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Abstract: Tuberculosis (TB) remains the top killer from an infectious globally causing an estimated 1.674.000 million deaths worldwide. In 2016, WHO estimates 600.000 cases of rifampicin-resistant TB of which 490.000 had multidrug-resistant (MDR) and less than half of them survive after receiving currently recommended WHO treatment regimens, illustrating weaknesses in current treatment approaches. We review progress and advances in the development of new and repurposed TB drugs, treatment trials and host-directed therapies. Updates are provided on phase 3 trials of the new compounds bedaquiline, delamanid, pretomanid; phase 2 trials of sutezolid, SQ-109, LCB01-0371, PBTZ-169; and five new drugs in phase 1 development. Approved or repurposed drugs undergoing further testing are rifampicin, rifapentine, clofazimine, and linezolid. Update on ongoing clinical trials, which aim to shorten TB treatment and improve treatment outcome is given. Several new or repurposed antimicrobial drugs are in advanced trial stages for MDR-TB, and five antimicrobial drug candidates are in phase 1 (Q203, TBI-166, OPC-167832, GSK 070, TBA-7371) and 5 in pre-clinical studies. Specific issues of safety and toxicity; drug-drug interactions; Therapeutic Drug Monitoring are reviewed. A wide range of candidate host-directed therapies (HDTs) and immune-based treatments are being investigated to accelerate the eradication of M.tb infection and for use as adjunctive therapy in shortening duration of treatment, preventing permanent lung injury and improving treatment outcomes of MDR-TB. Ongoing clinical trials of HDTs for TB treatment, the current HDT development pipeline and translational research efforts for advancing further HDT options are presented.

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Tuberculosis: Progress and advances in development of new drugs, treatment regimens and host-directed therapies.

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## Search strategy and selection criteria

We searched reports published in English between November 1st 2014 and November 1st 2017 on Google, Google Scholar, PubMed, and ClinicalTrials.gov using the search keywords 'tuberculosis', 'multi-drug-resistant (MDR)-TB', 'extensively-drug-resistant (XDR) TB', Latent TB, 'drugs', 'trials', 'host-directed therapy/therapies', 'biological therapies' and 'immune-based therapies', 'prevention', 'tuberculosis' plus 'clinical trials', 'biomarkers', and 'drug development'. Individual searches were also performed for the following new and repurposed TB drugs: Q203, SQ109, PBTZ169, bedaquiline, delamanid, clofazimine, levofloxacin, moxifloxacin, pretomanid, pyrazinamide, rifapentine, rifampicin, linezolid, delpazolid and sutezolid. Information on new drugs and compounds was reviewed from the WHO Annual TB Report 2017, websites of the Global Alliance for TB Drug Development (TB Alliance), Unitaid, Treatment Action Group (TAG), and the Stop TB Partnership Working Group for New TB Drugs. Search results which were found to be relevant to this review were selected. We also collated and synthesised information on the development of new TB drugs, treatment regimens and host-directed therapies through communications with various stakeholders including review of presentations and abstracts at the October 2017 conference of the International Union Against Tuberculosis and Lung Disease held in Guadalajara, Mexico.

#### **ABSTRACT**

Tuberculosis (TB) remains the top killer from an infectious globally causing an estimated 1.674.000 million deaths worldwide. In 2016, WHO estimates 600.000 cases of rifampicinresistant TB of which 490.000 had multidrug-resistant (MDR) and less than half of them survive after receiving currently recommended WHO treatment regimens, illustrating weaknesses in current treatment approaches. We review progress and advances in the development of new and repurposed TB drugs, treatment trials and host-directed therapies. Updates are provided on phase 3 trials of the new compounds bedaquiline, delamanid, pretomanid; phase 2 trials of sutezolid, SQ-109, LCB01-0371, PBTZ-169; and five new drugs in phase 1 development. Approved or repurposed drugs undergoing further testing are rifampicin, rifapentine, clofazimine, and linezolid. Update on ongoing clinical trials, which aim to shorten TB treatment and improve treatment outcome is given. Several new or repurposed antimicrobial drugs are in advanced trial stages for MDR-TB, and five antimicrobial drug candidates are in phase 1 (Q203, TBI-166, OPC-167832, GSK 070, TBA-7371) and 5 in pre-clinical studies. Specific issues of safety and toxicity; drug-drug interactions; Therapeutic Drug Monitoring are reviewed. A wide range of candidate hostdirected therapies (HDTs) and immune-based treatments are being investigated to accelerate the eradication of *M.tb* infection and for use as adjunctive therapy in shortening duration of treatment, preventing permanent lung injury and improving treatment outcomes of MDR-TB. Ongoing clinical trials of HDTs for TB treatment, the current HDT development pipeline and translational research efforts for advancing further HDT options are presented.

## **INTRODUCTION**

In 2016, there were an estimated 1.67 million deaths due to tuberculosis (TB), making the disease the infectious disease killer worldwide. The 2017 World Health Organization (WHO) Annual TB Report estimates 490.000 cases of multidrug-resistant (MDR-TB) of whom less than half survive after receiving currently recommended WHO treatment regimens, 1-6 revealing the dire need for new therapies and approaches for improving TB treatment outcomes. Many challenges remain in developing optimal TB treatment regimens. Recently, concerted efforts between many stakeholders have worked towards developing short course, better tolerated and effective treatment regimens. Several new or repurposed antimicrobial drugs are in advanced trial stages for MDR-TB, and nine antimicrobial drug candidates are in phase 1 and 2 trials. A range of candidate host-directed therapies and immune-based treatments are also being developed to accelerate the eradication of *Mycobacterium tuberculosis* (*Mtb*) infection, shorten the duration of treatment, prevent permanent lung injury and prevent new drug resistance.

In this article, we review advances and progress in the new and repurposed TB drug-development pipeline, host-directed therapies. We provide an update of ongoing clinical trials, aimed at shortening TB treatment, improving treatment outcomes in MDR-TB, and preventing TB in people with latent TB infection (LTBI). Results of trials assessing the efficacy of three new anti-TB drugs, bedaquiline, delamanid, and pretomanid are reviewed. Specific issues of safety and toxicity; drug-drug interactions; Therapeutic Drug Monitoring (TDM) and use people living with HIV, those with TB meningitis, pregnant women, and children are discussed.<sup>8-14</sup>

#### PROGRESS IN NEW TB DRUG DEVELOPMENT AND EVALUATION

Development of new and repurposed drugs and treatment regimens for TB has entered a promising phase.<sup>15-18</sup> The status of the pipeline for new anti-TB drugs up to November 1st 2017 is shown in **Figure 1**. The class of drugs, mechanisms of action and trial evaluation phase with relevant sponsor is shown on **Table 1**. PBTZ-169 will enter phase 2 EBA (Early Bactericidal Activity), new compound (Q203) completing a Phase I trial in 2017 and TBA-7371 entering phase 1. However, with these advances there have also been some setbacks: sutezolid (undergoing phase 2 trials) has to re-perform some phase 1 studies; the development of AZD5847 was officially ended (due to lack of demonstrated anti-TB

activity); the development of TBA-354 was discontinued (due to signs of neurotoxicity in the Phase I trial), <sup>19</sup> and SQ109 has not demonstrated anti-mycobacterial activity, (however it may still retain usefulness as a companion drug and therefore function to protect the action of core drugs by raising the resistance threshold). <sup>20</sup> There are twelve anti-TB drugs in clinical development for the treatment of drug-susceptible, MDR-TB or latent TB infection (LTBI), of which nine are new, and three are already approved or repurposed. **Table 2** provides a comprehensive list of the planned, ongoing and recently completed clinical trials on drug-susceptible and drug-resistant TB as of November 1st, 2017.

# **Drug-susceptible TB**

The WHO recommends treatment for drug-susceptible TB with a two-month intensive phase with daily quadruple first-line TB drugs (isoniazid, rifampin, pyrazinamide, ethambutol), followed by a 4-month continuation phase of isoniazid and rifampin. Shorter and simplified anti-TB regimens may increase patient adherence. Four-month standard regimens are, so far, only recommended in the American Thoracic Society guidelines for minimal disease, sputum smear, and culture negative cases. There are some ongoing studies to optimize the use of approved drugs and improving formulations, pill counts.<sup>21</sup> Of note new better tasting fixeddosed combination tablets are now available for paediatric use, which simplify dosing in children weighing less than 25kg,<sup>22</sup> while improving drug delivery and drug levels.<sup>23,24</sup> A study by Amagon et al. suggests a reduction of liver toxicity of the standard quadruple regimen when associated with methionine and vitamin B complex. 25 Isoniazid, a cornerstone of anti-TB medications, is included in high doses in the shorter MDR-TB regimen. Isoniazid resistance can lead to worse outcomes and higher relapse rates; several studies have been performed to identify strategies to treat isoniazid-monoresistant TB more effectively. <sup>26-28</sup> The on-going ACTG5312 trial is testing whether increasing the dosage of isoniazid can help to overcome existing low-level resistance to the drug. High-dose isoniazid is also being used in the NEXT-TB trial. The RIFASHORT, and STAND trials are focused on shortening the current pan- sensitive TB regimen, evaluating the utility of rifapentine, high dose of rifampicin and a completely new regimen. STAND trial accrual was not re-opened following release in early 2017 of the hold placed in October 2016, though follow-up continues on the 284 participants recruited so far. More studies are needed however; the ACTG is planning a new strategy trial for INH-monoresistant TB, A5373: Fighting Isoniazid Resistant Strains of TB (FIRST).

A recent phase 2 study demonstrated that although 20mg/kg of rifampicin did not increase efficacy it did not lead to increased adverse events.<sup>29</sup> The PanACEA trial tested four experimental arms with rifampin dosages of 35 mg/kg, 20 mg/kg, and 10 mg/kg in various regimens against the standard of care for drug-susceptible (DS-TB). The only arm to show significantly faster time to culture conversion (TTCC) in liquid media was the DS-TB standard of care with the rifampin dose increased to 35 mg/kg. Arms containing SQ109 and moxifloxacin failed to show superiority to the standard of care.<sup>30</sup>

Rifapentine, is being tested as a flat, not weight-based, dose of 1200 mg daily in a phase 3 study TBTC S31/ACTG A5349 as part of two four-month regimens for shortened treatment of DS-TB enrolling to date more than 1,400 of a target of 2,500 participants.<sup>31</sup> The first experimental regimen in this trial replaces rifampin with rifapentine and reduces the continuation phase to two months. The second experimental regimen is the same as the first, but replaces ethambutol with moxifloxacin and continues moxifloxacin for the continuation phase. The TRUNCATE-TB strategy phase 2c trial will test whether DS-TB treatment can be shortened to two months for some patients using combinations of new and repurposed drugs, including the rifamycins, utilising adaptive design.<sup>32</sup> Recently, the use of another rifamycin (rifabutin) was associated with improved treatment outcomes in rifabutin-susceptible cases.<sup>33</sup> The phase II Opti-Q study sets out to identify the optimal dose of levofloxacin, in patients with MDR-TB; results are expected in spring 2018. The study will evaluate levofloxacin doses of 11mg/kg, 14 mg/kg, 17 mg/kg, and 20 mg/kg, all taken daily for six months with an optimized background regimen.<sup>34</sup> Levofloxacin is also being used in the H-35265 trial, the NEXT trial, the STREAM trial, and in the MDR-END study.<sup>35</sup> Moxifloxacin is similarly being used in a number of ongoing trials and is being frequently utilized as a substitute for isoniazid or ethambutol in mono-resistant cases or patients with tolerability or contraindications. Resistance to the latest generation fluoroquinolones at the clinical breakpoint is still uncommon, a finding supporting current WHO recommendations to use moxifloxacin or gatifloxacin in the treatment of MDR-TB.<sup>36</sup>

## **Drug-resistant tuberculosis**

The updated classification of new anti-TB drugs by WHO is given in **table 3**,<sup>37</sup> The taxonomy of anti-TB drugs, and their combinations are undergoing a rapid transformation as a result of clinical trials and meta-analyses.<sup>38,39</sup> A 9–12-month standardised regimen is recommended by WHO for all patients with pulmonary MDR/rifampicin-resistant (RR)-TB

(excluding pregnant women and extrapulmonary cases) not previously treated with second line agents and susceptible to fluoroquinolones and aminoglycosides.<sup>37</sup> This regimen consists of an intensive phase with gatifloxacin/moxifloxacin, kanamycin/amikacin, ethionamide/prothionamide, clofazimine, high dose or 10mg/kg isoniazid (max 600mg a day), ethambutol and pyrazinamide for 4–6 months, followed by a continuation phase of 5 months with gatifloxacin/moxifloxacin, clofazimine, ethambutol, and pyrazinamide.<sup>40,41</sup> However, the appropriate management of such regimens is essential in order not to select for further resistance; adequate drug susceptibility testing should be provided for all cases, M/XDR-TB case management to highly experienced clinicians based on international guidelines is recommended. All these agents require a careful management in the context of individualised regimens under close clinical and laboratory monitoring.<sup>42-44</sup>

The "Bangladesh" shorter standardized regimen, achieved a relapse-free cure of 87.9% among 206 patients, this regimen achieved < 1% failure and 90% relapse-free cure. 45 Moreover, an update of this study has shown that 84.4% of the 515 patients had a bacteriologically favourable outcome. 40 The only difference between the Bangladesh regimen and the WHO shorter regimen is the substitution of gatifloxacin for moxifloxacin. A meta-analysis reported that shorter regimens were effective in treating MDR-TB; however, failure/relapse was associated with fluoroquinolone resistance with an OR of 46.46

Experience with the use of the shorter MDR-TB regimen remains limited, <sup>47-51</sup> and is conditionally recommended for MDR/RR-TB patients under specific eligibility criteria. The ongoing STREAM-1 Stage 1 phase 3 trial initiated in 2012 is evaluating the efficacy and safety of this regimen, final results from which are expected in 2018; interim results suggest failure at demonstrating non-inferiority; however, it is a good option for selected patients. The nine-month treatment regimen being tested achieved favourable outcomes in almost 80 percent of the patients treated. Severe adverse events were similar in both groups: however, a higher frequency of cardiac conduction disorders was recorded in the shorter regimen. The results suggest the nine-month regimen is very close to the effectiveness of the 20-24-month regimen recommended in 2011 WHO guidelines(under trial conditions), although it cannot be concluded that the nine-month regimen is non-inferior to the more protracted regimen. 78.1 percent of patients receiving the nine-month regimen achieved a favourable outcome, compared to 80.6 percent of patients receiving the 20-24-month regimen.<sup>52</sup> Whether bedaquiline could play a role in a shorter regimen is still under evaluation in the Stage 2 STREAM trial.

## Updates on bedaquiline and delamanid

By September 2017, an estimated 10,164 patients had received bedaquiline, two-thirds of whom are in South Africa.<sup>53</sup> Concerns about the safety of bedaquiline were based on the ten (late) deaths in the interventional arm of the registrational phase IIb C208 study, and the risk of cardiac toxicity. A retrospective, observational study of 428 DR-TB patients given bedaquiline-containing regimens in 15 countries under programmatic conditions suggests that the risk of QT prolongation appears less significant than initially envisaged. Sputum smear and culture conversion rates in MDR-TB cases were 88.7% and 91.2%, respectively, at the end of treatment. Bedaquiline was discontinued due to adverse events in 5.8% of cases. One patient died after having had electrocardiographic abnormalities, which were assumed not-bedaquiline related.<sup>54</sup>

Bedaquiline is used in the TB Alliance NIX-TB trial and appears useful in the treatment of XDR-TB, pre-XDR-TB, and treatment-intolerant or treatment-non-responsive MDR-TB. The NIX-TB trial is a single-arm, open-label trial of bedaquiline, pretomanid (formerly Pa-824), and linezolid (600 mg twice daily) given for six months, with an extra three months added if participants are sputum culture positive at four months.<sup>55</sup> As of October 2017, 103 participants are enrolled in the study, 70 had completed the six-month treatment course, and 31 had finished six months of follow-up. Four patients died—all in the first eight weeks. Relapse free cure to date was 26/30 (87%). All patients were culture negative at four months—65% were already negative by eight weeks.<sup>56</sup> NIX-TB will roll over in November 2017, into the new ZeNIX trial – dose-ranging for LZD.

The bedaquiline phase III study, STREAM Stage II, is ongoing and results are expected in December 2021.<sup>57</sup> Other important trials including bedaquiline are NEXT-TB study TB-PRACTECAL and endTB.<sup>58-60</sup> The NEXT study is an open-label trial of a 6–9-month injection-free regimen containing bedaquiline, ethionamide or high-dose isoniazid, linezolid, levofloxacin, and pyrazinamide, compared with the WHO-recommended 12-month shorter regimen for MDR-TB treatment.

The TB-PRACTECAL trial is a Phase II/III adaptive trial to evaluate the safety and efficacy of 6-month regimens that contain bedaquiline, pretomanid and linezolid, with or without moxifloxacin or clofazimine, for the treatment of adults with MDR-TB or XDR-TB. The endTB is a Phase III trial that will compare several regimens for treatment of MDR-TB or XDR-TB with the current WHO standard of care. The regimens being tested contain

bedaquiline or delamanid (or both), moxifloxacin or levofloxacin, and pyrazinamide plus linezolid or clofazimine (or both), in various combinations.

Initial findings from the ongoing NC-005 phase II trial which has seen its follow-up increased to month 24 was presented at the 2017 CROI suggest that a combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ) has both good bactericidal activity and safety. The TB Alliance is planning to test this regimen in a more substantial phase III trial, NC-008 (ZeNIX). The AIDS Clinical Trials Group (ACTG) study A5343 in its three arms adds bedaquiline, delamanid, and a combination of the two to the WHO-recommended shortened MDR-TB regimen (with clofazimine removed in each case as a result of the increased risk of QT prolongation when used with bedaquiline). The study will provide important information about the safety and pharmacokinetics of using these two new drugs together.

In a recent systematic review of 1,293 published cases treated with bedaquiline,<sup>53</sup> details on QT≥450 msec was available for 35/329 cases (10%) and QT≥500 msec for 42/1,293 cases (3.2%). In 44/1,293 (3,4%) cases bedaquiline was discontinued due to adverse events, while only 8/857 (0.9%) discontinued the drug specifically for QT prolongation (2 of these 8 cases being able to re-start it after temporary interruption).

## **Delamanid**

By September 2017, 688 patients had received Delamanid from Médecins sans Frontières (MSF) projects through its compassionate use program with the European Respiratory Society (ERS) TB Consilium. 62-64 The Otsuka Pharmaceutical Company delamanid phase III trial is listed as "completed" on ClinicalTrials.gov and top-line findings were presented at the Union World Conference on Lung Health in October 2017. The Otsuka delamanid studies provided consistent results with high proportion of favourable outcomes: phase 2 trial 204 (192 cases), 74.5%; 65 phase 2 trial 213 (339 cases), 81.4%, 66 and programmatic use in Latvia (19 cases), 84.2%. Results of the compassionate use cases are encouraging, with 53/66 cases (80%) achieving sputum culture conversion. 68

There is growing data to support the efficacy and safety of delamanid in children above the age of 6, Otsuka Trial 233 is on-going with 6 month pharmacokinetic (PK)/safety in all paediatric weight groups with results in 2020, following Trial 232 with 18day PK/safety in same weight groups, results due out in 2018.<sup>64,69,70</sup> Delamanid is also being tested in a number of new trials, most notably endTB (**Table 2**). The MDR-END trial (Seoul National

University hospital), which is evaluating a regimen containing delamanid, linezolid, levofloxacin, and pyrazinamide for 9 or 12 months. The same regimen as the MDR-END trial, with arms for various shorter durations, will be studied in the H-35265 trial.

Recently, there have been reports of treatment with delamanid and bedaquiline in combination; this was previously not recommended in the absence of evidence. However there is growing evidence that the combination may well be tolerated. There are two trials which are currently recruiting patients however results are not expected till 2020-1. Whilst WHO does not recommend this combination, it recognises that physicians may require guidance and has provided recommendations including active safety drug monitoring which may provide for more rapid and robust phase 4 safety data collection.

## **Pretomanid**

Pretomanid is a nitroimidazole developed by the Global Alliance for TB Drug Development (TB Alliance). It is currently being tested as part of three potential combination regimens for the treatment of both drug-susceptible and drug-resistant TB. The phase III STAND trial, which tests a four- or six-month combination of pretomanid, moxifloxacin, and pyrazinamide for the treatment of both DS and drug-resistant (DR)-TB, was cleared to resume enrolment and is following up 284 enrolled participants. It is one of the three drugs in the NIX-TB regimen. It will also be included for further study in people with XDR-TB, pre-XDR-TB and patients with non-responsive or treatment-intolerant MDR-TB. Pretomanid will also feature together with bedaquiline-moxifloxacin and pyrazinamide as a regimen in the TB Alliance's planned NC-008 trial. NC-008 SimpliciTB is a phase III trial that tests a regimen including pretomanid and bedaquiline. Promising results support the use of this BPaMZ (Bedaquiline, pretomanid, moxifloxacin and pyrazinamide) regimen from the NC-005 trial, <sup>77</sup> Pretomanid is also being studied in multiple arms of phase II/III TB-PRACTECAL study.

