

LANCET COMMISSION ON DRUG-RESISTANT TB: 2019 UPDATE

Epidemiology, pathogenesis, transmission, diagnosis and management of multi-drug-resistant and incurable tuberculosis

Authorship listing#:

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ABSTRACT

In 2017 the Lancet Respiratory Medicine Commission on Drug-Resistant TB (DR-TB) was published, which comprehensively reviewed and provided recommendations on various aspects of DR-TB. This 2019 update is complimentary to, and should be read in conjunction with, the detailed 2017 document. Addressing the DR-TB epidemic is critical. Multi-drug-resistant TB (MDR-TB), and resistance beyond MDR-TB, poses a major threat to global health security and is the only major airborne drug-resistant epidemic. The number of confirmed MDR cases over the last 5 years has almost doubled. DR-TB has a high mortality and is currently responsible for ~1 in 3 antimicrobial resistance (AMR) related deaths globally. Thus, DR-TB underpins the global AMR threat and TB should be prioritised as a key component of the global AMR response. DR-TB is associated with devastating economic consequences and it is estimated that it could cost the global economy US\$16.7 trillion between 2015 and 2050.

Several key new developments in the DR-TB landscape are outlined in this review. The WHO guidelines on treating DR-TB were updated in 2019 with a reclassification of second line anti-TB drugs. An injection-free MDR-TB treatment regimen is now recommended. Recent advances in treatment include the recognition of the safety and mortality benefit of bedaquiline, the finding that the 9-11 month injectable-based “Bangladesh regimen” was non-inferior to longer regimens, and promising interim results of a novel 6 month 3-drug regimen (bedaquiline, pretomanid, and linezolid). Studies of explanted lungs from patients with DR-TB have shown substantial drug-specific gradients across pulmonary cavities, suggesting that alternative dosing and drug delivery strategies are needed to reduce functional monotherapy at the site of disease. Several controversies are discussed including the optimal route of drug administration, optimal number of drugs constituting a regimen, selection of individual drugs for a regimen, duration of the regimen, and minimal desirable standards of antibiotic stewardship. Newer rapid nucleic acid amplification test platforms, including point-of-care systems that facilitate active case-finding, as discussed. The rapid diagnosis of resistance to other drugs, notably the fluoroquinolones, and detection of

resistance by targeted or whole genome sequencing is likely to change the diagnostic landscape in the near future.

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With the introduction of new drugs and molecular diagnostic technologies, the field of drug-resistant TB (DR-TB) has become an exciting and rapidly changing landscape. Results from recent clinical trials and systematic reviews¹, updated guidance from the WHO², and information about newer technologies prompted us to update the commission on DR-TB published in March 2017³. A literature search was conducted using the same search terms and selected publications were included from 31st January 2017 to up until 1st of April 2019 (a full reading list is provided in the online supplement). Only significant new developments and additional information not in the 2017 Commission are included in this update.

TERMINOLOGY

Given that second line injectable drugs (SLID) are no longer recommended to be part of a frontline MDR-TB (multi-drug resistant TB) regimen for most patients, the current definition of XDR-TB has become less clinically relevant⁴. In future it is likely that XDR-TB may be defined, likely based on outcome data, as resistance to one or more of the WHO group A drugs (see Table 1). Until this issue is clarified, we suggest using a term that specifies the group A drug to which the organism is resistant e.g. fluoroquinolone-resistant MDR-TB.

MEDICAL MANAGEMENT OF MDR-TB AND RESISTANCE BEYOND MDR-TB

Considering the 2019 WHO DR-TB guideline², and other available evidence, we have outlined our detailed recommendations to clinicians and health care workers for the medical management of MDR-TB (and resistance beyond MDR-TB) in Text box 1. Table 1 outlines the new WHO drug classification and summarises their guidelines about managing MDR-TB². Several specific aspects concerning management are discussed below.

