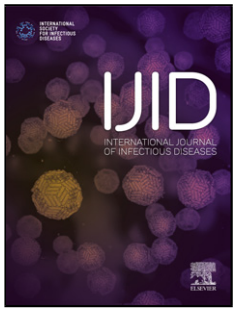

Title: The changing treatment landscape for MDR/XDR-TB - can current clinical trials revolutionise and inform a brave new world?

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PII: S1201-9712(19)30070-0
DOI: https://doi.org/10.1016/j.ijid.2019.02.006
Reference: IJID 3489

To appear in: *International Journal of Infectious Diseases*

Received date: 22 January 2019
Revised date: 4 February 2019
Accepted date: 9 February 2019

Please cite this article as: Honeyborne Isobella, Lipman Marc, Zumla Alimuddin, McHugh Timothy D.The changing treatment landscape for MDR/XDR-TB - can current clinical trials revolutionise and inform a brave new world?.*International Journal of Infectious Diseases* (2019), https://doi.org/10.1016/j.ijid.2019.02.006

IJID World TB Day Series article - March 2019

Invited viewpoint article

TITLE:

The changing treatment landscape for MDR/XDR-TB - can current clinical trials revolutionise and inform a brave new world?

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Keywords: Tuberculosis, drug resistance, MDR-TB, XDR-TB, clinical trials, treatment regimens

Word Count: 2,561 words

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Highlights:

1) **Multiple clinical trials are currently testing shortened drug regimens for MDR/XDR-TB, including with all oral regimens in study arms**
2) **Newly developed drugs such as Bdq and Dlm provide new treatment options for MDR/XDR-TB.**
3) **If trials are successful, treatment for MDR/XDR-TB could be reduced to 6-9 months as standard.**
4) **By 2022 best practice for managing MDR/XDR-TB will be informed by substantial clinical trial data**
5) **Re-purposing of existing drugs has proved useful in treatment of MDR/XDR-TB**

Tuberculosis (TB) is the top infectious disease cause of death worldwide. According to the latest World Health Organization Global Tuberculosis Report (WHO Report, 2018a), in 2017 TB was responsible for an estimated 1.3 million deaths among HIV-negative people and 300,000 deaths among HIV-positive people. There were 558,000 new cases of Rifampicin (Rif) resistant TB (RR-TB), 82% of which were resistant to at least Isoniazid as well (MDR-TB), and 8.5% with additional resistance to both a fluoroquinolone and a second-line injectable - extensively resistant (XDR-TB) (WHO Report, 2018a). These figures are alarming and emphasize that the chance of someone being cured and becoming disease free long-term decreases with increasing drug resistance, from over 85% for drug-susceptible TB (DS-TB), towards around half that with XDR-TB.

The relentless spread of MDR-TB and the high mortality rates are fuelled by the limited ability to test for resistance in resource-constrained settings, intermittent access to drugs, lack of useful alternative drugs, significant drug adverse effects, and poor adherence to medication continues. This in part reflects the inadequacy of the non-first line drug therapies for TB. To be effective, they need to be given for considerably longer; and therefore, the WHO guidelines for programmatic management of drug-resistant tuberculosis, updated in 2011 recommended that treatment for MDR-TB should remain at a staggering 20 months, including an injectable drug for at least 8 months and the use of a fluoroquinolone (WHO 2011). Up to that point, detection of resistant strains of *Mycobacterium tuberculosis* (*M.tb*) involved sophisticated culture-based susceptibility testing - often taking weeks to get results. In addition, these tests were generally not available in high TB incidence countries where there was the greatest need.

The landscape for detection of resistance was changed by introduction of rapid molecular tests such as lineprobe assays and the GeneXpert MTB-RIF Assay (Boehme et al., 2010) which simultaneously detects *M.tb* DNA and Rif-resistance. The GeneXpert system, for the first time, gave an option for the drug regimen to be better selected, by detection of Rif resistance in real time. Endorsed by the WHO (WHO 2010), it has successfully provided simple, effective detection MDR-TB, since Rif resistance is most commonly secondary to isoniazid (INH) resistance. Despite this, drug sensitivity testing for non-standard Rif mutations and other drugs remains a lengthy process requiring culture-based methods or increasingly the application of whole genome sequencing.

Following a diagnosis of MDR-TB it is estimated that only about two-thirds of treated cases have positive outcomes (Falzon et al., 2013). This is even worse for XDR-TB at 40% (Falzon et al., 2013) and reflects the lack of available options for healthcare workers to treat MDR/XDR-TB, poor tolerance and sub-optimal potency of the available regimens by patients.

