The Lancet Respiratory Medicine Commission : 2019 update: epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant and incurable tuberculosis

LANCET COMMISSION ON DRUG-RESISTANT TB: 2019 UPDATE

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

Authorship listing:

Keertan Dheda*, Tawanda Gumbo*, Gary Maartens*, Kelly E Dooley*, Aliasgar Esmail*, Megan Murray*, Jennifer Furin*, Edward A Nardell*, Leslie London*, Erica Lessem*, Jason Limberis, Grant Theron, Ruth McNerney, Stefan Niemann, David Dowdy, Annelies Van Rie, Jotam G Pasipanodya, Camilla Rodrigues, Taane G Clark, Frik A Sirgel, H Simon Schaaf, Kwok Chiu Chang, Christoph Lange, Payam Nahid, Bernard Fourie, Norbert Ndjeka, Andrew Nunn, GB Migliori, Zarir F Udwadia, C Robert Horsburgh Jr, Gavin J Churchyard, Dick Menzies, Anneke C Hesseling, James A Seddon, Marcus Low, Salmaan Keshavjee, Eric Nuermberger, Helen McIlleron, Kevin P Fennelly, Amina Jindani, Ernesto Jaramillo, Nesri Padayatchi, Clifton E Barry 3rd, Robin M Warren*

*Section editors; contributed equally

Affiliations:

1. Lung Infection and Immunity Unit, Department of Medicine, Division of Pulmonology and UCT Lung Institute, University of Cape Town, Groote Schuur Hospital, Cape Town, South Africa (Keertan Dheda Aliasgar Esmail, Jason Limberis, Ruth McNerney)
2. Center for Infectious Diseases Research and Experimental Therapeutics, Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA (Tawanda Gumbo, Jotam G Pasipanodya)
3. Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa (Gary Maartens, Helen McIlleron)
4. Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Kelly E Dooley, Eric Nuermberger)

5. Department of Global Health and Social Medicine, Harvard Medical School, Boston MA (Megan Murray, Jennifer Furin, Salmaan Keshavjee)

6. TH Chan School of Public Health (Jennifer Furin, Edward A Nardell)

7. Department of Medicine, Harvard Medical School, Boston, MA, USA (Leslie London)

8. School of Public Health and Medicine, University of Cape Town, Cape Town, South Africa (Leslie London)

9. Treatment Action Group, New York, NY, USA (Erica Lessem)

10. SA MRC Centre for Tuberculosis Research/DST/NRF Centre of Excellence for Biomedical Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Tygerberg, South Africa (Grant Theron, Frik A Sirgel, Robin M Warren)

11. Molecular and Experimental Mycobacteriology, Research Center Borstel, Borstel, Schleswig-Holstein, Germany (Stefan Niemann);

12. Division of Clinical Infectious Diseases, German Center for Infection Research (Stefan Niemann, Christoph Lange)

13. University of Cape Town, Cape Town, South Africa; and Tuberculosis Research Section, Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, MD, USA (C E Barry 3rd)

15. Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (David Dowdy)

16. University of North Carolina at Chapel Hill, Chapel Hill, NC, USA (Annelies Van Rie)

17. International Health Unit, Epidemiology and Social Medicine, Faculty of Medicine, University of Antwerp, Antwerp, Belgium (Annelies Van Rie)

18. Department of Microbiology, P.D. Hinduja National Hospital & Medical Research Centre, Mumbai, India (Camilla Rodrigues)

19. Faculty of Infectious and Tropical Diseases and Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK (Taane G Clark);

20. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa (H Simon Schaaf, Anneke C Hesseling)

21. Tuberculosis and Chest Service, Centre for Health Protection, Department of Health, Hong Kong SAR, China (Kwok Chiu Chang)

22. International Health/Infectious Diseases, University of Lübeck, Lübeck, Germany (Christoph Lange)

23. Department of Medicine, Karolinska Institute, Stockholm, Sweden (Christoph Lange)

24. Department of Medicine, University of Namibia School of Medicine, Windhoek, Namibia (Christoph Lange)

25. Division of Pulmonary and Critical Care, San Francisco General Hospital, University of California, San Francisco, CA, USA (Payam Nahid)

26. Pulmonary Department, Hinduja Hospital & Research Center, Mumbai, India (Zarir F Udwadia)

27. Schools of Public Health Medicine, Boston University, Boston, MA, USA (C Robert Horsburgh Jr)

28. Aurum Institute, Johannesburg, South Africa (Gavin J Churchyard)

29. School of Public Health, University of Witwatersrand, Johannesburg, South Africa (Gavin J Churchyard)

30. Advancing Treatment and Care for TB/HIV, South African Medical Research Council, Johannesburg, South Africa (Gavin J Churchyard)

