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Corresponding Author: Professor Alimuddin Zumla, PhD.FRCP.FRCPath

Corresponding Author's Institution: University College London Medical School,

First Author: Simon Tiberi, MD

Order of Authors: Simon Tiberi, MD; Nelita du Plessis, PhD; Gerhard Walzl, PhD; Michael J Vjecha, MD; Martin Rao, PhD; Francine Ntoumi, PhD.FRCP; Sayoki Mfinanga, PhD; Nathan Kapata, MPH; Peter Mwaba, PhD.FRCP; Timothy D McHugh, PhD; Giuseppe Ippolito, FRCP; Giovanni B Migliori, FRCP; Alimuddin Zumla, PhD.FRCP.FRCPath

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

Authors:

Simon Tiberi MD, Nelita du Plessis PhD, Gerhard Walzl PhD, Michael J. Vjecha MD, Martin Rao PhD, Francine Ntoumi FRCP, Sayoki Mfinanga PhD, Nathan Kapata MPH, Peter Mwaba FRCP, Timothy D McHugh PhD, Giuseppe Ippolito FRCP, Giovanni Batista Migliori FRCP, Markus J Maeurer FRCP, Alimuddin Zumla FRCP*

Institutional affiliations:

Division of Infection, Royal London Hospital, Barts Health NHS Trust, London, United Kingdom (Dr Simon Tiberi MD Email: Simon.Tiberi@bartshealth.nhs.uk)

South African Medical Research Council, Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. (Professor Gerhard Walzl PhD. FRCP Email: gwalzl@sun.ac.za and Dr Nelita du Plessis PhD. Email: nelita@sun.ac.za)

CDC TB Trials Consortium (TBTC) Core Science Group, Veterans Affairs Medical Center, Washington, DC, USA. (Dr Michael J. Vjecha MD. Email: mvjecha@sent.com)

Division of Therapeutic Immunology (TIM), Karolinska Institute, Stockholm, Sweden. (Professor Markus Maeurer PhD.FRCP. Email:markus.maeurer@gmail.com and Dr Martin Rao PhD. Email: martin.rao@gmail.com)

Fondation Congolaise pour la Recherche Medicale (FCRM), and Faculte des Sciences et Techniques, Universite M. Ngouabi, Brazzaville, Rep du Congo. (Professor Francine Ntoumi FRCP.PhD. Email: ffntoumi@hotmail.com fntoumi@fcrm-congo.com)

National Institute for Medical Research, Muhimbili Medical Research Centre, Dar es Salaam, Tanzania (Professor Sayoki Mfinanga PhD. Email: gsmfinanga@yahoo.com)

UNZA-UCLMS Research and Training Programme and Apex University, Lusaka, Zambia. (Professor Peter Mwaba PhD.FRCP Email: pbmwaba2000@gmail.com)

Institute of Public Health, Ministry of Health, Lusaka, Zambia (Dr Nathan Kapata MPH. Email: nkapata@gmail.com)

National Institute for Infectious Disease, L. Spallanzani, Rome, Italy. (Professor Giuseppe Ippolito MD. FRCP. Email: giuseppe.ippolito@inmi.it)

World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Istituto di Ricovero e Cura a Carattere Sceintifico, Tradate Italy. (Professor Giovanni-Battista Migliori MD. FRCP. Email: giovannibattista.migliori@fsm.it)

Centre for Clinical Microbiology, Division of Infection and Immunity, University College London, UK (Professor Timothy McHugh PhD Email: t.mchugh@ucl.ac.uk and Professor Alimuddin Zumla PhD. FRCP. Email: a.i.zumla@gmail.com)

NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK (Professor Alimuddin Zumla. Email. a.i.zumla@gmail.com)

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Correspondence:

Professor Sir Alimuddin Zumla PhD.FRCP
Division of Infection and Immunity, University College London and NIHR Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, United Kingdom
Email: a.i.zumla@gmail.com

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 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.

