor TSH

[1]This regrouping is intended to guide the design of conventional regimens; [2]Medicines in Groups A and C are shown by decreasing order of usual preference for use; [3]Streptomycin may substitute other injectable agents under specific conditions. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB); [4]Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin; [5]HIV-status must be tested and confirmed to be negative before thioacetazone is started. ARVs, antiretroviral; TSH, thyroid stimulating hormone; CNS, central nervous system; QTc, corrected QT interval.

successful treatment (7). Pill burden, drug toxicity, and the duration of treatment contribute to high rates of loss to follow-up and a high mortality in this population (8).

Current WHO guidelines group treatment for rifampicin resistant anti-TB therapies into four classes (*Table 1*) (13) and provide principles for designing appropriate MDR-TB treatment regimens (14). These regimens should include a minimum of four effective drugs (including an injectable agent) plus PZA which should be administered for an "intensive phase" of up to 8 months, followed by a "continuation phase" for minimum total treatment duration of 20 months (14,15). More recently the WHO has recommended that, when certain pre-requisites can be fulfilled, a shorter MDR-TB regimen of 9–12 months can be used in selected patients (13), and repurposed drugs such as linezolid may be used where appropriate (13).

The results of prospective outcome studies, including randomized controlled trials are underway (16). The WHO guidelines also recommend that when an effective drug regimen cannot be constituted because of drug toxicity or resistance, newer agents such as bedaquiline and delamanid may be used (13).

However, treatment of drug-resistant TB (DR-TB) remains challenging, and is more complex in patients with co-morbid disease where there is a limited evidence base to guide clinical practice. This review focuses on the challenges of treating drug-resistant TB in special populations, including in HIV-TB co-infected persons, pregnant women, patients with liver and renal dysfunction, diabetes, and those who are critically ill.

Management of drug-resistant TB in patients co-infected with HIV

Management of drug-resistant TB in the HIV-infected patient presents significant challenges due to shared toxicity between anti-HIV and TB drugs (*Table 2*). Greater potential for drug toxicity, HIV-related end-organ disease, pharmacokinetic drug-drug interactions, and immune reconstitution inflammatory syndrome (IRIS), especially involving the central nervous system, all contribute to the high mortality seen in MDR-TB-HIV co-infected patients (29,30).

New drugs used in the treatment of MDR-TB such as bedaquiline and linezolid have changed the face of MDR treatment; however, significant adverse event profiles require that these agents be used with caution, particularly in the setting of HIV where the potential for drug interactions is significant (see *Table 2*). The WHO has recently endorsed the use of dolutegravir as part of a first-line ART regimen (31). This agent is not only more effective and better tolerated, but is also expected to be safe for co-administration with newer agents such as bedaquiline and delamanid (32,33).

Timing of initiating antiretroviral therapy (ART) in drug-resistant TB-HIV co-infection

Antiretroviral therapy improves survival in patients with MDR-TB (29,34,35). The WHO recommends that newly diagnosed MDR-TB/HIV co-infected patients should initiate ART within the first 8 weeks of starting effective MDR-TB treatment irrespective of CD4+ count (36). As with drug-sensitive TB, patients with CD4+ counts <50 cells/mm^3 should initiate ARVs within 2 weeks of starting MDR-TB treatment (37-39), unless if they are suspected to have TB meningitis (in which case initiation of ARVs should be deferred due to the risk of developing potentially fatal IRIS) (40,41).

Bedaquiline (Bdq) use in the drug-resistant TB-HIV co-infected patient

Bedaquiline (trade name Sirturo) is a diarylquinoline and the first new anti-TB drug on the market in over 40 years. This orally administrated medication acts via a novel mechanism that selectively inhibits mycobacterial adenosine triphosphate synthase (42,43). Bedaquiline is known to cause prolongation of the QTc interval, and while a phase IIB trial demonstrated higher rates of culture conversion in the bedaquiline arm, there were also more deaths in those receiving the study drug (44). Although this was not felt to be drug related, bedaquiline use warrants regular ECG monitoring.