31. Montreal Chest Institute, McGill University, Montreal, QC, Canada (Dick Menzies)

32. Pulmonary Clinical Medicine Section, Division of Intramural Research, National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda, MD, USA (Kevin P Fennelly)

35. World Health Organization, Geneva, Switzerland (Ernesto Jaramillo)

36. CAPRISA MRC HIV-TB Pathogenesis and Treatment Research Unit, Durban, South Africa (Nesri Padayatchi)

37. Istituti Clinici Maugeri, IRRCS, Tradate, Italy (GB Migliori)

39. University of Pretoria, Department of Medical Microbiology, Pretoria, South Africa (Bernard Fourie)

40. Drug-Resistant TB, TB & HIV at National Department of Health, South Africa (Norbert Ndjeka)

41. Medical Research Council Clinical Trials Unit at UCL, London, UK (Andrew Nunn)

43. St. George's University of London, Institute of Infection and Immunity, London, UK (Amina Jindani)

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 reviews[1], updated guidance from the WHO[2], 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 relevant[3,4]. 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-TB[2]. 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 outcomes[1]. In addition, injectable agents are commonly associated with reduced adherence and serious adverse events[5], especially in children[6,7].

ii) **Optimal number of drugs:** The optimal number of proven or likely effective drugs to be used in a regimen remains unclear. The PETTS study[8] and a recent patient-level meta-analysis[1] 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 given[2]. 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[9-14]. Delamanid has been designated a Group C drug[15] (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 linezolid[16] and more prolonged treatment[17] could result in better outcomes, but 30 to 40% of patients interrupt linezolid due to adverse events[18]. 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 patients[19,20].

The current WHO guidelines also makes provision, given recent trial results[21-24], 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 approach[26], 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 amplification[27] and the rights of individuals versus communities have recently been extensively debated[28-30].

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 treatment[31,32]. 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-TB[33]. 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 countries[34]. 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 shortly[36], 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 concentrations[43]. 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 resistance[44-46]. Studies on the impact of therapeutic drug monitoring of second-line drugs are needed[35,47]. 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 older[35]. 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 avibactam[48], tedizolid[49], once a week tigecycline, and minocycline[50], 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 inhibitors[53] such as benzothiazole[54].

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.

Table 1: 2018 WHO-recommended grouping of MDR-TB drugs and a summary of WHO MDR-TB guidance[2]	
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].

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 load[55].
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-CT[56]) may be used to quantify disease burden (bilateral involvement, presence of cavitary disease, number and severity of zones affected[57,58] 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 cavity[44]. • 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[60]. • 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 prognosis[35]
Program-related factors	• Access to efficacious drugs** • Adherence-supporting measures • Absolute pill burden (HIV and TB drugs) • Adverse events and their detection and management	• Programmatic measures to support adherence, social support, and detection and management of adverse events may impact outcomes and prognosis[26,61] • 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

	• Social support: food security; access to shelter; access to gainful employment	

*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 features[67]).
  (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-analysis[1] 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-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)[69-71]. However there is currently limited evidence about the efficacy of delamanid for the treatment of MDR-TB[15].
- 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 package[26].
- 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 regimen[74,75]. 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 arms[2]). 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.