INTRODUCTION

In 2016, there were an estimated 1.67 million deaths due to tuberculosis (TB), making the disease the infectious disease killer worldwide.[1] 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.[7] 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.[8-14]

PROGRESS IN NEW TB DRUG DEVELOPMENT AND EVALUATION

Development of new and repurposed drugs and treatment regimens for TB has entered a promising phase.[15-18] 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),[19] 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).[20] 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.[21] Of note new better tasting fixed-dosed combination tablets are now available for paediatric use, which simplify dosing in children weighing less than 25kg,[22] while improving drug delivery and drug levels.[23,24] 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.[26-28] 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.[29] 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.[30]

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.[31] 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.[32] Recently, the use of another rifamycin (rifabutin) was associated with improved treatment outcomes in rifabutin-susceptible cases.[33] 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.[34] Levofloxacin is also being used in the H-35265 trial, the NEXT trial, the STREAM trial, and in the MDR-END study.[35] 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.[36]

Drug-resistant tuberculosis

The updated classification of new anti-TB drugs by WHO is given in **table 3**,[37] The taxonomy of anti-TB drugs, and their combinations are undergoing a rapid transformation as a result of clinical trials and meta-analyses.[38,39] 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.[37] 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.[40,41] 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.[42-44]

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,[47-51] 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.[52] 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.[53] 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.[54]

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.[55] 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.[56] 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.[57] Other important trials including bedaquiline are NEXT-TB study TB-PRACTECAL and endTB.[58-60] 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.[61] 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,[53] 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%.[67] 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.[64,69,70] 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.[71,72] There are two trials which are currently recruiting patients however results are not expected till 2020-1.[73,74] 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.[75,76]

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,[77] 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.[78] Encouraging evidence is also available for a large programmatic study in Brazil.[79] 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 ß-lactamases) renders these compounds less

appealing, even though some appear very active with excellent tolerability and safety.[80-82] Linezolid, an oxazolidinone, has demonstrated anti-mycobacterial efficacy and is included in many drug trial regimens;[83] 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.[84]

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).[85] 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.[86] 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.[87] PHOENIX will begin Q1 2018 as an open label study.[88] TB-CHAMP will enrol 1,556 children age 5 and younger at sites in South Africa.[89]

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 TNFα 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.[88]

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.[90,91] 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.[90,91] 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.[92] 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 anti-mycobacterial 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.[93,94] 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 anti-inflammatory properties,[96] improve TB lung pathology and prevent immune reconstitution inflammatory syndrome (IRIS) in TB/HIV co-infection.[97] Survival benefits have been demonstrated for TB meningitis,[98] although other clinical forms of TB have not shown a consistent benefit from adjunctive corticosteroid treatment.[99]

Eicosanoid modulators

Eicosanoids are generated by cyclooxygenase (COX) and lipoxygenase (5-LOX) metabolism of arachidonic acid to generate prostaglandins and leukotriene,[100] respectively. Selective COX-2 inhibitors decrease unproductive inflammation and improve survival in murine TB by direct anti-mycobacterial activity.[101-102] COX2-inhibition is however, also associated with cell necrosis, which favours *Mtb* survival.[103] 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.[104] 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.[105]

Cholesterol-lowering drugs

In addition to lipid-lowering properties, statins possess potent anti-inflammatory activities[106] with beneficial effects in TB.[107] 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.[108-109] Statin usage by newly diagnosed type-2 diabetics did however, not prevent development of TB,[110] 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.[111] PDE inhibitors accelerate lung sterilization, reduce lung inflammation and promote lung repair by potentiating isoniazid bactericidal activity, limiting TNFα production and reducing macrophage activation.[112-113] There is insufficient data on the clinical and immunological impact of PDE inhibitors and further research is required.[114]

