**LANCET COMMISSION ON DRUG-RESISTANT TB: 2019 UPDATE**

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

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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 2017. A literature search was conducted using the same search terms and selected publications were included from 31st January 2017 to up until 15st of January 2019. 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 relevant3,4. In future it is likely that XDR-TB may be defined, based on prognostic 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**

Taking into account the WHO Guidelines published in December 2018, which we endorse, 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 on managing MDR-TB2. Several aspects of medical 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. In addition, injectable agents are commonly associated with reduced adherence and serious adverse events5, especially in children6,7.

ii) **Optimal number of drugs:** The optimal number of proven or likely effective drugs to be used in a regimen remains unclear. The PETTS study8 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 in which the three group A drugs are preferably given2. 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 studies9-14. Delamanid has been designated a Group C drug15 (Text Box 1). The use of specific drugs will be guided by susceptibility readouts and drug-specific mycobactericidal and sterilising activity. Risk-benefit ratio is also a consideration. For example, higher doses of linezolid16 and more prolonged treatment17 could result in better outcomes, but 30 to 40% of patients interrupt linezolid due to adverse events18. The optimal indication, dose, frequency and duration of linezolid remains unclear. Lack of consensus is reflected in practice on the ground; in South Africa, for example, linezolid 600mg daily is given for two months as part of a shorter 9-11 month bedaquiline-based regimen (whilst awaiting second line DST results to exclude FQ resistance) or for six months as part of a longer regimen depending on risk factors outlined in Text Box 1. The WHO, by contrast, recommends 600mg/daily for six months, and in a research context, the NIX study successfully used 1200mg/daily for six months in most patients19,20.

The current WHO guidelines also makes provision, given recent trial results21-24, for the limited use of the WHO shorter course 9 to 12 month regimen mentioned in the 2016 WHO guidelines (which does not contain bedaquiline or linezolid but includes a SLID) whilst scale-up of newer drugs is ongoing (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 a several 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 including the efficacy of and optimal duration of pretomanid (see 25 for updated list of clinical trials).

v) **Drug susceptibility testing and the minimal standard of antibiotic stewardship:** Ideally, the current minimal diagnostic standard for management of MDR-TB should include confirmation of resistance to rifampicin, isoniazid, and fluoroquinolones, and is limited by the availability of standardised DSTs. 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 approach26, to use standardised or quasi-individualised regimens. As a minimum in any setting, the presence of fluoroquinolone resistance should be ascertained prior to initiating MDR-TB treatment (South Africa being an example where this is being successfully implemented). The regimen can then be 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 amplification27 and the rights of individuals versus communities have recently been extensively debated28-30.

**DIAGNOSIS OF DRUG-RESISTANT TB**

Substantially reducing the burden of MDR-TB will necessitate active case finding as ≥95% or more of transmission has already occurred prior to MDR-TB cases self-declaring themselves for treatment31,32. In addition to targeted screening, e.g. close contacts, one recent study indicated the feasibility of using new portable battery-operated molecular tools such as Xpert Edge and Xpert Omni for targeted community-based active case finding for MDR-TB33. Xpert Ultra, a version of Xpert that is more sensitive but less specific than the generation 4 cartridge, is now the frontline diagnostic being used in TB many endemic countries34. Its drawbacks include limited positive predictive value for rifampicin resistance (when the prevalence of resistance is under 10%)35 and the lack of clarity on how to handle trace positive results. Newer versions of the line probe assay are likely to emerge, and the GeneXpert DR-TB cartridge is due to be released shortly36, which will detect resistance to isoniazid, fluoroquinolones, and SLIDs. It is likely that susceptibility to other drugs will be added on as technology progresses. Next generation whole genome sequencing can provide comprehensive mutational analysis allowing drug susceptibility profiles for many second-line drugs to be simultaneously determined 37-42. 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 may have good correlations with minimum inhibitory drug concentrations43. The clinical impact of extended 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 risk of site-of-disease functional monotherapy and prevent amplification of resistance44-46. Studies on the impact of therapeutic drug monitoring of second-line drugs are needed35,47. Additionally, 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 older35. There is new evidence that specific combinations of newer drugs may rapidly interrupt transmission (Edward Nardell; personal communication). Recent publications using the hollow fibre and other models have suggested that certain repurposed drugs including ceftazidime avibactam48, tedizolid49, once a week tigecycline, and minocycline50, may hold promise for the treatment of DR-TB. 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) 51,52, the cell wall biosynthesis inhibitor OPC167832, and DprE1 inhibitors53 such as benzothiazole54.