Bedaquiline is well tolerated (45) and has demonstrated both safety and efficacy in HIV co-infected patients (46). The WHO-recommended first-line antiretroviral therapy (ART) regimens include nevirapine and efavirenz, both of which induce CYP3A4, and the second-line regimens include ritonavir-boosted protease inhibitors, which inhibit CYP3A4. Drug-drug interaction studies of HIV-infected patients on steady state ART, where a single dose of Bdq was given, found that nevirapine, lopinavir-ritonavir (LPV/r), and efavirenz were associated with no effect, an increase (significance unclear), and a decrease in the area under the curve, respectively (47). However, single doses of bedaquiline may under-estimate the magnitude of interactions experienced when bedaquiline reaches steady-state. Population pharmacokinetic studies modelling the data from single dose Bdq and antiretroviral drug-drug interaction studies estimated the following changes in Bdq exposure at steady-state: LPV/r—3-fold increase; efavirenz—decreased by 52%; nevirapine—no significant effect (11,48). A study of patients on ART being treated with Bdq for drug-resistant TB confirmed the findings of the population pharmacokinetic studies on interactions with nevirapine and LPV/r (49). Bdq should not be used with efavirenz, and caution needs to be exercised when using with LPV/r, with close monitoring for Bdq toxicity. Other potential ART options for co-administration with Bdq are the integrase strand transfer inhibitors raltegravir or dolutegravir together with dual nucleoside reverse

Table 2 Shared toxicity between anti-TB therapy and antiretroviral agents

Description of adverse event	Responsible anti-retroviral agent/s	Responsible anti-tuberculous agent/s	Consideration
Renal toxicity	TDF	Aminoglycosides*, Cm*	TDF causes renal failure with hypophosphatemia and proteinuria. Avoid in HIV-infected persons with renal impairment; avoid TDF in patients receiving aminoglycosides and Cm; serum creatinine should be checked before switching patients onto TDF after completion of aminoglycoside; caution is advised when administering TDF or aminoglycosides in patients with underlying co-morbidities such as diabetes mellitus or in patients who are receiving concomitant nephrotoxic agents such as NSAIDS and amphotericin B; if TDF is necessary monitoring of serum creatinine is required
Electrolyte derangement	TDF	Aminoglycosides*, Cm*	Minimise exacerbating factors such vomiting, diarrhoea, dehydration, diuretics, etc.
Hepatitis/ hepatotoxicity	NVP*, EFV*, PI* (especially RTV), NRTI*	Z*, Bdq* (17), PAS, FQ, Eto	When severe (ALT ≥3× ULN with symptoms or ALT >5× ULN) stop both ARVs and anti-TB agents, consider a non-hepatotoxic TB regimen; exclude other contributing or causative factors such as alcohol abuse, viral aetiologies, and other drug toxicity; the risk of NVP hepatotoxicity is highest in the first 3 months of starting therapy with higher risk in patients with CD4 >250 (18); the risk of NVP hepatotoxicity is lower if VL is suppressed (19)
Myelosuppression	AZT*	Lzd* (20), H	Stop Lzd if myelosuppression occurs. Blood transfusion is indicated if haemoglobin falls below 8 g/dL (9,10); avoid co-administration of AZT and Lzd; adverse events should be managed with a combination of temporary or permanent suspension of linezolid, dose reduction, and/ or symptom management (21); dose reduction to 300 mg daily may be associated with fewer neuropathic effects but may be associated with sub therapeutic levels (22); consider stopping co-trimoxazole
Peripheral neuropathy	ddI*, d4T*	Lzd* (23), Cs, H*, Eto, E	Avoid use of D4T or ddI in combination with Cs or Lzd; use pyridoxine as prophylaxis in patients receiving Cs, H and Lzd
QT prolongation	PI, EFV	Bdq* (24), Mfx* (25), Cfz*, Lfx (26)	Close monitoring of QTc is recommended when using these agents in combination; Lfx is associated with less QT prolongation compared to Mfx
Central nervous system toxicity	EFV*	Cs*, H, Eto/Pto, FQ, Lzd	EFV toxicity generally occurs in first 2–3 weeks of treatment; concurrent use of EFV with CS needs close monitoring; Lzd can rarely (<0.5%) cause serotonin syndrome especially when combined with serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
Headache	AZT*, EFV*	Cs*, Bdq* (17)	Headaches may be self-limited in case of AZT, EFV and Cs; advise analgesia and hydration
Nausea and vomiting	RTV*, d4T*, NVP	Eto*, PAS*, H, Bdq (17), E, Z	Many drugs will cause some degree of nausea; if persistent consider drug induced pancreatitis or hepatitis
Lactic acidosis	d4T*, ddI*, AZT, 3TC	Lzd (27)	High index of suspicion needed to detect hyperlactatemia to prevent overt symptoms of lactic acidosis
Pancreatitis	d4T, ddI	Lzd (20)	Avoid co-administration where possible; if pancreatitis occurs discontinue the relevant ARVs
Diarrhoea	PI*, ddI*	PAS*, FQ*, Eto*	For mild diarrhoea, anti-motility drugs can be used; may be self-limited. Exclude opportunistic infections
Optic neuritis	ddI	E*, Lzd* (28), Eto	Stop all suspected agents causing optic neuritis
Hypothyroidism	d4T	Eto*, PAS*	Monitor TSH for patients receiving these agents
Joint pain	NA	Z*, Bdq*, FQ*	Mild symptoms can be managed by simple analgesia