REFERENCES

1. The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017: Nafees Ahmad, Shama D Ahuja OWA, Jan W C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos,, Digamber Behera AB, Greg P Bisson, Martin Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Geisa F Carlessso,, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *The Lancet* 2018; S0140-6736(18)31644-1.
2. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis 2018 update (pre-final text): World Health Organization, 2018.
3. Lange C, Chesov D, Furin J, Udwadia Z, Dheda K. Revising the definition of extensively drug-resistant tuberculosis. *Lancet Respir Med* 2018; **6**(12): 893-5.
4. Migliori GB, Global Tuberculosis N. Evolution of programmatic definitions used in tuberculosis prevention and care. *Clin Infect Dis* 2018.
5. Zhao Y, Fox T, Manning K, et al. Improved treatment outcomes with bedaquiline when substituted for second-line injectable agents in multidrug resistant tuberculosis: a retrospective cohort study. *Clin Infect Dis* 2018.
6. Shean K, Streicher E, Pieterson E, et al. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. *PloS one* 2013; **8**(5): e63057.
7. Seddon JA, Schaaf HS, Marais BJ, et al. Time to act on injectable-free regimens for children with multidrug-resistant tuberculosis. *Lancet Respir Med* 2018; **6**(9): 662-4.
8. Cegielski JP, Kurbatova E, van der Walt M, et al. Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance. *Clin Infect Dis* 2016; **62**(4): 418-30.
9. Olayanju O, Limberis J, Esmail A, et al. Long-term bedaquiline-related treatment outcomes in patients with extensively drug-resistant tuberculosis from South Africa. *Eur Respir J* 2018; **51**(5).
10. Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *The New England journal of medicine* 2014; **371**(8): 723-32.
11. Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: a retrospective cohort study. *Lancet Respir Med* 2018.
12. Lee M, Lee J, Carroll MW, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *The New England journal of medicine* 2012; **367**(16): 1508-18.
13. Ndjeka N, Conradie F, Schnippel K, et al. Treatment of drug-resistant tuberculosis with bedaquiline in a high HIV prevalence setting: an interim cohort analysis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2015; **19**(8): 979-85.
14. Borisov SE, D'Ambrosio L, Centis R, et al. Outcomes of patients with drug-resistant-tuberculosis treated with bedaquiline-containing regimens and undergoing adjunctive surgery. *J Infect* 2018.
15. von Groote-Bidlingmaier F, Patientia R, Sanchez E, et al. Efficacy and safety of delamanid in combination with an optimised background regimen for treatment of multidrug-resistant tuberculosis: a multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trial. *Lancet Respir Med* 2019.
16. Millard J, Pertinez H, Bonnett L, et al. Linezolid pharmacokinetics in MDR-TB: a systematic review, meta-analysis and Monte Carlo simulation. *J Antimicrob Chemother* 2018.
17. Vazquez JA, Arnold AC, Swanson RN, Biswas P, Bassetti M. Safety of long-term use of linezolid: results of an open-label study. *Ther Clin Risk Manag* 2016; **12**: 1347-54.
18. Zhang X, Falagas ME, Vardakas KZ, et al. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. *J Thorac Dis* 2015; **7**(4): 603-15.
19. Francesca Conradie AD, Pauline Howell, Daniel Everitt, Angela Crook, Carl Mendel, Erica Egizi, Joanna Moreira, Juliano Timm, Timothy McHugh, Genevieve Wills, Christo Van Niekerk, Mengchun Li,

Morounfolu Olugbosi, Melvin Spigelman. Sustained high rate of successful treatment outcomes: Interim results of 75 patients in the Nix-TB clinical study of pretomanid, bedaquiline and linezolid. The 49th Union Conference on Lung Health; 2018 25th October 2018; Hague, Netherlands: The Union; 2018.
20. Clinical Guidelines & Standard Operating Procedure for the Implementation of the Short & Long DR-TB regimens for Adults, Adolescents and Children. Westerncape.gov.za: Department of Health, Western Cape Government.
21. Van Deun A, Aung KJM, Halim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010; **182**: 684-92.
22. Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2014; **18**(10): 1188-94.
23. Trebucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2018; **22**(1): 17-25.
24. Position Statement on the Continued Use of the Shorter MDR-TB Treatment Regimen following an Expedited Review of the STREAM Stage 1 Preliminary Results. Geneva: The World Health Organization, 2018.
25. Lange C, Chesov D, Heyckendorf J, Leung CC, Udwadia Z, Dheda K. Drug-resistant tuberculosis: An update on disease burden, diagnosis and treatment. *Respirology* 2018; **23**(7): 656-73.
26. Organization WH. Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. . Geneva: World Health Organization, 2017.
27. Ismail NA, Omar SV, Joseph L, et al. Defining Bedaquiline Susceptibility, Resistance, Cross-Resistance and Associated Genetic Determinants: A Retrospective Cohort Study. *EBioMedicine* 2018; **28**: 136-42.
28. Gupta R, Wells CD. Pan-tuberculosis regimens: re-framing the argument. *Lancet Respir Med* 2018; **6**(7): e28.
29. Dheda K, Gumbo T, Lange C, Horsburgh CR, Jr., Furin J. Pan-tuberculosis regimens: an argument against. *Lancet Respir Med* 2018; **6**(4): 240-2.
30. Wallis RS, Cohen T, Menzies NA, Churchyard G. Pan-tuberculosis regimens: an argument for. *Lancet Respir Med* 2018; **6**(4): 239-40.
31. Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med* 2017.
32. Kendall EA, Fofana MO, Dowdy DW. Burden of transmitted multidrug resistance in epidemics of tuberculosis: a transmission modelling analysis. *Lancet Respir Med* 2015; **3**(12): 963-72.
33. Dheda K, Esmail A, Pooran A, Randall P, Calligaro G, Meldau R, Mottay L. Quantifying infectiousness of undiagnosed tuberculosis cases and the impact of enhanced community-based active case finding strategy using novel diagnostic tools – a randomized controlled trial (XACT-II). 44th Annual Department of Medicine Research Day; 2018 20th of September 2018; University of Cape Town; 2018.
34. Dorman SE, Schumacher SG, Alland D, et al. Xpert MTB/RIF Ultra for detection of *Mycobacterium tuberculosis* and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *The Lancet Infectious diseases* 2018; **18**(1): 76-84.
35. WHO. Rapid Implementation of the Xpert MTB/RIF diagnostic test: Technical and operational 'How-to' Practical considerations. Geneva, Switzerland: World Health Organisation, 2011.
36. Xie YL, Chakravorty S, Armstrong DT, et al. Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis. *The New England journal of medicine* 2017; **377**(11): 1043-54.
37. Dheda K, Limberis JD, Pietersen E, et al. Outcomes, infectiousness, and transmission dynamics of patients with extensively drug-resistant tuberculosis and home-discharged patients with programmatically incurable tuberculosis: a prospective cohort study. *Lancet Respir Med* 2017; **5**(4): 269-81.
38. Organisation WH. The use of next-generation sequencing technologies for the detection of mutations associated with drug resistance in Mycobacterium tuberculosis complex: technical guide. Geneva, 2018.

