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Drug Resistant Tuberculosis: Challenges and Progress

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Background

Treatment of drug susceptible TB conducted under strong national TB programs (NTPs) using standard four drug therapy and directly observed therapy (DOT) has led to relapse-free cure rates over 95% and dramatic national declines in TB incidence. This success has required consistent allocation of substantial money and resources. Conversely, poorly organized and underfunded NTPs result in unsupervised and inappropriate treatment, leading to treatment failure and the development of drug resistance, which is then spread to others [1]. The management of drug-resistant TB (DR-TB) is much more difficult than drug-susceptible TB, leading to epidemic spread of DR-TB in several countries. Drug resistance represents a major threat to global TB control and in this section we will explore new drugs and treatment regimens being developed to treat this deadly, communicable disease. Failure to control DR-TB could have disastrous consequences [2].

Multidrug-resistant TB (MDR-TB) is defined as TB that is resistant isoniazid (INH) and rifampin [3]. According to the Centers for Disease Control (CDC), in 2013 there were 95 new cases of confirmed MDR-TB in the U.S., representing 1.2% of the total 9582 new TB cases reported, and 92% of the MDR-TB patients were foreign-born [4]. Per the World Health Organization (WHO) Global Tuberculosis Report, there were an estimated 480,000 new cases of MDR-TB in the world in 2013, accounting for 3.5% of the total estimated 9 million TB cases [3]. Estimates are used because many of the countries with high MDR-TB incidence lack the resources and investment to accurately diagnosis drug resistance on a national scale. Actual notifications were received for 136,412 people with MDR-TB or rifampicin-resistant TB, and of these, 96,617 (71%) were started on treatment. Treatment outcomes are available for 52,206 patients from 2011 with 48% reported as successfully

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completing treatment. The WHO estimates that 210,000 of the 480,000 MDRT-TB patients died. While these numbers represent improvement, global control of MDR-TB remains dismal: less than one-third are diagnosed, about one-fifth are treated, and about 5% successfully complete treatment. The overwhelming majority of MDR-TB patients in the world are likely to have poor outcomes, causing great suffering and continued transmission.

A small subset, estimated at 9% of people with MDR-TB, have extensively drug-resistant TB (XDR-TB). XDR-TB is defined as MDR-TB with additional resistance to any fluoroquinolone and to at least one of three injectable agents (kanamycin, amikacin, or capreomycin). One hundred countries reported a case of XDR-TB in 2013, and of the 1269 patients reported in the 2011 cohort only 284 (22%) completed their treatment successfully and 438 (35%) patients died [3].

Resistance mechanisms and current approaches to treatment

Soon after the discovery and initial use of streptomycin to treat TB in the 1940s it became clear that single drug therapy led to the rapid development of drug resistance, resulting in high failure rates [5, 6]. This recognition led to the development of combination therapy using at least two active drugs to prevent resistance [7]. It was also noted that treatment beyond seemingly successful treatment - resolution of symptoms and microbiological clearance - was necessary to avoid relapse. The addition of INH, an agent with potent early bactericidal activity, led to effective combination therapy with high success rates after treatment for 18-24 months [8]. The introduction of rifampicin allowed a dramatic shortening of the treatment course to 6-9 months [9]. Ethambutol, an oral agent with relatively low toxicity, offered protection when drug resistance to INH or rifampicin was present. Finally, the addition of pyrazinamide reliably allowed for shortening of treatment course to 6 months for the majority of cases (for review, see [10]).

While the phenomenon of drug resistance was quickly recognized, the underlying biological mechanisms were only recently elucidated. This has allowed for a progressive shift from culture-based, “phenotypic” drug resistance testing to mutation-based genotypic resistance testing. It is noteworthy that all drug resistance mutations found today are based on spontaneous chromosomal alterations. Mutations in drug target proteins are fairly restricted to confined gene loci and can easily be detected. Examples include the *rpoB* and *gyrA* genes, conferring resistance to rifampicin and fluoroquinolones, respectively. They can be quickly identified by semi-automated nuclear acid amplification tests (NAAT). A remarkable example, that is revolutionizing TB diagnosis, is the Xpert MTB/RIF (Cepheid), a fully-automated platform capable of NAAT testing for *M. tuberculosis* and rifampicin resistance within 2 hours [11]. In contrast to target protein mutations, mutations in prodrug-activating enzymes are much more heterogeneous [12], making them more difficult to capture in automated systems.