*Drugs most likely to contribute towards toxicity. Cm, capreomycin; H, isoniazid, PAS, para-amino salicylic acid; Z, pyrazinamide; Bdq, bedaquiline; Lzd, linezolid; Eto, ethionamide; Pto, prothionamide; FQ, fluoroquinolones; Mfx, moxifloxacin, Lfx, levofloxacin E, ethambutol; Cs, Cycloserine; TDF, tenofovir; EFV, efavirenz; ddI, didanosine; d4T, stavudine; PI, protease inhibitor; 3TC, lamivudine; NVP, nevirapine; RTV, ritonavir; AZT, zidovudine; QTc, corrected QT interval; TSH, thyroid stimulating hormone; CNS, central nervous system.

transcriptase inhibitors (NRTIs); however, these agents are not widely available in many resource-limited settings. In settings where integrase strand transfer inhibitors are unavailable, and where an effective ART regimen cannot otherwise be constructed, the use of triple NRTIs may be an option for co-administration with Bdq. However, this regimen should only be used after virologic suppression has been achieved (50).

Use of linezolid and other oxazolidinones in the drug-resistant TB-HIV co-infected patient

Linezolid, an oxazolidinone, binds to the 70S initiation complex of bacterial ribosomes and disrupts protein synthesis. It is orally administered and has demonstrated effective anti-mycobacterial activity *in vitro* and in animal studies. Case series and several systematic reviews have shown that MDR and XDR-TB regimens incorporating linezolid have improved clinical outcomes (23,51,52), and high culture conversion rates have been reported in compassionate use programs in South Africa where 56% of the cohort was HIV co-infected (46).

There is potential for significant worsening of HIV-related neuropathy and bone marrow dysfunction in the presence of linezolid, particularly anaemia when co-administered with zidovudine, and peripheral neuropathy when combined with stavudine (29). Provided these red flags are considered, linezolid can be used for MDR-TB treatment in the HIV co-infected patient with careful monitoring. While 600 mg daily is the standard dose of linezolid in drug-resistant TB regimens, 300 mg daily may reduce potential for adverse events (22). However, acquired drug resistance is more likely with a lower starting dose (52). Further studies are needed to determine the optimal dose to maintain culture conversion, minimize adverse events, and prevent amplification of resistance.

Several retrospective case series of HIV-infected patients with MDR and XDR-TB receiving linezolid as part of their regimen have demonstrated promising culture conversion rates, but high rates of associated drug-related adverse events, mainly due to peripheral neuropathy, anemia, and optic neuritis (53). However, improved treatment outcomes with linezolid may justify the use of this drug in patients co-infected with HIV. Therapeutic drug monitoring using dried blood spot analysis (54), measuring plasma concentrations (55) and measuring the cytochrome c oxidase/citrate synthase activity ratio from peripheral blood (56), if available, could play a helpful role in maximizing efficacy of linezolid, while limiting toxicity, but prospective studies are required. HIV-infected patients receiving linezolid should receive pyridoxine prophylaxis, particularly when linezolid is co-administered with other potentially neurotoxic drugs such as high-dose isoniazid (especially in MDR-TB patients with *inhA* mutations where high dose isoniazid is being used). Peripheral neuropathy often occurs after 3 months of treatment (57). These patients must be monitored closely for subjective neuropathy symptoms as well as by neurological assessment for peripheral neuropathy including measurement of vibration sense at each follow up visit. In the event of bone marrow suppression, a dose reduction can be attempted in addition to correcting other contributory factors such as concomitant nutritional deficiency and cessation of other myelotoxic drugs (such as sulfamethoxazole and trimethoprim); if blood counts do not improve, linezolid should be discontinued.