39. Coll F, Phelan J, Hill-Cawthorne GA, et al. Genome-wide analysis of multi- and extensively drug-resistant Mycobacterium tuberculosis. *Nat Genet* 2018; **50**(2): 307-16.
40. Ezewudo M, Borens A, Chiner-Oms A, et al. Integrating standardized whole genome sequence analysis with a global Mycobacterium tuberculosis antibiotic resistance knowledgebase. *Sci Rep* 2018; **8**(1): 15382.
41. Miotto P, Tessema B, Tagliani E, et al. A standardised method for interpreting the association between mutations and phenotypic drug resistance in Mycobacterium tuberculosis. *Eur Respir J* 2017; **50**(6).
42. Consortium CR, the GP, Allix-Beguec C, et al. Prediction of Susceptibility to First-Line Tuberculosis Drugs by DNA Sequencing. *The New England journal of medicine* 2018; **379**(15): 1403-15.
43. Ruesen C, Riza AL, Florescu A, et al. Linking minimum inhibitory concentrations to whole genome sequence-predicted drug resistance in Mycobacterium tuberculosis strains from Romania. *Sci Rep* 2018; **8**(1): 9676.
44. Dheda K, Lenders L, Magombedze G, et al. Drug Penetration Gradients Associated with Acquired Drug Resistance in Tuberculosis Patients. *Am J Respir Crit Care Med* 2018.
45. Dheda. K, Lenders L, Gumbo T. New Insights into the Pathogenesis of Drug-Resistant TB and Implications for Clinical Management Keystone Symposia: Tuberculosis Co-Morbidities and Immunopathogenesis; 2016; Keystone Resort , Keystone, Colorado, USA; 2016.
46. Sarathy J DV, et al. Fluoroquinolone efficacy against tuberculosis is driven by penetration into lesions and activity against resident bacterial populations. *Antimicrob Agents Chemother* 2019; **in press**.
47. Park SI, Oh J, Jang K, et al. Pharmacokinetics of Second-Line Antituberculosis Drugs after Multiple Administrations in Healthy Volunteers. *Antimicrob Agents Chemother* 2015; **59**(8): 4429-35.
48. Deshpande D, Srivastava S, Chapagain M, et al. Ceftazidime-avibactam has potent sterilizing activity against highly drug-resistant tuberculosis. *Sci Adv* 2017; **3**(8): e1701102.
49. Srivastava S, Deshpande D, Nuermberger E, et al. The Sterilizing Effect of Intermittent Tedizolid for Pulmonary Tuberculosis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2018; **67**(suppl_3): S336-S41.
50. Deshpande D, Pasipanodya JG, Srivastava S, et al. Minocycline Immunomodulates via Sonic Hedgehog Signaling and Apoptosis and Has Direct Potency Against Drug-Resistant Tuberculosis. *J Infect Dis* 2018.
51. Lu P, Asseri AH, Kremer M, et al. The anti-mycobacterial activity of the cytochrome bcc inhibitor Q203 can be enhanced by small-molecule inhibition of cytochrome bd. *Sci Rep* 2018; **8**(1): 2625.
52. Hoagland DT, Liu J, Lee RB, Lee RE. New agents for the treatment of drug-resistant Mycobacterium tuberculosis. *Adv Drug Deliv Rev* 2016; **102**: 55-72.
53. Chikhale RV, Barmade MA, Murumkar PR, Yadav MR. Overview of the Development of DprE1 Inhibitors for Combating the Menace of Tuberculosis. *J Med Chem* 2018; **61**(19): 8563-93.
54. Venugopala KN, Khedr MA, Pillay M, et al. Benzothiazole analogs as potential anti-TB agents: computational input and molecular dynamics. *J Biomol Struct Dyn* 2018: 1-13.
55. Shenai S, Ronacher K, Malherbe S, et al. Bacterial Loads Measured by the Xpert MTB/RIF Assay as Markers of Culture Conversion and Bacteriological Cure in Pulmonary TB. *PloS one* 2016; **11**(8): e0160062.
56. Malherbe ST, Shenai S, Ronacher K, et al. Persisting positron emission tomography lesion activity and Mycobacterium tuberculosis mRNA after tuberculosis cure. *Nat Med* 2016; **22**(10): 1094-100.
57. Te Riele JB, Buser V, Calligaro G, et al. Relationship between chest radiographic characteristics, sputum bacterial load, and treatment outcomes in patients with extensively drug-resistant tuberculosis. *Int J Infect Dis* 2019; **79**: 65-71.
58. Montes Ruiz-Cabello M, Guirao Arrabal E, Caminero Luna JA. PET/CT for evaluation of the response to therapy and follow-up of patients with tuberculosis. *Med Clin (Barc)* 2017; **149**(9): 420-1.
59. Romanowski K, Balshaw RF, Benedetti A, et al. Predicting tuberculosis relapse in patients treated with the standard 6-month regimen: an individual patient data meta-analysis. *Thorax* 2018.
60. Kurbatova EV, Taylor A, Gammino VM, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis* 2012; **92**(5): 397-403.
61. Global Tuberculosis Report: World Health Organization, 2018.