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.[115] Signalling via immune checkpoints inhibit T- and B-cell function[116]. Checkpoint inhibitors have been successfully employed in various cancers, specifically the monoclonal antibodies nivolumab and ipilimumab, against PD-1 and CTLA-4, respectively.[117] Inhibition of CTLA-4 enhances immune responses without improving bacillary clearance. Polymorphisms in *CTLA-4* were linked to TB susceptibility.[118] Inhibition of the PD1/PD-L1 pathway enhances *Mtb*-specific responses in humans,[119] but not in mice.[120] Immune checkpoint inhibition treatment can result in development of active TB disease. This is likely due to excessive inflammation and increased focal necrosis.[121] 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.[122] VitD3 deficiency is a risk factor for development of TB disease,[123] although a randomised control trial failed to show a profound effect on TB treatment outcome.[124] 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,[125] deficiency strongly predicts the risk of incident TB amongst TB household contacts (HHC) and supplementation (with zinc) improves TB treatment outcomes.[126] The vitA derivative, all-trans-retinoic acid (ATRA), decreased *Mtb* burden by reducing cellular cholesterol and inducing phagosomal acidification.[127] These favourable outcomes could however not be repeated in other TB treatment studies.[128]

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.[129] Imatinib, a tyrosine kinase inhibitor, reduces bacterial load and lung pathology, likely by enhancing autophagy, phagosomal acidification and myeloid cell mobilization,[130-131] 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.[132] AMPK is activated by metformin, a type-2 diabetes drug,[133] that reduces bacterial burden and ameliorates lung pathology in mice and humans by enhancing autophagy and increasing ROS production.[92] 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.[134]

Cellular therapy

Cellular therapy has shown promise in the cancer field,[135] and is being investigated for use as adjunct therapy for drug-resistant TB.[136] Mesenchymal stromal cells (MSC) are non-hematopoietic progenitor cells with immunomodulatory and antibacterial properties,[137-138] that improve immune responses and lung pathology in human and murine TB.[139-140] Another immunotherapeutic approach involves modulation of immune regulatory cells, specifically myeloid-derived suppressor cells (MDSC)[141-142] MDSC are increased in TB, display T-cell immunosuppressive properties,[143-145] 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, TNFα, IL6, chemokines and stimulation of macrophage polarization.[146-147] 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-α is essential to granuloma integrity, macrophage antimicrobial activity and ROS-mediated *Mtb* killing.[150] TNF-α can however, also trigger cell necrosis and exacerbate inflammation, thereby aggravating TB pathology.[151] TNF-α blockers and anti-TNF-α monoclonal antibodies, such as thalidomide and infliximab, successfully control severe TB .[152] On the other hand, TNF-α inhibition destabilizes granulomas, reactivates *Mtb* bacilli and increases the risk of TB disease.[153] IFN-γ is important to protective anti-TB immunity and administration has nominal benefit in drug-sensitive,[154] and drug-resistant TB.[155]