Patients with renal dysfunction who are receiving linezolid with potentially myelosuppressive ARVs are especially at risk for thrombocytopenia and dose adjustment should be considered in patients with creatinine clearance of <30 mL/min (58,59). The major mechanism of linezolid-associate neuropathy is mitochondrial toxicity, since linezolid interferes with mitochondrial protein synthesis (60,61). If peripheral neuropathy develops while on linezolid, dose reduction may be considered depending in the clinical context including rapidity of progression, severity, regimens. Thus, if neuropathy is minimal and stabilizes upon dose reduction, linezolid may be continued in select cases (62). Any evidence of optic neuritis warrants immediate discontinuation of linezolid, as this is usually irreversible (63). Close follow up with serial monthly visual acuity measurements and colour vision assessment is advised when using linezolid together with ethambutol (64).

Linezolid, whilst effective in the treatment of DR-TB, has substantial myelotoxicity and neurotoxicity resulting in almost a third of requiring dose reduction or discontinuation of linezolid altogether (65). By contrast, tedizolid, a newer oxazolidinone currently registered for skin and soft tissue infections in the USA and European Union (66), is less myelotoxic than linezolid in short-term studies (67). Animal studies have demonstrated no evidence of neuropathy (68,69). Population based pharmacokinetic models have shown that over the course of a dosing interval (using standard therapeutic doses), free plasma concentrations of tedizolid fell below the toxic concentrations for causing mitochondrial protein synthesis suppression in 84% (70)

vs. 38% of linezolid-treated patients (56,71). Tedizolid, in the hollow fibre model, has shown anti-tuberculous efficacy equivalent to that of rifampicin and moxifloxacin. Clinical trials in patients with DR-Tb are now warranted.

Sutezolid is another oxazolidinone that is efficacious against *M.tb* in rat models where it shortened treatment by 1 month compared to linezolid, which failed to show a treatment shortening effect (72). The maximum bactericidal activity of sutezolid is estimated to be twice that of linezolid, with a favourable safety profile in whole blood culture models (73). Furthermore, sutezolid has bactericidal activity against both intra and extracellular mycobacteria (74). In a phase 1 study sutezolid has been shown to be potentially safer than linezolid when given to healthy volunteers at a dose of 600 mg twice daily for 28 days with no reports of hematologic, neurologic or biochemical toxicity (73). However, more recently, 6-month rat toxicity studies have raised concerns about the longer term safety profile of sutezolid. Both tedizolid and sutezolid are compatible with antiretrovirals and other TB drugs. Collectively, the available evidence suggests that these agents may be more efficacious and have a lower adverse event rate, but this requires confirmation in phase 2 and 3 studies pending safety clarifications about sutezolid.

Delamanid use in the drug-resistant TB-HIV co-infected patient

Delamanid is an orally administered agent that acts by inhibiting mycolic acid synthesis in the mycobacterial cell wall (75). It has demonstrated promising results in drug-resistant TB, showing increased rates of sputum culture conversion and improved clinical outcomes (76-78). Phase III clinical trials have been completed but, disappointingly, the delaminid failed to show improved outcomes when added to an optimized background regimen. Clinical drug-drug interaction studies have been performed on healthy volunteers and co-administration with tenofovir and efavirenz did not affect delamanid exposure, but lopinavir/ritonavir co-administration significantly increased delamanid exposure (79). These results are of uncertain significance.

Delamanid is known to cause prolongation of the QTc interval via the DM-6705 metabolite, and therefore regular ECG monitoring is required. Formation of the DM-6705 metabolite is regulated by serum albumin, and delamanid is consequently contraindicated in hypoalbuminemia (albumin <28 g/L), which is a frequent finding in HIV-infected individuals, particularly in advanced disease, and may be a predictor for progression to AIDS and death (80,81). Low serum albumin may also be more commonly found in patients with TB-HIV co-infection (82). Unfortunately, this may limit delamanid's use in the HIV co-infected population despite having a safe drug-drug interaction profile with first-line antiretroviral medications (83). Additionally, delamanid is administered as twice daily dosing, 30-minutes after a standard meal (84). This twice-daily dosing may impact adherence (85) and require additional resources to ensure drug administration under observation. Delamanid is potentially efficacious and well tolerated in children aged 6 years and older (86), however controlled studies are lacking in the pediatric population.