## Repurposed drugs

Clofazimine, an anti-leprosy drug, has demonstrated sterilising and treatment shortening potential. Its improved version TBI-166 has entered phase 1 trials and is hoped will not produce skin discolouration.<sup>78</sup> Encouraging evidence is also available for a large programmatic study in Brazil.<sup>79</sup> Carbapenems may have a future role in the treatment of tuberculosis. However, a lack of an active oral formulation and the necessity of combining amoxicillin-clavulanate (to protect it from \( \beta-lactamases) renders these compounds less

appealing, even though some appear very active with excellent tolerability and safety. <sup>80-82</sup> Linezolid, an oxazolidinone, has demonstrated anti-mycobacterial efficacy and is included in many drug trial regimens; <sup>83</sup> however, its toxicity profile does not allow for its use beyond drug-resistant TB. Sutezolid and delpazolid are two newer generation oxazolidinones in early clinical trials which are hoped to be just as effective as linezolid but less toxic. Efflux pump inhibitors like verapamil may have a role in lowering resistance and boosting antimicrobial activity of drugs like bedaquiline. <sup>84</sup>

## UPDATES ON TB DRUGS FOR PREVENTIVE THERAPY

Clinicians and patients have long desired shorter, more tolerable, and safer alternatives for treatment of latent *Mtb* infection (LTBI) than standard daily isoniazid for 9 or more months. In 2011, the landmark phase III trial Study 26 conducted by the US Centres for Disease Control and Prevention (CDC) Tuberculosis Trials Consortium (TBTC) in 7,731 participants established the safety and non-inferiority of once weekly rifapentine given with isoniazid for 12 weeks (the 3HP regimen) compared with nine months of daily isoniazid (9H). ACTG A5279 is assessing the safety and effectiveness of 1 month daily course of rifapentine and isoniazid versus nine months of daily isoniazid for the prevention of active TB in HIV-positive people with LTBI. Results are expected in early 2018. Several other studies on the combination of rifapentine and isoniazid and of rifapentine alone under different durations and dosing schedules, in high endemic settings, and in pregnant/postpartum women and in children, are ongoing or planned.

To date, no randomized controlled LTBI treatment trials have determined how to eradicate latent infection with drug-resistant (DR) *Mtb* strains. As a result, clinical practice has varied widely, and the WHO *Guidelines on the Management of Latent Tuberculosis Infection* identify "adequately powered randomized controlled trials to define the benefits and harms of treatment of MDR-TB contacts as an urgent research priority. Three clinical trials investigating preventive therapy for individuals exposed to DR-TB are underway or will open soon. The V-QUIN and TB-CHAMP studies, which both opened in 2016, are double-blind cluster-randomized phase 3 trials evaluating the safety and efficacy of six months of daily levofloxacin versus placebo for preventing TB among household contacts of MDR-TB. V-QUIN will enrol 2,006 adults and children at sites in Vietnam. PHOENIX will begin Q1 2018 as an open label study. TB-CHAMP will enrol 1,556 children age 5 and younger at sites in South Africa.

The ACTG and IMPAACT networks are partnering on the PHOENIX study (A5300B, I2003B), a cluster randomized open-label phase III trial opening in early 2018 that will compare the safety and efficacy of 26 weeks of twice-daily delamanid versus 9 months of daily isoniazid for preventing TB over two years of follow-up among household contacts of patients with MDR-TB. The study will enrol over 3,450 household contacts from an estimated 1,725 households. Eligible household contacts include adults and children over five years of age who are HIV positive, at high risk of disease progression (e.g., on TNF $\alpha$  treatment), or have a positive Tuberculin skin test or Interferon gamma release assay result; children ages 0–5 are eligible regardless of TST or IGRA status.<sup>88</sup>

#### ADVANCES AND PROGRESS IN HOST-DIRECTED THERAPIES

Effective host immunity limits *Mtb* from causing disease in the majority of individuals. Waning host defence leads to increased susceptibility to developing disease and poor treatment outcomes as illustrated by the case of *Mtb*/HIV co-infection. Augmentation of beneficial immune responses may serve as useful adjunct therapy to TB drug treatment regimens. Host-directed therapy (HDT) approaches are now a focus for use as adjunct treatment options for MDR-TB, for shortening treatment duration, limiting immunopathology by modulating aberrant *Mtb* induced immune responses, and improving treatment outcomes. Immunotherapy is revolutionizing cancer treatment and similar host pathways operational in TB are being investigated. Three main approaches are being taken forward for HDTs as adjunct therapy for TB treatment: (i) amplification of host immunity, (ii) modulation of inflammation to reduce lung tissue destruction and (iii) killing of *Mtb*.

**Table 4** lists the HDT development pipeline for adjunct TB treatment. Small-molecule drugs and enzymes that have therapeutic value in metabolic diseases are being investigated for their usefulness as HDT. Metformin has been shown to augment immune effector function and reduction of *Mtb* burden in preclinical TB models. Other HDTs being evaluated are over the counter drugs commonly used, safe and cheap drugs such aspirin, indomethacin, as well as vitamins and biological compounds e.g. flavonoids and stilbenoids. Administering therapeutic antibodies targeting cell surface molecules of *Mtb* infected cells or those that neutralise circulating proteins detrimental to protective immunity are HDT options for use as adjuncts with anti-TB treatment regimens to achieve immune-modulation and enhanced antimycobacterial effects. The role of exosomes may enhance anti-*Mtb* immune reactivity and could play an overall role in immuno-modulation. T and B cells have also been shown to

release exosomes which contain T-cell receptors (TCRs) or B-cell receptors (BCRs), respectively, in addition to MHC-peptide complexes, miRNA and fragments of DNA as well as apoptosis inducers such as Fas ligand. Translational studies are being developed will incorporate novel technologies, such as tissue-embedded microchips and *ex vivo* 3D culture models for evaluating HDTs in conjunction with anti-TB drugs. 95

#### TB IMMUNOTHERAPEUTIC TARGETS

#### Glucocorticoids

Glucocorticoids and receptor agonists, such as dexamethasone and prednisone, have antiinflammatory properties, <sup>96</sup> improve TB lung pathology and prevent immune reconstitution inflammatory syndrome (IRIS) in TB/HIV co-infection. <sup>97</sup> Survival benefits have been demonstrated for TB meningitis, <sup>98</sup> although other clinical forms of TB have not shown a consistent benefit from adjunctive corticosteroid treatment. <sup>99</sup>

#### Eicosanoid modulators

Eicosanoids are generated by cyclooxygenase (COX) and lipoxygenase (5-LOX) metabolism of arachidonic acid to generate prostaglandins and leukotriene, <sup>100</sup> respectively. Selective COX-2 inhibitors decrease unproductive inflammation and improve survival in murine TB by direct anti-mycobacterial activity. <sup>101-102</sup> COX2-inhibition is however, also associated with cell necrosis, which favours *Mtb* survival. <sup>103</sup> Zileuton, a 5-LOX inhibitor, approved for use in asthma, increases PGE2 and inhibits leukotrienes to limit type I IFN-mediated lung pathology. It improves survival of *Mtb*-infected mice. <sup>104</sup> The eicosanoid pathway thus represents a complex target of TB HDT as the effect is likely dependent on infection stage, as PGE2 has protective effects early during infection but impairs anti-TB immunity during later stages. <sup>105</sup>

# **Cholesterol-lowering drugs**

In addition to lipid-lowering properties, statins possess potent anti-inflammatory activities<sup>106</sup> with beneficial effects in TB.<sup>107</sup> As adjunctive therapy in murine TB, statins shorten the time to culture negativity by 1 month, reduce tissue pathology, decrease the proportion of culture-positive relapse cases and enhance bacterial killing.<sup>108-109</sup> Statin usage by newly diagnosed type-2 diabetics did however, not prevent development of TB,<sup>110</sup> and further studies are required.

## **PDE** inhibitors

Inhibitors of phosphodiesterase (PDE)-3, PDE4 and PDE5, such as cilostazol, roflumilast, sildenafil and tadalafil, increase levels of cyclic-adenosine-monophosphate or cyclic guanosine monophosphate. PDE inhibitors accelerate lung sterilization, reduce lung inflammation and promote lung repair by potentiating isoniazid bactericidal activity, limiting TNF $\alpha$  production and reducing macrophage activation. There is insufficient data on the clinical and immunological impact of PDE inhibitors and further research is required.

### **Immune checkpoint inhibitors**

The use of immune-oncological products such as anti-programmed cell death-1 (PD-1) and anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) have been clinically promising in the treatment of solid cancers. Immune regulatory checkpoints are perturbed in TB and linked to T-cell exhaustion. Signalling via immune checkpoints inhibit T- and B-cell function Checkpoint inhibitors have been successfully employed in various cancers, specifically the monoclonal antibodies nivolumab and ipilimumab, against PD-1 and CTLA-4, respectively. Inhibition of CTLA-4 enhances immune responses without improving bacillary clearance. Polymorphisms in *CTLA-4* were linked to TB susceptibility. Inhibition of the PD1/PD-L1 pathway enhances *Mtb*-specific responses in humans, the but not in mice. Immune checkpoint inhibition treatment can result in development of active TB disease. This is likely due to excessive inflammation and increased focal necrosis. Trials on the use of checkpoint inhibitors which block the PD1/PD-L1 pathway as adjunt to TB therapy are being considered.

#### **Vitamins**

Vitamin D3 (vitD3) moderately accelerates time to sputum conversion. <sup>122</sup> VitD3 deficiency is a risk factor for development of TB disease, <sup>123</sup> although a randomised control trial failed to show a profound effect on TB treatment outcome. <sup>124</sup> Further trials are required to accurately define the value of vitD3 as TB HDT. Vitamin A (vitA) possesses host immunomodulatory potential and *in vitro* anti-mycobacterial capabilities, <sup>125</sup> deficiency strongly predicts the risk of incident TB amongst TB household contacts (HHC) and supplementation (with zinc) improves TB treatment outcomes. <sup>126</sup> The vitA derivative, all-trans-retinoic acid (ATRA), decreased *Mtb* burden by reducing cellular cholesterol and inducing phagosomal acidification. <sup>127</sup> These favourable outcomes could however not be repeated in other TB treatment studies. <sup>128</sup>

## **Kinase modulators**

Targeting cancer drugs such tyrosine kinase inhibitors are being evaluated in preclinical models of TB, with considerable success. Several protein kinase inhibitors are available for clinical use. The interest in diabetes mellitus pathology and increasing autophagy, phagosomal acidification and myeloid cell mobilization, and is currently being tested for its safety and immunogenicity as repurposed TB treatment. Adenosine monophosphate-activated protein kinase (AMPK) regulates cellular energy levels, T-cell differentiation and development of memory. AMPK is activated by metformin, a type-2 diabetes drug, that reduces bacterial burden and ameliorates lung pathology in mice and humans by enhancing autophagy and increasing ROS production. Metformin adjunctive treatment however failed to improve sterilizing activity and TB relapsed in mice, with no significant effect being reported for culture conversion rates in diabetes mellitus patients with TB.

# Cellular therapy

Cellular therapy has shown promise in the cancer field, <sup>135</sup> and is being investigated for use as adjunct therapy for drug-resistant TB. <sup>136</sup> Mesenchymal stromal cells (MSC) are non-hematopoietic progenitor cells with immunomodulatory and antibacterial properties, <sup>137-138</sup> that improve immune responses and lung pathology in human and murine TB. <sup>139-140</sup> Another immunotherapeutic approach involves modulation of immune regulatory cells, specifically myeloid-derived suppressor cells (MDSC) <sup>141-142</sup> MDSC are increased in TB, display T-cell immunosuppressive properties, <sup>143-145</sup> and harbour *Mtb*, suggesting that MDSC-targeting strategies should also be considered in TB HDT design. The promise of use T-cell therapy, with or without T-cell receptor (TCR) manipulations to increase affinity for antigen has shown promise for CMV treatment, and could be beneficial in TB. Low-dose chemotherapy i.e. with cyclophosphamide can reduce circulating regulatory T cells (Tregs), and may allow for effective cellular immune responses to be established.

## Micro-RNA

miRNA are small non-coding RNAs regulating gene expression and can affect host immunity to Mtb infection through modulation of inflammation, TNF $\alpha$ , IL6, chemokines and stimulation of macrophage polarization. There is emerging evidence that miRNAs could serve as cancer immunotherapy and could serve as therapeutic targets in TB.  $^{148-149}$ 

## Cytokines and proteases

TNF- $\alpha$  is essential to granuloma integrity, macrophage antimicrobial activity and ROS-mediated Mtb killing. TNF- $\alpha$  can however, also trigger cell necrosis and exacerbate inflammation, thereby aggravating TB pathology. TNF- $\alpha$  blockers and anti-TNF- $\alpha$  monoclonal antibodies, such as thalidomide and infliximab, successfully control severe TB. On the other hand, TNF- $\alpha$  inhibition destabilizes granulomas, reactivates Mtb bacilli and increases the risk of TB disease. TFN- $\gamma$  is important to protective anti-TB immunity and administration has nominal benefit in drug-sensitive, and drug-resistant TB.

Although several HDTs show promise in pre-clinical studies, insufficient information is available to gauge the impact of HDTs on key immune functions during different phases of *Mtb* infection and disease. The timing of specific HDTs could be crucial as pro- and anti-inflammatory immune mechanisms play important roles during different stages of TB. The challenge remains to identify cost-effective and safe approaches rapidly. Evaluations of HDTs in randomized clinical trials in different geographical and clinical settings are required.

## **CONCLUSIONS**

Steady progress is being made in the development of new and repurposed TB drugs, treatment trials and host-directed therapies. Several new or repurposed antimicrobial drugs are in advanced trial stages for MDR-TB, and five antimicrobial drug candidates are in phase 1 (Q203, TBI-166, OPC-167832, GSK 070, TBA-7371) and 5 in pre-clinical studies. Results of several phase 3 trials of the new compounds bedaquiline, delamanid, pretomanid and phase 2 trials of sutezolid, SQ-109, LCB01-0371, PBTZ-169 are eagerly awaited. A range of candidate host-directed therapies (HDTs) and immune-based treatments are being investigated to accelerate the eradication of *Mtb* infection and for use as adjunctive therapy in shortening duration of treatment, preventing permanent lung injury and improving treatment outcomes of MDR-TB.

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## **CONFLICTS OF INTEREST**

All authors have ongoing research activities on various treatment aspects of TB.

## **AUTHOR CONTRIBUTIONS**

Prof Alimuddin Zumla initiated the idea, developed the first draft outline and subsequent and final drafts of the manuscript. All authors contributed to sections relevant according to their expertise, helped refine the text and content.

# **LEGENDS TO TABLES AND FIGURE**

Table 1: TB Drugs development pipeline

Table 2: Planned, ongoing and recently completed clinical trials on drugs sensitive and drug resistant tuberculosis (as of November 2017) (courtesy of CDC TB Trials Consortium)

Table 3: WHO categorisation of second-line anti-tuberculosis drugs recommended for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis

Table 4. Host-directed therapies in TB -Developmental pipeline: Ongoing clinical trials and translational research

Figure 1. Global New TB Drug development pipeline

## **REFERENCES**

- Global tuberculosis report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NCSA 3.0 IGO. http://www.who.int/tb/publications/global\_report/en/. Accessed 30/10/2017
- 2. Ahmad Khan F, Salim MAH, du Cros P, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017 Jul 27; **50**(1). pii: 1700061. doi: 10.1183/13993003.00061-2017.
- 3. Mitnick CD, White RA, Lu C, et al. on behalf of the Collaborative Group for Analysis of Bacteriology Data in MDR-TB Treatment. Multidrug-resistant tuberculosis treatment failure detection depends on monitoring interval and microbiological method. *Eur Respir J* 2016 Oct; **48**(4): 1160-1170. doi: 10.1183/13993003.00462-2016. Epub 2016 Sep 1.
- 4. 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 Apr; **5**(4): 269-281. doi: 10.1016/S2213-2600(16)30433-7. Epub 2017 Jan 19.
- 5. Günther G, Lange C, Alexandru S, et al. Treatment Outcomes in Multidrug-Resistant Tuberculosis. *N Engl J Med* 2016 Sep 15; **375**(11): 1103-5.
- 6. Zignol M, Dean AS, Falzon D, et al. Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. *N Engl J Med* 2016 Sep 15; **375**(11): 1081-9.
- 7. Zumla A, Abubakar I. Clinical trial research in focus: overcoming barriers in MDR-TB clinical trials. *Lancet Respir Med* 2017 Apr; **5**(4): 247-248. doi: 10.1016/S2213-2600(17)30079-6.
- 8. Zuur MA, Akkerman OW, Davies Forsman L, et al. Fixed-dose combination and therapeutic drug monitoring in tuberculosis: friend or foe? *Eur Respir J* 2016 Oct; **48**(4): 1230-1233. doi: 10.1183/13993003.00833-2016. Epub 2016 Sep 1.
- 9. Alffenaar JC, Migliori GB, Gumbo T. Multidrug-resistant tuberculosis: pharmacokinetic and pharmacodynamic science. *Lancet Infect Dis* 2017 Sep; **17**(9): 898. doi: 10.1016/S1473-3099(17)30449-8.
- 10. Nahid P, Droman E, Alipanah N, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America clinical practice guidelines: treatment of drug-susceptible Tuberculosis. *Clin Infect Dis* 2016; **63**: 853–67.

- 11. Alffenaar JC, Tiberi S, Verbeeck RK, Heysell SK, Grobusch MP. Therapeutic drug monitoring in tuberculosis: practical application for physicians. *Clin Infect Dis* 2017 Jan 1; **64**(1): 104-105.
- 12. Lienhardt C, Nahid P, Rich ML, et al. Target regimen profiles for treatment of tuberculosis: a WHO document. *Eur Respir J* 2017 Jan 25; **49**(1). http://www.who.int/tb/publications/TRP\_profiles/en/
- 13. TB Alliance. https://www.tballiance.org. Accessed 20/10/2017
- 14. STOP TB. http://www.stoptb.org. Accessed 20/10/2017
- 15. 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 Mar; **5**(4): 291-360. pii: S2213-2600(17)30079-6.
- 16. Lienhardt C, Lönnroth K, Menzies D, et al. Translational Research for Tuberculosis Elimination: Priorities, Challenges, and Actions. *PLoS Med* 2016 Mar 2; **13**(3): e1001965.
- 17. Sulis G, Centis R, Sotgiu G, et al. Recent developments in the diagnosis and management of tuberculosis. *NPJ Prim Care Respir Med* 2016 Nov 3; **26**: 16078.
- 18. Heemskerk AD, Bang ND, Mai NT, et al. Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. *N Engl J Med* 2016 Jan 14; **374**(2): 124-34. doi: 10.1056/NEJMoa1507062.
- 19. http://www.tballiance.org/news/phase-1-clinical-trial-tb-drug-candidate-tba-354-discontinued. Accessed 21/10/2017.
- 20. Caminero JA, Piubello A, Scardigli A, Migliori GB. Proposal for a standardised treatment regimen to manage pre- and extensively drug-resistant tuberculosis cases. *Eur Respir J* 2017 Jul 5; **50**(1). pii: 1700648. doi: 10.1183/13993003.00648-2017. Print 2017 Jul.
- 21. Aseffa A, Chukwu JN, Vahedi M, et al. Group. Efficacy and Safety of 'Fixed Dose' versus 'Loose' Drug Regimens for Treatment of Pulmonary Tuberculosis in Two High TB-Burden African Countries: A Randomized Controlled Trial. *PLoS One* 2016 Jun 20; **11**(6): e0157434.
- 22. New fixed-dose combinations for the treatment of TB in children. http://www.who.int/tb/FDC\_Factsheet.pdf. Accessed 20/10/2017
- 23. Seddon JA, Schaaf HS. Drug-resistant tuberculosis and advances in the treatment of childhood tuberculosis. *Pneumonia (Nathan)* 2016 Nov 24; **8**: 20.
- 24. Wu J, Liao S, Sun Z. Treating tuberculosis with high doses of anti-TB drugs: mechanisms and outcomes. *Ann Clin Microbiol Antimicrob* 2017 Oct 3; **16**(1): 67.