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

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Figure 1

New TB Drugs Development Pipeline **(courtesy of Michael Vjecha and WGNTBD)**

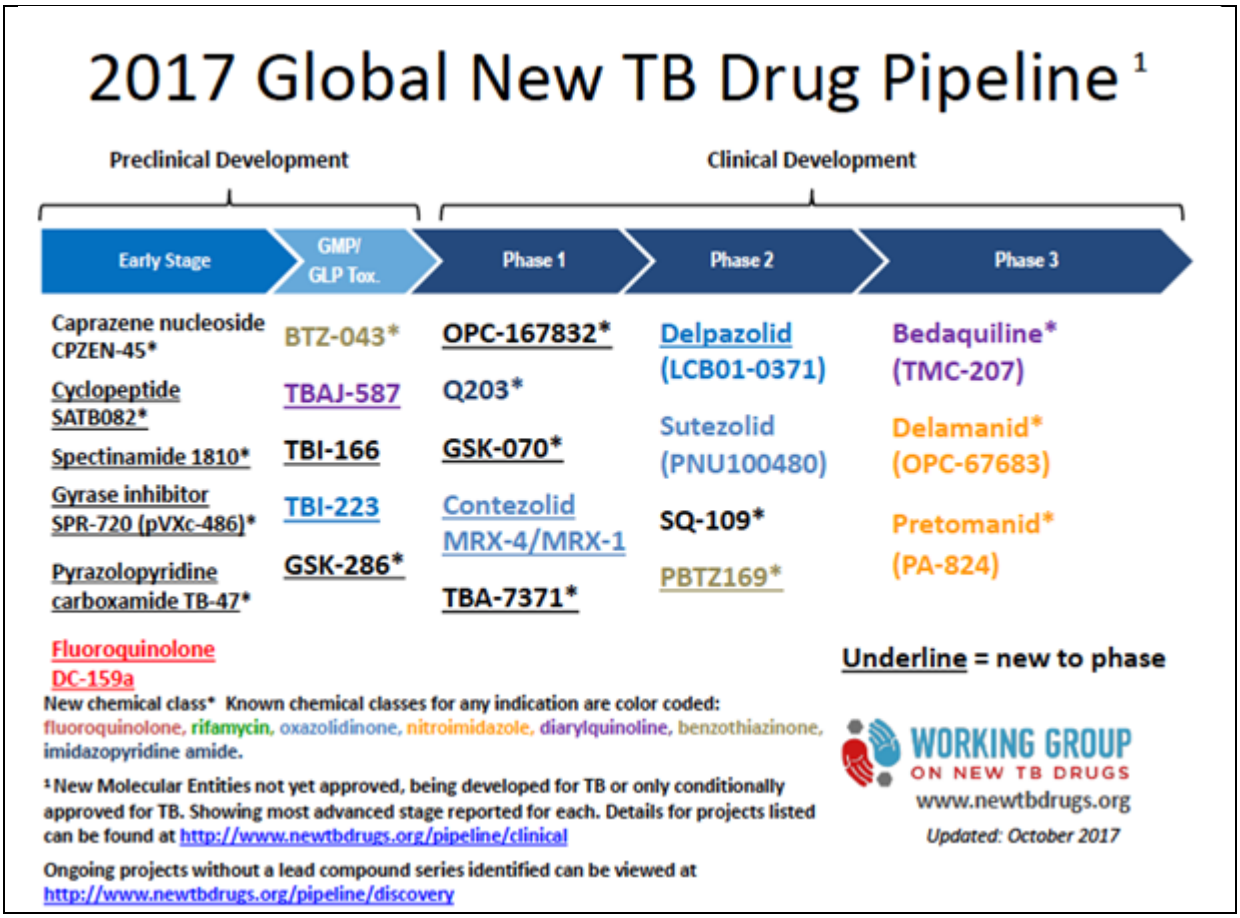

Table 1:

TB Drugs development pipeline -Class of drug, target, phase of trial and sponsor

(Adapted from TAG Report http://www.pipelinereport.org/sites/default/files/2017%20Pipeline%20Report%20Final.pdf)