Standard therapy for drug-susceptible TB: mechanisms and resistance

INH has excellent early bactericidal activity resulting in a rapid drop in CFU after beginning treatment [13]. It is a prodrug, which is activated by the catalase peroxidase KatG. The activated INH forms chemical entities with NAD(P)⁺ coenzymes and inhibits the target

protein InhA, an enoyl-acyl carrier protein which takes part in mycolic acid synthesis. Mutations in the *katG* gene confer high-level INH resistance. The most common single base mutation S315T leads to decreased INH substrate affinity at expense of only modest reduction in overall catalase activity [13]. Other mutations, including missense and deletions, have been described. Alternatively, increased expression of *inhA* caused by alterations in the promoter region is associated with low level INH resistance as well as cross resistance to ethionamide [14, 15].

Rifampicin has excellent sterilizing activity allowing for shorter treatment without relapse [16]. Rifampicin interferes with RNA synthesis by inhibition of the RNA polymerase RpoB. Resistance occurs spontaneously at a frequency of 1×10^{-7} to 10^{-8} bacilli via a single mutation in a well-defined region of the gene, which makes it detectable by molecular assays [17]. In contrast to INH, rifampicin mono-resistance is uncommon [18], making it a useful surrogate marker for MDR-TB [11, 19].

Pyrazinamide (PZA) is utilized for its sterilizing activity, which allowed for reduction in treatment length to 6 months. It is a prodrug that is activated by pyrazinamidase, coded for by *pncA*. The resultant pyrazinoic acid inhibits fatty acid synthetase 1 [20]. The majority of described resistance mutations are found scattered over the *pncA* gene, which makes rapid molecular detection difficult [21]. Furthermore, the pH dependence of PZA activity makes culture-based phenotypic drug resistance testing challenging.

Ethambutol is primarily used to prevent acquired drug resistance in the setting of unknown INH resistance. It is usually discontinued once drug-susceptibility is confirmed. Ethambutol inhibits the gene product of the *embCAB* cluster, which codes for an arabinosyl transferase necessary for arabino-galactan synthesis, a constituent of the mycobacterial cell wall [22]. Resistance mutations leading to overexpression or structural alteration have been identified [23].

Current treatment regimen for MDR-TB – second line agents

Treatment regimens for MDR-TB are complex. They rely on drugs with reduced efficacy and increased toxicity. Individual regimens are compiled in a stepwise approach, based on the WHO group scheme and taking drug susceptibility test results into account (Table 1). To start, a drug with preserved activity is picked from group 1. Due to limited activity, PZA and ethambutol should only be used as an adjunct to the regimen. Then, an injectable agent and a fluoroquinolone are added. Group 4 and 5 drugs are used to complement a regimen total of 4 drugs with the potential addition of PZA. The following paragraphs briefly describe mechanism and clinical utility of established second-line drugs [24].

Aminoglycosides and the cyclic polypeptide **capreomycin** interfere with protein synthesis on the ribosomal level. High resistance rates for streptomycin limit its use, and kanamycin or amikacin are the preferred agents. The most common resistance mutations affect the genes coding for 16S rRNA (*rrs*) and confer resistance to both kanamycin and amikacin [25]. The activity of capreomycin is only partly affected by these mutations and may still be of clinical use. Mutations in *tlyA*, which codes for a methyl rRNA transferase, results in loss of rRNA methylation and has been associated with capreomycin resistance [26]. There have been

varying reports about different cross resistance patterns among the aminoglycosides and cyclic peptides. A systematic molecular study revealed several different mutations conferring a heterogeneous pattern of cross-reactivity, which cautions against generalizations about cross-resistance without phenotypic testing. [27].

Levofloxacin, moxifloxacin and gatifloxacin are the most studied **fluoroquinolones**. They target the DNA gyrase which is necessary for uncoiling of the circular chromosome during replication. It is coded for by two genes, *gyrA* and *gyrB*. Resistance is caused by a single base substitution in a confined location known as quinolone-resistance-determining region (QRDR) [28]. Fluoroquinolones reach high tissue levels and have clinical efficacy similar to INH [29]. They have been included in MDR-TB regimens for decades, and due to their efficacy and favorable side effect profile they remain a cornerstone of MDR-TB therapy [30-32].