**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 (including therapeutic drug monitoring) 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: 2018 WHO-recommended grouping of MDR-TB drugs and a summary of WHO MDR-TB guidance2** | |
| **WHO Grouping** | **Anti-tuberculous drug** |
| **Group A:**  Include all three medicines (unless they cannot be used) | Levofloxacin OR Moxifloxacin (Lfx / Mfx) |
| Bedaquiline (Bdq) |
|  |
| Linezolid (Lzd) |
| **Group B:**  Add both medicines (unless they cannot be used) | Clofazimine (Cfz) |
| Cycloserine OR Terizidone (Cs / Trd) |
| **Group C:**  Add to complete the regimen and when medicines from Groups A and B cannot be used | Ethambutol (E) |
| Delamanid (Dlm) |
| Pyrazinamide (Z) |
| Imipenem-cilastin OR Meropenem (Ipm-Cln / Mpm) |
| Amikacin (OR Streptomycin) (Am (S)) |
| Ethionamide OR Prothionamide(Eto / Pto) |
| *p-*aminosalicylic acid (PAS) |
| **Summary of the WHO guideline on treatment regimens for drug-resistant tuberculosis** | |
| 1. An all oral regimen to be used in most patients 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 beginning 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 with group A and B drugs. 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 must be used. 3. An all-oral bedaquiline-based shorter (9-12 month) regimen may be explored under operational research conditions. 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 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, or, in whom resistance to fluoroquinolones and second-line injectable agents has been excluded; this regimen may be less effective compared to the longer regimen 24. | |

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| **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** | * Mycobacterial load * Drug-specific resistance profile * The number and relative efficacy of mycobactericidal and sterilising drugs * Strain type | * Time to positivity (sputum culture), smear status, and Xpert Ultra Ct values may be used as a marker for mycobacterial load55. |
| **Host factors** | * HIV co-infection * Diabetes mellitus * Weight < 50 kg or low BMI * Previous TB * Radiological disease burden/ extent (including disseminated TB) * Genetic factors * Substance abuse | * Chest radiography (and sometimes CT or PET-CT56) may be used to quantify disease burden (bilateral involvement, presence of cavitary disease, number and severity of zones affected57,58 may be associated with worse outcome)59. * There is poor penetration of drugs into thick walled cavities and sputum DST correlates poorly with samples that are obtained directly from the cavity44. * HIV co-infection (especially in the context of unsuppressed viral load), diabetes mellitus (especially if uncontrolled) and weight < 50kg are all associated with poor outcomes60. * Genetics may impact a number of factors that determine PK profiles and ability to eradicate infection including absorption, metabolism, excretion, adaptive immunity, immunopathology etc. * Substance abuse is associated with a poorer prognosis35 |
| **Program-related factors** | • Access to efficacious drugs\*\*  • Adherence-supporting measures  • Absolute pill burden (HIV and TB  drugs)  • Adverse events and their detection and management  • Social support: food security; access to shelter; access to gainful employment | * Programmatic measures to support adherence, social support, and detection and management of adverse events may impact outcomes and prognosis26,61   • Short-term costs, such as procuring medications, may be a major challenge in some  settings, but 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 |

\*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 would apply to drug-sensitive TB).

\*\*Programmes must have access to newer group A and C drugs and use them according to the new guidelines. Where unavailable there should be a clear pathway 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# 62).
* **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 62. Actively monitor for toxicity especially to linezolid (~30% reduce the dose or stop the drug 63,64,65,66). 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 features67).

**(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 2). 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 (see Table 2) 68.
* **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-basedgenotypic 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)69-71. However there is currently limited evidence about the efficacy of delamanid for the treatment of MDR-TB15.
* Meropenem or imipenem/ cilastin should be administered with 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 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 72
* Psychosocial, adherence, and financial support are critical elements of the treatment package26.
* Patients should be actively monitored for adverse drug reactions, which are common 73.
* 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 regimen74,75. 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 76. 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 12 month 2016 WHO shorter course regimen containing a SLID but not containing bedaquiline or linezolid): whilst scale-up of newer drugs and diagnostics continues, as an interim option, the WHO has recommended that this regimen can be used on a discretionary basis (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 2,77. There should be clear plans to 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 n umber 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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