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	II/III	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	II	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	I	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
Rifamycins: Rifapentine - P - RPT (Sanofi)								
	TBTC 28X	NCT00694629	2HPZE (20 v. 15 v. 10 mg/kg/d) v. 2HRZE	II	320	TBTC (Dorman)	Results ATS 2013, AJRCCM 2015	1200 mg P safe/tolerable, flat dosing better
	RIFAQUIN	ISRCTN44153044	2MRZE/2M_3P_3 800 v. 2MRZE/4M_3P_3 1200 v. 2HRZE/4HR	III	1095	MRC/UK, EDCTP	Results IUATLD 2013, NEJM Oct 2014	4 mo inferior, 6 mo non-inferior, both safe/tolerable
	RioMAR	NCT00728507	2HP_2ZM v. 2HRZE (P = 7.5 mg/kg)	II	216	JHU (Dorman)	Results CROI 2014 93, PLoS One May 2016	Early stop 56% accrual, HPZM better by liquid media
	A6311	NCT01574638	P 15 mg/kg v. 20 mg/kg qd or bid ± egg [HIV- healthy volunteers]	I	48	ACTG (Dooley)	Results CROI 2014 816, AAC 2015	Higher AUCs/intolerance w/doses up to 1800 mg
	Sanofi	NCT01690403	21d pK P 600 mg q wk + Atripla [HIV+ healthy volunteers]	I	36	Sanofi	Results CROI 2014 493	EFV 600 mg OK with once-weekly P (10 mg/kg)
	FDA Cape Town Trial	NCT00814671	2P_1 (600 v. 450 mg) HZE v. 2HRZE	II	153	JHU (Dorman/Dawson)	Results IUATLD 2014	Safe/tolerable but no difference cx conversion
	A6279	NCT01404312	LTBI: HP (10 mg/kg) qd x30d pK substudy: P + EFV [HIV+]	III	3000	ACTG (Chaisson)	pK Results CROI 2014 105, results Q1 2018	EFV OK with daily P (10 mg/kg)
	TBTC 31 / A5348	NCT02410772	2HP_{1200}ZE/2HP v. 3$HP_{1200}ZM_{800}$ v. 2HRZE/4HR [HIV-/+, ages 13 and up, sparse PK]	III	2500	TBTC/ACTG	Opened Jan 2016, enrol thru Q4 2018	Includes DDI PK P/EFV in 31 + 90 HIV+ in 2 stages
	TBTC 31 / A5348 PK	NCT02563327	Intence PK: 2HP_{1200}ZE/2HP v. 3$HP_{1200}ZM_{800}$ v. 2HRZE/4HR [HIV-/+]	II	60	TBTC/ACTG	Opened Jan 2016, enrol 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-/+]	I/II	82	IMPAACT (Mathad)	Opened Feb 2017, enrol thru Q1 2018	
	CORTI8	NCT02735590	LTBI: 3HP_{900} weekly v. no intervention [↑risk by transcriptomics, HIV- adults]	III	3200	UCT (Hatherill)	Opened July 2016, results 2018	15 month follow-up
	WHIP3TB	NCT02980016	LTBI: 3HP weekly Y1 v. 3HP weekly Y1&Y2 v. 6H Y1 daily	III	4000	Aurum Inst. (Churchyard)	Opened Nov 2016, results Sep 2019	
	TBTC 36	n/a	LTBI PK/safety: P (25-36 mg/kg) + H (10-15 mg/kg) in ages <2, 2-5, 6-12 [HIV-/+]	II	80	TBTC/Sanofi (Hesseling)	Opens Q1 2018	New water dispersible tablet co-formulation
Rifamycins: High-dose Rifampin - R - RIF								
	HIGHRIF1	NCT01392911	2 wk max tolerability dosage, 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. 15 v. 10 mg/kg	II	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. 900 (15 mg/kg) v. 600 (10 mg/kg)	II	150	EDCTP/PanACEA	Results InterTB Oct 2014	15 + 20 mg/kg safe/tolerable, pK variability