In contrast to DS-TB, where treatment is informed by carefully conducted trials to determine combination treatment efficacy, until 2016 therapy for MDR/XDR-TB was largely empirical and based on expert opinion. The WHO treatment guidelines for drug-resistant tuberculosis, released in 2016 reflected the first big shift in treatment recommendations for MDR-TB, informed by several observational studies in multiple countries (WHO 2016). Cohort studies in Bangladesh recruited 206 patients with MDR-TB and after consecutively testing 6 different drug combinations, found 9 months' treatment with gatifloxicin (Gfx), clofazimine (Cfz), ethambutol (Emb) and pyrazinamide (Pza), supplemented by prothionamide (Pto), kanamycin (Km) (injectable) and high-dose isoniazid (INH) resulted in a relapse-free cure in 87.9% (CI 82.7-91.6) of individuals (Van Deun et al., 2010). Several meta-analyses including one of 9,153 patients from 32 observational studies identified treatments associated with improved response, such as the use of later-generation fluoroquinolones, and use of 4 or more likely-effective drugs during the intensive treatment phase, though concluded in highlighting the urgent need for randomised trials (Ahuja et al., 2012). The positive results seen in cohort studies led to a change in the WHO guidelines to recommend that RR-TB and MDR-TB treatment time could be reduced from 20 months to 9-12 months provided that patients have had no previous treatment with second-line TB drugs and where resistance to fluoroquinolones and second-line injectable drugs was excluded or not expected (WHO 2016).

The STREAM trial

The change in WHO guidelines in 2016 was informed by the non-randomised cohort studies, and again highlighted the lack of controlled clinical trial data. Although in 2012, the STREAM trial had started recruitment as the first-ever phase III, randomised controlled clinical trial testing a shorter MDR-TB regimen, even the early data were only available in 2017. It was to be the first open-label, multi-centre study setup to test the safety and effectiveness of a 'shorter regimen' (40-48 weeks) (based on the Bangladesh cohort study findings) and to compare it to the 18-24 months previous standard. The drug regimen was the same as the Bangladesh study except that Gfx was replaced with Moxifloxacin (Mfx) and the study included people living with HIV (Nunn et al., 2014).

The preliminary results of STREAM stage 1 were released in late 2017 at the 48th Union World Conference on Lung Health and followed by WHO key changes to treatment of multidrug- and rifampicin-resistant tuberculosis in August 2018 (WHO 2018b). Although not fully supporting non-inferiority, when compared to the standard treatment for MDR-TB, the STREAM stage 1 trial results reported that under trial conditions a nine-month regimen could be effective in 78.1% of those with MDR-TB compared to 80.6% of those on the standard 20 month's treatment. It should be noted that, under clinical trial conditions, the 20-month treatment arm outperformed the expected 54% success generally recorded in non-trial conditions. There are several potential further benefits to be considered for shorter regimens such as improved compliance, less side-effects due to taking the drugs for a shorter period, and potential cost reductions (demonstrated in the preliminary analysis for the Ethiopia site for both patients and the health system). There was no difference found in the number of patients with adverse events in the study versus the control. Based on the findings of the preliminary analysis, the WHO recommendations for using shorter course therapy under specific circumstances remain in place to date (WHO 2018b).

Two further studies evaluated the Bangladesh regimen for 12 months (with a minimum intensive phase of 4 months). Both found favourable outcomes (Kuaban et al., 2015) (Piubello et al., 2014).

STREAM trial stage 2

The 9-month regimen did not contain any novel drugs but was composed entirely of historically-tested drugs. Encouragingly it revealed that even without new anti-bacterial agents improved outcomes were possible for many patients presenting with MDR-TB.

STREAM stage 2 extends the results of STREAM stage 1, by introducing trial arms for MDR-TB that replace the injectable drug with bedaquiline (Bdq) (Sirturo, TMC207). Bdq, first discovered in 2004, was fast-tracked by the FDA and approved for use, in combination with other drugs, for treatment of MDR and XDR-TB in 2012. The drug is currently being tested in STREAM stage 2 and other clinical trials, but there are some potentially serious adverse-effects. These include QT prolongation on patient's

electrocardiograms (ECG); and a reported increased risk of death in the Bdq arm of a phase 2b clinical trial (Diacon et al., 2014). This led to initial caution by the WHO in recommending its use. This was despite the investigators within the study not attributing the increased number of deaths to the use of Bdq. In support of this, a large retrospective cohort study of individuals with MDR/XDR-TB in South Africa, found that adding Bdq to a treatment regimen was associated with a reduction in all-cause patient mortality (Schnippel et al., 2018). Having a pill-only regimen would be a considerable additional advantage for patients, when taken together with the reduced treatment time. Additionally, the study has a 6-month treatment arm. It cannot be overstated the significant advance if some patients with MDR-TB could be treated for the same duration as currently recommended for fully DS-TB. The study started enrolling in March 2018 and the results are likely to be available in 2021.