- 25. Amagon K, Awodele O, Akindele AJ. Methionine and vitamin B-complex ameliorate antitubercular drugs-induced toxicity in exposed patients. *Pharmacol Res Perspect* 2017 Oct; **5**(5). doi: 10.1002/prp2.360.
- 26. Santos G, Oliveira O, Gaio R, Duarte R. Effect of Isoniazid Resistance on the Tuberculosis Treatment Outcome. *Arch Bronconeumol* 2017 Jul 13. pii: S0300-2896(17)30215-6.
- 27. Gegia M, Winters N, Benedetti A, van Soolingen D, Menzies D. Treatment of isoniazid-resistant tuberculosis with first-line drugs: a systematic review and meta-analysis. *Lancet Infect Dis* 2017 Feb; **17**(2): 222-234. doi:10.1016/S1473-3099(16)30407-8.
- 28. Stagg HR, Lipman MC, McHugh TD, Jenkins HE. Isoniazid-resistant tuberculosis: a cause for concern? *Int J Tuberc Lung Dis* 2017 Feb 1; **21**(2): 129-139. doi: 10.5588/ijtld.16.0716.
- 29. Jindani A, Borgulya G, de Patino IW, et al. A randomised Phase II trial to evaluate the toxicity of high-dose rifampicin to treat pulmonary tuberculosis. *Int. J. Tuberc. Lung Dis* 2016; **20**(6): 832–838.
- 30. Boeree MJ, Heinrich N, Aarnoutse R, et al. High-dose rifampicin, moxifloxacin, and SQ109 for treating tuberculosis: a multi-arm, multi-stage randomized controlled trial. *Lancet Infect Dis* 2017 Jan; **17**(1): 39–49. doi:10.1016/S1473- 3099(16)30274-2.
- 31. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02410772. BTC Study 31: Rifapentine-containing Tuberculosis Treatment Shortening Regimens (S31/A5349). Available from: https://clinicaltrials.gov/ct2/show/record/NCT02410772. Accessed 15/10/2017.
- 32. Papineni, P., Phillips, Q. Lu, Cheung Y.B, Nunn A, Paton N. TRUNCATE-TB: an innovative trial design for drug-sensitive tuberculosis. *Int J Infect Dis* 2016 Apr; **45**(Supp. 1): 404.
- 33. Lee H, Ahn S, Hwang NY, et al. Treatment outcomes of rifabutin-containing regimens for rifabutin sensitive multidrug-resistant pulmonary tuberculosis. *Int J Infect Dis* 2017 (in press)
- 34. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT01918397. Efficacy and Safety of Levofloxacin for the Treatment of MDR-TB (Opti-Q); 2013 August 5. Available from: https://clinicaltrials.gov/ct2/show/NCT01918397. Accessed 20/10/2017
- 35. Treatment Shortening of MDR-TB Using Existing and New Drugs (MDR-END) https://clinicaltrials.gov/ct2/show/NCT02619994. Accessed 20/10/2017

- 36. Zignol M, Dean AS, Alikhanova N, et al. Population-based resistance of *Mycobacterium tuberculosis* isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. *Lancet Infect Dis* 2016; **16**: 30190–30196. (http://www.ncbi.nlm.nih.gov/pubmed/27397590, accessed 14 October 2017.
- 37. Falzon D, Schünemann H. J, Harausz E, et al. WHO treatment guidelines for drugresistant tuberculosis, 2016 update." *Eur Respir J* 2017 Mar 22; **49**(3): pii: 1602308. doi: 10.1183/13993003.02308-2016.
- 38. Tiberi S, Scardigli A, Centis R, et al. Classifying new anti-tuberculosis drugs: rationale and future perspectives. *Int J Infect Dis* 2017 Mar; **56**: 181-184.
- 39. Caminero JA, Scardigli A. Classification of antituberculosis drugs: a new proposal based on the most recent evidence. *Eur Respir J* 2015; **46**(4): 887–93.
- 40. Aung K, Van Deun A, Declerq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 55 consecutive patients. *Int J Tuberc Lung Dis* 2014 Oct; **18**(10): 1180-7. doi: 10.5588/ijtld.14.0100.
- 41. Piubello A, Harouna S, Souleymane MB, et al. High cure rate with standardized short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuber Lung Dis* 2014; **18**: 1188–94.
- 42. Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Zumla A, Migliori GB. WHO recommendations on shorter treatment of multidrug-resistant tuberculosis. *Lancet* 2016 Jun 18; **387**(10037): 2486-7.
- 43. Sotgiu G, Tiberi S, Centis R, et al. Applicability of the shorter 'Bangladesh regimen' in high multidrug-resistant tuberculosis settings. *Int J Infect Dis* 2017 Mar; **56**: 190-193.
- 44. Sotgiu G, Tiberi S, D'Ambrosio L, et al. International Carbapenem Study Group. Faster for less: the new "shorter" regimen for multidrug-resistant tuberculosis. *Eur Respir J* 2016 Nov; **48**(5): 1503-1507.
- 45. Van Deun A, Maug A, Salim A, et al. Short, highly effective, and inexpensive standardised, treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010; **182**: 684–92.
- 46. Ahmad Khan F, Salim MAH, du Cros P, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017 Jul; **50**(1): 1700061; doi: 10.1183/13993003.00061-2017.

- 47. Chesov D, Ciobanu N, Lange C, Heyckendorf J, Crudu V. High-dose isoniazid in the shorter-course multidrug-resistant tuberculosis regimen in the Republic of Moldova. *Eur Respir J* 2017 Oct 12; **50**(4). pii: 1701340. doi: 10.1183/13993003.01340-2017.
- 48. van der Werf MJ, Ködmön C, Catchpole M. Shorter regimens for multidrug-resistant tuberculosis should also be applicable in Europe. *Eur Respir J* 2017 Jun 1; **49**(6). pii: 1700463. doi: 10.1183/13993003.00463-2017.
- 49. Yassin MA, Jaramillo E, Wandwalo E, et al. Investing in a novel shorter treatment regimen for multidrug-resistant tuberculosis: to be repeated. *Eur Respir J* 2017 Mar 22; **49**(3). pii: 1700081. doi: 10.1183/13993003.00081-2017.
- 50. Barry PM, Lowenthal P, True L, et al. Benefit of the Shorter MDR TB Treatment Regimen in California and Modified Eligibility Criteria. *Am J Respir Crit Care Med* 2017 Jul 17. doi: 10.1164/rccm.201701-0013LE. [Epub ahead of print]
- 51. Chee CBE, KhinMar KW, Sng LH, Jureen R, Cutter J, Lee VJM et al. The shorter multidrug-resistant tuberculosis treatment regimen in Singapore: are patients from South-East Asia eligible? *Eur Respir J* 2017 Aug 10; **50**(2). pii: 1700753. doi: 10.1183/13993003.00753-2017.
- 52. http://www.ctu.mrc.ac.uk/news/2017/preliminary\_results\_from\_stream\_trial\_provide\_in sight\_into\_shorter\_treatment\_for\_multidrug\_resistant\_tuberculosis. Accessed 27/10/2017
- 53. Country Updates [Internet]. DR-TB STAT; updated 2017 April. Available from: http://drtb-stat.org/country-updates/. Accessed 15/10/2017
- 54. Borisov SE, Dheda K, Enwerem M, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. *Eur Respir J* 2017 May 21; **49**(5). pii: 1700387. doi: 10.1183/13993003.00387-2017.
- 55. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02333799. A Phase 3 Study Assessing the Safety and Efficacy of Bedaquiline Plus PA-824 Plus Linezolid in Subjects With Drug Resistant Pulmonary Tuberculosis; 2015 January 6. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02333799?term=bedaquiline&rank=6. Accessed 15/10/207
- 56. Conradie F, Diacon AH, Everitt D, et al. The NIX-TB trial of pretomanid, bedaquiline and linezolid to treat XDR-TB. Abstract Number: 80LB. February 13–16, 2017 | Seattle, Washington http://www.croiconference.org/sessions/nix-tb-trial-pretomanid-bedaquiline-and-linezolid-treat-xdr-tb. Accessed 15/10/2017
- 57. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02409290. The Evaluation of a Standard Treatment Regimen of Anti-

- tuberculosis Drugs for Patients with MDR-TB (STREAM); 2015 March 31. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02409290?term=stream&rank=8. Accessed 15/10/2017
- 58. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02454205. An Open-label RCT to Evaluate a New Treatment Regimen for Patients with Multi-drug Resistant Tuberculosis (NEXT); 2015 May 22. Available from: https://www.clinicaltrials.gov/ct2/show/NCT02454205?term=bedaquiline&rank=28. Accessed 15/10/2017
- 59. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier. Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s) (TB-PRACTECAL); 2015 October 15. Available from: https://clinicaltrials.gov/ct2/show/NCT02589782. Accessed 15/10/2017
- 60. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02754765. Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB). Available from: https://clinicaltrials.gov/ct2/show/NCT02754765. Accessed 15/10/2017
- 61. Dawson R, Harris K, Conradie A, et al. Efficacy Of Bedaquiline, Pretomanid, Moxifloxacin & PZA (BPAMZ) Against DS- & MDR-TB (Abstract 724LB). Paper presented at: Conference on Retroviruses and Opportunistic Infections; 2017 February 13–16; Seattle (WA). Available from: http://www.croiconference.org/sessions/ef cacy-bedaquiline-pretomanid- moxi oxacin-pza-bpamz-against-ds-mdr-tb. Accessed 18/10/2017
- 62. Pontali E, Sotgiu G, Tiberi S, D'Ambrosio L, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical analysis of the evidence. *Eur Respir J* 2017 (in press)
- 63. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance (WHO/HTM/TB/2014.23). Geneva: WHO; 2014. Available from:
- http://apps.who.int/iris/bitstream/10665/137334/1/WHO\_HTM\_TB\_2014.23\_eng.pdf. Accessed 18/10/2017.
- 64. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. *Eur Respir J* 2016; **48**(3): 938–43.
- 65. Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013; **41**(6): 1393-400.

- 66. New Treatments for Drug-Resistant TB Get a Boost. Posted on October 23, 2017 Article by Betsy McKay, published in the Wall Street Journal, 13 Oct 2017 7:00 A.M. ET. Available from: http://www.resisttb.org/?page\_id=1086. Accessed 31/10/2017.
- 67. Kuksa L, Barkane L, Hittel N, Gupta R. Final treatment outcomes of MDR- and XDR-TB patients in Latvia receiving delamanid containing regimens. *Eur Respir J* 2017. (in press)
- 68. Hafkin J, Hittel N, Martin A, Gupta R. Early outcomes in MDR and XDR-TB patients treated with delamanid under compassionate use. *Eur Respir J* 2017 Jul 27; **50**(1). pii: 1700311.
- 69. Hafkin J, Frias M, Hesseling A, et al. Pharmacokinetics and safety of delamanid in pediatric MDR-TB patients: ages 6–17 years. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). San Diego, California. 2015 September 18-21.
- 70. Hafkin J, Frias M, De Leon A, et al. Long-term safety, tolerability and pharmacokinetics of delamanid in pediatric MDR-TB patients, ages 12–17 years. 46th Union World Conference on Lung Health. Cape Town, South Africa. 2015 December 2-6.
- 71. Maryandyshev A, Pontali E, Tiberi S, et al. Bedaquiline and Delamanid Combination Treatment of 5 Patients with Pulmonary Extensively Drug-Resistant Tuberculosis. *Emerg Infect Dis* 2017 Oct; **23**(10). doi: 10.3201/eid2310.170834.
- 72. Tadolini M, Lingtsang RD, Tiberi S, et al. First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline. *Eur Respir J* 2016; **48**(3): 935–8.
- 73. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02583048. Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis Full Text View ClinicalTrials.gov. Available from:

https://clinicaltrials.gov/ct2/show/NCT02583048?term=NCT02583048&rank=1. Accessed 28/09/2017.

- 74. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02754765. Evaluating Newly Approved Drugs for Multidrug-resistant TB Full Text View ClinicalTrials.gov. Available from:
- https://clinicaltrials.gov/ct2/show/NCT02754765. Accessed 28/09/2017.
- 75. WHO best-practice statement on the off-label use of bedaquiline and delamanid for the treatment of multidrug-resistant tuberculosis. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available from:

http://apps.who.int/iris/bitstream/10665/258941/1/WHO-HTM-TB-2017.20-eng.pdf. Accessed 05/10/2017.

- 76. Active tuberculosis drug-safety monitoring and management (aDSM). Framework for implementation. (WHO/HTM/TB/2015.28) [Internet]. Geneva, World Health Organization; 2015. Available from:
- http://apps.who.int/iris/bitstream/10665/204465/1/WHO\_HTM\_TB\_2015.28\_eng.pdf. Accessed 05/10/2017.
- 77. Dawson R, Harris K, Conradie A, et al. Efficacy of bedaquiline, pretomanid, moxifloxacin & PZA (BPAMZ) against DS- & MDR-TB. Conference Dates and Location: February 13–16, 2017 | Seattle, Washington. Abstract Number: 724LB. Accessed 31/10/2017.
- 78. Lu Y, Zheng M, Wang B, et al. Clofazimine analogs with efficacy against experimental tuberculosis and reduced potential for accumulation. *Antimicrob Agents Chemother* 2011; **55**: 5185–93.
- 79. Dalcolmo M, Gayoso R, Sotgiu G, et al. Effectiveness and safety: of clofazimine in multidrug-resistant tuberculosis a nationwide report from Brazil. *Eur Respir J* 2017 Mar 22; **49**(3). pii: 1602445. doi: 10.1183/13993003.02445-2016.
- 80. Tiberi S, Sotgiu G, D'Ambrosio L, et al. Comparison of effectiveness and safety of imipenem/clavulanate- versus meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016 Jun; **47**(6): 1758-66.
- 81. Tiberi S, Payen MC, Sotgiu G, et al. Effectiveness and safety of meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB. *Eur Respir J* 2016; **47**(4):1235–43.
- 82. Diacon AH, van der Merwe L, Barnard M, et al. b-Lactams against Tuberculosis—new trick for an old dog? *N Engl J Med* 2016; **375**(4): 393–4.
- 83. Sotgiu G, Pontali E, Migliori GB. Linezolid to treat MDR-/XDR-tuberculosis: available evidence and future scenarios. *Eur Respir J* 2015; **45**(1): 25–9.
- 84. Te Brake LHM, de Knegt GJ, de Steenwinkel JE, et al. The Role of Efflux Pumps in Tuberculosis Treatment and Their Promise as a Target in Drug Development: Unraveling the Black Box. *Annu Rev Pharmacol Toxicol* 2017 Jul 17. doi: 10.1146/annurev-pharmtox-010617-052438. [Epub ahead of print].
- 85. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *N Engl J Med* 2011; **365**(23): 2155–66. doi: 10.1056/NEJMoa1104875.

- 86. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva: World Health Organization; 2015. Available from: http://www.who.int/tb/publications/ltbi\_document\_page/en/. Accessed 15/10/2017.
- 87. Australian New Zealand Clinical Trials Registry [Internet]. Trial ID ACTRN12616000215426, The V-QUIN MDR Trial: a randomized controlled trial of six months of daily levofloxacin for the prevention of tuberculosis among household contacts of patients with multi-drug resistant tuberculosis; 2016 June 20. Available from: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=369817. Accessed 31/10/2017.
- 88. Harrington, Mark (Treatment Action Group, New York, NY). Personal communication
- with: Mike Frick (Treatment Action Group, New York, NY). 2017 May 30.
- 89. Tuberculosis child multidrug-resistant preventive therapy: TB CHAMP trial ISRCTN92634082 DOI 10.1186/ISRCTN92634082. Available from: http://www.isrctn.com/ISRCTN92634082. Accessed 31/10/2017.
- 90. Zumla A, Chakaya J, Hoelscher M, et al Towards host-directed therapies for tuberculosis. *Nat Rev Drug Discov* 2015; **14**(8): 511-2.
- 91. Wallis RS, Maeurer M, Mwaba P, et al. Tuberculosis Advances in Development of New Drugs, Treatment Regimens, Host-Directed Therapies and Biomarkers. *Lancet Infect Dis* 2016; **16**: 4. e34-e46. doi: 10.1016/S1473-3099(16)00070-0.
- 92. Singhal A, Jie L, Kumar P, et al. Metformin as adjunct antituberculosis therapy. *Sci Transl Med* 2014; **6**(263): 263ra159.
- 93. Ventimiglia LN, Alonso MA. Biogenesis and Function of T Cell-Derived Exosomes. *Front Cell Dev Biol* 2016 Aug 17; **4**: 84. doi: 10.3389/fcell.2016.00084.
- 94. Colombo M, Raposo G, Thery C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu Rev Cell Dev Biol* 2014; **30**: 255-89.
- 95. Caballero D, Blackburn SM, de Pablo M, Samitier J, Albertazzi L. Tumour-vessel-on-achip models for drug delivery. *Lab Chip* 2017 Sep 1. doi: 10.1039/c7lc00574a. [Epub ahead of print].
- 96. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol* 2017; **17:** 233–247.
- 97. Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13:** 223–237.
- 98. Bourgi K, Fiske C, Sterling TR. Tuberculosis Meningitis. *Curr Infect Dis Rep* 2017; **19:** 39.

- 99. Simmons CP, Thwaites GE, Quyen NT, et al. The Clinical Benefit of Adjunctive Dexamethasone in Tuberculous Meningitis Is Not Associated with Measurable Attenuation of Peripheral or Local Immune Responses. *J Immunol* 2005; **175**: 579–590.
- 100. Ricciotti E, FitzGerald GA. Prostaglandins and Inflammation. *Arterioscler Thromb Vasc Biol* 2011; **31:** 986–1000.
- 101. Vilaplana C, Marzo E, Tapia G, Diaz J, Garcia V, Cardona PJ. Ibuprofen therapy resulted in significantly decreased tissue bacillary loads and increased survival in a new murine experimental model of active tuberculosis. *J Infect Dis* 2013; **208**: 199–202.
- 102. Tonby K, Wergeland I, Lieske NV, Kvale D, Tasken K, Dyrhol-Riise AM. The COX-inhibitor indomethacin reduces Th1 effector and T regulatory cells *in vitro* in *Mycobacterium tuberculosis* infection. *BMC Infect Dis* 2016; **16:** 599. doi: 10.1186/s12879-016-1938-8.
- 103. Divangahi M, Chen M, Gan H, et al. *Mycobacterium tuberculosis* evades macrophage defenses by inhibiting plasma membrane repair. *Nat Immunol* 2009; **10:** 899–906.
- 104. Mayer-Barber KD, Andrade BB<sup>1</sup>, Oland SD et al. Host-directed therapy of tuberculosis based on interleukin-1 and type I interferon crosstalk. *Nature* 2014; **511:** 99–103.
- 105. Rangel Moreno J, Estrada García I, De La Luz García Hernández M, Aguilar Leon D, Marquez R, Hernández Pando R.. The role of prostaglandin E2 in the immunopathogenesis of experimental pulmonary tuberculosis. *Immunology* 2002; **106:** 257–266.
- 106. McCullough PA. The Anti-inflammatory Effects of Statins. *N Engl J Med* 2001; **345**: 1209–1211.
- 107. Lai CC, Lee MT, Lee SH, Hsu WT, Chang SS, Chen SC. Statin treatment is associated with a decreased risk of active tuberculosis: an analysis of a nationally representative cohort. *Thorax* 2016; **71:** 646–651.
- 108. Dutta NK, Bruiners N, Pinn ML, et al. Statin adjunctive therapy shortens the duration of TB treatment in mice. *J Antimicrob Chemother* 2016; **71:** 1570–1577.
- 109. Skerry C, Pinn ML, Bruiners N, Pine R, Gennaro ML, Karakousis PC. Simvastatin increases the in vivo activity of the first-line tuberculosis regimen. *J Antimicrob Chemother* 2014; **69:** 2453–2457.
- 110. Kang YA, Choi NK, Seong JM. The effects of statin use on the development of tuberculosis among patients with diabetes mellitus. *Int J Tuberc Lung Dis* 2014; **18:** 717–724.
- 111. Boswell-Smith V, Spina D, Page CP. Phosphodiesterase inhibitors. *Br J Pharmacol* 2006; **147:** S252–S257.

- 112. Maiga M, Ammerman NC, Maiga MC et al. Adjuvant host-directed therapy with types 3 and 5 but not type 4 phosphodiesterase inhibitors shortens the duration of tuberculosis treatment. *J Infect Dis* 2013; **208:** 512–19.
- 113. Subbian S, Tsenova L, Holloway J et al. Adjunctive Phosphodiesterase-4 Inhibitor Therapy Improves Antibiotic Response to Pulmonary Tuberculosis in a Rabbit Model. *EBioMedicine* 2016; **4:** 104–14.
- 114. Serafini P, Meckel K, Kelso M et al. Phosphodiesterase-5 inhibition augments endogenous antitumor immunity by reducing myeloid-derived suppressor cell function. *J Exp Med* 2006; **203**: 2691–2702.
- 115. Jayaraman P, Jacques MK, Zhu C et al. TIM3 Mediates T Cell Exhaustion during *Mycobacterium tuberculosis* Infection. *PLoS Pathog* 2016; **12:** e1005490.
- 116. Dyck L, Mills KHG. Immune checkpoints and their inhibition in cancer and infectious diseases. *Eur J Immunol* 2017; **47:** 765–79.
- 117. Iwai Y, Hamanishi J, Chamoto K, Honjo T. Cancer immunotherapies targeting the PD-1 signaling pathway. *J Biomed Sci* 2017 Apr 4; **24**(1): 26. doi: 10.1186/s12929-017-0329-9.
- 118. Kirman J, McCoy K, Hook S et al. CTLA-4 Blockade Enhances the Immune Response Induced by Mycobacterial Infection but Does Not Lead to Increased Protection. *Infect Immun* 1999; **67:** 3786–92.
- 119. Jurado JO, Alvarez IB, Pasquinelli V et al. Programmed Death (PD)-1:PD-Ligand 1/PD-Ligand 2 Pathway Inhibits T Cell Effector Functions during Human Tuberculosis. *J Immunol* 2008; **181:** 116–25.
- 120. Barber, D. L., Mayer-Barber, K. D., Feng, C. G., Sharpe, A. H. & Sher, A. CD4 T cells promote rather than control tuberculosis in the absence of PD-1-mediated inhibition. *J Immunol* 2011; **186:** 1598–607.
- 121. Fujita K, Terashima T, Mio T. Anti-PD1 Antibody Treatment and the Development of Acute Pulmonary Tuberculosis. *J Thorac Oncol* 2016; **11:** 2238–40.
- 122. Sato S, Tanino Y, Saito J et al. The relationship between 25-hydroxyvitamin D levels and treatment course of pulmonary tuberculosis. *Respir Investig* 2012; **50:** 40–45.
- 123. Huang SJ, Wang XH, Liu ZD, Cao WL, Han Y, Ma AG. Vitamin D deficiency and the risk of tuberculosis: a meta-analysis. *Drug Des Devel Ther* 2016; **11:** 91–102.
- 124. Martineau AR, Timms PM, Bothamley GH, et al. High-dose vitamin D(3) during intensive-phase antimicrobial treatment of pulmonary tuberculosis: a double-blind randomised controlled trial. *Lancet* 2011; **377:** 242–50.