	MAMS-TB-01	NCT01785186	HR_{35}ZE ~~v. HR2G~~ ~~v. HR_{50}ZG~~ v. HR_{35}ZM v. HRZE	II	368	EDCTP/PanACEA	Results CROI 2015 95LB, Lancet ID 2017	TTCC R_{35} < R_{50} at 12wk MGIT only, ↑ liver AEs R_{35}
	n/a	NCT02387242	WBA: R (30 mg/kg) v. R (20 mg/kg) v. R (10 mg/kg) [healthy]	II	18	NUH Singapore (Paton)	Opened Feb 2015, results Sep 2015	
	HIRIF	NCT01408914	2HR_{1200}ZE v. 2HR_{900}ZE v. 2HR_{600}ZE	II	180	Harvard (Mitnick)	Results Apr 2016	
	RIFAVIRENZ	NCT01986543	2R (20 mg/kg)HZE + EFV 600 or 800/d v. 2R (10 mg/kg)HZE + EFV 600/d	II	105	ANRS	Results Apr 2017	
	RIFASHORT	NCT02581527	2HR_{1200}ZE/2HR_{1200} v. 2HR_{1000}ZE/2HR_{1000} v. 2HRZE/4HR [HIV-]	III	820	St. George's/INTERTB	Opened Feb 2017, results Jan 2020	
Rifamycins: Rifabutin - B - RBT								
	EARNEST Substudy	NCT01663168	pK Safety B_3 v. B_7 + LPV/r (24 wks) [HIV+ on ART]	II	140	MRC/UK (Uganda sites)	pK substudy results pending	
	A6280	NCT01601626	2HBZE/4RH + LPV/r 200 mg +/- RAL vs. 2HRZE/4RH + LPV/r 400 mg	II	71	ACTG (Benson)	Stage 1 results IAS 2017	
	APT	NCT02256696	12 wk: 2Pa_{200}BHZ/1Pa_{200}BH v. 2Pa_{200}RHZ/1Pa_{200}RH v. 2HRZE/1HR [DS]	II	183	JHU (Dooley/Dawson)	Accrual 28, reopening May 2017 after Pa hold	
	TB Host-Directed Rx	NCT02968927	2HBZE/4BH -/+ Everolimus v. Auranofin v. VitD3 v. CC11060 (PDE4inh) [DS, HIV-]	III	200	Aurum Inst.(Wallis)	Opened Nov 2016, results Mar 2018	
	A6289	n/a	2-stage dose-range open label: HRZU v. HBZU v. HRZE [DS only] [HIV-/+]	II	182	ACTG (Luetkemeyer)	On hold (Sep 2016)	
Nicotinic Acids: High-dose Isoniazid - H - INH								
	A6312	NCT01936831	1 wk EBA H 16 v. 10 v. 5 mg/kg/d in INH-A resistant TB	EBA	265	ACTG (Dooley/Diacon)	N=227, results Q3 2018	
Fluoroquinolones: Levofloxacin - Lx, Gatifloxacin - G - Gx, Moxifloxacin - M - Mx								
	RIFAQUIN	ISRCTN44153044	2RMZE/2M_3P_3 800 v. 2RMZE/4M_3P_3 1200 v. 2HRZE/4HR	III	1095	MRC/UK, EDCTP	Results IUATLD 2013, NEJM Oct 2014	4 mo inferior, 6 mo non-inferior, both safe/tolerable
	OFLOTUB	NCT00216385	2HRZG/2RHG v. 2HRZE/4HR	III	1836	EU/WHO	Results IUATLD 2013, NEJM Oct 2014	4 mo inferior, both arms safe/tolerable
	RioMAR	NCT00728507	2HP_2ZM v. 2HRZE (P = 7.5 mg/kg)	II	216	JHU (Dorman)	Results CROI 2014 93, PLoS One May 2016	Early stop 56% accrual, HPZM better by liquid media
	ReMOX	NCT00864383	2HRZM/2HRM v. 2RMZE/2RM v. 2HRZE/4HR	III	1931	TB Alliance/PanACEA	Results ICAAC 2014, NEJM Oct 2014	4 mo arms inferior, both safe/tolerable
	MAMS-TB-01	NCT01785186	HR_{35}ZE ~~v. HR2G~~ ~~v. HR_{50}ZG~~ v. HR_{35}ZM v. HRZE	II	372	EDCTP/PanACEA	Results CROI 2015 95LB, Lancet ID 2017	HR2G + HR_{35}ZG arms dropped Mar 2014