62. WHO. WHO updated references on management of drug-resistant tuberculosis: guidelines for the programmatic management of drug-resistant tuberculosis—2011 update. Geneva: World Health Organization, 2011.
63. Lange C, Abubakar I, Alffenaar JW, et al. Management of patients with multidrugresistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement: ERS Publications, 2014.
64. Fox GJ, Anh NT, Nhung NV, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2017; **21**(3): 297-302.
65. Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; **40**(6): 1430-42.
66. Chang KC, Yew WW, Tam CM, Leung CC. WHO group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis. *Antimicrob Agents Chemother* 2013; **57**(9): 4097-104.
67. Guglielmetti L, Jaspard M, Le Du D, et al. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. *Eur Respir J* 2017; **49**(3).
68. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis, 2016 update. *WHO/HTM/TB/201604* 2016.
69. Kim CT, Kim TO, Shin HJ, et al. Bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis: a multicentre cohort study in Korea. *Eur Respir J* 2018; **51**(3).
70. Li Y, Sun F, Zhang W. Bedaquiline and delamanid in the treatment of multidrug-resistant tuberculosis: Promising but challenging. *Drug Dev Res* 2018.
71. Pontali E, Sotgiu G, Tiberi S, et al. Combined treatment of drug-resistant tuberculosis with bedaquiline and delamanid: a systematic review. *Eur Respir J* 2018; **52**(1).
72. Garcia-Prats AJ, Rose PC, Draper HR, et al. Effect of Coadministration of Lidocaine on the Pain and Pharmacokinetics of Intramuscular Amikacin in Children With Multidrug-Resistant Tuberculosis: A Randomized Crossover Trial. *Pediatr Infect Dis J* 2018; **37**(12): 1199-203.
73. Muller B, Chihota VN, Pillay M, et al. Programmatically selected multidrug-resistant strains drive the emergence of extensively drug-resistant tuberculosis in South Africa. *PLoSOne* 2013; **8**(8): e70919.
74. Harausz EP, Garcia-Prats AJ, Law S, et al. Treatment and outcomes in children with multidrug-resistant tuberculosis: A systematic review and individual patient data meta-analysis. *PLoS Med* 2018; **15**(7): e1002591.
75. Osman M, Harausz EP, Garcia-Prats AJ, et al. Treatment Outcomes in Global Systematic Review and Patient Meta-Analysis of Children with Extensively Drug-Resistant Tuberculosis. *Emerg Infect Dis* 2019; **25**(3): 441-50.
76. Taneja R, Garcia-Prats AJ, Furin J, Maheshwari HK. Paediatric formulations of second-line anti-tuberculosis medications: challenges and considerations. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2015; **19 Suppl 1**: 61-8.
77. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). Licence: CC BY-NC-SA 3.0 IGO. http://www.who.int/tb/publications: World Health Organization, 2018.