- 125. Greenstein RJ, Su L, Brown ST. Vitamins A & D Inhibit the Growth of Mycobacteria in Radiometric Culture. *PLoS One* 2012; **7:** e29631.
- 126. Aibana O, Franke MF, Huang CC et al. Impact of Vitamin A and Carotenoids on the Risk of Tuberculosis Progression. *Clin Infect Dis* 2017; **65:** 900–09.
- 127. Wheelwright M, Kim EW, Inkeles MS, et al. All-trans retinoic acid-triggered antimicrobial activity against *Mycobacterium tuberculosis* is dependent on NPC2. *J Immunol* 2014; **192:** 2280–90.
- 128. Lawson L, Thacher TD, Yassin MA et al. Randomized controlled trial of zinc and vitamin A as co-adjuvants for the treatment of pulmonary tuberculosis. *Trop Med Int Health* 2010; **15:** 1481–90.
- 129. Wu P, Nielsen TE, Clausen MH. FDA-approved small-molecule kinase inhibitors. *Trends Pharmacol Sci* 2015; **36:** 422–39.
- 130. Bruns H, Stegelmann F, Fabri M. et al. Abelson Tyrosine Kinase Controls Phagosomal Acidification Required for Killing of *Mycobacterium tuberculosis* in Human Macrophages. *J Immunol* 2012; **189:** 4069–78.
- 131. Napier RJ, Norris BA, Swimm A et al. Low doses of imatinib induce myelopoiesis and enhance host anti-microbial immunity. *PLoS Pathog* 2015; **11:** e1004770.
- 132. Blagih J, Coulombe F, Vincent EE, et al. The energy sensor AMPK regulates T cell metabolic adaptation and effector responses *in vivo*. *Immunity* 2015; **42:** 41–54.
- 133. Meng S, Cao J, He Q et al. Metformin Activates AMP-activated Protein Kinase by Promoting Formation of the αβγ Heterotrimeric Complex. *J Biol Chem* 2015 Feb 6; **290**(6): 3793-802. doi:10.1074/jbc.M114.604421.
- 134. Lee YJ, Yim JJ, Han SK et al. The effect of metformin on culture conversion in tuberculosis patients with diabetes mellitus (dm). *Am J Respir Crit Care Med* 2017; **195**: A2109.
- 135. Payne KK, Bear HD, Manjili MH. Adoptive cellular therapy of cancer: exploring innate and adaptive cellular crosstalk to improve anti-tumor efficacy. *Future Oncol* 2014; **10**: 1779–94.
- 136. Parida SK, Axelsson-Robertson R, Rao MV, et al. Totally drug-resistant tuberculosis and adjunct therapies. *J Intern Med* 2015; **277:** 388–405.
- 137. Vladimirovna IL, Sosunova E, Nikolaev A, Nenasheva T. Mesenchymal Stem Cells and Myeloid Derived Suppressor Cells: Common Traits in Immune Regulation. *J Immunol* Res 2016; **2016**: 7121580. doi: 10.1155/2016/7121580. Epub 2016 Jul 27.

- 138. Nenasheva T, Nikolaev A, Diykanov D et al. The introduction of mesenchymal stromal cells induces different immunological responses in the lungs of healthy and *M. tuberculosis* infected mice. *PloS One* 2017; **12:** e0178983. doi: 10.1371/journal.pone.0178983.
- 139. Skrahin A, Jenkins HE, Hurevich H et al. Effectiveness of a novel cellular therapy to treat multidrug-resistant tuberculosis. *J Clin Tuberc Mycobact Dis* 2016; **4:** 21–27.
- 140. Skrahin A, Ahmed RK, Ferrara G et al. Autologous mesenchymal stromal cell infusion as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis: an open-label phase 1 safety trial. *Lancet Respir Med* 2014; **2:** 108–22.
- 141. Tobin, R. P., Davis, D., Jordan, K. R. & McCarter, M. D. The clinical evidence for targeting human myeloid-derived suppressor cells in cancer patients. *J Leukoc Biol* 2017; **102:** 381–91.
- 142. Tamadaho, R. S. E., Hoerauf, A. & Layland, L. E. Immunomodulatory effects of myeloid-derived suppressor cells in diseases: role in cancer and infections. *Immunobiology* 2017. doi:10.1016/j.imbio.2017.07.001
- 143. du Plessis N, Loebenberg L, Kriel M et al. Increased frequency of myeloid-derived suppressor cells during active tuberculosis and after recent *Mycobacterium tuberculosis* infection suppresses T-cell function. *Am J Respir Crit Care Med* 2013; **188**: 724–32.
- 144. Knaul J, Jörg S, Oberbeck-Mueller D et al. Lung-residing myeloid-derived suppressors display dual functionality in murine pulmonary tuberculosis. *Am J Respir Crit Care Med* 2014; **190:** 1053–66.
- 145. El Daker S, Sacchi A, Tempestilli M et al. Granulocytic Myeloid Derived Suppressor Cells Expansion during Active Pulmonary Tuberculosis Is Associated with High Nitric Oxide Plasma Level. *PLoS One* 2015 Apr 16; **10**(4): e0123772. doi: 10.1371/journal.pone.0123772.
- 146. Ahluwalia PK, Pandey RK, Sehajpal PK, Prajapati VK. Perturbed microRNA Expression by *Mycobacterium tuberculosis* Promotes Macrophage Polarization Leading to Pro-survival Foam Cell. *Front Immunol* 2017 Feb 8; **8**: 107. doi: 10.3389/fimmu.2017.00107.
- 147. Rajaram MV, Ni B, Morris JD et al. *Mycobacterium tuberculosis* lipomannan blocks TNF biosynthesis by regulating macrophage MAPK-activated protein kinase 2 (MK2) and microRNA miR-125b. *Proc Natl Acad Sci* 2011; **108:** 17408–13.
- 148. Paladini L, Fabris L, Bottai G et al. Targeting microRNAs as key modulators of tumor immune response. *J Exp Clin Cancer Res* 2016; **35:** 103. doi: 10.1186/s13046-016-0375-2.
- 149. Dorhoi A, Iannaccone M, Farinacci M, et al. MicroRNA-223 controls susceptibility to tuberculosis by regulating lung neutrophil recruitment. *J Clin Invest* 2013; **123**: 4836–48.

- 150. Flynn JL, Chan J, Triebold KJ et al. An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. *J Exp Med* 1993; **178:** 2249–54.
- 151. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001; **345:** 1098–104.
- 152. Wallis RS, van Vuuren C, Potgieter S. Adalimumab treatment of life-threatening tuberculosis. *Clin Infect Dis* 2009; **48:** 1429–32.
- 153. Wang Q, Wen Z, Cao Q. Risk of tuberculosis during infliximab therapy for inflammatory bowel disease, rheumatoid arthritis, and spondyloarthropathy: A meta-analysis. *Exp Ther Med* 2016; **12:** 1693–704.
- 154. Dawson R, Condos R, Tse D, et al. Immunomodulation with recombinant interferongamma1b in pulmonary tuberculosis. *PloS One* 2009; **4:** e6984. doi: 10.1371/journal.pone.0006984.
- 155. Khan TA, Mazhar H, Saleha S et al. Interferon-Gamma Improves Macrophages Function against *M. tuberculosis* in Multidrug-Resistant Tuberculosis Patients. *Chemother Res and Pract* 2016; **2016**: 7295390. doi: 10.1155/2016/7295390. Epub 2016 Jul 12.

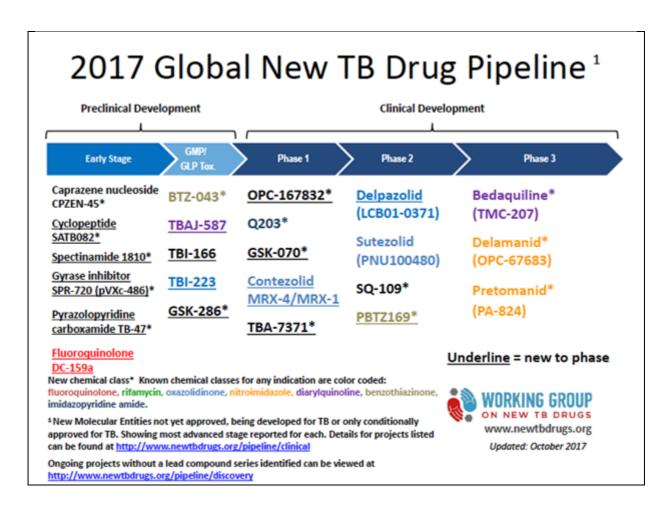


Table 1:

TB Drugs development pipeline -Class of drug, target, phase of trial and sponsor (Adapted from TAG Report <a href="http://www.pipelinereport.org/sites/default/files/2017%20Pipeline%20Report%20Final.pdf">http://www.pipelinereport.org/sites/default/files/2017%20Pipeline%20Report%20Final.pdf</a>)

Drug	Class	Target	Sponsor(s)	Phase	Notes
bedaquiline	diarylquinolone	ATP synthase	Janssen, TB Alliance, NIAID, AMRC, The Union, Unitaid, USAID	III	Conditional marketing approval
delamanid	nitroimidazole	Inhibit cell wall synthesis and cell respiration	Otsuka, NIAID, Unitaid	III	Conditional marketing approval
pretomanid	nitroimidazole	Inhibit cell wall synthesis and cell respiration	TB Alliance	III	
sutezolid	oxazolidinone	Protein synthesis 23s ribosome	Sequella, NIAID, Medicines Patent pool, TB alliance	IIa	Early bactericidal activity significant reduction in counts of colony-forming units in EBA study.
SQ109	1,2-ethylene diamine	Inhibit cell wall synthesis MmpL3	Infectex, Sequella, PanACEA	П/Ш	May be synergic with bedaquiline. Two SQ109- containing arms in a PanACEA trial testing high-dose rifampin were stopped early because pre-specified efficacy thresholds were not met.
PBTZ169	DprE1 inhibitor	Inhibit cell wall synthesis	Nearmedic, iM4TB, BMGF	II	synergies with bedaquiline and clofazimine
delpazolid LCB01-0371	oxazolidinone	Protein synthesis 23s ribosome	LegoChem Biosciences	П	A phase II safety and early bactericidal activity study of the drug is expected to be completed in late 2017.
Q203	imidazopyridine	Cytochrome bc complex	Qurient, Infectex, PanACEA	I	A phase I dose- escalation study is under way and an EBA study is expected to start before the end of 2017.
TBI-166	rimenophenzine	Outer membrane, bacterial respiratory chain and ion transporters	Institute of Materia Medica, TB Alliance	I	
OPC-167832	DprE1 inhibitor	Inhibit cell wall synthesis	Otsuka, BMGF	Ι	Co-developed with delamanid

GSK 070, GSK 3036656	oxaborole	Protein synthesis Leucyl-tRNA Synthetase	GlaxoSmithKline	I	
TBA7371	DprE1 inhibitor	Inhibit cell wall synthesis	Eli Lilly, Foundation for Neglected Disease Research	I	

**BMGF**: Bill and Melinda Gates Foundation; NIAID: National Institute of Allergy and Infectious Diseases (U.S.A); PanACEA: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics; SAMRC: South African Research Council; The Union: International Union Against Tuberculosis and Lung Disease; USAID: The U.S. Agency for International Development.

Table 2 Planned, ongoing and recently completed clinical trials on drugs sensitive and drug resistant tuberculosis (as of November, 2017) (courtesy of CDC TB Trials Consortium)