	A6307	NCT01589497	2 wk EBA RMZE v. RZE v. HRZE	EBA	69	ACTG (Bisha)	Completed Feb 2016, results CROI 2017 79	INH had no EBA, even by D2 (? Lower load sputa)
	STREAM Stage 1	ISRCTN78372190	4MCEZHKPro/6MCZE v. local DR regimen [DR]	III	400	IUATLD/MRC/DFID/USAID	Interim results IUATLD 2017	
	NC-006 STAND	NCT02342886	4$Pa_{100/200}$MZ v. 8Pa_{100}MZ v. 8Pa_{200}MZ v. 2HRZE/4HR [DS, DR 6Pa_{200}MZ only]	III	284	TB Alliance	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]	II	100	NIAID/TBTC (Horsburgh)	Follow-up completed, results Q2 2018	
	NexGen EBA	NCT02371681	4 wk EBA: 1MRHZ [serial F-FDG PET scans, DS only]	II	350	NIAID (Barry/Diacon)	Opened Jan 2015, results Nov 2017	
	NExT-6001	NCT02454205	6-8LzJLxZ[H or Eth or Ter) v. 6-8KMZ(Eth or Ter)/16-18MZ(Eth or Ter) [DR]	II/III	300	UCT/Stellenbosch (Dheda)	Opened Oct 2015, results Jan 2019	
	TBTC 31 / A5348	NCT02410772	2HP_{1200}ZE/2HP v. 3$HP_{1200}ZM_{800}$ v. 2HRZE/4HR [HIV-/+, ages 13 and up, sparse PK]	III	2500	TBTC/ACTG	Opened Jan 2016, enrol thru Q4 2018	Includes DDI PK P/EFV in 31 + 90 HIV+ in 2 stages
	TBTC 31 / A5348 PK	NCT02563327	Intence PK: 2HP_{1200}ZE/2HP v. 3$HP_{1200}ZM_{800}$ v. 2HRZE/4HR [HIV-/+]	II	60	TBTC/ACTG	Opened Jan 2016, enrol thru Q4 2018	
	MDR-END	NCT02619994	9 or 12D + $Lx_{750/1000}$ + $Lz_{900/2M+500}$ + Z v. 24OBR [DR, quinolone sensitive]	II	238	Seoul Nat. Univ. Hospital	Opened Jan 2016, results Dec 2019	
	TB-PRACTECAL	NCT02589782	2 stage: 6JPaMLz v. 6JPaLzC v. 6JPaLz v. 24OBR [DR, XDR]	II/III	630	MSF Holland/UCL/LSHTM	Opened Jan 2017, results Mar 2021	Belarus, South Africa, Uzbekistan
	STREAM Stage 2	NCT02409290	MCEZHKPro v. JLvCEZHPro v. JLvCZHK v. local DR regimen [DR]	III	1155	IUATLD/MRC/USAID/TBA	Opened Apr 2016, results Apr 2021	
	endTB	NCT02754765	9JLzMZ v. 9JLzCLxZ v. 9JLzDLxZ v. 9DCMZ v. 24OBR [DR, quinolone sensitive]	III	750	MSF France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	V-QUIN MDR	ACTRN12600021541	LTBI: 6$Lx_{250/500/750}$ v. placebo (blinded) [DR contacts, ≥15 rand/screen all, HIV+/-]	III	2006	Australia NHMRC (Fox)	Opened 2016, results 2019	Vietnam (multiple sites)
	TB-CHAMP	n/a	LTBI: 6$Lx_{15-20\ mg/kg/d}$ v. placebo (blinded) [DR contacts, ages 0-5, HIV+/-]	III	1565	MRC/DFID/Wellcome	Opens 2017, results 2019	South Africa (Stellenbosch and 3 other sites)
	NC-008 SimpliciTB	n/a	4JPaMZ v. 2HRZE/4RH [DS], 6JPAMZ [DR]	III	150/150	TB Alliance	Opens 2018	
Diarylquinolines: Bedaquiline - TMC-207 - J (Janssen/TB Alliance)								
	n/a	NCT01341184	pK single dose J + RFB, J + RFM [healthy volunteers]	I	32	NIAID (CWRU)	Completed 2012, results pending	