Phase 3 Trials with new and re-purposed drugs

Delamanid (Dlm) was made available by Otsuka and used in the Otsuka trial 213 to determine the efficacy of Dlm in treating MDR-TB in combination with other drugs for 6 months. It was a multi-centre study where 341 patients received Dlm in addition to an optimised standard treatment, whilst 170 received placebo instead of Dlm. Although use of Dlm led to quicker culture conversion, favourable results at 24 months were similar between the placebo and Dlm arms. These results were first presented at the 48th Union World Conference in 2017 and recently fully reported (von Groote-Bidlingmaier et al., 2019).

Pretomanid (Pa), a drug with a novel mechanism, has shown good efficacy against *in vitro* tested TB isolates resistant to other drugs (Lenaerts et al., 2005); whilst animal studies suggested it is active against both replicating and non-replicating *M. tuberculosis* (Tyagi et al., 2005). Notably Pa appears to have less side-effects than Bdq (Ginsberg et al., 2015) (Dawson et al., 2015) making it an excellent candidate to test in new MDR and XDR-TB regimens.

Linezolid (Lzd), active against gram positive bacterial organisms and licenced to treat MRSA, has been used off-label for MDR/XDR-TB with some success. It is a new drug that can be added to the limited

treatment options for patients. Studies in 2012 suggested that Lzd was effective in patients with no other treatment options left: 79% culture-converted after 4 months using the drug (Lee et al., 2012). This was also supported by PET/CT imaging in both macaques and humans using Lzd monotherapy for XDR-TB (Coleman et al., 2014). However, there were issues regarding patient tolerance and adverse events, such as optic neuropathy. Recent meta-analyses suggest that Lzd is positively associated with MDR-TB treatment success (Collaborative Group for the Meta-Analysis of Individual Patient Data in et al., 2018) (Sotgiu et al., 2012).

Several clinical trials are testing the efficacy and safety of combinations of new and re-purposed drugs and their results will be known in 2-3 years. TB Alliance in partnership with PanACEA is evaluating a Bdq, Pa, Mfx and Pza regimen (SimpliciTB) and attempting to show efficacy treating for 6 months using an all oral treatment course for MDR-TB. The results won't be available until 2022.

The NexT-5001 trial, run by the University of Cape Town, is testing 6-9 months of Bdq, Lzd, Levofloxicin (Lfx), Pza and either high-dose INH or ethionamide (Eto) or terizidone (Trd) daily (an all oral regimen) versus a conventional empiric injection-based regimen consisting of an intensive phase of 6-8 months kanamycin (Km), Mfx, Pza, Eto, Ter daily and an 18 month continuation phase of Mfx, Pza, Ter for both MDR and XDR-TB cases. The results of this study should be available in early 2019.

The endTB study (a partnership between Partners in Health, Médecins Sans Frontières, Interactive Research & Development and financial partner UNITAID) is testing whether using the new drugs Dlm and Bdq can benefit patients by providing a shorter, less toxic and injection-free treatment course for MDR-TB. The study results are projected to be available in 2022. The regimens consist of 5 combinations of drugs including Bdq, Lzd, Mfx, Pza, Cfz, Dlm, Lfx all for 9 months.

Notably the WHO report released in 2018 gave a revised grouping of TB medicines recommended for use in longer MDR-TB regimens with agents selected grouped into 3 categories and chosen in descending order from A to C. Medicines to be prioritised are in Group A: Lfx/Mfx, Bdq and Lzd. This

highlights the expected benefit of adding Bdq and Lzd to the MDR-TB regimen despite some of the potential toxicities of these drugs. Those in group B are added next: Cfz, Trd/cycloserine and then group C, which are selected to complete the regimen and when agents from A and B cannot be used: Emb, Dlm, Pza, imipenem-cilastatin, meropenem, amikacin (streptomycin), Eto/Pto, p-amino salicyclic acid. There are also recommendations for regimen design to take into account whether there are drug-susceptibility testing results available, the preference for an oral drug over an injectable and the drug resistance levels in the local population (WHO 2018b). A summary of the drugs described in this article are given in Table I.