Management of drug-resistant TB in pregnancy

The burden of TB in pregnant women is substantial (87), with prevalence estimates amongst pregnant and post-partum women ranging from 0.06% to 7.2%, and as high as 11% in HIV-infected women in a high-burden setting (87-89). Women may be more vulnerable to TB disease during pregnancy and in the post-partum period. T-helper 1 (Th-1)/Th-2 ratio is reduced during pregnancy, thus potentially increasing susceptibility to new infection and reactivation of TB. In the early post-partum period, Th-1 suppression may be reversed (88). This may be associated with exacerbation of symptoms akin to the immune reconstitution syndrome seen in HIV patients after ART therapy is commenced (90). TB during pregnancy is also associated with poor outcomes, including an increased risk of preterm birth, low birth weight, intrauterine growth restriction, and perinatal death (91,92).

A decision on the timing of treatment for drug-resistant TB and the construction of a drug-resistant TB regimen during pregnancy should take into consideration the gestational age of the foetus, and should weigh the risks of the teratogenic effects of anti-TB treatment carefully against potential benefit to the mother (14). Ideally, all pregnant women should be started on treatment as soon as possible. However, as most teratogenicity occurs during the first trimester, in selected cases where the clinical condition of the mother is stable and where there is minimal radiological disease, treatment may be deferred until the second trimester. This strategy must be accompanied by close clinical follow-up as drug-resistant TB in pregnancy can have an accelerated course.

Guidance for treatment of MDR-TB in pregnancy

Table 3 FDA based classification of drugs used for MDR-TB treatment during pregnancy

MDR-TB drug	FDA classification
Pyrazinamide	C
Fluoroquinolones: levofloxacin; moxifloxacin; ofloxacin	C
Aminoglycosides: kanamycin; amikacin; streptomycin	D
Capreomycin	C
Ethionamide/prothionamide	C
Cycloserine/terizidone	C
Para-aminosalicylic acid	C
High-dose isoniazid	C
Clofazimine	C
Linezolid	C
Amoxicillin/clavulanate	B
Clarithromycin	C
Imipenem/cilastatin	C
Meropenem	B
Bedaquiline	B
Delamanid	Not FDA approved

FDA pregnancy categories: A—human studies demonstrate no risk; B—animal studies demonstrate no risk, no human studies; C—animal studies demonstrate risk, no human studies; D—human studies demonstrate risk; X—contraindicated in pregnancy.

comes only from case reports and case series. While some women choose to terminate pregnancy due to the possible teratogenicity of anti-TB treatment, case series suggest that favourable outcomes are achievable (93,94). In the largest series of MDR-TB treatment in pregnancy (n=38), 60% of patients were cured, 21% of patients had pregnancy-associated complications including vaginal bleeding and spontaneous abortion, and no teratogenic effects were seen in the infants (94).

Ideally, the regimen for MDR-TB in pregnancy will consist of at least four second-line anti-TB drugs that are likely to be effective against the infecting strain, plus pyrazinamide. Most of the second line anti-TB agents are pregnancy class C per the US Food and Drug Administration (FDA; *Table 3*). Aminoglycosides, specifically amikacin and kanamycin, are FDA class D, and should be excluded from TB treatment regimens during pregnancy, especially within the first 20 weeks, because of the risk of ototoxicity and foetal malformation. In selected cases with severe disease with no available alternatives, these agents can be used with close monitoring but should be deferred until after 20 weeks (95). Capreomycin, a polypeptide with similar activity to aminoglycosides, is an FDA class C drug with a reduced toxicity profile. In severe cases of multidrug-resistant TB where aminoglycoside treatment must be given at the outset, capreomycin is the injectable agent of choice (95), and can be given thrice weekly to decrease drug exposure to the foetus. Ethionamide is generally avoided as it can increase the risk of nausea and vomiting associated with pregnancy. These drugs can be reintroduced after delivery to strengthen the regimen in the immediate postpartum period. The WHO has not recommend the use of bedaquiline and delamanid in pregnancy due to the lack safety and efficacy data (96). Delamanid, in animal studies, has been shown to be potentially teratogenic and should be avoided until more data is available (97) whereas bedaquiline has been demonstrated to be safe in animal reproduction studies (category B), and may be considered for individual women who have contra-indications to aminoglycoside use or in whom an effective regimen cannot otherwise be constructed (24,98). With regards to breast feeding, smear positive mothers should discontinue breast feeding if possible. Both bedaquiline and delamanid are excreted in breast milk in animal studies and therefore, the decision to discontinue the drug or nursing, as an alternative, should depend on the clinical context.