Please see attached pdf and excel sheet for clearer version

Drug(s)	Trial Name	NCT / WHO #	Arms	Ph	N	Group(s)	Status	Results
017			Ailio	- ""		Oloup(s)	otatus	Results
	ns: Rifapentine - P - Ri	, ,						
	TBTC 29X		2HPZE (20 v. 16 v. 10 mg/kg/d) v. 2HRZE	- 1	320	TBTC (Dorman) MRC/UK_EDCTP	Results ATS 2013, AJRCCM 2015 Results IJATLD 2013, NEJM Oct 2014	1200 mg P safe/tolerable, flat dosing better
	RIFAQUIN RIOMAR	ISRCTN44153044 NCT00728507	2MRZE/2MgP <sub>2</sub> 800 v. 2MRZE/4M <sub>1</sub> P <sub>1</sub> 1200 v. 2HRZE/4HR 2HP <sub>1</sub> ZM v. 2HRZE (P = 7.5 mo/kg)	- 1	1095	JHU (Dorman)	Results IDATED 2013, NEJM Oct 2014 Results CROI 2014 93, PLoS One May 2016	4 mo inferior, 6 mo non-inferior, both safe/tolerable Early stop 56% accrual. HPZM better by liquid media
	A6311		P 16 malka v. 20 malka ad or bld ± egg. [HIV- healthy volunteers]		48	ACTG (Dooley)	Results CROI 2014 915, PLOS ONE May 2016  Results CROI 2014 816, AAC 2015	Higher AUCs/Intolerance widoses up to 1800 mg
	Sanofi	NCT01690403	21d pK P 800 mg q wk + Atripia [HIV+ healthy volunteers]		36	Sanofi	Results CROI 2014 493	EFV 600 mg OK with once-weekly P (10 mg/kg)
		NCT00814671	2P <sub>+</sub> (800 v. 460 mg) HZE v. 2HRZE		153	JHU (Dorman/Dawson)	Results IUATLD 2014	Safe/tolerable but no difference cx conversion
		NCT01404312	LTBI: HP (10 mg/kg) ad x30d pK substudy: P + EFV (HIV+)	- 1	3000	ACTG (Chaisson)	pK Results CROI 2014 105, results Q1 2018	EFV OK with daily P (10 mg/kg)
	TBTC 31 / A6349	NCT02410772	2HP <sub>1200</sub> ZE/2HP v. 3HP <sub>1200</sub> ZM <sub>400</sub> v. 2HRZE/4HR [HIV-/+, ages 13 and up, sparse PK]	-	2500	TBTC/ACTG	Opened Jan 2016, enroll thru Q4 2018	Includes DDI PK P/EFV in 31 + 90 HIV+ in 2 stages
	TBTC 31 / A6349 PK	NCT02563327	Intense PK: 2HP+200ZE/2HP v. 3HP+200ZM400 v. 2HRZE/4HR [HIV-/+]		60	TBTC/ACTG	Opened Jan 2016, enroll thru Q4 2018	Intensive PK P, M
	IMPAACT 2001	NCT02651259	LTBI PK/safety: HP (10 mg/kg) q wk x 12 [pregnant/postpartum, ≥ 18 yrs, HIV-/+]	M	82	IMPAACT (Mathad)	Opened Feb 2017, enroll thru Q1 2018	
(	CORTIS	NCT02735590	LTBI: 3HP <sub>900</sub> weekly v. no intervention [†risk by transcriptomics, HIV- adults]		3200	UCT (Hatherill)	Opened July 2016, results 2018	15 month follow-up
	WHIPSTB	NCT02980016	LTBI: 3HP weekly Y1 v. 3HP weekly Y1&Y2 v. 6H Y1 daily		4000	Aurum Inst. (Churchyard)	Opened Nov 2016, results Sep 2019	
	TBTC 36	n/a	LTBI PK/cafety: P (26-36 mg/kg) + H (10-16 mg/kg) in ages <2, 2-5, 6-12 [HIV-/+]	1.0	80	TBTC/Sanofi (Hesseling)	Opens Q1 2018	New water dispersible tablet co-formulation
Rifamyel	ns: High-dose Rifampi	n - R - RIF						
•		NCT01392911	2 wk max tolerability docage, Pk, EBA R to 35 mg/kg	EBA	68	EDCTP/PanACEA	Results IUATLD 2013, AJRCCM Feb 2015	35 mg/kg safe/tolerable, no gr4/5 events, min LFT↑
	RIFATOX	ISRCTN55670677	2HRZE with R 20 v. 16 v. 10 mg/kg	1	300	St. George's/INTERTB	Results IUATLD 2013, IJTLD Jun 2016	20 mg/kg safe/tolerable, dose-related ↑ LFTs < gr3
	HIGHRIF2	NCT00760149	2R 1200 (20 mg/kg) v. 800 (16 mg/kg) v. 600 (10 mg/kg)	100	150	EDCTP/PanACEA	Results InterTB Oct 2014	15 + 20 mg/kg safe/tolerable, pK variability
	MAM8-TB-01	NCT01785186	HR <sub>M</sub> ZE <del>v. HRZQ v. HR<sub>M</sub>ZQ</del> v. HR <sub>M</sub> ZM v. HRZE	1.0	368	EDCTP/PanACEA	Results CROI 2015 95LB, Lancet ID 2017	TTCC R <sub>35</sub> < R <sub>30</sub> at 12wk MGIT only, † liver AEs R <sub>35</sub>
ſ	nia	NCT02387242	WBA: R (30 mg/kg) v. R (20 mg/kg) v. R (10 mg/kg) [healthy]	1.0	18	NUH Singapore (Paton)	Opened Feb 2015, results Sep 2015	
	HIRIF	NCT01408914	2HR <sub>1200</sub> ZE v. 2HR <sub>900</sub> ZE v. 2HR <sub>000</sub> ZE	1	180	Harvard (Mitnick)	Results Apr 2016	
	RIFAVIRENZ	NCT01986543	2R (20 mg/kg)HZE + EFV 800 or 800/d v. 2R (10 mg/kg)HZE + EFV 600/d	1	105	ANRS	Results Apr 2017	
	RIFASHORT	NCT02581527	2HR <sub>1200</sub> ZE/2HR <sub>1200</sub> v. 2HR <sub>1000</sub> ZE/2HR <sub>1000</sub> v. 2HRZE/4HR [HIV-]		820	St. George's/INTERTB	Opened Feb 2017, results Jan 2020	
Rifamyel	ns: Rifabutin - B - RBT							
•		NCT01663168	pK 8afety B <sub>3</sub> v. B <sub>7</sub> + LPV/r (24 wks) [HIV+ on ART]	100	140	MRC/UK (Uganda sites)	pK substudy results pending	
	-		2HBZE/4RH + LPV/r 200 mg +/- RAL vs. 2HRZE/4RH + LPV/r 400 mg	i i	71	ACTG (Benson)	Stage 1 results IAS 2017	
	APT	NCT02256696	12 wk: 2Pa <sub>200</sub> BHZ/1Pa <sub>200</sub> BH v. 2Pa <sub>200</sub> RHZ/1Pa <sub>200</sub> RH v. 2HRZE/1HR [DS]	100	183	JHU (Dooley/Dawson)	Accrual 28, reopening May 2017 after Pa hold	
	TB Host-Directed Rx	NCT02968927	2HBZE/4BH -/+ Everollmus v. Auranofin v. VitD3 v. CC11060 (PDE4inh) [D8, HIV-]		200	Aurum Inst.(Walls)	Opened Nov 2016, results Mar 2018	
	A6289	n/a	2-stage dose-range open label: HRZU v. HBZU v. HRZE [DS only] [HIV-/+]	1.0	182	ACTG (Luetkemeyer)	On hold (8ep 2016)	
Nicotinic	Acids: High-dose Isor	niazid - H - INH						
			1 wk EBA H 16 v. 10 v. 5 mg/kg/d in INH-A recictant TB	EBA	265	ACTG (Dooley/Diacon)	N=227, results Q3 2018	
						The factor of th		
			in - G - Gx, Moxifloxacin - M - Mx				Results IUATLD 2013, NEJM Oct 2014	
	RIFAQUIN OFLOTUB	NCT00216385	2RMZE/2M <sub>2</sub> P <sub>2</sub> 800 v. 2RMZE/4M <sub>1</sub> P <sub>1</sub> 1200 v. 2HRZE/4HR 2HRZG/2RHG v. 2HRZE/4HR	- 1	1095	MRC/UK, EDCTP EU/WHO	Results IUATLD 2013, NEJM Oct 2014 Results IUATLD 2013, NEJM Oct 2014	4 mo inferior, 6 mo non-inferior, both safe/tolerable 4 mo inferior, both arms safe/tolerable
	RIOMAR	NCT00216363 NCT00728507	2HP-ZM v. 2HRZE (P = 7.5 ma/ka)	- 1	216	JHU (Dorman)	Results CROI 2014 93, PLoS One May 2016	Early stop 56% accrual, HPZM better by liquid media
	ReMOX	NCT00/2650/ NCT00864383	2HRZM/2HRM v. 2RMZE/2RM v. 2HRZE/4HR	- 1	1931	TR Allance/PanACEA	Results ICAAC 2014 NEJM Oct 2014	4 mo arms inferior, both safe/tolerable
	MAMS.TR.01	NCT01785186	HRuze <del>v. HRze v. Hr. Ze</del> v. HRuzM v. HRze	- 7	372	EDCTP/PanACEA	Results CROI 2015 95LB, Lancet ID 2017	HRZQ + HR <sub>ss</sub> ZQ arms dropped Mar 2014
	A6307		2 WK EBA RMZE V. RZE V. HRZE	EBA	69	ACTG (Bishal)	Completed Feb 2016, results CROI 2017 79	INH had no EBA, even by D2 (? Lower load sputa)
			4MCEZHKProi6MCZE v. local DR regimen (DR)	1	400	IUATLD/MRC/DFID/USAID	Interim results IUATLD 2017	, , , , , , , , , , , , , , , , , , , ,
	NC-008 STAND	NCT02342886	4PananamMZ v. 6PanamMZ v. 6PanamMZ v. 2HRZE/4HR [DS. DR 6PanamMZ only]	1	284	TB Allance	Completed early, results late 2017	
	OPTI-Q	NCT01918397	Lx (14 v. 17 v. 20 mg/kg/d) + OBT v. Lx (11 mg/kg/d) + OBT [DR]	1.0	100	NIAID/TBTC (Horsburgh)	Follow-up completed, results Q2 2018	
	NexGen EBA	NCT02371681	4 wk EBA: 1MRHZ [serial F-FDG PET scans, D8 only]	1	350	NIAID (Barry/Diacon)	Opened Jan 2015, results Nov 2017	
ſ	NExT-6001	NCT02454205	8-8LzJLxZ(H or Eth or Ter) v. 6-8KMZ(Eth or Ter)/16-18MZ(Eth or Ter) [DR]	IVII	300	UCT/Stellenbosch (Dheda)	Opened Oct 2015, results Jan 2019	
	TBTC 31 / A6349	NCT02410772	2HP <sub>1200</sub> ZE/2HP v. 3HP <sub>1200</sub> ZM <sub>600</sub> v. 2HRZE/4HR [HIV-/+, ages 13 and up, sparse PK]	100		TBTC/ACTG	Opened Jan 2016, enroll thru Q4 2018	Includes DDI PK P/EFV in 31 + 90 H/V+ in 2 stages
	TBTC 31 / A6349 PK	110100710110			2500	101011010		includes point in the First Country in a studen
	IDIO OIT ADDAOTIN	NCT02563327	Intense PK: 2HP <sub>1200</sub> ZE/2HP v. 3HP <sub>1200</sub> ZM <sub>400</sub> v. 2HRZE/4HR [HIV-/+]	1	2500 60	TBTC/ACTG	Opened Jan 2016, enroll thru Q4 2018	TEMOS DOTT RETAINED TO THE TEMOSES
	MDR-END		Infence PK: 2HP <sub>1306</sub> ZE/2HP v. 3HP <sub>1306</sub> ZM <sub>860</sub> v. 2HRZE/4HR [HIV-I+] 8 or 12D + Lx <sub>7501300</sub> + Lz <sub>5002M+300</sub> + Z v. 240BR [DR, quinoione sensitive]	1			Opened Jan 2016, enroll thru Q4 2018 Opened Jan 2016, results Dec 2019	TRANSPORTER TO THE TOTAL TO THE TRANSPORT
		NCT02563327		-	60	TBTC/ACTG	-,	Belarus, South Africa, Uzbekistan
	MDR-END	NCT02563327 NCT02619994	8 or 12D + Lx <sub>10x1000</sub> + Lx <sub>00x004+000</sub> + Z v. 24OBR [DR, quincione sensitive] 2 ctage: 6JPaMLz v. 6JPaLz v. 8JPaLz v. 24OBR [DR, XDR] MCEZHKPro v. JLvCEZHPro v. JLvCZHK v. local DR regimen [DR]	i	60 238	TBTC/ACTG Seoul Nat. Univ. Hospital	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021	•
	MDR-END TB-PRACTECAL STREAM Stage 2	NCT02563327 NCT02619994 NCT02589782 NCT02409290 NCT02754765	8 or 12D + Lx <sub>1001000</sub> + Lx <sub>001001+000</sub> + Z v. 24OBR [DR, quinoione sensitive] 2 dtage: 6JPaMLz v. 6JPaLz v. 8JPaLz v. 24OBR [DR, XDR] MCEZHKPro v. JLvCEZHPro v. JLvCZHK v. local DR regimen [DR] 8JLzMZ v. 6JLzCLxZ v. 6JLzDLxZ v. 8DCMZ v. 24OBR [DR, quinoione sensitive]	II IVII	60 238 630	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCL/LSHTM	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021	•
	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR	NCT02563327 NCT02619994 NCT02589782 NCT02409290 NCT02754765 ACTRN126000215	8 or 12D + Lx <sub>1801000</sub> + Lx <sub>801001+300</sub> + Z v. 24OBR [DR, quinoione sensitive] 2 dtage: 8JPaMLz v. 8JPaLz v. 8JPaLz v. 24OBR [DR, XDR] MCEZHKPro v. JLvCEZHPro v. JLvCZHK v. local DR regimen [DR] 8JLzMZ v. 8JLzCLxZ v. 8JLzDLxZ v. 8DCMZ v. 24OBR [DR, quinoione sensitive] 4LTBL: 8Lx <sub>801800100</sub> v. placebo (blinded) [DR contacts, ≥15 randiscreen all, HIV+F)	II IVII II	60 238 630 1155 750 2006	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCULSHTM IUATLD/MRC/USAID/TBA MSF France/Harvard Australia NHMRC (Fox)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021 Opened Dec 2016, results Sep 2020 Opened 2016, results 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhistan, Kyrgyzstan, Lesotho, Penu Vietnam (multiple sites)
	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR TB-CHAMP	NCT02563327 NCT02519994 NCT02589782 NCT02409290 NCT02754765 ACTRN126000215 n/a	8 or 12D + Lx <sub>1001000</sub> + Lx <sub>001004+N00</sub> + 2 v. 240BR [DR, quinoione sensitive] 2 stage: &IPaMLz v. &IPALZ v. &IPALZ v. 240BR [DR, XDR] MOEZHKPR v. JLvOEZHP v. JLvOZHK v. local DR regimen [DR] SULTMZ v. &ILTCLIX v. &ILTCLIX v. &ISOCMZ v. 240BR [DR, quinoione sensitive] HITBLE &Lx <sub>000000700</sub> v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lx <sub>000000700</sub> v. placebo (plinded) [DR contacts, 265 html++]	I MI II II	60 238 630 1155 750 2006 1565	TBTC/ACTG Seoul Nat. Liniv. Hospital MSF Holland/UCL/LSHTM IUATLD/MRC/USA/D/TBA MSF France/Harvard Australia NHMRC (Fox) MRC/DFID/Wellcome	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened And 2016, results Apr 2021 Opened And 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opened 2017, results 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhstan, Kyngyzstan, Lesotho, Peru
	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR	NCT02563327 NCT02619994 NCT02589782 NCT02409290 NCT02754765 ACTRN126000215	8 or 12D + Lx <sub>1801000</sub> + Lx <sub>801001+300</sub> + Z v. 24OBR [DR, quinoione sensitive] 2 dtage: 8JPaMLz v. 8JPaLz v. 8JPaLz v. 24OBR [DR, XDR] MCEZHKPro v. JLvCEZHPro v. JLvCZHK v. local DR regimen [DR] 8JLzMZ v. 8JLzCLxZ v. 8JLzDLxZ v. 8DCMZ v. 24OBR [DR, quinoione sensitive] 4LTBL: 8Lx <sub>801800100</sub> v. placebo (blinded) [DR contacts, ≥15 randiscreen all, HIV+F)	I MI II II	60 238 630 1155 750 2006 1565	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCULSHTM IUATLD/MRC/USAID/TBA MSF France/Harvard Australia NHMRC (Fox)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021 Opened Dec 2016, results Sep 2020 Opened 2016, results 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhistan, Kyrgyzstan, Lesotho, Penu Vietnam (multiple sites)
	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR TB-CHAMP	NCT02563327 NCT02619994 NCT02589782 NCT02499290 NCT0274765 ACTRN126000215 nla	8 or 12D + Littories + Literian-No + 7 v. 240BR [DR, quincione sensitive] 2 stages: &IPAMLY v. &IPALETO v. &IPALE v. 340BR [DR, XDR] MCEZHKPro v. JLVCAZHV rov. JLVCZHK v. Local DR regimen [DR] 8 JLLMZ v. &ILLCLXZ v. &ILLCLXZ v. &IDAMZ v. 140B [DR, quincione sensitive] 14 LTBS: &Literian-Sensitive v. Discate (unined) [DR contacts, 215 randiscreen all HIV++] LTBS: &Literian-Sensitive v. piacebo (blinded) [DR contacts, 215 randiscreen all HIV++] 4 JPAMZ v. 2HRZEHRH [DS], &JPAMZ [DR]	I MI II II	60 238 630 1155 750 2006 1565	TBTC/ACTG Seoul Nat. Liniv. Hospital MSF Holland/UCL/LSHTM IUATLD/MRC/USA/D/TBA MSF France/Harvard Australia NHMRC (Fox) MRC/DFID/Wellcome	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened And 2016, results Apr 2021 Opened And 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opened 2017, results 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)
Diaryiquii	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplicitB	NCT02563327 NCT02619994 NCT02589782 NCT02599782 NCT0274765 ACTRN126000215 nla TMC-207 - J (Ja	8 or 12D + Littories + Literian-No + 7 v. 240BR [DR, quincione sensitive] 2 stages: &IPAMLY v. &IPALETO v. &IPALE v. 340BR [DR, XDR] MCEZHKPro v. JLVCAZHV rov. JLVCZHK v. Local DR regimen [DR] 8 JLLMZ v. &ILLCLXZ v. &ILLCLXZ v. &IDAMZ v. 140B [DR, quincione sensitive] 14 LTBS: &Literian-Sensitive v. Discate (unined) [DR contacts, 215 randiscreen all HIV++] LTBS: &Literian-Sensitive v. piacebo (blinded) [DR contacts, 215 randiscreen all HIV++] 4 JPAMZ v. 2HRZEHRH [DS], &JPAMZ [DR]	I MI II II	60 238 630 1155 750 2006 1565	TBTC/ACTG Seoul Nat. Liniv. Hospital MSF Holland/UCL/LSHTM IUATLD/MRC/USA/D/TBA MSF France/Harvard Australia NHMRC (Fox) MRC/DFID/Wellcome	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened And 2016, results Apr 2021 Opened And 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opened 2017, results 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)
Diaryiqui	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-GUIN MDR TB-CHAMP NC-008 SimplioITB nollnes: Bedaquilline -	NCT02563327 NCT02619994 NCT02589782 NCT02409290 NCT02754765 ACTRN126000215 nla TMC-207 - J (Ja NCT01341184	8 or 12D + Lxtsurson + Lzeuczet-Nov + Yv. 24OBR [DR, quinoione sensitive] 2 diage: 8JPaMLz v. 8JPaLz v. 8JPaLz v. 24OBR [DR, XDR] MOEZHKPO v. JLVOEZHPO v. JLVOEZH V. IOCAI DR regimen [DR] 8JLZMZ v. 8JLZDLXZ v. 8JLZDLXZ v. 8DCMZ v. 24OBR [DR, quinoione sensitive] VITBL: 8LXsusseriov v. placebo (blinded) [DR contacts, 215 randiscreen all, HIV++] LTBL: 8LXsign sense v. placebo (blinded) [DR contacts, ages 0-5, HIV++] 4JPaMZ v. 2HRZEI4RH [D0], 8JPAMZ [DR] INBSBNTTB Alliance)	I MI II II	60 238 630 1155 750 2006 1565 150/150	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCLU.8HTM IUATLD/MRG/USA/IDFA Australia N-HIARC (Fox) MRC/DFID/Welcome TB Allance	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021 Opened Apr 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opens 2017, results 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhistan, Kyrgyzstan, Lesotho, Penu Vietnam (multiple sites)
Diaryiquii	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplicitB nolines: Bedaquiline - n/a	NCT02563327 NCT02619994 NCT02589782 NCT02409290 NCT02754765 ACTRN126000215 nlb nlb TMC-207 - J (Ja NCT01341184	8 or 12D + Littorion + Littorion+No + Y.v. 24OBR [DR, quincione sensitive] 2 clage: & JPaMLz v. & JPaLz V. & JPALz v. 24OBR [DR, XDR] MOEZHKFO v. JLIVOEZHFO v. JLIVOEZH V. IOCAI DR regimen [DR] 8 JLEMZ v. & SILEDLIZ v. & JRIDDLIZ v. & JOCHZ v. Z4OBR [DR, quincione sensitive] 4 LTBL: & Littorion v. placebo [blinded] [DR contacts, 215 randiscreen all, HIV+H] LTBL: & Littorion analog. V. placebo [blinded] [DR contacts, ages 0-5, HIV+H] 4 JPAMZ v. 2HRZE4HR [D0], & JPAMZ [DR] insesn/TB Alliance) pK clingle doce J + RFB, J + RFM [healthy volunteers]	1	60 238 630 1155 750 2006 1565 150/150	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland UCLLSHTM IUATLOMRCUGAID/TBA MSF FranceHannard Australia NHMRC (Fox) MRCIDFIDIW elcome TB Allance NIAID (CWRU)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021 Opened Apr 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opens 2017, results 2019	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru  Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)
Diaryiqui	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-Q-QUIN MDR TB-C-HAMP NC-008 SimpliciTB nollnes: Bedaquiline - n/a NC-008	NCT02563327 NCT02519994 NCT02599782 NCT02409290 NCT02754765 ACTRN126000215 nlb nlb TMC-207 - J (Ja NCT01341184 NCT01691534	8 or 12D + Lx <sub>1901000</sub> + Lx <sub>1901004+M0</sub> + 2 v. 24OBR [DR, quinoine sensitive] 2 dtage: 8JPaMLz v. 8JPaLz V. 8JPaLz v. 24OBR [DR, XDR] MCEZHKPRO v. JLvOEZHPO v. JLvOEJDR regimen [DR] 8JLEMZ v. 8JLZDLZ v. 8JLZDLZ V. 8DCMZ v. 24OBR [DR, quinoine sensitive] 6LTBI: 8Lx <sub>190100000</sub> v. piscebo [binded] [DR contacts, 215 randiscreen all, HIV+1-] LTBI: 8Lx <sub>1901000000</sub> v. piscebo [binded] [DR contacts, ages 0-5, HIV+1-] 4JPaMZ v. 2HAZEJHRH [DS], 8JPAMZ [DR] inssenTB Alliance) pK clingle doze J + RFB, J + RFM [realthy volunteers] 2 wk EBA JPAZ, JPAZC, JPaC, JZC, Z, C	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	60 238 630 1155 750 2006 1565 150/150	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland UCL/LSHTM IUAT LDMRCUGAID/TBA MSF France Hannard Australia NHMRC (Fox) MRC/DFID/Welcome TB Allance NIAID (CWRU) TB Allance	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021 Opened Apr 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opens 2017, results 2019 Opens 2018 Completed 2012, results pending Results CROI 2014 97LB, AJRCCM Jan 2015	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaz best, mod QT effect, C no activity
Diaryiquii	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplicitB Inclines: Bedaquiline - nia NC-005	NCT02563327 NCT02619994 NCT02589782 NCT02409290 NCT02754765 ACTRN126000215 n/b n/b NCT01341184 NCT01691534 NCT02193776	8 or 12D + Lx <sub>1001100</sub> + Lx <sub>1001001+N0</sub> + Y.v. 24OBR [DR. quinoine sensitive] 2 ctage: &IPAMLY v. &IPALETO v. &IPALE v. X-DOBR [DR. XDR] MCEZHKPro v. JLvCeZHPro v. JLvCeZHK v. local DR regimen [DR] SULEMZ v. &ILECLEZ v. &ILECLEZ v. &IDACED (Blinder) [DR quinoine sensitive] i-LTBI: &Lx <sub>10010000000</sub> v. placebo (blinded) [DR contacts, x/5 randiscreen all HIV+/-] LTBI: &Lx <sub>10010000000</sub> v. placebo (blinded) [DR contacts, x/5 randiscreen all HIV+/-] 4JPAMC v. Z-HRZEHAH [DD], &JPAMZ [DR] INBSSNITE Alliance) pt (single dose J + RFB, J + RFM [healthy volunteers] 2 wk EBA JPAZ, JPAZO, JPAO, JZO, Z. C. 88CC: J(400 mg/id x14d, 200 mg/im)PaZ v. J(200 mg/id)PaZ (+ M in DR) v. HRZE	1	60 238 630 1155 750 2006 1565 150/150 32 105 240	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCUL/SHTM IUATLD/MRC/USA/D/TBA MSF France/havand Australia NHMRC (Fox) MRC/DF/D/Welcome TB Allance NIAID (CWRU) TB Allance TB Allance	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Agr 2016, results Mar 2021 Opened Agr 2016, results Agr 2020 Opened 2016, results 2019 Opened 2016, results 2019 Opens 2018  Completed 2012, results pending Results CROI 2014 97UB, AJRCCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaz best, mod QT effect, C no activity
Diaryiquii	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-Quin MDR TB-CHAMP NC-908 SimpliciTB inolines: Bedaquilline - n/a NC-909 NC-905 NC-905 NC-905 NC-905 NX-NX-TB NExT-5001	NCT02563327 NCT0259994 NCT02599792 NCT02599792 NCT02409290 NCT02754765 NB	8 or 12D + Lxtpurion + Lzwozdw-Mo + 2 v. 24 OBR [DR, quinolone sensitive] 2 clage: & JPaMLz v. & JPaLz v. & JPaLz v. 24 OBR [DR, XDR] MOEZHKFO v. JLvOEZHFO v. JLvOEZHFO v. Closd DR regimen [DR] 8 JLZMZ v. & JLZCLZ v. & JLZDLZ v. & DOCMZ v. 24 OBR [DR, quinolone sensitive] 4 TEB: & Lxtpaneomo v. placebo (plinded) [DR contacts, 215 randiscreen all, HIV+H] LTB: & BLxtpaneomo v. placebo (plinded) [DR contacts, 295 and socreen all, HIV+H] 4 JPaMZ v. 24 RZE44RH [D0], & JPAMZ [DR]  1088801TB Alliance) pK single dose J + RFB, J + RFM [realthy volunteers] 2 wk EBA JPAZ, JPAZO, JPAG, JZC, Z, C 8 SCC: J(400 mgld xHz) Quong thelipaZ v. J(200 mgld)PAZ (+ M in DR) v. HRZE clingle arm pkfusfety Japaneos: & H + OBR [DR]  8 JPA <sub>200</sub> (LZD (800 mg bid) [single arm, XDR] 8 -BLZLVZIH or Eth or Ter) v. 6+8KMZ(Eth or Ter) //16-18MZ(Eth or Ter) [DR]	1   1   1   1   1   1   1   1   1   1	60 238 630 1155 750 2006 1565 150/150 32 105 240 5	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland UCQLLSHTM IUATLD MRG. UCAJAD/TBA MSF FRANCEHANVARI Australia NHARC (Fox) MRC/DFID/Welcome TB Allance NIAID (CWRU) TB Allance Janossen TB Allance Janossen TB Allance UCT/Stellenbosch (Dheds)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened Jan 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opens 2017, results 2019 Opens 2018 Completed 2012, results pending Results CROI 2014 8718, JARCOM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Mar 2015, results deckt Nov 2017 Opened Mar 2015, results Jan 2019	Belarus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vieham (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPAZ best, mod QT effect, C no activity  BPAMZ + BPAZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs
Diaryiqui	MDR-END TB-PRACTECAL STREAM Stage 2 endTB V-Quin MDR TB-C-HAMP NC-008 SimplioITB nollnes: Bedaquilline - n/a NC-008 NC-005 NC-005 NC-006 NC-007 NC-TB NEXT-5001 TB-PRACTECAL	NCT0259327 NCT0251994 NCT0251994 NCT02599782 NCT0279275 ACTRN126000215 nb nb TMC-207 - J (Ja NCT01341194 NCT01391194 NCT01591534 NCT01259523 NCT0259523 NCT0259523 NCT0254525 NCT0258523	8 or 12D + Lx <sub>1001100</sub> + Lx <sub>1001001+N00</sub> + Y.v. 24OBR [DR, quinoine sensitive] 2 ctage: & RyPAMLY v. &PyPaLZ v. &PyPaLZ v. X4OBR [DR, XDR] MCEZHKPro v. JLvCeZHPro v. JLvCeZHK v. local DR regimen [DR] MCLEMY v. &LxCeLZ v. &LtaDLoz v. 80CMZ v. 24OBR [DR, quinoine sensitive] i-LTB1: &Lx <sub>10010001000</sub> v. placebo (plinded) [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>10010000100</sub> v. placebo (plinded) [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>10010000100</sub> [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>10010000010</sub> [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>10010000000</sub> [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>10010000000</sub> [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>10010000000</sub> [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>100100000000</sub> [DR contacts, x15 randiscreen all H1/+-) LTB1: &Lx <sub>1001000000000000000000000000000000000</sub>	1	60 238 630 1155 750 2006 1565 150150 32 105 240 5 200 300 630	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCL/LGHTM MSF France-Hanand Australia NHMRC (Fox) MRC/DF/DIW-elcome TB Allance NIAID (CWRU) TB Allance TB Allance UCT/Stellenbosch (Dheda) MSF Hollande UCT/Stellenbosch (Dheda)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Apr 2021 Opened Apr 2016, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opens 2017, results 2019 Opens 2018  Completed 2012, results pending Results CROI 2014 97LB, AJRCCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Apr 2015, follow-up thru Nov 2017 Opened Ond 2015, results Jan 2019 Opened John 2015, results Jan 2019 Opened John 2017, results Jan 2019	Belanus, South Africa, Uzbekistan Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vletnam (multiple sites) South Africa (Stelenbosch and 3 other sites) BPAZ best, mod QT effect, C no activity BPAMZ + BPAZ had highest BA; low AEs in 8 wks
Diaryiqui	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-QUIN MDR TB-CHAMP NC-908 SimplicitB nollines: Bedaquilline - n/a NC-908 NC-908 NC-908 NC-908 NX-TB NX-TB NX-TB NX-TB TB-PRACTECAL STREAM stage 2	NCT02563327 NCT0259994 NCT02599792 NCT02599792 NCT02754755 ACTRM126000215 nb nb TMC-207 - J (Ja NCT01341184 NCT01341184 NCT01391534 NCT02395523 NCT02395523 NCT02395992 NCT02459250 NCT02459250 NCT02459250	8 or 12D + Lx <sub>1001100</sub> + Lx <sub>1001001+N00</sub> + Y.v. 24OBR [DR, quinoine sensitive] 2 stapes: &PPAMLY v. &PPALEO v. &PPALE v. 24OBR [DR, XDR] MOEZHKPro v. JLvCeZHPro v. JLvC2HK v. 10cal DR regimen [DR] MULHAZ v. &BJLCLKZ v. &JLCLKZ v. &OCMZ v. 24OBR [DR, quinoine sensitive]  **LTBS: &Lx <sub>200000070</sub> v. placebo (plinded) [DR contacts, 245 and screen all HIV++]  LTBS: &Lx <sub>4000000070</sub> v. placebo (plinded) [DR contacts, 245 and screen all HIV++]  *LTBS: &Lx <sub>4000000000</sub> v. placebo (plinded) [DR contacts, 265 and screen all HIV++]  ### APPAMZ v. 2+HRZEHRH [D0], &JPAMZ [DR]  #### [Peatitry volunteers]  ### (Peatitry volunteers)  ### (Peatitry volun	1	60 238 630 1155 750 2006 1565 150/150 32 105 240 5 200 630 1155	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCLU.GHTM MSF France/Hanard Australia NHMRC (Fox) MR.O.D.F.ID.W. elcome TB Alliance NIAID (CWRU) TB Alliance TB Alliance Janasen TB Alliance UCT/Gtellenbosch (Dheda) MSF Holland/UCLU.GHTM IUATL.DIMR.G.U.Q.AID.TEA	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Opene 2017, results 2019 Opene 2018  Completed 2012, results pending Results CROI 2014 97LB, AJRCCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Feb 2015, follow-up thru Nov 2018 Opened Mar 2015, switch to ZeMIX Nov 2017 Opened Oct 2015, results Jan 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Mar 2021	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belanus, South Africa, Uzbekistan
Diaryiqui	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplicitB nollines: Bedaquilline - n/a NC-005 NC-005 N/a NC-005 N/a NIX-TB NEXT-5001 TB-PRACTECAL STREAM stage 2 C211	NCT02563327 NCT0259994 NCT0259992 NCT02599792 NCT0259775 ACTRN126000215 nla nla TMC-207 - J (Ja NCT01591534 NCT01591534 NCT01691534 NCT0169154	8 or 12D + Lxtsurion + Lxtsution+No + Y.v. 24OBR [DR, quinoine sensitive] 2 clage: &IPaMLz v. &IPaLz v. &IPaLz v. 24OBR [DR, XDR] MOEZHKPR v. JLVOEZHPR v. JLVOZHK v. IOCAI DR regimen [DR] SULTMZ v. &ILTCLIX v. &ILTCLIX v. &IDACMZ v. 24OBR [DR, quinoine sensitive]  ILTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++] LTBL: &Lxtsussum v. placebo (plinded) [DR contacts, 245 and screen all HIV++]  WE EBA JPAZ, JPAZC, JPAC, JZC, Z, C  &WE EBA JPAZ, JPAZC, JPAC, JZC, Z, C  &UPAS, LTBL: &Lxtsussum v. placebo (plinded) [DR]  &IPAS, LT	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	60 238 630 1155 750 2006 1565 150/150 32 105 240 5 200 300 630 1155 60	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holiand/UCLU.BHTM IUATLD/MRC/USA/IDFBA MSF France-Harward Australia NHMRC (Fox) MRC/DF/D/Welcome TB Alliance  NIAID (CWRU) TB Alliance TB Alliance UCT/Gtellance UCT/Gtellance UCT/Gtellance UCT/Gtelland/UCLU.BHTM IUATLD/MRC/USA/IDTBA Janasen	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Opene 2017, results 2019 Opene 2017, results 2019 Opene 2018  Completed 2012, results pending Results CROI 2014 PTUB, AJROCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Sep 2015, follow-up thru Nov 2018 Opened Mar 2015, switch to ZeNIX Nov 2017 Opened Oct 2015, results Jan 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Mar 2021 Opened May 2016, results Mar 2021 Opened May 2016, results Mar 2021	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (mutiple sites)  South Africa (Stelenbosch and 3 other sites)  BPAZ best, mod QT effect, C no activity  BPAMZ + SPAZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belanus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa
Diaryiquii	MDR-END TB-PRACTECAL STREAM stage 2 endTB v-Quin MDR TB-CHAMP NC-008 SimplicitB inolines: Bedaquilline - n/a NC-005 n/a NC-005 n/a NEXT-5001 TB-PRACTECAL STREAM stage 2 C211 endTB	NCT02563327 NCT0259994 NCT02599792 NCT02699792 NCT02699792 NCT02697976 NCT02697976 NCT03697979 NCT03697979 NCT03697979 NCT02693799 NCT02693779 NCT02693779 NCT02693778 NCT02693782 NCT02693782 NCT02693782 NCT02693782 NCT02697820 NCT02694782 NCT02694782 NCT02694782 NCT02694782 NCT02694782	8 or 12D + Lxtsurson + Lzeuczel+No + Yv. 24OBR [DR, quinoione sensitive] 2 clage: &IPaMLz v. &IPaLz v. &IPaLz v. 24OBR [DR, XDR] MOEZHKPRO v. JLVOEZHPO v. LIVOZHK v. IOCAI DR regimen [DR] 8 ULTAZ v. &ILTCLX v. &ILTDLX v. &IPALz v. 24OBR [DR, quinoione sensitive] 4 UTBL: &Lxtsussorov v. placebo (plinded) [DR contacts, 215 randiscreen all HIV+H] LTBL: &Lxtsussorov v. placebo (plinded) [DR contacts, 215 randiscreen all HIV+H] LTBL: &LXtsussorov v. placebo (plinded) [DR contacts, ages 0-5, HIV+H] 4 UTBL: &ILXtsussorov v. placebo (plinded) [DR contacts, ages 0-5, HIV+H] 9 IN (BRA) PAZ, JAZ, JAZ, JAZ, JAZ, JAZ, JAZ, JAZ, J	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	60 238 630 1155 750 2006 1565 150/150 32 105 240 5 200 630 1155 60 750	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCLU.SHTM IUATLD/MRG/USA/DTBA MSF FranceHanand Australia N-HMRG (Fox) MRG/DF/ID/Welcome TB Alliance TB Alliance Janusen TB Alliance UCT/Stellenbosch (Dheda) MILATLD/MRG/USA/DTBA Janusen MILATLD/MRG/USA/DTBA Janusen MSF FranceHanand	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Opene 2017, results 2019 Opene 2017, results 2019 Opene 2018  Completed 2012, results pending Results CROI 2014 97U.B, AJRCCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Sep 2015, follow-up tru Nev 2018 Opened Mar 2015, switch to ZeNIX Nov 2017 Opened Oct 2015, results Jan 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Mar 2021 Opened May 2016, results Mar 2021 Opened May 2016, results Mar 2021 Opened Dec 2016, results Mar 2021	Belarus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belarus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
Diaryiqui	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-Quin MDR TB-CHAMP NC-908 SimpliciTB inolines: Bedaquilline - n/a NC-905 NC-905 NC-905 NC-905 NC-905 TB-PRACTECAL STREAM stage 2 C211 endTB A6343 DELIBERATE	NCT0259327 NCT0251994 NCT0251994 NCT0259375 NCT02754755 AGTRN12600215 Nb TMC-207 - J [Ja NCT01341194 NCT01341194 NCT01691534 NCT0134194 NCT01259375 NCT02356523 NCT02589782	8 or 12D + Littorion + Lawician-No. + 2 v. 24 OBR [DR, quinolone sensitive] 2 clage: & JPaMLz v. & JPaLz v. & JPaLz v. 24 OBR [DR, XDR] MOEZHKFO v. JLIVOEZHFO v. JLIVOZHK v. (local DR regimen [DR] 8 JLAMZ v. & JLIZCLZ v. & JLIZDLZ v. & SOCMZ v. 24 OBR [DR, quinolone sensitive] 4 TEB: & Lixing making v. placebo (plinded) [DR contacts, 215 randiscreen all, HIV+h] LTB: & BLiright making v. placebo (plinded) [DR contacts, 295 and socreen all, HIV+h] 4 JPaMZ v. 2HRZEH4RH [D0], & JPAMZ [DR]  1088801TB Allilance) pK single dose J + RFB, J + RFM [realthy volunteers] 2 with EBA JPAZ, JPAZO, JPAG, JZO, Z, C 8 SCC: J(400 mgld xHJZ yBAZO, V. 200 mg thipPaZ v. J(200 mgld)PaZ (+ M in DR) v. HRZE clingle arm pit/Lasfey Japanese: 84 + OBR [DR] 8 JPA <sub>200</sub> (JZD (800 mg bid) [single arm, XDR] 8 -BLZILVZ[H or Eth or Ter] v. 6+8KMZ[Eth or Ter] VIF-18MZ[Eth or Ter] [DR] 2 clage: & JPAMLz v. & JPAZD v. & JPAZ v. X-JOSR [DR, XDR] MCEZHKFOR v. JLIVCZEJR v. JLIVZEJK K. (local DR regimen [DR] PKIJAMZ v. & JLIZCLIZ v. & BLZDLZ v. & JOSR [DR, Quinolone sensitive] pK DDI QT 8J v. 80 v. & JD + OBR [DR] [PH/V]  8 JLAMZ v. & BLZCLIZ v. & JLZDLZ v. & BORMZ (JR) [DR, quinolone sensitive] pK DDI QT 8J v. 80 v. & JD + OBR [DR] [PH/V]	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	60 238 630 1155 750 2006 1565 150150 32 105 240 5 200 300 630 1155 60 750 84	TBTCIACTG Seoul Nat. Univ. Hospital MSF Holand/UCULGHTM MSF France-Hanand Australia NHMRC (Fox) MRCIDFIDIW elcome TB Allance NIAID (CWRU) TB Allance TB Allance UCT/Stellenbosch (Dheda) MSF Holland/UCLLSHTM IUATLDIMRCUSAIDITBA Janssen MSF France-Hanand ACTG (Maartens/Dooley)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened Jan 2016, results Dep 2020 Opened Dec 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Opened 2017, results 2019 Opened 2012, results pending Results CROI 2014 87/LB, AJROCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Sep 2015, results Jan 2017 Opened Mar 2015, switch to ZeNIX Nov 2017 Opened Mar 2015, results Jan 2019 Opened Jan 2017, results Mar 2021 Opened May 2016, results Jan 2021 Opened May 2016, results Mar 2021	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belanus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Results 2018
Diaryiqui (	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-QUIN MDR TB-CHAMP NC-908 SimplicitB nollines: Bedaquilline - n/a NC-908 NC-90	NCT02563327 NCT02519994 NCT0259992 NCT02499290 NCT02499290 ACTRAN126000215 n/b n/b TTMC-207 - J (Ja NCT01341194 NCT01391934 NCT02395623 NCT02395623 NCT0239590 NCT02495290 NCT02495290 NCT02495290 NCT02495290 NCT02589048 n/b	8 or 12D + Liteures + Liteures + V. 240BR [DR, quinoine sensitive] 2 ctage: &IPAMLY v. BPALTO V. &IPALTO V. AUGR [DR, CDR]  MCEZHKPro v. JLVCEZHPro v. JLVCZHK v. local DR regimen [DR]  MLTEX v. SILCCLXZ v. SILCDLXZ v. 80CMZ v. 240BR [DR, quinoine sensitive]  LTBI: &Liteures v. biacteb (ulnded) [DR contacts, 215 and screen all HIV+/-]  LTBI: &Liteures v. biacteb (ulnded) [DR contacts, 215 and screen all HIV+/-]  LTBI: &Liteures v. biacteb (ulnded) [DR contacts, 215 and screen all HIV+/-]  LTBI: &Liteures v. biacteb (ulnded) [DR contacts, 215 and screen all HIV+/-]  LTBI: &Liteures v. biacteb (ulnded) [DR contacts, 215 and screen all HIV+/-]  LTBI: &Liteures v. biacteb (ulnded) [DR contacts, 215 and screen all HIV+/-]  WE SIDE APPAL V. HRESHAH [DO], &IPAMZ [DR]  INSBANTER Alliance]  2 wie EBA JPAZ, JPAZO, JPAG, JZO, Z, C  SSCC: J(400 mgid x14d, 200 mg tiv/PaZ v. J(200 mgid/PaZ (+ M in DR) v. HRZE clingle am pi/losteby Japanese: &I + OBR [DR]  &JPAZ, LZD (800 mg bid) [cinqle amx, JZD (BR) [DR]  &JPAZ, LZD (800 mg bid) [cinqle amx, JZD (BR) [DR], JZD (BR)  MCEZHKPro v. JLVCEZHPro v. JLVCZHK v. local DR regimen [DR]  PI/lashby: A age dishal + OBR [DR, Quinci DR Regimen [DR]  PI/lashby: dose-range J + OBR [DR] [PI/IV+/-]  PK/lashby: dose-range J + OBR [DR, C-18 yrs, HI/IV+]	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	60 238 630 1155 750 2006 1565 150150 32 105 240 5 200 300 630 1155 60 750 84 72	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holland/UCLU.GHTM MSF France/Harvard Australia NHMRC (Fox) MRC/DF/DIW-elcome TB Allance NIAID (CWRU) TB Allance Janasen TB Allance UCT/Stellenbosch (Dheda) MSF Hollande UCT/Stellenbosch (Dheda) Janasen TS Allance UCT/Stellenbosch (Dheda)	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Opene 2017, results 2019 Opene 2018  Completed 2012, results pending Results CROI 2014 97LB, AJRCCM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Feb 2015, follow-up thru Nov 2018 Opened Mar 2015, saltich to ZeMIX Nov 2017 Opened Ox 2015, results Jan 2019 Opened Jan 2017, results Mar 2021 Opened May 2016, results Mar 2021 Opened May 2016, results Mar 2021 Opened May 2016, results Dep 2020 Opened Jan 2016, fine pending 2010	Belarus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellerbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belarus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
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Diaryiquii i	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplicitB nollines: Bedaquilline - n/a NC-005 NC-005 N/a NIX-TB NEXT-5001 TB-PRACTECAL STREAM stage 2 C211 endTB A6343 DELIBERATE P1108 NC-007 ZeNIX	NCT02563327 NCT0259994 NCT02599792 NCT02599792 NCT02599792 NCT02754755 ACTRM126000215 nb nb TMC-207 - J (Ja NCT01341184 NCT01341184 NCT01349153 NCT02355623 NCT02355623 NCT02355756 NCT02599792 NCT02599793 NCT02599792 NCT025	8 or 12D + Liteurien + Lawicien+No + Y.v. 240BR [DR, quinoine sensitive] 2 stages: &IPAMLY v. &IPALEZ V. &IPALE V. 240BR [DR, Quinoine sensitive] MCEZHKPro v. JLVCEZHPro v. JLVCZHK v. IOCAI DR regimen [DR] MILIMZ V. &ILICLIX V. &ILICLIX V. &IDACE V. A40BR [DR, quinoine sensitive] HLTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] Sales (Placebo v. PRE), J. RFM [realthy volunteers] 2 vis EBA JPAZ, JPAZ, JPAC, JPC, ZC, Z. C 88CO: J4600 mgl dxl 440, 200 mgl bdl) [stript arm, XDR] 8.4LzLLVZH or Eth or Terl v. 6-6KMZ[Eth or Terly16-18MZ[Eth or Terly [DR] 2 ctages: &IPAMLY v. &IPALEZ v. &IPALE v. XADER [DR, XDR] MCEZHKPro v. JLVCEZHPro v. JLVCZHK v. local DR regimen [DR] PIVIBATely: 4 age strata J + OBR [DR, 240 ps 0 - 18] [HIV-H]  \$RICHARY v. SILICLIX v. SILICLIX v. SOCME v. X-DOBR [DR, quinoine sensitive] PK/feately: dose-range J + OBR [DR, D-18 yrs, HIV-H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]	1	32 105 105 1565 150/150 32 105 240 5 200 300 630 1155 60 750 84 72 180	TBTCIACTG Seoul Nat. Univ. Hospital MSF Holland/UCLU.GHTM IUATLDIMRG/USAID/TBA MSF France/Harvard Australia NHMRC (Fox) MRCIDFIDIWelcome TB Alliance  NIAID (CWRU) TB Alliance Janussen TB Alliance UCT/Stellenbosch (Dhedis) MSF Holland/UCLU.GHTM IUATLDIMRG/USAID/TBA Janussen MSF France/Harvard ACTG (Maartens/Dooley) MPAACT (Hesseling) TB Alliance	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Openes 2017, results 2019 Openes 2018  Completed 2012, results pending Results CROI 2014 97LB, AJRCOM Jan 2015 FU to M24 ongoing, results CROI 2017 LB724 Opened Feb 2015, follow-up thru Nov 2018 Opened Mar 2015, switch to ZeMIX Nov 2017 Opened Mar 2015, results Jan 2019 Opened Jan 2017, results Mar 2021 Opened Apr 2016, results Mar 2021 Opened May 2016, results Jan 2021 Opened May 2016, results Jan 2021 Opened May 2016, results Jan 2021 Opened May 2017, results Jan 2021	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belanus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Results 2018
Diaryiquii	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplioiTB inolines: Bedaquilline - n/a NC-005 n/a NIX-TB NEXT-5001 TB-PRACTECAL STREAM stage 2 C211 endTB ASS45 DELIBERATE P10-007 ZeNIX NC-008 SimplioiTB Iszoles: Pretomanid - I n/a	NCT02563327 NCT0259994 NCT02599792 NCT02599792 NCT02599792 NCT02754755 ACTRM126000215 nb nb TMC-207 - J (Ja NCT01341184 NCT01341184 NCT01349153 NCT02355623 NCT02355623 NCT02355756 NCT02599792 NCT02599793 NCT02599792 NCT025	8 or 12D + Liteurien + Lawicien+No + Y.v. 240BR [DR, quinoine sensitive] 2 stages: &IPAMLY v. &IPALEZ V. &IPALE V. 240BR [DR, Quinoine sensitive] MCEZHKPro v. JLVCEZHPro v. JLVCZHK v. IOCAI DR regimen [DR] MILIMZ V. &ILICLIX V. &ILICLIX V. &IDACE V. A40BR [DR, quinoine sensitive] HLTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] LTBS: &Luspassense v. placebo (plinded) [DR contacts, 245 and screen all HIV+H] Sales (Placebo v. PRE), J. RFM [realthy volunteers] 2 vis EBA JPAZ, JPAZ, JPAC, JPC, ZC, Z. C 88CO: J4600 mgl dxl 440, 200 mgl bdl) [stript arm, XDR] 8.4LzLLVZH or Eth or Terl v. 6-6KMZ[Eth or Terly16-18MZ[Eth or Terly [DR] 2 ctages: &IPAMLY v. &IPALEZ v. &IPALE v. XADER [DR, XDR] MCEZHKPro v. JLVCEZHPro v. JLVCZHK v. local DR regimen [DR] PIVIBATely: 4 age strata J + OBR [DR, 240 ps 0 - 18] [HIV-H]  \$RICHARY v. SILICLIX v. SILICLIX v. SOCME v. X-DOBR [DR, quinoine sensitive] PK/feately: dose-range J + OBR [DR, D-18 yrs, HIV-H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]  4 arms: 8 or 2 LZD (200 areas (double blind) + J <sub>200000</sub> + Pa <sub>200</sub> [DR, 214, HIV+H]	1	32 105 105 1565 150/150 32 105 240 5 200 300 630 1155 60 750 84 72 180	TBTCIACTG Seoul Nat. Univ. Hospital MSF Holland/UCLU.GHTM IUATLDIMRG/USAID/TBA MSF France/Harvard Australia NHMRC (Fox) MRCIDFIDIWelcome TB Alliance  NIAID (CWRU) TB Alliance Janussen TB Alliance UCT/Stellenbosch (Dhedis) MSF Holland/UCLU.GHTM IUATLDIMRG/USAID/TBA Janussen MSF France/Harvard ACTG (Maartens/Dooley) MPAACT (Hesseling) TB Alliance	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened Dec 2016, results Dep 2020 Opened 2015, results 2019 Opened 2017, results 2019 Opene 2017, results 2019 Opene 2018  Completed 2012, results pending Results CROI 2014 \$71.8, AURCOM Jan 2015 FU to M24 ongoing, results CROI 2017 L8724 Opened Sep 2015, follow-up Brow Nov 2018 Opened Mar 2015, switch to ZeNIX Nov 2017 Opened Oct 2015, results Jan 2019 Opened Apr 2015, results Mar 2021 Opened May 2016, results Mar 2021 Opened May 2016, results Mar 2021 Opened Aug 2016, siersults Apr 2021 Opened Aug 2016, fesults Sep 2020 Opened Aug 2016, fire sults Jan 2021 Opened Aug 2016, fire sults Jan 2021 Opened Aug 2016, fire sults Jan 2021 Openes Nov 2017, results Jan 2021 Opens 2018  Completed Dec 2012, results pending	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belanus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Results 2018  Halt, India, South Africa
Diaryiquii	MDR-END TB-PRACTECAL STREAM stage 2 endTB V-QUIN MDR TB-CHAMP NC-008 SimplioiTB inolines: Bedaquilline - n/a NC-005 n/a NDX-TB NEXT-5001 TB-PRACTECAL STREAM stage 2 C211 endTB ASS45 DELIBERATE P10.097 ZeNIX NC-008 SimplioiTB Jazoles: Preformanid - I n/a	NCT02563327 NCT0259994 NCT0259992 NCT02794795 ACTRM126000215 n/a n/a TMC-207 - J (Ja TMC-207 - J (Ja NCT0314194 NCT013913776 NCT0235623 NCT0235623 NCT023537399 NCT02454205 NCT02454205 NCT02594725 NCT02454205 NCT02594725 NC	8 or 12D + Liteuries + Lawicies-No. + 7 v. 240BR [DR, quincione sensitive] 2 clage: & BPaMLz v. & BPALZ v. & BPALZ v. 240BR [DR, XDR] MOEZHKPRO v. J. LVOEZHPO v. & LPALZ v. 240BR [DR, Quincione sensitive] 8 LTBL v. & BLICELX Z. & BLICELX V. & BOCMZ v. 240BR [DR, quincione sensitive] 8 LTBL & BLusswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] LTBL: & BLusswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] LTBL: & BLusswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] LTBL: & BLUSswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] LTBL: & BLUSswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] LTBL: & BLUSswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] LTBL: & BLUSswamere v. Discrebo (blinded) [DR contacts, 245 and screen all HIV++] PK & BAMIZ v. 244RE [DR], J. RFM [Dreathy volunteers] 2 vik EBA JPAZ, JPAZC, JPAC, JZC, Z, C 8 APPAZ, JPAZC, JPAC, JPAC, JPAC, JPAZC, JPAC,	1	60 238 630 1155 750 2006 1565 150/150 32 105 240 5 200 300 630 1155 60 750 84 72 180 150/150	TBTC/ACTG Seoul Nat. Univ. Hospital MSF Holiand/UCLU.BHTM IUATLD/MRC/USA/D/TBA MSF France/Harvard Australia NHMRC (Fox) MRC/DF/D/Welcome TB Alliance NIAID (CWRU) TB Alliance Janasen TB Alliance UCT/Bteller/basch (Dheda) MSF Holiand/UCLU.BHTM IUATLD/MRC/USA/D/TBA Janasen MSF France/Harvard ACTF (Maratens/Docley) MSF France/Harvard ACTF (Maratens/Docley) TB Alliance TB Alliance	Opened Jan 2016, results Dec 2019 Opened Jan 2017, results Mar 2021 Opened Jan 2017, results Mar 2021 Opened John, results Apr 2021 Opened 2016, results Dep 2020 Opened 2016, results 2019 Opened 2016, results 2019 Openes 2017, results 2019 Openes 2017, results 2019 Openes 2017, results 2019 Openes 2018  Completed 2012, results pending Results CROI 2014 PTUB, AJROCOM Jan 2015 FU Ib M24 ongoing, results CROI 2017 LB724 Openes Feb 2015, follow-up thru Nov 2018 Opened Mar 2015, switch to ZeNIX Nov 2017 Opened Oct 2015, results Mar 2021 Opened Apr 2016, results Mar 2021 Opened May 2016, results Jan 2021 Opened May 2016, results Jan 2021 Opened May 2017, results Jan 2021 Openes May 2017, results Jan 2021 Openes 2018	Belanus, South Africa, Uzbekistan  Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Vietnam (multiple sites)  South Africa (Stellenbosch and 3 other sites)  BPaZ best, mod QT effect, C no activity  BPaMZ + BPaZ had highest BA; low AEs in 8 wks  Interim results CROI 2017 80LB, effective, 27% AEs  Belanus, South Africa, Uzbekistan  India, Phillipines, Russia, South Africa Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru Results 2018