Cycloserine and its structural analog terizidone, have activity against gram-positive bacteria and mycobacteria. They inhibit peptidoglycan synthesis by interfering with Ala-racemase and DAla-DAla synthetase. Their use is limited by CNS toxicity caused by partial NMDA receptor agonism. Resistance mechanisms are not well defined. Overexpression of the target racemase AlaA, which serves as a cycloserine “sink” has been described as a major resistance mechanism in experimental mycobacteria [33].

Ethionamide and prothionamide are thioamide drugs. Prodrug activation occurs by independent enzymes EthA and KatG. Like INH, Ethionamide and prothionamide target InhA to inhibit fatty acid synthesis. Mutations in the *inhA* promoter region cause high-level ethionamide resistance in conjunction with low-level INH resistance [15]. Patient tolerance can be challenging due to gastrointestinal side effects, and they are associated with hypothyroidism.

Beta-lactams are listed as Group 5 drugs, agents with unclear benefit. Inconsistent reports exist about the early bactericidal activity of amoxicillin-clavulanate [34, 35], but clinicians have used it as adjunct therapy in the treatment of MDR-TB for some time [36]. *M. tuberculosis* expresses a beta-lactamase, BlaC, which was identified as the major determinant that renders *M. tuberculosis* resistant to beta-lactams [37], but it is susceptible to inhibition by currently available beta-lactamase inhibitors clavulanate, tazobactam and sulbactam. The combination of carbapenems which act as slow substrates, and beta-lactamase inhibitors has been shown to have potent activity against otherwise drug-resistant strains [38].

Similar to other bacteria, peptidoglycan is an important constituent of the mycobacterial cell wall. It consists of longitudinal polysaccharide trunks which bear branches of oligopeptide side-strands. These oligopeptides branches are cross-linked by transpeptidase enzymes to form a stable mesh. Recently, alternative cross linking catalyzed by a different group of enzymes, the L_D transpeptidases has been found to be the dominant type of peptidoglycan of *M. tuberculosis* [39]. The L_D transpeptidases are effectively inhibited by carbapenems [40] and case series of patients treated with the combination of meropenem and clavulanate as part of an MDR regimen demonstrated promising results [41-43]. One major draw-back is

the need for intravenous infusion of meropenem. Therefore, the introduction of the oral carbapenems tebipenem and biapenem, which were shown to have activity against a collection of 21 MDR and XDR isolates [44], has raised considerable interest.

Clinical Trials

Given the poor performance of standard MDR-TB therapy along with its limited evidence base, there has been a substantial effort over the past decade to develop both new drugs and regimens specifically for DR-TB. Of note, most of the drugs used in the current treatment of MDR-TB have not been tested as single agents or in combination in randomized clinical trials. In addition to achieving relapse-free cure, an equally important part of therapeutic strategies for TB is preventing the development of drug-resistance, and treatment of all forms of TB requires the use of combination regimens [45]. The classic approach to TB drug development, in which a single new drug is tested in combination with an optimized background regimen, has resulted in the approval of two new anti-TB drugs: bedaquiline and delamanid. **Bedaquiline** is an oral diarylquinoline, a new class of antimycobacterial drugs that inhibit ATP synthase [46]. In 2012, it was approved by the FDA for the treatment of MDR-TB [47]. The approval was based on a two-stage phase 2b study. Phase 2b studies provide preliminary efficacy evidence, and usually utilize sputum culture conversion to negative as the primary outcome (unlike phase 3 trials, which follow patients for relapse). The first phase conducted from 2007 to 2008 in South Africa enrolled 47 newly-diagnosed MDR-TB patients treated with individualized therapy based on WHO guidelines and additionally randomized to receive bedaquiline vs placebo for a total of 8 weeks [48]. The study found significantly shorter times to sputum culture conversion at 8 weeks: 48% in the bedaquiline group vs 9% in the placebo group. There were no significant differences in severe adverse events, and absolute values for corrected QT interval were all less than 500 msec -an earlier phase 2a trial had demonstrated an increase in corrected QT among patients taking bedaquiline [49]. The second phase of the Phase 2b study enrolled 160 patients in Brazil, India, Latvia, Peru, the Philippines, Russia, South Africa, and Thailand. Patients were randomly assigned to receive either bedaquiline or placebo for 22 weeks, in addition to a five-drug regimen [50]. Patients in the bedaquiline group had significantly shorter time to culture conversion compared to placebo (83 vs. 125 days, $p < 0.001$), and higher rates of sputum culture conversion: 79% vs. 58% at 24 weeks ($p=0.008$). While the authors reported no significant differences in adverse events, there were 10 deaths out of 79 patients (13%) in the bedaquiline group compared with 2 out of 81 patients (2%) in the placebo group. Nine of the 10 deaths occurred after completion of study drug, there was no association with QT prolongation, and none were considered to be related to bedaquiline [50]. The deaths led to the addition of a black-box warning regarding the increased risk of death as well as QT prolongation [51]. Additionally, the CDC published provisional guidelines recommending that bedaquiline be used only for MDR-TB patients “when an effective regimen cannot otherwise be provided” [52]. Preliminary reports suggest that in those situations, including XDR-TB, bedaquiline can be an effective addition to DR-TB regimens [53].