XDR-TB

What about XDR-TB? The STREAM trials exclude patients with XDR-TB. However, NiX-TB using an open-label design, and commenced in 2015, is the first pill-only trial for XDR-TB. It is testing a combination of novel and re-purposed drugs; and moves away from using current, conventional anti-TB drugs completely with its combination of Bdq, Lzd and Pa (BPaL) (TB Alliance). Also it aims to reduce treatment time to 6-9 months. If successful the study could transform the treatment of XDR-TB by providing an injection-free regimen. The preliminary results reported at CROI 2017 were promising, with 86.7% of 30 patients relapse-free during 6 months follow-up, and the toxicity due to Lzd being manageable (Conradie et al., Croi 2017). Since it was open-label, the NiX-TB trial could be adapted, based on early study outcomes. This has informed another TB Alliance Trial - ZeNix, which began recruiting in 2018. It is also testing BPaL but with different arms, including a reduced Lzd concentration to better determine the balance between efficacy and toxicity. It is recruiting patients with both MDR and XDR-TB.

The Médecins Sans Frontières (MSF) sponsored study TB-PRACTECAL study is testing 3 different treatment arms including combinations of Bdq, Pa, Mfx, Lzd, Cfz for 6 months, with a comparator treatment being the locally accepted standard of care, consistent with the WHO recommendation. The results are expected in 2021 and includes individuals with XDR-TB.

An additional study, running at the same sites as the endTB study, is the endTB-Q study for individuals with fluoroquinolone resistance and includes a 6-month arm and a 9-month arm with no quinolone included in the regimen. All of the clinical trials discussed here are summarised in Table 2.

Summary

Based on both already published results and ongoing studies it is clear the landscape is changing in a positive way for treatment of both MDR and XDR-TB. The new clinical trials will provide a rigorous assessment of the drugs that are currently available in Phase III or beyond, and generate a large data set from multiple countries that can better inform the management of drug-resistant TB. Once trials have informed the optimal regimens some risks and issues will still need to be resolved. These will include how to financially support usage of drugs, such as Lzd and Bdq, in resource-constrained settings with their substantially higher costs, and potential issues of patient-adherence outside of the clinical trial setting, particularly with all oral regimens. There is also the compromise between restricting the use of new drugs to minimise the development of resistance, and making them available at scale to enhance available regimens. With increasing demand for these drugs, the potential for generic drug production to reduce costs plus the encouragement of 'goodwill' by partnerships with pharmaceutical companies, it is hoped that these issues can be overcome.

In parallel with bactericidal drugs there is also the potential for adjunctive therapies. Host-directed therapies could potentially be used in synergy with optimised drug regimens to boost or protect the host tissues or cells. Therapies could include corticosteroids, TNF-α inhibitors, phosphodiesterase inhibitors and matrix-metalloproteinases (Ordonez et al., 2014), as well as infusion of autologous mesenchymal stromal cells (Skrahin et al., 2014). With recent advances in rapid molecular drug susceptibility testing (Xie et al., 2017) and judicious prescribing stewardship of the newly available drugs, including an all oral treatment regimen (WHO 2018b) we anticipate a substantial impact on the treatment of MDR and XDR-TB as new recommendations emerge from ongoing clinical trials.

Conflict of interest: IH and TDMcH receive funding for participation in SimpliciTB, NiX-TB, ZeNix (TB Alliance) and TB-PRACTECAL (Médecins Sans Frontières). AZ and ML have no conflict of interest.

Funding Source: This publication is part the PANDORA-ID-NET (RIA 2016E-1609) and CANTAM2 (RegNet2015-1045), EACCR2 (RegNet2015-1104) Networks of Excellence grants funded by the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme, which is supported by Horizon 2020, the European Union's Framework Programme for Research and Innovation. The views and opinions of authors expressed herein do not necessarily state or reflect those of EDCTP.

Ethical approval: Not applicable

Acknowledgements: IH, TDMcH and AZ are members of the PANDORA-ID-NET Consortium and members of Central Africa Network on Tuberculosis (CANTAM2), East African Consortium for Clinical Research (EACCR2). All three consortia are supported by the European and Developing Countries Clinical Trials Partnership (EDCTP2) programme. All three consortia are supported by the European and Developing Countries Clinical Trial Partnership (EDCTP).