- i) **Route of administration (oral versus parenteral):** Almost all patients should receive an oral MDR-TB regimen. In a recently published meta-analysis, kanamycin and capreomycin, but not amikacin, were reported to be associated with worse outcomes¹. However, amikacin causes permanent deafness and other serious adverse events⁵, especially in children⁶, and may be associated with reduced adherence.
- ii) **Optimal number of drugs:** The optimal number of proven or likely effective drugs to be used in a regimen remains unclear. The PETTS study⁷ and a recent patient-level meta-analysis¹ suggested that outcomes were better with five or more effective drugs; however, there were few patients on two or more group A drugs. The WHO recommends at least four drugs when using a regimen including the three group A drugs². However, the optimal number of drugs in a regimen will depend on several factors (outlined in Table 2) including the mycobactericidal and sterilising activity of the drugs used, disease extent, and drug susceptibility test (DST) profiles.
- iii) **Which specific drugs and the optimal duration of each drug?** The WHO has strongly recommended, based on moderate quality evidence, a group A backbone around which an oral MDR-TB regimen should be constructed, as these drugs have been associated with substantial improvements in mortality *and* treatment outcomes, mainly in observational studies^{8,9}. A large South African study showed that bedaquiline substantially reduced mortality, which was an important finding as the phase 2 trial showed an increase mortality in the bedaquiline arm (likely a chance finding as almost all of the deaths occurred after bedaquiline was stopped). Delamanid has been designated a Group C drug after disappointing results in a phase 3 trial¹⁰ (Text Box 1). The use of specific drugs will be guided by susceptibility and drug-specific mycobactericidal and sterilising activity. Risk-benefit ratio is also important. For example, higher doses of linezolid given for longer durations could result in better outcomes, but 30 to 40% of patients interrupt linezolid due to adverse events¹¹. The optimal indication, dose, frequency and duration of linezolid remains unclear.

The WHO recommends 600mg/daily for six months, whilst the NIX study successfully used 1200mg/daily for six months in most patients¹². The current WHO guidelines also makes provision for the use of the “Bangladesh”-like shorter course 9-11 month regimen, which was non-inferior to the old long regimen in a recent trial¹³. The South African NTP has replaced the SLID with bedaquiline in a 9-11 month regimen, which should improve outcomes⁵ (Text box 1 and Table 1).

iv) **Duration of the regimen:** The optimal duration of therapy for MDR-TB has not yet been determined and will depend on the presence of one or more prognostic factors outlined in Table 2. Indeed, variable regimen durations are used for programmatic management of DR-TB in different parts of the world (Text Box 1). It also remains unclear how long after culture conversion the regimen should be continued and which biomarkers can inform the optimal duration of treatment in different sub-groups of patients, including those with severe and non-severe disease, the latter including most children. Ongoing clinical trials, e.g. NExT, end-TB, STREAM Stage 2, Nix-TB, ZeNix, and SimpliciTB and SmART Kids (IMPAACT 2020) will help to answer these questions (see ¹⁴ for updated list of clinical trials).

v) **Drug susceptibility testing and the minimal standard of antibiotic stewardship:** Ideally, the diagnostic standard for management of MDR-TB should include confirmation of resistance to rifampicin, isoniazid, and fluoroquinolones. Diagnostic testing for susceptibility to bedaquiline, linezolid, pyrazinamide and ethambutol is neither widely available nor validated; this capacity is urgently needed. Until then, clinicians in most high-burden settings will continue, in the interests of a patient-centred approach, to use standardised or quasi-individualised regimens. The regimen can then be further individualised based on the results of the available second line DST.

Another suggested approach is to use a pan-TB regimen to treat all forms of rifampicin-resistant TB with one regimen without preceding DST. The merits and drawbacks of this approach, including the

risk of resistance amplification¹⁵ and the rights of individuals versus communities, have recently been extensively debated^{16,17}.

DIAGNOSIS OF DRUG-RESISTANT TB

Substantially reducing the burden of MDR-TB will necessitate active case finding as $\geq 95\%$ of transmission has already occurred prior to diagnosis by passive case finding³. In addition to targeted screening, e.g. of close contacts, a completed study has confirmed the feasibility of using new portable battery-operated devices for nucleic acid amplification tests for targeted community-based active case finding⁷ for MDR-TB (NCT03168945; submitted). Xpert Ultra, a version of Xpert that is $\sim 5\%$ more sensitive (expected to pick up more cases of TB and hence rifampicin-resistant TB at population level) but less specific than the generation 4 cartridge, is now the frontline diagnostic being used in TB many endemic countries¹⁸. Its drawbacks include limited positive predictive value for rifampicin resistance (when the prevalence of resistance is under 10%) and the lack of clarity on how to handle trace positive results. The GeneXpert DR-TB cartridge is due to be released shortly, which will detect resistance to isoniazid, fluoroquinolones, and SLIDs¹⁹. It is likely that susceptibility to other drugs will be added on as new prototypes and new assays emerge. Next generation whole genome sequencing can provide comprehensive mutational analysis allowing drug susceptibility profiles for many second-line drugs to be simultaneously determined²⁰⁻²³. However, major limitations include the poor predictive value for some drugs, e.g. clofazimine and cycloserine, and the poor sensitivity when using sputum rather than a culture isolate as a sample (meaning that results from a culture isolate are generally only available after 4 to 8 weeks of empiric treatment). Some mutations have good correlations with minimum inhibitory drug concentrations³. It is encouraging that a standardised platform for phenotypic DST and MIC determination of 14 drugs, including bedaquiline and delamanid, has been developed²⁴. Critical concentration cut points for second-line drugs have recently been updated by the WHO²⁵. The