Lastly, in view of the toxic effects of MDR-TB drugs to the expectant mother and the foetus, it is critically important to offer individualised, long term and effective contraception (e.g., Depo-Provera or an intra-uterine contraceptive device) to all women of child bearing age who are receiving treatment for DR-TB.

Management of drug-resistant TB in patients with renal impairment

Renal failure may be due to a concomitant medical problem or may be a result of previous treatment for DR-TB with an aminoglycoside. Dosing of drugs should be adjusted per patient's creatinine clearance (an estimate of the glomerular filtration rate) (*Table 4*). For several drugs, the WHO has suggested that the dose and/or the interval between dosing should be adjusted for patients with creatinine clearance

less than <30 mL/min or those receiving haemodialysis (14). While some clinicians have had to previously persist with thrice-weekly dosage of aminoglycosides because of the lack of alternative options, the availability of newer drugs such as bedaquiline should render this practice obsolete. In clinical practice, it is now not uncommon to use Bdq when there is aminoglycoside-associated toxicity.

Tenofovir, an antiretroviral agent, can cause renal dysfunction and severe electrolyte wasting with life-threatening hypokalaemia when administered with aminoglycosides or capreomycin as both concentrate in the proximal convoluted tubules; co-administration should be avoided (110-112) (see *Table 1*). In rare cases where this combination cannot be avoided, special emphasis must be placed on correction of underlying factors that may potentiate toxicity such as diarrhoea, dehydration, diuretic use and concomitant administration of other nephrotoxic medications (113). Co-administration of these agents also warrants close monitoring of creatinine, serum potassium and aminoglycoside drug levels if available; in the event of electrolyte wasting or worsening renal dysfunction, both drugs should be stopped until the patient is electrolyte replete. In patients of African heritage, the risks of iatrogenic nephrotoxicity may be greater due to the background prevalence of HIVAN (HIV associated nephropathy) (113,114). In such patients, the use of tenofovir and/or aminoglycoside should be avoided, especially, in patients with advanced HIV (115,116) and nephrotic range proteinuria (115,117).

Management of drug-resistant TB in patients with liver dysfunction

Although technically a first-line drug, pyrazinamide is the most hepatotoxic agent employed in the DR-TB regimen. Patients with significant chronic liver disease should not receive pyrazinamide. Isoniazid has been used high doses (16–18 mg/kg) in cases of MDR-TB with low-level INH resistance (conferred by the *inhA* mutation), and although no evidence of a greater likelihood of acute hepatotoxicity was found in patients with normal liver function (118), its use in patients with concomitant stable chronic liver disease at high doses has not been studied. We recommend that it should be excluded from MDR-TB regimens in patients with chronic liver disease except in selected cases. Of the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, while the fluoroquinolones are rarely implicated in hepatitis.

All second-line drugs can be used in chronic stable liver disease, but close monitoring of liver enzymes is mandatory, and significant deterioration in liver function should trigger immediate withdrawal of the offending drug. The source of other causes for liver dysfunction, including viral hepatitis and alcohol consumption, should be addressed and treated to prevent further complications during treatment. In cases of acute hepatitis, anti-TB treatment should be deferred until hepatitis has stabilized. When formulating a regimen in patients with chronic liver dysfunction, a combination of 4 non-hepatotoxic drugs should ideally be used with the inclusion of a fluoroquinolones to ensure efficacy of the regimen (14).

In patients receiving TB treatment, chronic hepatitis B infection is considered a risk factor for hepatotoxicity (119). Patients who are sero-positive for hepatitis B e antigen are more prone to hepatotoxicity compared to patients who are hepatitis e antigen negative (120). If treatment for hepatitis B infection is indicated, ART should be initiated with the combination of at least two agents active against hepatitis B, e.g., tenofovir and emtricitabine or lamivudine (121,122). Entecavir can be considered in place of tenofovir in patients with renal dysfunction (dose adjustment may be required) (122). In HIV/HCV co-infection drug interactions and overlapping toxicities with MDR-TB agents must be considered (121).

Management of drug-resistant TB in patients with diabetes mellitus

The prevalence of diabetes mellitus has increased substantially worldwide, with an estimated 415 million adults suffering from diabetes in 2015. The rates of type II diabetes also appear to be increasing in developing regions such as sub-Saharan Africa and India (123). Diabetes mellitus confers a 3-fold increased risk of developing active TB (124,125), and is associated with worse TB treatment outcomes, including delayed sputum culture conversion, and higher rates of treatment failure, relapse and recurrence (126-128). Furthermore, TB itself can induce glucose intolerance resulting in worsening glycaemic control (129).