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Table 1: Summary of the drugs in this article including existing, re-purposed, re-used and new drugs

Drug	*Acronym*	*Mode of action*	*Existing/New/re-purposed/re-used To Tuberculosis treatment*	*Original use*
Amikacin	Ami	Aminoglycoside. Inhibits protein synthesis	Re-purposed	Gram-negative infections resistant to gentamicin
Bedaquiline	Bdq	Blocks proton pump for ATP synthase of mycobacteria	New	N/A
Clofazimine	Cfz	Inhibits bacterial proliferation + increases bacterial phospholipase A2 which are toxic	Re-purposed	Leprosy
Cycloserine	Cs	Inhibits cell wall synthesis	Existing	N/A
Delamanid	Dlm	Blocks manufacture of mycolic acids, destabilising the bacterial cell wall	New	N/A
Ethambutol	Emb	Obstructs formation of the bacterial cell wall	Existing	N/A
Ethionamide	Eto	Inhibits InhA, thought to inhibit synthesis of mycolic acid	Existing	N/A
Gatifloxicin	Gfx	Inhibits bacterial DNA gyrase and topisomerase IV	Re-purposed	Gram-negative and positive organisms Respiratory tract and eye infections
Imipenem-cilistatin	I/C	Inhibition of cell wall synthesis	Re-purposed	Aerobic & anaerobic Gram-positive and Gram-negative infections
Isoniazid	Inh	Inhibits mycolic acid synthesis	Existing	N/A
*Kanamycin**	Km	Aminoglycoside. Inhibits protein synthesis	Existing	N/A
Levofloxicin	Lfx	Inhibitor of DNA gyrase, a type II topoisomerase	Re-purposed	Wide range of bacterial infections
Linezolid	Lzd	Suppresses bacterial protein production	Re-purposed	Gram positive infections
Meropenem	Mem	Inhibition of cell wall synthesis	Re-purposed	Aerobic & anaerobic Gram-positive and Gram-negative infections
Moxifloxicin	Mfx	Inhibitor of DNA gyrase, a type II topoisomerase	Re-purposed	Wide range of infections, including CAP
p-amino salicylic acid	PAS	Precise mechanism not fully characterised	Re-used	N/A
Pretomanid	Pa	Cell wall inhibition and respiratory toxicity	New	N/A
Prothionamide	Pto	Inhibits InhA and mycolic acid synthesis	Re-used (interest waned due to poor tolerability)	N/A
Pyrazinamide	Pza	Cause accumulation of pyrazinoic acid inside the bacillus	Existing	N/A
Streptomycin		Aminoglycoside. Inhibits protein synthesis	Existing	N/A
Terizidone	Trd	Inhibits cell wall synthesis (a structural analogue of cycloserine)	Existing	N/A

CAP – community acquired pneumonia *August 2018 WHO guidance on MDR-TB recommended that Kanamycin should no-longer be used to treat MDR-TB

Table 2 – Summary of trials described in this article

Trial, Sponsor & recruitment countries	Study Design	MDR/XDR patients recruited	Shortest treatment duration under test	Recruitment started	Results available/ estimated to be available	Key points
Otsuka 213 (NCT01424670) Sponsor: Otsuka Countries (7): Estonia/Latvia/Lithuania/Peru Moldova/Philippines/South Africa	Recruited: 511 participants 341 received Dlm + OBR **OR** 170 received placebo + OBR	MDR only	18-24 mths	2011	2017	18-69 years No clinically relevant difference between the 2 study arms
STREAM stage 1 (ISRCTN78372190) Sponsor: IUATLD, Inc Countries (4): Vietnam/Mongolia/Ethiopia/ South Africa	Recruited: 424 participants WHO standard (18-24 mths) **OR** Mfx, Cfz, Emb, Pza, Pto, Km & high dose Inh (40-48 wks)	MDR only	9 mths	2012	Preliminary results: 2017 Full results: mid-2018	Includes adults ≥18 yrs 78.1% efficacy in 9 month arm vs 80.6% in control arm
STREAM stage 2 (NCT02409290) Sponsor: IUATLD, Inc Countries (8): Mongolia/Ethiopia/South Africa Moldova/Georgia/India/ Uganda	Target: 1155 participants A: WHO standard B: Cfz, E, Mfx, Pza (40 wks)+ INH, Km, Pto (1st 16 wks) C: Bdq, Cfz, E, Lfx, Pza (40 wks) + Inh & Pto (1st 16 wks) D: Bdq. Cfz, Lfx, Pza (28 wks), + Inh & Km (1st 8 wks)	MDR only	7 mths	2016	2021	Includes children ≥15 yrs Includes an oral only study arm
endTB (NCT02754765) Sponsor: MSF Countries (7): Georgia/India/South Africa/Peru Kazakhstan/Lesotho/Pakistan	Target: 750 participants 1: Bdq, Lzd, Mfz, Pza (9 mths) 2: Bdq, Cfz, Lzd, Lfx, Pza (9 mths) 3. Bdq, Dlm, Lzd, Lfx, Pza (9 mths) 4. Dlm, Cfz, Lzd, Lfx, Pza (9ths) 5. Dlm, Cfz, Mfz, Pza (9ths)	MDR only	9 mths	2016	2022	Includes children ≥15 yrs Testing 5 new all oral 9 month regimens