clinical impact of targeted and whole genome sequencing technology, and the clinical benefit over more limited molecular readouts (such as that in the Xpert DR-TB cartridge) requires clarification.

PK/PD ASPECTS, AND NEWER DRUG REGIMENS AND AGENTS

Recent studies using explanted human lungs have confirmed the existence of substantial drug-specific gradients across pulmonary cavities suggesting that alternative dosing and drug delivery strategies are needed to reduce functional monotherapy at the site of disease, and prevent amplification of resistance. Studies on the impact of therapeutic drug monitoring of second-line drugs are needed. Newly-available PK and safety data from children now allow us to use BDQ in children age > 6 years and DLM in children 3 years or older. A FDA advisory panel has approved the use of pretomanid as part of a combination regimen with bedaquiline and linezolid, in adults, for the treatment of pulmonary XDR-TB, and treatment-intolerant or nonresponsive MDR-TB²⁶.

Recent publications using the hollow fibre and other models have suggested that certain repurposed drugs including ceftazidime avibactam, tedizolid, once a week tigecycline, and minocycline, may hold promise for the treatment of DR-TB^{27,28}. Promising new agents that have partially or fully completed or are in phase 1 clinical trials include mycobacterial respiratory chain inhibitors such as Q203 (imidazopyridine), the cell wall biosynthesis inhibitor OPC167832, and DprE1 inhibitors such as benzothiazole.

CONCLUSION

Although DR-TB threatens to derail the already fragile TB control programmes across the world, it is exciting and encouraging that new public health strategies, diagnostic technologies, drugs, and interventions to prevent resistance amplification are emerging. Together with poverty alleviation

and political will, exemplified by the recent UN General Assembly High Level meeting on ending TB, these advances portend the ability to end the scourge of DR-TB.

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Table 1: 2019 WHO-recommended grouping of MDR-TB drugs and a summary of WHO MDR-TB guidance²

<u>WHO Grouping</u>	Anti-tuberculous drug
<u>Group A:</u> Include all three drugs (unless they cannot be used)	Levofloxacin <u>OR</u> Moxifloxacin (Lfx / Mfx)
	Bedaquiline (Bdq)
	Linezolid (Lzd)
<u>Group B:</u> Add both drugs (unless they cannot be used)	Clofazimine (Cfz)
	Cycloserine <u>OR</u> Terizidone (Cs / Trd)
<u>Group C:</u> Add to complete the regimen and when drugs from Groups A and B cannot be used	Ethambutol (E)
	Delamanid (Dlm)
	Pyrazinamide (Z)
	Imipenem-cilastin <u>OR</u> Meropenem (Ipm-Cln / Mpm)
	Amikacin (<u>OR</u> Streptomycin) (Am (S))
	Ethionamide <u>OR</u> Prothionamide(Eto / Pto)
	<i>p</i> -aminosalicylic acid (PAS)
Summary of the WHO guideline on treatment regimens for drug-resistant tuberculosis	
<p>1) The regimen should comprise all three Group A agents and at least one Group B agent, such that at least four likely effective drugs are included at the initiation of treatment. If only one or two Group A agents are used both Group B agents should be included in the regimen. Group C agents should be used when an effective regimen (4 likely effective agents) cannot be can be constituted using group A and B drugs.</p> <p>2) A regimen consisting of at least four likely effective drugs in the initial phase (bedaquiline used for 6 months) and at least three likely effective drugs after the initial phase should be used.</p> <p>3) An all-oral bedaquiline-based shorter (9-12 month) regimen may be explored under operational research conditions.</p>	

4) The standardised shorter MDR-TB regimen (requiring daily injections for at least four months) may be offered to eligible patients (instead of the longer regimen in 1 above) who to those who agree to a briefer treatment duration of 9-12 months provided they had not been previously treated for more than one month with second-line medicines, and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded; this regimen may be less effective compared to the longer regimen .