Preliminary evidence suggests that that there may be an association between diabetes and MDR-TB (130,131). More recently, diabetes has also been shown to increase the risk of primary infection with MDR-TB and is associated with delayed sputum conversion (132,133). Evidence is emerging to suggest that diabetes mellitus may also play a role in the development of drug resistant TB (134,135).

Table 4 Dosing of MDR-TB agents in patients with renal impairment

Mycobacterial agent and usual dose	Degree of renal impairment (Cr clearance)	Renal replacement therapy	Special prescriber points
Aminoglycosides (99-101) (Cm, Km, Am) 15–20 mg/kg	Dosing should be adjusted to achieve undetectable plasma trough levels at all levels of renal impairment	Dosing should be adjusted to achieve undetectable plasma trough levels	Must be AVOIDED if possible; main route of clearance is renal; 3x/week *vs.* daily has no difference in oto/nephrotoxicity; dose adjustment and therapeutic drug monitoring required due to toxicity risk and changes in drug clearance over time; monitoring should include regular U&Es to assess renal function along with clinical assessment, audiometry
Pyrazinamide (102-104) 25–30 mg/kg/day 1.5 g for 50 kg, 2 g for >50 kg	≥30 mL/min: no dose adjustment required; <30 mL/min: 25–30 mg/kg three times per week	25–30 mg/kg three times/week after dialysis	Can be used safely in renal disease; main route of clearance is hepatic with active metabolites undergoing some renal clearance; monitor LFTs for hepatotoxicity; monitor for gout due to reduced uric acid clearance in renal failure
Ethambutol (103-105), 15–25 mg/kg/day (103)	≥30 mL/min: No dose adjustment required; <30mL/min: 15–25 mg/kg three times per week	15–25 mg/kg three times a week; dialysis does not eliminate drug significantly	AVOID use if possible; main route of clearance is renal; ocular toxicity is a significant concern in patients with renal disease
Ethionamide (106), 15–20 mg/kg/day in divided doses	No dose adjustment required	No dose adjustment required	Main route of clearance is hepatic; monitor for neuropathy and hepatotoxicity
Cycloserine (106), 10–15 mg/kg/day in divided doses	≥30 mL/min: no dose adjustment required; <30 mL/min: 250 mg daily or 500 mg alternate days	250 mg daily or 500 mg alternate days given after hemodialysis	AVOID if possible in renal disease. As the main route of clearance is renal; Increased risk of significant neurotoxicity; plasma level monitoring should be used if available
Para-aminosalicylic acid (PAS) (106) 8–12 g/day	No dose adjustment required	Hemodialysis eliminates it's the active metabolite. Dosing should therefore be given post dialysis	Use with extreme caution in renal disease as the main route of clearance is renal; increased risk of acidosis and gastrointestinal side effects
Linezolid 600 mg/day	No dose adjustment required	No dose adjustments required	Main route of clearance is hepatic with some renal clearance; increased risk of haematological toxicity and peripheral neuropathy
Isoniazid (103,107), 16–18 mg/kg	No dose adjustment required	No dose adjustments required; hemodialysis does not eliminate drug significantly	Co-administer with pyridoxine
Clofazamine (106), 100 mg daily	No dose adjustment needed	No dose adjustment needed	Monitor QTc when used concurrently with other QTc prolonging agents like bedaquiline, delamanid and fluoroquinolones in patients with renal insufficiency
Fluoroquinolones (108) moxifloxacin 400 mg daily; levofloxacin (108,109) 750–1,000 mg daily	Moxifloxacin: no dose adjustments needed; levofloxacin: 30–50 mL/min (750–1,000 mg), <30 mL/min (750–1,000 mg three times per week)	Moxifloxacin: no dose adjustments necessary; levofloxacin: 750–1,000 mg alternate days	Moxifloxacin is predominantly cleared by the hepatobiliary route while levofloxacin has significant renal clearance in addition; there may be a higher risk of neurotoxicity and tendinopathies when using fluoroquinolones in advanced renal insufficiency; avoid concomitant administration of antacids, phosphate binders, calcium, iron or aluminium containing medications to avoid mal-absorption

The thresholds for the diagnosis of diabetes in patients with DR-TB/HIV co-infection remain the same as the general population (136), however, special considerations need to be afforded when using HbA1c, which may underestimate poor glycaemic control (HbA1C may be modulated by HIV that decreases red blood cell life span, NRTI use may increase mean corpuscular volume, and results are discordant at CD4 counts (<500 cells/mL) (137-139). Thus, fasting plasma glucose (FPG) may be more in this population.