Table continues on next page

Drug(s)	Trial Name	NCT / WHO #	Arms	Ph	N	Group(s)	Status	Results
	NC-003	NCT01691534	2 WK EBA JPaZ, JPaZC, JPaC, JZC, Z, C	lla	105	TB Allance	Results CROI 2014 97LB, AJRCCM Jan 2015	BPaZ best, mod QT effect, C no activity
	NC-006	NCT02193776	88CC: J(400 mg/d x14d, 200 mg tw)PaZ v. J(200 mg/d)PaZ (+ M in DR) v. HRZE	IIb	240	TB Allance	FU to M24 ongoing, results CROI 2017 LB724	BPaMZ + BPaZ had highest BA; low AEs in 8 wks
	NC-008 STAND	NCT02342886	4Pa <sub>100/200</sub> MZ v. 8Pa <sub>100</sub> MZ v. 8Pa <sub>200</sub> MZ v. 2HRZE/4HR [DS, DR 6Pa <sub>200</sub> MZ only]	III	284	TB Allance	Completed early, results late 2017	
	APT	NCT02256696	12 wk: 2Pa <sub>200</sub> BHZ/1Pa <sub>200</sub> BH v. 2Pa <sub>200</sub> RHZ/1Pa <sub>200</sub> RH v. 2HRZE/1HR [DS]	II	183	JHU/UCT (Dooley/Dawson)	N=28, reopening May 2017 after Pa hold	
	NIX-TB	NCT02333799	8JPa <sub>300</sub> /LZD (600 mg bld) [single arm, XDR]	III	200	TB Allance	Opened Mar 2015, switch to ZeNIX Nov 2017	Interim results CROI 2017 80LB, effective, 27% AEs
	TB-PRACTECAL	NCT02589782	2 stage: &JPaMLz v. &JPaLzC v. &JPaLz v. 240BR [DR, XDR]	IVIII	630 180	MSF Holland (Nyang'wa)	Opened Jan 2017, results Mar 2021 Opens Nov 2017, results Jan 2021	Belarus, South Africa, Uzbekistan
	NC-007 ZeNIX NC-008 SimplicITB	NCT03086486 n/a	4 arms: 8 or 2 LZD <sub>1200 or 600</sub> (double blind) + J <sub>2001100</sub> + Pa <sub>200</sub> [DR, ≥14, HIV+/-] 4JPaMZ v. 2HRZEJ4RH [DS], 8JPAMZ [DR]		150/150	TB Allance TB Allance	Opens Nov 2017, results Jan 2021 Opens 2018	
Mirolos	dazoles: Delamanid - (			-	150/150	16 Andree	Opera 2010	
MILLORINI	Trial 204	NCT00685360	D (200 ma bid v. 100 ma bid) + OBR (DR)		481	Otsuka	Completed	NEJM Jun 2012. Eur Resp J Jun 2013
	Trial 213	NCT01424670	2D (100 mg bid)+OBR / 4D (200 mg qd)+OBR v. Spiacebo+OBR [DR]	ii.	511	Otsuka	Completed June 2016, results 2017	The state of the s
	Trial 232	NCT01856634	18d PK: 4 peds cohorts D <26, 26, 50, 100 mg bid + OBR x 10 d [DR]	1	36	Otsuka	Opened July 2013, results 2018	Cape Town/Philippines
	Trial 233	NCT01859923	8M PK/8afety: 4 peds cohorts D <25, 26, 50, 100 mg bid + OBR x 8 mo [DR]	II	36	Otsuka	Opened Aug 2013, results 2020	Cape Town/Philippines
	MDR-END	NCT02619994	8 or 12D + Lx <sub>(8601000</sub> + Lz <sub>(6001284-900</sub> + Z v. 240BR [DR, quincione sensitive]	II	238	Seoul Nat. Univ. Hospital	Opened Jan 2016, results Dec 2019	
	endTB	NCT02754765	8JLzMZ v. 8JLzCLxZ v. 8JLzDLxZ v. 8DCMZ v. 240BR [DR, quinolone sensitive]	Ш	750	M8F France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	A6343 DELIBERATE	NCT02583048	pK DDI QT 6J v. 8D v. 8JD + OBR [DR] [HIV-/+]	II	84	ACTG (Maartens/Dooley)	Opened Aug 2016, 51 enrolled	Results 2018
	IMPAACT 2006	n/a	PK/cafety: cingle arm 8D + (oral)OBR [DR, 0 - 18, HIV-/+]	M	48	IMPAACT (Dooley)	Opens 2018, results Apr 2021	Botswana, India, South Africa, Tanzania
	A6366 A6300B / I2003B	n/a n/a	8D(100 bid)+LZD(300 qd/800 qd/1200 qod) + OBR (oral) v. 8D + OBR (inj.) [DR] PHOENix LTBI: 8D v. 9H [DR contacts, age 6 and up] [HIV-/+]	lla III	240 3452	ACTG (Benson) ACTG/IMPAACT	Opens Q1 2018 Opens Q1 2018	
					3452	ACIG/MPAACI	Opens Q1 2018	
Oxazoli			fizer → Sequella + TB Alliance)				Security of	
	n/a	NCT00990990 NCT01225540	Safefy/WBA U (100, 300, 600, 1200 mg bid) x 14d, 28d +/- Z d 27-28 2 wk EBA + WBA U (600 mg bid v. 1200 mg qd) v. HRZE	FRA	59	Pfizer Pfizer	Completed	1200 mg qd > 600 mg bld, ↑ LFTs
	n/a A6288	NCT01225640 n/a	2 wk EBA + WBA 0 (800 mg bid v. 1200 mg qd) v. HKZE 2-stage dose-range open label: UHRZ v. UHTZ v. HRZE [DS only] [HIV-/+]	EBA	59 182	Pfizer ACTG (Luetkemever)	Results IAS 2012 THLBB02, PLOS Apr 2014 On hold (Sep 2016)	1200 mg qu > 600 mg bid, Tr EP 15
Over-**				"	182	AUTO (Lucisemeyer)	SH IMB (OCH 2010)	
Oxazoli	dinones: Linezolid - L2		175 MM			Secretary Date Descript		
	J-1310-028-523 LIN-CL001	NCT01994460 NCT02279875	LZD (600 mg/d, 2 wk v 4 wk) + 2HRZ/4HR v. 2HRZE/4RH [DS only] [HIV-] 2 wk EBA/8afety LZD (1200 ad. 600 bid. 600 ad. 300 bid. 300 ad) [DS only]	III EBA	429 113	Seoul Nat. Univ. Hospital TB Alliance	Opened Jan 2014, results end 2016 Opened Nov 2014, results Eeb 2017	New dose strategies tested in study extension
	NIX-TB	NCT02333799	2 WK EBA/safety LZD (1200 qd, 800 bid, 800 qd, 300 bid, 300 qd) [DS only]  8BPa <sub>mol</sub> LZD (800 mg bid) [single arm, XDR]	EBV	200	TB Allance	Opened Nov 2014, results Feb 2017  Opened Mar 2015, switch to ZeNIX Nov 2017	New dose strategies tested in study extension Interim results CROI 2017 80LB, effective, 27% AEs
	NEXT-5001	NCT02333799 NCT02454205	8-9LzJLxZ(H or Eth or Ter) v. 6-9KMZ(Eth or Ter)/16-18MZ(Eth or Ter) [DR]	I/II	300	UCT/Stellenbosch (Dheda)	Opened Mar 2015, switch to ZeNIX Nov 2017  Opened Oct 2015, results Jan 2019	mannifesors ortor 2017 book, effective, 27% AES
	MDR-END	NCT02619994	9 or 12D + Lx <sub>780/1000</sub> + Lz <sub>800x294+000</sub> + Z v. 24OBR [DR, quinoione sensitive]	II.	238	Seoul Nat. Univ. Hospital	Opened Jan 2016, results Dec 2019	
	TB-PRACTECAL	NCT02589782	2 stage: 8JPaMLz v. 8JPaLzC v. 8JPaLz v. 240BR [DR, XDR]	II/III	630	MSF Holland (Nyang'wa)	Opened Jan 2017, results Mar 2021	Belarus, South Africa, Uzbekistan
	endTB	NCT02754765	8JLzMZ v. 8JLzCLvZ v. 8JLzDLvZ v. 8DCMZ v. 240BR [DR, quinoione sensitive]	Ш	750	MSF France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	A5358	n/a	8D(100 bid)+LZD(300 qd/800 qd/1200 qod) + OBR (oral) v. 8D + OBR (inj.) [DR]	lla	240	ACTG (Benson)	Opens Q1 2018	
	NC-007 ZeNIX	NCT03086486	4 arms: 8 or 2 LZD <sub>1200 or 600</sub> [double blind] + J <sub>2001100</sub> + Pa <sub>200</sub> [DR, ≥14, HIV+/-]	Ш	180	TB Allance	Opens Nov 2017, results Jan 2021	
Oxazoli	dinones: Delpazolid - L	.CB01-0371 - DZD	- Dz (LegoChem)					
	LCB01-0371-16-2-01	NCT02836483	2 wk EBA Dz (800 mg qd v. 800 mg bld v. 400 mg bld) [DS only]	EBA	64	LegoChem Biosciences	Opened Dec 2016, results Q1 2018	
Iminoph	enazines: Ciofazimine	- Lamprene - CF	Z - C (Novartis)					
	NC-003	NCT01691534	2 wk EBA JPaZ, JPaZC, JPaC, JZC, Z, C	EBA	105	TB Allance	Results CROI 2014 97LB, AJRCCM Jan 2015	BPaZ best, mod QT effect, C no activity
	STREAM Stage 1	ISRCTN78372190	4MCEZHKPro/6MCZE v. local DR regimen [DR]	III	400	IUATLD/MRC/DFID/USAID	Interim results IUATLD 2017	
	TB-PRACTECAL	NCT02589782	2 stage: 8JPaMLz v. 8JPaLzC v. 8JPaLz v. 24OBR [DR, XDR]	IVIII	630	MSF Holland/UCL/LSHTM	Opened Jan 2017, results Mar 2021	Belarus, South Africa, Uzbekistan
	STREAM Stage 2	NCT02409290	MCEZHKPro v. JLxCEZHPro v. JLxCZHK v. local DR regimen [DR]	Ш	1155	IUATLD/MRC/USAID/TBA	Opened Apr 2016, results Apr 2021	
	CLAM320B2202	2015-004440-19	C (60 or 100 mg qd) + OBR v. OBR [DR] 8JLzMZ v. 8JLzCLvZ v. 8JLzDLvZ v. 8DCMZ v. 24OBR [DR, quincione sensitive]	IVIII	380	Novartis	Trial suspended 2017	Lithuania/Latvia/Russia/Peru/Philippines/RSA/Thailnd
	endTB A6382 Clo-FAST	NCT02754765 n/a	2 stage: (4C <sub>50</sub> v. 4C <sub>100</sub> v. 4placebo) + 4HRZE / 2placebo v. 2placebo v. 2HR	III IIc	750 400	MSF France/Harvard ACTG (Metcalfe)	Opened Dec 2016, results Sep 2020 Opens Q1 2018, follow up to M18	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
-1-			2 6tage. (40% v. 40% v. 49180600) + 411122 / 29180600 v. 29180600 v. 2111		400	ACTO (Melcale)	Opens Q1 2016, follow up to M16	
Ethylen	e diamines: SQ-109 - 0							
	8Q109-01 MAM8-TB-01	NCT01218217 NCT01785186	EBA Q (76 v. 160 v. 300 mg qd) ± R	EBA	90 372	EDCTP/PanACEA EDCTP/PanACEA	Completed 2012, JAC Jan 2015 Completed Q1 2015, results CROI 2015 95LB	Safeitolerable, no QT signal, 2C19 induction HRZQ + HR <sub>w</sub> ZQ arms dropped Mar 2014
	m/mo-10=/1	NG101/85186	HR <sub>10</sub> ZE <del>v. HRZQ v. HR<sub>10</sub>ZQ v</del> . HR <sub>20</sub> ZM v. HRZE 8Q + OBR v. OBR [DR]	IIb/III	140	Infectex/Sequella	Results 2017 (7 sites Russia)	Safe/tolerable, 80% 6M 3CxC v. 61% controls
Indidaga	nuridinas: COSS Tala			MATERIAL PROPERTY.	140	cciewoequeia	mana surr (r arca mused)	Sale actions, our out out over 1. 5176 COTIONS
imidazo	pyridines: Q203 - Tele n/a	cebec (Qurient)	PK. safety, dose range: single + multiple doses [freathy volunteers]		,	Infectex/Qurient	Opened March 2016, results pending	
	Na G203-TB-PI-U8001	n/a n/a	PK, cafety, dose range: cingle + murtiple doses [neathy volunteers]  PK, cafety, dose range: cingle doses [neathy volunteers]	la la	56	Outlent US	Opened March 2016, results pending Opened Aug 2015, completed Feb 2016	
ĺ	G203-TB-PI-U8002	NCT02858973	PK, safety, dose range: multiple doses [healthy volunteers, placebo, blinded]	lb	24	Qurient US	Opened August 2016, results end 2017	
	STEP	n/a	Optimized dose R and Z + arm with Q203 v. 2HRZE/4RH [D8]	I c	600	EDCTP/PANACEA/Qurient	Opens Q1 2018	Univ. of Munich
3 4 000	ostvrii Derivative: OP		•					
J,+ Call	n/a	n/a	PK. safety, dose range, EBA studies	н	,	Otsuka	4 studies to open Oct 2016 through 2017	
Dancolo			.,,,,					
Denzoth	niazinones (DprE1 inhib PBTZ189-Z00-C01-1	(tor): PBTZ169 (I	Nearmedic Plus LLC) PK, cafety, dose range healthy volunteers		35	Nearmedic Plus	Opened Jan 2016, results Nov 2016	
	PBTZ168-Z00-C01-1 PBTZ169	NC103036163 n/a	PR, carety, dose range nearthy volunteers  EBA [DR]			Nearmedic Plus Nearmedic Plus	Opened Jan 2016, results Nov 2016 Opens late 2017	14 sites Russia
Date :						The state of the s	apara ana avril	
neta-lac			(with amoxicillin/clavulanate), Meropenem - M <sub>AC</sub> (with amoxicillin/clavulanate)			Test (Disease)	Council Con 2014 and Con 2014	U
	TASK-001 Faropenem-TB	NCT02349841 NCT02381470	2 wk EBA: M (2 gm IV tid) + AC tid v. F (800 mg po tid) + AC tid v. HRZE 6d EBA: F (400 mg po tid) + AC (500/126 mg po tid) v. H <sub>ass</sub> v. Z (2 gm) [DS]	EBA EBA		Task (Diacon)/GSK NUH Singapore (Paton)	Opened Sep 2014, results CPTR Apr 2016 Opens July 2017, results Mar 2018	Meropenem <sub>AC</sub> showed EBA, F <sub>AC</sub> low exposures Philipines, Singapore
			see Land 1. (who mig po may a Mo (see 120 mg po may v. n 200 v. 2 (2 gm) [D3]	cen	20	mon orgapore (Fatori)	System only 2017, results Midf 2010	· ····porica, origapore
Thiazoll	des: Nitazoxanide - Ni		And PRACTICAL VICTOR CONTRACTOR C					
	NTZ001	NCT02684240	2 wk EBA: N (1000 mg bld) + HRZE v. HRZE (DS, HIV-)	EBA	30	Comel/GHESKIO (Pape)	Opened Feb 2016, results late 2017	Halt
2 Month	Treatment Shortening							
	TRUNCATE-TB	n/a	MAMS 2(multiple new regimens) v. 2HRZE/4HR	II/III	900	MRC/UCL (Paton/Phillips)	Opens Q1 2017, results 2019	Thailand, Indonesia, Philipines, Singapore
4 Month	Treatment Shortening	Strategies [Mini	mai DS < 16 yrs]					
	SHINE	ISRCTN63579542	2HRZ(E)/2HR v. 2HRZE/4HR [D3, < 16 yrs, minimal disease, HIV-/+]	III	1200	MRC/UCL/DFID (Glbb)	Opened Q3 2016, results 2020	India, Uganda, South Africa, Zambia

Please see attached pdf and excel sheet for clearer versions

# Table 3: WHO categorisation of second-line anti-tuberculosis drugs recommended for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis<sup>37</sup>

# **Group A: fluoroquinolones**

- Levofloxacin
- Moxifloxacin
- Gatifloxacin

# **Group B: second-line injectable agents**

- Amikacin
- Capreomycin
- Kanamycin
- (Streptomycin)

# **Group C: other core second-line agents**

- Ethionamide/prothionamide
- Cycloserine/terizidone
- Linezolid
- Clofazimine

# **Group D: add-on agents** (not part of the core MDR-TB regimen)

#### **D**1

- Pyrazinamide
- Ethambutol
- High-dose isoniazid

### **D2**

- Bedaquiline
- Delamanid

#### **D3**

- Para-aminosalicylic acid
- Imipenem plus cilastatin (requires clavulanate)
- Meropenem (requires clavulanate)
- Amoxicillin plus clavulanate
- (Thioacetazone)\*