Table 2: Factors that may impact prognosis, outcomes, and the risk to benefit ratio of treatment, and should be considered when deciding on the duration of treatment, minimum number of likely effective drugs, and the selection of individual drugs in regimens for MDR-TB*

Category	Contributing factors	Comments
Mycobacterial factors	<ul style="list-style-type: none"> • Mycobacterial load • Drug-specific resistance profile • The number and relative efficacy of mycobactericidal and sterilising drugs • Strain type 	<ul style="list-style-type: none"> • Time to positivity (sputum culture), smear status, and Xpert Ultra Ct values are useful surrogate markers of mycobacterial load.
Host factors	<ul style="list-style-type: none"> • HIV co-infection • Diabetes mellitus • Weight < 50 kg or low BMI • History of prior TB • Radiological disease burden/ disease extent (including disseminated TB) • Genetic factors • Substance and alcohol abuse 	<ul style="list-style-type: none"> • Chest radiography (and sometimes CT or PET-CT) may be used to quantify disease burden (bilateral involvement, presence of cavitory disease, number and severity of zones affected may be associated with worse outcome)²⁹. • There is poor penetration of drugs into thick walled cavities and sputum DST correlates poorly with samples that are obtained directly from the cavity. • HIV co-infection (especially in the context of unsuppressed viral load), diabetes mellitus (especially if uncontrolled) and weight < 50kg are all associated with poor outcomes. • Genetics may impact a number of variables that determine PK profiles including absorption, metabolism, excretion, adaptive immunity, immunopathology etc. • Substance abuse is associated with a poorer prognosis
Program-related and other factors	<ul style="list-style-type: none"> • Access to effective drugs** • Adherence-promoting measures • Pill burden (HIV and TB drugs) • Drug-related adverse events and toxicity 	<ul style="list-style-type: none"> • Programmatic measures to support adherence, social support, and detection and management of adverse events may impact outcomes and prognosis • Support should be provided to ensure all patients have access to the best possible care, which may reduce long-term costs associated with poor treatment outcomes

	<ul style="list-style-type: none"> • Social support: food security, access to shelter, and access to gainful employment 	
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*More aggressive treatment with 5 likely effective drugs and prolonged duration of treatment (of the regimen or individual drugs) may be justifiable in patients with one or more of these risk factors or descriptors (the same principles would apply to drug-sensitive TB).

**Programmes must have access to newer group A and C drugs and use them as outlined in the new guidelines. When unavailable there should be a clear pathway and plan in place to obtaining them.

Legend: HIV: Human immunodeficiency virus; ct: cycles threshold; CT: computed tomography; PET-CT: positron emission tomography – computed tomography.

DST= drug susceptibility testing.

Textbox 1. Recommended principles to be used when designing a regimen for the medical management of MDR-TB and resistance beyond MDR-TB including in those with pulmonary TB, extra-pulmonary TB, and in children^{\$}