Rifampicin, when used for drug sensitive TB, enhances the metabolism of sulphonylureas (140), and when co-administered with metformin may exaggerate hypoglycaemia via increased expression of organic cation transporter (OCT-1) (141). Newer anti-diabetic agents such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitor are potentially safer when co-administered with rifampicin for drug-sensitive or INH-monoresistant TB (141). The optimal dose for rifamycins is currently under review and several studies are evaluating the impact of increased rifamycin dosage (142), which may further amplify these effects. Additionally, metformin may induce more pronounced gastrointestinal side-effects when co-administered with anti-tuberculous agents such as ethionamide, para-amino salicylic acid and clofazimine, and can rarely cause lactic acidosis (143). Caution should be instituted when using nephrotoxic agents such as aminoglycosides, and neurotoxic agents such as linezolid, in patients with established diabetes. QTc monitoring is advised when using bedaquiline and/or delamanid concurrently with hypoglycaemic agents such sulphonylureas and glinides since these agents' function by inhibiting ATP-dependent potassium channels thus delaying repolarization which leads to prolongation of QTc (144). Furthermore, special consideration also needs to be afforded when using bedaquiline with potentially hepatotoxic hypoglycaemic agents such as thiazolidinediones (145).

The pharmacological management drug-resistant TB remains similar for diabetic and non-diabetic patients; however, this may need reconsideration in view of the increased treatment failure rates seen in patients with uncontrolled diabetes (146,147). Optimal glycaemic control may result in better outcomes. It is therefore recommended that diabetic patients are treated aggressively to achieve optimal control (148). The use of modern insulin or insulin analogues must be utilized where necessary, especially in the early phase of TB treatment (149), however, caution needs to be exercised when treating patients with tight glycaemic control, and to ensure that health systems are well equipped to monitor the patient and prevent adverse events such as hypoglycaemia (150). Furthermore, patients with TB may have poor appetite due to TB itself or due to the adverse effects of the various anti-TB agents. This may cause marked changes in weight (initially weight loss followed by weight gain during TB treatment), which could potentially cause further problems with optimal dosing of anti-glycaemic agents. Patients with diabetes are known to have increased rates of TB relapse and recurrence (127,151,152), and should therefore be appropriately counselled and followed up.

Management of drug-resistant TB in the intensive care unit

In high-burden settings, TB is frequently diagnosed in the ICU, even in patients without a respiratory indication for admission such as trauma or emergency surgery (153). A proportion of these patients will have drug-resistant TB. The management of drug-resistant TB in the ICU is challenging, complicated by pharmacokinetic concerns such as poor gastric absorption, high rates of organ dysfunction, and drug toxicity. Concomitant renal failure precludes the use of aminoglycosides. Therapeutic drug monitoring (TDM) should be used whenever possible, and may timely adjustment of drug therapy (154,155). Rifampicin absorption is often stochastic and preliminary studies demonstrate that levels are often very low in patients admitted to the intensive care unit (156). TDM for second-line agents such as linezolid, fluoroquinolones and injectable drugs is expensive and not widely available (156). Newer methods such as utilization of dried blood spot (DBS) may overcome logistical challenges, thereby making TDM for drugs like linezolid and moxifloxacin more cost effective.

Infection control is critical and patients should be isolated in individual negative-pressure rooms, and managed with an endotracheal suctioning system without disconnection (closed suctioning) and a bacterial (HME) filter in the expiratory limb of the ventilator circuit. Appropriate infection control precautions should be observed, and during or after high-risk situations such as endotracheal tube changes or during extubation.

Conclusions

Access to more accurate diagnostic techniques, including Xpert MTB/RIF Ultra testing, is continually improving, even in resource-poor areas. This promises to enhance

detection rates of multi-drug resistant TB. Better detection of drug-resistance combined with ever increasing rates of co-morbid disease means that increasing numbers of more complex cases are likely to be seen. This review provides guidance on management of drug-resistant TB in special situations including co-morbid disease, pregnancy, and critical illness. However, good evidence to support management decisions in these sub-groups is scanty as these patients are often excluded from clinical trials. Further research is necessary to guide practice and support clinical decision-making in these patient sub-groups, and in different clinical settings (including those that are resource constrained).

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Footnote

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