<sup>\*</sup>HIV negative status required before administering thioacetazone. Not to be administered to HIV-positive individuals

# Authors suggest Table 4 be placed as APPENDIX - ONLINE SUPPLEMENTAL MATERIAL

Table 4. Host-directed therapies in TB -Developmental pipeline: Ongoing clinical trials and translational research

Candidate(s)/Strategies	Description	Remarks	Reference
A. Clinical development pl	hase (for TB)		
N-acetylcysteine	N-acetylcysteine plus RIZE to exert simultaneous anti-TB and anti-oxidative (tissue-protective) effect in patients with active pulmonary TB	Phase 2 clinical trial underway in Brazil	ClinicalTrials.gov identifier: NCT03281226
Azithromycin	Adjunctive HDT with standard TB/MDR-TB regimens to treat pulmonary TB – for reducing overt inflammation in patients' lungs (and potentially systemic inflammation also)	Phase 2 clinical trial underway in the Netherlands	ClinicalTrials.gov identifier: NCT03160638
Everolimus, Auranofin, Vitamin D3 or CC-11050	Adjunctive HDT with 2 months of isoniazid, rifabutin, pyrazinamide and ethambutol followed by 4 months of isoniazid and rifabutin (modified drug regimen) to improve treatment efficacy and clinical outcomes in pulmonary TB	Phase 2 clinical trial underway in South Africa	ClinicalTrials.gov identifier: NCT02968927
Mycobacterium w	Used as an immunomodulatory agent to induce beneficial effects in patients with pulmonary TB following antibacterial therapy	Phase 3 clinical trial underway in India	ClinicalTrials.gov identifier: NCT00265226
Vitamin D3	Used as a supplement to help resolve inflammation or to induce productive intracellular defence mechanisms i.e. antimicrobial peptide production. Multiple vitamin D3 doses are evaluated	Several intermediate to advanced clinical trials (phases 2-4) underway in South Africa, Korea, India and the UK	ClinicalTrials.gov identifiers: NCT03011580 NCT01992263 NCT02880982 NCT02169570
Dexamethasone	Adjunctive corticosteroid used as an anti-inflammatory agent to resolve cytokine storm and tissue destruction in patients with TB, including TB meningitis	Phase 3 two clinical trials underway in Vietnam and Indonesia	ClinicalTrials.gov identifiers: NCT03100786 NCT03092817
Nitazoxanide	Tested in clinical trials for early anti-mycobacterial activity.	Phase 2 clinical trial underway in Haiti	ClinicalTrials.gov identifier:

Nyaditum Resae®	However, nitazoxanide may also exert its effects via autophagy, as shown in the preclinical study by Gupta <i>et al.</i> , 2016  Heat-killed <i>Mycobacterium manresesis</i> to induce generation of memory Tregs as a mechanism of avoiding overt TB-associated inflammation. Safety study in children; given as a probiotic capsule	Phase 1 clinical trial underway in Spain	NCT02684240  ClinicalTrials.gov identifier: NCT02581579
Recombinant human IL-2	Given subcutaneously to patients with MDR-TB as adjunct to standard chemotherapy for modulating T-cell activity	Phase 2/3 clinical trial underway in China	ClinicalTrials.gov identifier: NCT03069534
GX-70	Safety study of DNA vaccine combining genes encoding Mtb antigens as well as the human Flt3 ligand for immunomodulation in patients with TB who failed treatment or experience disease relapse	Phase 1 clinical trial underway in Korea	ClinicalTrials.gov identifier: NCT03159975
Etoricoxib +/- H56:IC31	Etoricoxib is a COX2 inhibitor, and would increase the production of the anti-inflammatory lipid mediator prostaglandin E2 (PGE2). Combination of etoricoxib and H56:IC31 (subunit vaccine with adjuvant) is expected reduce non-specific inflammation while inducing targeted anti-TB immune responses. This is evaluated in patients with MDR-TB	Phase 1 clinical trial underway in Norway	ClinicalTrials.gov identifier: NCT02503839
B. Developmental pipeline-	Basic/translational research phase		<u> </u>
Resveratrol	A plant-derived natural phenol, resveratrol can activate the sirtuin 1 (SIRT1) protein for enhancing anti-TB treatment efficacy, and augmenting intracellular immune functions	Preclinical evidence in cell lines and mouse model of TB along with standard drug treatment, resulting in improved control of bacterial burden, reduced pathology and abatement of chronic inflammation	1
Denileukin diftitox	An engineered protein which combines IL-2 and diphtheria toxin, it can be administered with anti-TB drugs in order to potentiate the immune response by depleting suppressive milieu	Preclinical evidence in a mouse model of TB along with standard drug treatment, resulting in enhanced drug efficacy	2

		T	<del>                                     </del>
	in the granuloma	concomitant with reduced regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)	
Gefinitib	A tyrosine kinase inhibitor which can augment intracellular immune functions and block suppressive activity to restrict <i>Mtb</i> growth while enhancing effector immune responses	Gefitinib was found to block STAT3 expression and increase lysosomal biogenesis thus activity, which improves intracellular bacterial killing, antigen processing and presentation	3
Inhibitors of histone modifying enzymes	Histone deacetylase (HDAC) I/II inhibitor trichostatin A (TSA) and histone acetyltransferase (HAT) inhibitors can modulate the expression of matrix metalloproteinases that drive pathology in TB	Tested in human cell lines infected with <i>Mtb</i> . TSA shown to selectively inhibit HDAC I/II, resulting in reduced production of MMP-1/3, with a more pronounced effect by HAT inhibitors	4
Vγ2Vδ2 T-cell therapy	Adoptive transfer of gamma delta T cells for eradication of <i>Mtb</i> -infected cells and bacterial reservoirs in the host	Vγ2Vδ2 TCR+ T cells (gamma-delta) were adoptively transferred to nonhuman primates infected with <i>Mtb</i> , resulting in heavily reduced bacterial dissemination	5
Interleukin 37	A cytokine belonging to the IL-1 family which can tailor protective immune responses without causing tissue damage in TB	Preclinical evidence in cell lines and mouse model of BCG infection showing that IL-37 augments protective immune responses and decreased tissue pathology, while reducing the bacterial burden. A higher number of Th1 cells and lesser Th17 cells as well as Tregs were also observed	6
Anti-IL-6 therapy	A pleiotropic cytokine that has an indispensable role at the early stages of <i>Mtb</i> infection, IL-6 overproduction in advanced TB	Preclinical evidence that mice challenged with virulent <i>Mtb</i> or its cell wall derivative	7-11

	disease mediates long-term pulmonary complications and potentially death. Reduction in systemic IL-6 levels can be achieved using bovine lactoferrin (BLF) or monoclonal antibodies targeting the IL-6 pathway (siltuximab, tocilizumab)	TDM managed much better with subsequent treatment with BLF, which lead to reduced pathology, reduced IL-6 levels in the lung as well as improved bacterial burden control. Anti-IL-6 therapy has also clinically beneficial in managing patients with ARDS, solid cancers and systemic inflammatory response syndrome	
Anti-IL-17-therapy	IL-17 is dominantly a pro- inflammatory cytokine which like IL-6 is highly necessary to initiate protective anti-TB immune responses but exaggerated levels later on can be deleterious to the host. Timing of therapeutically targeting the IL-17 pathway is crucial and can complement anti-TB drug therapy	Clinical experience of anti-IL-17 therapy in patients with autoimmune diseases has been mixed; some respond very well while other do not. Several reagents exist: secukinumab, ixekizumab (anti-IL-17) and brodalumab (anti-IL-17 receptor) while newer candidates are in development. Best responses to IL-7 blockade has been observed among patients with psoriasis. Further clinical trials are needed to assess safety and efficacy, including in TB	12,13
Ezetimibe  Aroylated phenylenediamines	Ezetimibe is 2-azetidinone cholesterol absorption inhibitor that has deleterious effects on the intracellular life cycle of <i>Mtb</i> , and can augment anti-TB drug therapy	Ezetimibe was shown to reduce the growth of intracellular <i>Mtb</i> using in vitro cell culture studies that. Also, white blood cells from patients who were treated with ezetimibe (for lowering blood cholesterol levels) displayed reduced capacity to support mycobacterial growth	14
Just a priori justiculuminos	postar parametro groun	and the showing	

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(APDs)	inducers of antimicrobial peptides i.e. LL-37, APDs can be crucial in the intracellular control of <i>Mtb</i> growth	have 20 to 30-fold induction of LL-37, and evaluated in a preclinical rabbit model of shigellosis, resulting in full recovery of the animals. Highly applicable to TB	
Inhibitors of heme oxygenase-1 (HO-1)	Reduced the intracellular growth of <i>Mtb</i> by potentiating T-cell activity	Administration of tin protoporphyrin IX, an HO-1 inhibitor together with anti-TB drugs to <i>Mtb</i> -infected mice resulted in reduced bacterial burden, with a concomitant activation of T cells	16
Indomethacin	COX2 inhibitor which can modulate T-cell response, but may need to be co-administered with an immune-potentiating agent	Preclinical evidence in PBMCs from patients with TB showed that indomethacin reduced Th1 and Treg numbers, along with <i>Mtb</i> antigen-specific cytokine production	17
Agonists of CD40 and TLR4	Stimulation of CD40 and TLR4 can lead to release of pro- inflammatory cytokines instrumental in activating the adaptive immune response	Preclinical evidence in primary cells as well as a mouse model of TB showed that CD40/TLR4 stimulation, along with anti-TB drugs greatly reduced bacterial burden while activating Th1 and Th17 immune responses, with a role played IL-2 and IL-6 production by dendritic cells	18
Loperamide	A pharmacological agent used for controlling diarrhoea, loperamide can augment intracellular immune functions to restrict <i>Mtb</i> growth and augment T-cell activity	Preclinical evidence in human and murine macrophages showed that loperamide can induce autophagy and decrease mycobacterial growth and increase TNF-α production.  Loperamide also increased the colocalisation of	19

		Microtubule- associated proteins 1A/1B light chain 3, which is involved in autophagolysosome formation, with <i>Mtb</i> bacilli	
Nitazoxanide (NTZ)	A broad-spectrum drug used for treated parasitic and viral infections, NTZ is also an inducer of autophagy and thus has promising HDT attributes for use in TB drugs regimens	Preclinical evidence in a mouse model of TB showed that inhaled NTZ, in conjunction with a standard TB drug regimen lead to a significant decrease in pulmonary <i>Mtb</i> load, while displaying signs of lung tissue regeneration	20
All-trans retinoic acid (ATRA), 1,25(OH)2-vitamin D3, and α-galactosylceramide (αGalCer)	These biological compounds can potentiate intracellular immune functions, the antigen processing machinery and allow T-cell activation leading to effective killing of <i>Mtb</i> -infected host cells	Preclinical evidence in a mouse model of TB showed that administration of ATRA, vitamin D3 and αGalCer lead to enhance antimycobacterial activity, reduced relapse rates as well as increased TNF-α production in the lungs	21
Inhibitors of phosphodiesterase-4 (PDE-4)	Inhibition of PGE-4 i.e. by Rolipram (Imodium) or CC- 3052, can increase the efficacy of standard TB drugs	Preclinical evidence in mouse model of TB showed that CC-3052-mediates inhibition of PDE-4 augmented isoniazid activity, leading to enhanced bacterial clearance and reduced lung pathology, concomitant with downregulation of inflammation-associated gene expression	22
Inhibitors of Src family kinases	These non-receptor tyrosine kinases are involved in various physiological processes and have many cellular interactions partners, and are also involved in oncogenesis. Abrogation of Src kinase activity leads to reduced mycobacterial growth and promotes antigen processing and	Preclinical evidence in cell culture and the guinea pig model of TB showed that administration of AZD0530 lead to decreased lung <i>Mtb</i> burden, improved intracellular antigen	23

	intracellular immune effector functions	processing and decreased bacterial survival while promoting xenophagy – the process of one cell 'devouring' another	
Inhaled RNA interference (RNAi) therapeutics	RNAi-mediated suppression of host gene expression in lung, mainly associated with hyperinflammation or mycobacterial persistence can augment standard TB drug treatment	Various genetic targets, including genes that allow <i>Mtb</i> persistence in macrophages, immunological targets which promote Th2 and Treg activity, activation of suppressive immune cells can be silenced in order to establish necessary effector function	24
Toxoplasma gondii GRA-7 protein (dense granular protein 7)	Could be used as an adjuvant to activate intracellular antimicrobial functions for killing <i>Mtb</i> , in conjunction with standard drug therapy	Preclinical evidence of augmenting Myd88-dependent immune activation in <i>T. gondii</i> (intracellular pathogen) infection	25
CMV/EBV antigens	Measuring host response to CMV and EBV serves as an indication of immunological fitness in patients with TB, and can help select individuals who can respond to immune-based interventions	Tested in a clinical study of over 200 patients with pulmonary TB. Response to drug therapy in addition to strong IFN-γ responses to CMV/EBV antigens were indicative of extended survival	26
Mtb/HIV-bispecific T-cell receptor (TCR)	Tested in T cells from an HLA-A*02+ healthy individual, shedding light on the applicability of CD8+ TCRs for adoptive cell therapy	Amino acid modifications in the CDR3 loop of a bispecific ( <i>Mtb</i> Ag85B/HIV Env) TCR reduced affinity for MHC-I-peptide complex and abrogated cytokine production.  Knowledge can be instrumental for developing T-cell therapies for TB/HIV	27

CD4+ TCR motifs for shared	TCRs that can recognise a broad	TCRVβ sequences	28
Mtb antigen recognition	range of <i>Mtb</i> epitope can be used	from 22 individuals	
	in developing T-cell products for	with LTBI analysed	
	infusion into patients	using grouping of	
		lymphocyte	
		interactions by	
		paratope hotspots	
		(GLIPH), leading to	
		identification of motifs	
		that allow for binding	
		to shared antigenic	
		ligands	

#### FOR TABLE 4 ABOVE AS SUPPLEMENTAL ONLINE APPENDIX

- 1. Cheng CY, Gutierrez NM, Marzuki MB, et al. Host sirtuin 1 regulates mycobacterial immunopathogenesis and represents a therapeutic target against tuberculosis. *Sci Immunol* 2017; **2**(9).
- 2. Gupta S, Cheung L, Pokkali S, et al. Suppressor Cell-Depleting Immunotherapy With Denileukin Diftitox is an Effective Host-Directed Therapy for Tuberculosis. *J Infect Dis* 2017; **215**(12): 1883-7.
- 3. Sogi KM, Lien KA, Johnson JR, Krogan NJ, Stanley SA. The Tyrosine Kinase Inhibitor Gefitinib Restricts Mycobacterium tuberculosis Growth through Increased Lysosomal Biogenesis and Modulation of Cytokine Signaling. *ACS Infect Dis* 2017; **3**(8): 564-74.
- 4. Moores RC, Brilha S, Schutgens F, Elkington PT, Friedland JS. Epigenetic Regulation of Matrix Metalloproteinase-1 and -3 Expression in Mycobacterium tuberculosis Infection. *Front Immunol* 2017; **8**: 602.
- 5. Qaqish A, Huang D, Chen CY, et al. Adoptive Transfer of Phosphoantigen-Specific gammadelta T Cell Subset Attenuates Mycobacterium tuberculosis Infection in Nonhuman Primates. *J Immunol* 2017; **198**(12): 4753-63.
- 6. Liu H, Zheng R, Wang P, et al. IL-37 Confers Protection against Mycobacterial Infection Involving Suppressing Inflammation and Modulating T Cell Activation. *PLoS One* 2017; **12**(1): e0169922.
- 7. Actor JK. Lactoferrin: A Modulator for Immunity against Tuberculosis Related Granulomatous Pathology. *Mediators of inflammation* 2015; **2015**: 409596.
- 8. Welsh KJ, Hwang SA, Boyd S, Kruzel ML, Hunter RL, Actor JK. Influence of oral lactoferrin on Mycobacterium tuberculosis induced immunopathology. *Tuberculosis* 2011; **91 Suppl 1**: S105-13.
- 9. Yang DH. The Biological Effects of Interleukin-6 and Their Clinical Applications in Autoimmune Diseases and Cancers. *Rheumatica Acta: Open Access* 2017; **1**(1): 11.

- 10. Masui-Ito A, Okamoto R, Ikejiri K, et al. Tocilizumab for uncontrollable systemic inflammatory response syndrome complicating adult-onset Still disease: Case report and review of literature. *Medicine (Baltimore)* 2017; **96**(29): e7596.
- 11. Morrondo CD, Zarza LP, Gil JG, Pinto Tasende JA, Diez PD, Lopez JM. Benefit of Tocilizumab Therapy for Adult-Onset Still Disease Complicated With Acute Respiratory Distress Syndrome. *J Clin Rheumatol* 2016; **22**(5): 291-3.
- 12. Mourik BC, Lubberts E, de Steenwinkel JEM, Ottenhoff THM, Leenen PJM. Interactions between Type 1 Interferons and the Th17 Response in Tuberculosis: Lessons Learned from Autoimmune Diseases. *Front Immunol* 2017; **8**: 294.
- 13. de Carvalho AV, Duquia RP, Horta BL, Bonamigo RR. Efficacy of Immunobiologic and Small Molecule Inhibitor Drugs for Psoriasis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Drugs R D* 2017; **17**(1): 29-51.
- 14. Tsai IF, Kuo CP, Lin AB, et al. Potential effect of ezetimibe against Mycobacterium tuberculosis infection in type II diabetes. *Respirology* 2017; **22**(3): 559-66.
- 15. Ottosson H, Nylen F, Sarker P, et al. Potent Inducers of Endogenous Antimicrobial Peptides for Host Directed Therapy of Infections. *Sci Rep* 2016; **6**: 36692.
- 16. Costa DL, Namasivayam S, Amaral EP, et al. Pharmacological Inhibition of Host Heme Oxygenase-1 Suppresses Mycobacterium tuberculosis Infection In Vivo by a Mechanism Dependent on T Lymphocytes. *MBio* 2016; **7**(5).
- 17. Tonby K, Wergeland I, Lieske NV, Kvale D, Tasken K, Dyrhol-Riise AM. The COX-inhibitor indomethacin reduces Th1 effector and T regulatory cells in vitro in Mycobacterium tuberculosis infection. *BMC Infect Dis* 2016; **16**(1): 599.
- 18. Khan N, Pahari S, Vidyarthi A, Aqdas M, Agrewala JN. Stimulation through CD40 and TLR-4 Is an Effective Host Directed Therapy against *Mycobacterium tuberculosis*. *Front Immunol* 2016; **7**: 386.
- 19. Juarez E, Carranza C, Sanchez G, et al. Loperamide Restricts Intracellular Growth of Mycobacterium tuberculosis in Lung Macrophages. *Am J Respir Cell Mol Biol* 2016; **55**(6): 837-47.
- 20. Gupta A, Meena J, Sharma D, et al. Inhalable Particles for "Pincer Therapeutics" Targeting Nitazoxanide as Bactericidal and Host-Directed Agent to Macrophages in a Mouse Model of Tuberculosis. *Mol Pharm* 2016; **13**(9): 3247-55.
- 21. Mourik BC, Leenen PJ, de Knegt GJ, et al. Immunotherapy Added to Antibiotic Treatment Reduces Relapse of Disease in a Mouse Model of Tuberculosis. *Am J Respir Cell Mol Biol* 2017; **56**(2): 233-41.
- 22. Subbian S, Koo MS, Tsenova L, et al. Pharmacologic Inhibition of Host Phosphodiesterase-4 Improves Isoniazid-Mediated Clearance of *Mycobacterium tuberculosis*. *Front Immunol* 2016; **7**: 238.
- 23. Chandra P, Rajmani RS, Verma G, Bhavesh NS, Kumar D. Targeting Drug-Sensitive and -Resistant Strains of Mycobacterium tuberculosis by Inhibition of Src Family Kinases Lowers Disease Burden and Pathology. *mSphere* 2016; **1**(2).

- 24. Man DK, Chow MY, Casettari L, Gonzalez-Juarrero M, Lam JK. Potential and development of inhaled RNAi therapeutics for the treatment of pulmonary tuberculosis. *Adv Drug Deliv Rev* 2016; **102**: 21-32.
- 25. Koh HJ, Kim YR, Kim JS, Yun JS, Jang K, Yang CS. Toxoplasma gondii GRA7-Targeted ASC and PLD1 Promote Antibacterial Host Defense via PKCalpha. *PLoS Pathog* 2017; **13**(1): e1006126.
- 26. Nagu T, Aboud S, Rao M, et al. Strong anti-Epstein Barr virus (EBV) or cytomegalovirus (CMV) cellular immune responses predict survival and a favourable response to anti-tuberculosis therapy. *Int J Infect Dis* 2017; **56**: 136-9.
- 27. Zhou CY, Wang RN, Wen Q, et al. Alanine Mutagenesis in the Complementarity Determining Region 3 of the MTB and HIV-1 Peptide-Bispecific T Cell Receptor Beta Chain Affects Ligand Recognition. *Front Immunol* 2017; **8**: 983.
- 28. Glanville J, Huang H, Nau A, et al. Identifying specificity groups in the T cell receptor repertoire. *Nature* 2017; **547**(7661): 94-8.