Similar to bedaquiline, **delamanid** was studied as a single drug added to an optimized background regimen. Delamanid is derived from the nitroimidazole class of compounds that

have been shown to inhibit mycolic acid synthesis. A phase 2b trial, with 2 month sputum culture conversion as the primary efficacy endpoint, enrolled 481 patients with pulmonary MDR-TB in nine countries. Patients were randomized to receive either delamanid or placebo for 2 months in combination with a background regimen [54]. A significantly higher proportion of patients in the delamanid vs placebo group achieved culture conversion by 2 months (45.4% vs 29.6%, $p = 0.008$). Adverse events were similar in the groups, but there was a significant, dose-dependent increase in the frequency of QT prolongation with 3.8% of placebo, 9.9% of delamanid 100mg group, and 13.1% of delamanid 200mg group patients with QT prolongation [54]. A follow-up observational study, found favorable outcomes, defined as cure or completion of treatment, in 75% of patients who received delamanid for 6 or more months compared to 55% who received 2 months or less [55].

Another drug that has been successfully utilized and studied as a single drug addition to the traditional DR-TB regimens is **linezolid**. Developed as an oxazolidinone, which inhibits protein synthesis by binding the 23S rRNA in the 50S ribosomal subunit of bacteria, linezolid demonstrated in-vitro activity against *M. tuberculosis* [56] and was adopted early-on for the treatment of highly resistant TB [57]. A randomized trial of 41 patients with sputum culture-positive XDR-TB conducted in South Korea from 2008-2011 in which patients received linezolid at a dose of 600mg daily in addition to an optimized background regimen found that 87% of patients had sputum culture conversion to negative during the first 6 months of linezolid treatment [58]. Notably, 82% of patients had significant adverse events including 21 cases of peripheral neuropathy, 7 episodes of myelosuppression, 7 cases of optic neuropathy, and 1 case of rhabdomyolysis. Additionally *M. tuberculosis* isolates from 4 patients developed linezolid resistance during treatment through acquired mutations in either 23S rRNA or ribosomal protein L3 [58]. Two other oxazolidinones are under development for the treatment of TB with the hope of developing a potent drug with a lower side effect profile. Sutezolid is a linezolid analog and has undergone phase 1 and 2 testing, with the latter demonstrating bactericidal activity, although lower than standard therapy [59]. AZD5847 is a second generation oxazolidinone that has recently undergone phase 2 testing with results expected in late 2015.

While both bedaquiline and delamanid have been licensed using a “single drug” approach, they still have limited safety and effectiveness data, and even less evidence for combinations of the two drugs [60]. This is especially important given the side effect profiles, including QT prolongation, which could limit their use in combination treatments. Although single drug studies are still ongoing, the experience with bedaquiline and delamanid highlights the limitations of this approach: decades are needed to identify therapeutic advances [61].

Alternative approaches to DR-TB clinical drug development

Citing the practical challenges of implementing MDR-TB treatment based on WHO guidelines, the Damien Foundation, a nongovernmental organization based in Bangladesh conducted a prospective observational study during which they used treatment outcomes and adverse drug reactions to guide adjustments in MDR-TB treatment with the goal of developing a well-tolerated, effective, and inexpensive regimen [62]. The study included 427 culture-confirmed MDR-TB patients in 6 successive cohorts of patient over 10 years,