	6. WHO standard (18-24 mths)					
endTB-Q **Sponsor: MSF** **Countries (7):** **Georgia/India/South Africa Kazakhstan/Lesotho Pakistan/Peru**	Target: 500 participants 1: Bdq, Dlm, Cfz, Lzd (6 mths) 2: Bdq, Dlm, Cfz, Lzd (9 mths) 3: WHO standard	MDR/XDR	6 mths	2019	2022	Includes children ≥15 yrs Includes a 6 month regimen
NiX-TB **(NCT02333799)** **Sponsor: GATB** **Countries (1):** **South Africa**	Recruited: 109 participants Bdq, Pa, Lzd (6 mths) + option of 9 mths for those still culture positive at 6 mths	Non-responsive MDR Treatment intolerant MDR XDR	6 mths	2015	Preliminary results: 2017 Full results: expected Feb 2019	Includes children ≥14 yrs Study has an adaptive design to incorporate new treatments if they become available during the trial
ZeNiX **(NCT03086486)** **Sponsor: GATB** **Countries (4):** **Georgia/South Africa Russia/Moldova**	Target: 180 participants 1. 1200mg Lzd, Pa, Bdq (26 wks) 2. 1200mg Lzd (9 wks) + Pa & Bdq for 26 wks 3. 600mg Lzd, Pa & Bdq for 26 wks 4. 600mg Lzd (9 wks) +Pa & Bdq for 26 weeks	Non-responsive MDR Treatment intolerant MDR XDR	26 wks	2018	2022	Includes children ≥14 yrs If week 16 sample remains culture positive treatment may be increased to 39 weeks
TB-PRACTECAL **(NCT02589782)** **Sponsor: MSF** **Countries (3):** **Uzbekistan/South Africa/Belarus**	Target: 630 participants 1. Bdq, Pa, Mfz, Lzd (6 mths) 2. Bdq, Pa, Lzd, Cfz (6 mths) 3. Bdq, Pa, Lzd (6 mths) 4. WHO standard	MDR/XDR	6 mths	2017	2021	Includes adults ≥18 yrs All oral study arms
NExT-5001 **(NCT02454205)** **Sponsor: UCT** **Countries (1):** **South Africa**	Target: 300 participants 1.Km, Mfz, Pza, Eto, Trd (6-8 mths) 4 oral drugs will continue after 2 consecutive negative for 18 mths without Km 2.Lzd, Bdq, Lfx, Pza + Eto OR high dose Inh OR Trd (6-9 mths)	MDR only	6 mths	2015	2019	Includes adults ≥18 yrs Includes an oral only study arm
SimpliciTB (NC-008) **(NCT03338621)** **Sponsor: GATB**	Target: 450 participants Bdq, Pa, Mfz, Pza (6mths)	MDR only	6 mths	2018	2022	Includes adults ≥18 yrs Includes an oral only study arm

Countries (10) across: Africa/Asia/Europe/South America						

Bedaquiline (Bdq), Clofazimine (Cfz), Delamanid (Dlm), Ethambutol (Emb), Ethionamide (Eto), Isoniazid (Inh), Kanamycin (Km), Levofloxicin (Lfx), Linezolid (Lzd), Moxifloxicin (Mfx), Pretomanid (Pa), Prothionamide (Pto), Pyrazinamide (Pza), terizidone (Trd) OBR – optimised background regimen Mths – months Wks – weeks, Otsuka – Otsuka Pharmaceutical Development & Commercialization, Inc, GATB – Global Alliance for drug development
IUATLD – International Union Against Tuberculosis and Lung Disease, MSF - Médecins Sans Frontières, UCT – University of Cape Town