- **ROUTE OF ADMINISTRATION:** Use an all-oral regimen (*see note below on WHO-recommended Bangladesh-like shorter course regimen).
- **NUMBER OF DRUGS:** Ideally use five drugs (minimum 4) to which the strain has proven or likely susceptibility (drugs previously taken for ≥ 1 month are generally avoided; use at least 3 [preferably 4] likely effective drugs in the continuation phase[#]).
- **INDIVIDUAL COMPONENTS OF THE REGIMEN:**
 - (i) Use a backbone of the 3 Group A drugs i.e. a later-generation fluoroquinolone e.g. levofloxacin (less QT prolongation but safety relative to moxifloxacin unclear), linezolid, and bedaquiline. The optimal duration of individual drugs like linezolid and bedaquiline remain unclear but they are generally used for at least 6 months (based only on end-points used in clinical trials; in practice extension of bedaquiline to ≥ 9 months may be undertaken particularly in late culture converters and those with poor prognostic features).
 - (ii) Add additional group B drugs (e.g., cycloserine [terizidone], and/ or clofazimine).
 - (iii) Add additional Group C drugs, if necessary (based on toxicity and resistance profiles), so that 5 likely effective drugs make up the regimen. In the meta-analysis¹ PAS and ethionamide were associated with worse outcomes, and using drugs to which there was known resistance was associated only with increased toxicity, including for pyrazinamide.
- **DURATION OF TREATMENT:** The optimal duration of the multi-drug regimen remains unclear. Current practice when treating MDR-TB (using a Group A backbone) varies from 9 to 11 months to the WHO-recommended 18 to 20 months (e.g. in South Africa both the 9-11 month and the 18-20 month regimen are used depending on the clinical context and factors outlined in Table S1; online supplement). The optimal duration of treatment will depend on several factors including mycobacterial burden (and time of culture conversion), disease extent, disease site, co-morbidities (e.g. HIV and diabetes), previous treatment, country setting, local resistance profiles, and patient preference etc.
- **EMPIRIC versus INDIVIDUALISED:** To optimise outcomes, and to prevent resistance amplification and accelerated loss of newer drugs, drug susceptibility-guided treatment for individual drugs is preferred over empiric treatment regimens. To minimise resistance amplification sputum-based genotypic testing for second-line resistance, particularly FQs, is recommended. Regimens should be further optimized based on drug susceptibility results when they become available.
- Delamanid (Group C) can be used together with bedaquiline, if required, to make up the 5 drug regimen (monitor QT interval). However there is currently limited evidence about the efficacy of delamanid for the treatment of MDR-TB¹⁰.
- Meropenem or imipenem/ clavulanic acid (generally given as oral Augmentin[®]).
- A SLID (amikacin or streptomycin; group C drugs) may be used if an appropriate regimen of 4 to 5 likely effective drugs cannot be constructed provided baseline and follow-up screening for hearing loss and renal toxicity is accessible. We recommend that an indwelling intravenous catheter

be used for administration of amikacin and/or a carbapenem. If inaccessible, we recommend that amikacin be given intramuscularly together with a local anaesthetic agent.

- Psychosocial, adherence, and financial support are critical elements of the treatment package.
- Patients should be actively monitored for adverse drug reactions, which are common .
- A single drug should not be added to a failing regimen.
- The HIV status should be determined, and ART initiated in all HIV-infected patients (within 8 weeks; 2 weeks in advanced HIV). Dolutegravir is safe when used together with the new MDR regimen containing a group A backbone.
- Surgical intervention maybe offered in appropriate patients who have failed treatment or are at high risk of relapse.
- **CHILDREN:** use *all* the same principles as outlined above including an all-oral regimen³⁰. Bedaquiline can be used from 6 years of age. Delamanid is safe and effective from 3 years of age and prioritised in children (data down to birth will be available soon). Lack of optimal diagnostics and child-friendly formulations remain a major challenge . In children <6 years of age, if delamanid is unavailable, PAS (or a child-friendly linezolid formulation if available) can be given instead of the SLID.
- ***WHO-recommended shorter RR/ MDR-TB course regimen** (9 to 11 month 2016 WHO shorter course regimen containing a SLID but not containing bedaquiline or linezolid): whilst scale-up of newer drugs and diagnostics continues, the WHO has recommended that this regimen can be used (in the STREAM trial, it was found to be non-inferior to the conventional 18-20 month WHO regimen but bacteriologic outcomes were worse with the shorter regimen and there was a trend to worse outcomes in HIV-infected persons in both arms²). We suggest that this regimen be used as an exception and provided there is (i) no proven or likely resistance to any component of the regimen (except isoniazid), (ii) there is access to baseline and longitudinal monitoring for hearing loss, (iii) FQ and SLID resistance have been excluded, and (iv) patients have been counselled about the risks of this regimen and agree to receive it ². There should be a clear programmatic plan for transitioning to an all-oral Group A-based regimen.

FQ= fluoroquinolone; MDR-TB= multi-drug resistant TB; SLID=second-line injectable drug.

^{\$}Adapted with permission from Dheda K, Lancet, 2016 & Dheda K, Lancet Resp Med, 2017

[#] Continuation phase: some group A drugs like bedaquiline and/ or linezolid may only be given for a limited period (e.g. ~6 months) and thus the period beyond this point may only contain a limited number of drugs. Depending on the length of the regimen and how long each drug is used, in specific instances, there may not be a continuation phase.

^{*} See main text for the composition of WHO-recommended shorter course regimen.

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