beginning in 1997. The final regimen, known as the “**Bangladesh Regimen**” consisted of an intensive phase including kanamycin, clofazimine, gatifloxacin, ethambutol, high dose INH, PZA, and prothionamide given for 4 months (or until culture conversion), followed by a continuation phase of clofazimine, gatifloxacin, ethambutol, and PZA given for 5 months. Patients were follow for 2 years and relapse-free cure was obtained in 170 of 206 patients (82.5%) [62]. A follow-up study that included 515 patients treated with the same regimen demonstrated treatment success in 435 of 515 patients (84.5%) [63]. To validate the remarkable outcomes of the Bangladesh regimen, the British Medical Research Council (MRC) is conducting a phase III randomized controlled clinical trial, called **STREAM 1** to test this regimen against standard therapy [64]. The trial began in July 2012 in Ethiopia, Mongolia, South Africa and Vietnam and completed enrollment in early 2015. It marks the first successful randomized clinical trial of a DR-TB regimen. The Bangladesh regimen also highlights drug repurposing. Initially synthesized in 1954 as a TB drug [65], but primarily used since for the treatment of leprosy, **clofazimine** has made a surprising comeback as an important drug for the treatment DR-TB. Given promising retrospective data [66], Tang et al. conducted a prospective, randomized controlled study in China, enrolling 105 patient with sputum culture-positive MDR-TB [67] to receive either a WHO-based regimen with or without the addition of clofazimine. Treatment success (cure or treatment completion) was significantly higher in the clofazimine group (74% vs 54%, $p=0.04$). One unique side effect of clofazimine is a reddish-brown skin discoloration that is usually reversible with discontinuation, and 94% of patients in the clofazimine group developed skin discoloration.

Given the limitations of studying single drugs and the success of the Bangladesh studies, a regimen-based approach is now favored in which new, old and re-purposed drugs are given in various combinations in order to identify a drug combinations that can be used for treating TB and MDR-TB [68, 69]. This approach has been supported by regulatory agencies, including the U.S. FDA [70] and is being adapted by a number of clinical trials as described in Table 2 below [71, 72]. Some of the trials focus on finding a “universal regimen” that can be used for patients with pan-susceptible and drug-resistant forms of TB. The development of **pretomanid**, a new nitroimidazole, followed this approach. Unlike the phase 2b trials of bedaquiline and delamanid, which added a single drug to an optimized background regimen, pretomanid was investigated as part of a totally new TB regimen for both drug susceptible and DR-TB. The regimen, consisting of pretomanid, PZA, and moxifloxacin, was studied in a randomized controlled phase 2b trial of 207 patients with drug-susceptible pulmonary TB [73]. In addition, there was an MDR-TB arm that received the same regimen. The combination, which was safe and well-tolerated with superior bactericidal activity, is now being tested in the phase 3 “**STAND**” trial enrolling patients with drug susceptible and MDR-TB [74]. Other trial strategies focus on using novel methodologic strategies for identifying regimens based on early safety and efficacy indicators. The **PanACEA** research group in using the Multi-Arm Multi-Stage (MAMS) design to allow for several different treatment regimens to be evaluated in a single trial [75, 76]. These approaches have been adapted from clinical trials in cancer [77], and it is hoped that they can not only identify full regimens instead of single drugs, but also rapidly identify candidate regimens to move forward into phase III trials and thus shave years off of the time it takes to advance programmatic use of new drugs [78].

While trials of new drugs and regimens for TB and DR-TB are advancing at a historic pace, the future control of DR-TB will require a clearer understanding of the mechanisms and impact of drug resistance to better inform trial design. Currently, the limited knowledge that exists about the clinical implications of drug-resistance mutations has led to a situation in which mechanisms of resistance play little role in regimen selection or design. For example, there have been limited data published showing there may be cross-resistance between bedaquiline and clofazimine [79], which could have profound implications for DR-TB regimens that plan to use both drugs together. Understanding resistance goes beyond identifying specific mutations, such as *rpoB*, but rather takes a holistic approach that incorporates epistasis and bacterial fitness [80]. Epistasis is the phenomenon of multiple genetic interactions that create a phenotype, such that a single mutation can manifest in different ways depending on the modifying gene interactions of the genetic background [81]. Fitness is the concept that mutations can have a physiological cost, affecting the growth rate or virulence of the mutated bacilli. In depth understanding of these complex interactions is now possible with whole genome sequencing (WGS). The goal is to combine genetic and clinical information to create supranational surveillance for emerging resistance and guide the construction of future DR-TB regimens.

Conclusion

Antimicrobial resistance is a natural evolutionary process, which in the case of *M. tuberculosis* is based on spontaneous chromosomal mutations, meaning that well-designed combination drug regimens provided under supervised therapy will prevent the emergence of drug-resistant strains. Unfortunately, limited resources, poverty and neglect has led to the emergence of DR-TB throughout the world, particularly in the most vulnerable populations. The international community has responded with financial and scientific support leading to new rapid diagnostics, new drugs and regimens in advanced clinical development, and an increasingly sophisticated understanding of resistance mechanisms and their application to all aspects of TB control and treatment. While the obstacles are enormous, it is an exciting time based on optimism for substantial improvements for patients with DR-TB. Ultimately, for long-range success we must not lose sight of the patient, for all new drugs and scientific advancements will be for naught if TB patients do not receive adequate, well-supervised care.

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-Antimicrobial resistance is a natural evolutionary process, which in the case of *M. tuberculosis* is based on spontaneous chromosomal mutations, meaning that well-designed combination drug regimens provided under supervised therapy will prevent the emergence of drug-resistant strains.

-Unfortunately, limited resources, poverty and neglect has led to the emergence of DR-TB throughout the world, particularly in the most vulnerable populations.

-The international community has responded with financial and scientific support leading to new rapid diagnostics, new drugs and regimens in advanced clinical development, and an increasingly sophisticated understanding of resistance mechanisms and their application to all aspects of TB control and treatment.

-While the obstacles are enormous, it is an exciting time based on optimism for substantial improvements for patients with DR-TB.

-Ultimately, for long-range success we must not lose sight of the patient, for all new drugs and scientific advancements will be for naught if TB patients do not receive adequate, well-supervised care.

Table 1WHO group scheme of *M. tuberculosis* drugs

Group 1	Group 2	Group 3	Group 4	Group 5
First line drugs	Injectable drugs	Fluoroquinolones	Oral bacteriostatic second-line drugs	Drugs with unclear efficacy
Isoniazid, rifampicin, pyrazinamide, ethambutol	Kanamycin, amikacin, streptomycin, capreomycin, viomycin	Moxifloxacin, levofloxacin, gatifloxacin, ofloxacin	Pro-/ethionamide, Cycloserine and Terizidone, PAS, thiacetazone	Clofazimine, amoxicillin/clavulanic acid, clarithromycin, linezolid, imipenem

Table 2
Current and planned Phase III and pragmatic clinical trials of new regimens for DR-TB

Trial Name	Trial Number	Description	Trial Group	Enrolment Status
STREAM 1	ISRCTN78372190	4MCEZHKPro/5MCZE vs local regimen	MRC	Opened July 2012, results expected late 2017
STREAM 2	NCT02409290	4MCEZHKPro/5MCZE vs 4BLCEZHPro/5BLCEZ vs 2BLCZHK/4BLCZ Vs local regimen	IUATLD/MRC	Opens Q3 2015
Trial 213	NCT01424670	6D + OBR vs Placebo + OBR	Otsuka Pharmaceuticals	Opened Sept 2011, Results 2017
NIX-TB (XDR)	NCT02333799	6BPALzd (single arm)	TB Alliance	Opened Feb 2015
STAND NC-006/A5344	NCT02342886	6PaMZ (single arm for DR-TB)	TB Alliance/ACTG	Opened Feb 2015
Opti-Q	NCT01918397	L + OBR (high dose vs standard dose)	U.S. NIH	Opened January, 2015
NeXT	NCT02454205	LzdBLEthHZ (combination based on mutational analysis – given for 6-9 months) vs local regimen	South Africa MRC	Opened June, 2015
TB-PRACTECAL		6BPALzdM vs 6BPALzdC vs 6BPALzd vs local regimen	Medecins Sans Frontiers (MSF)	Expected start Q3 2015
END-TB		Various combinations of BDQ-PA_924, LZD, CFZ, LFX, MFX, PZA	UNITAID-Partners In Health, MSF	Protocol development

Abbreviations: M, moxifloxacin; C, clofazimine; E, ethambutol; Z, pyrazinamide; H, isoniazid; K, kanamycin; Pro, prothionamide; B, bedaquiline; D, delamanid; OBR, optimized background regimen; Pa, pretomanid; Lzd, linezolid; L, levofloxacin; Eth, ethionamide;