	NC-003	NCT01691534	2 wk EBA JPaZ, JPaZC, JPaC, JZC, Z, C	IIa	105	TB Alliance	Results CROI 2014 97LB, AJRCCM Jan 2015	BPaZ best, mod QT effect, C no activity
	NC-005	NCT02193776	SSCC: J(400 mg/d x14d, 200 mg tiw)PaZ v. J(200 mg/d)PaZ (+ M in DR) v. HRZE	IIb	240	TB Alliance	FU to M24 ongoing, results CROI 2017 LB724	BPaMZ + BPaZ had highest BA; low AEs in 8 wks
	n/a	NCT02365623	single arm pK/safety Japanese: 6J + OBR [DR]	II	5	Janssen	Opened Feb 2015, follow-up thru Nov 2018	
	NIX-TB	NCT02333799	6JPa_{200}/LZD (600 mg bid) [single arm, XDR]	II	200	TB Alliance	Opened Mar 2015, switch to ZeNIX Nov 2017	Interim results CROI 2017 80LB, effective, 27% AEs
	NExT-6001	NCT02454205	6-8LzJLvZ[H or Eth or Ter) v. 6-8KMZ(Eth or Ter)/16-18MZ(Eth or Ter) [DR]	II/III	300	UCT/Stellenbosch (Dheda)	Opened Oct 2015, results Jan 2019	
	TB-PRACTECAL	NCT02589782	2 stage: 6JPaMLz v. 6JPaLzC v. 6JPaLz v. 24OBR [DR, XDR]	II/III	630	MSF Holland/UCL/LSHTM	Opened Jan 2017, results Mar 2021	Belarus, South Africa, Uzbekistan
	STREAM Stage 2	NCT02409290	MCEZHKPro v. JLvCEZHPro v. JLvCZHK v. local DR regimen [DR]	III	1155	IUATLD/MRC/USAID/TBA	Opened Apr 2016, results Apr 2021	
	C211	NCT02354014	PK/Safety: 4 age strata J + OBR [DR, ages 0 - 18] [HIV-]	II	60	Janssen	Opened May 2016, results Mar 2021	India, Philipines, Russia, South Africa
	endTB	NCT02754765	9JLzMZ v. 9JLzCLxZ v. 9JLzDLxZ v. 9DCMZ v. 24OBR [DR, quinolone sensitive]	III	750	MSF France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	A5343 DELIBERATE	NCT02583048	pK DDI QT 6J v. 6D v. 6JD + OBR [DR] [HIV-/+]	II	84	ACTG (Maartens/Dooley)	Opened Aug 2016, 51 enrolled	Results 2018
	P1108	n/a	PK/safety: dose-range J + OBR [DR, 0-18 yrs, HIV-/+]	II	72	IMPAACT (Hesseling)	Opens Jun 2017	Haiti, India, South Africa
	NC-007 ZeNIX	NCT03086486	4 arms: 8 or 2 $LZD_{1200\ or\ 600}$ [double blind] + $J_{200/100}$ + Pa_{200} [DR, ≥14, HIV+/-]	III	180	TB Alliance	Opens Nov 2017, results Jan 2021	
	NC-008 SimpliciTB	n/a	4JPaMZ v. 2HRZE/4RH [DS], 6JPAMZ [DR]	III	150/150	TB Alliance	Opens 2018	
Nitroimidazoles: Pretomanid - PA-824 - Pa (TB Alliance)								
	n/a	NCT01674218	PaM QT study [5 arms, crossover, healthy volunteers]	I	75	NIAID/DMID	Completed Dec 2012, results pending	
	A6306	NCT01571414	PK: Pa with LPV/r, EFV, RIF [HIV-]	I	48	ACTG (Dooley)	Results CROI 2013 188LB, AAC 2014	RIF + EFV ↓ [Pa], LPV/r no effect
	NC-002	NCT01498419	SSCC: 2 Pa (100 v. 200 mg) MZ v. 2HRZE [DS + DR]	II	230	TB Alliance	Lancet Mar 2015	

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	IIa	105	TB Alliance	Results CROI 2014 97LB, AJRCCM Jan 2015	BPaZ best, mod QT effect, C no activity
	NC-005	NCT02193776	SSCC: J(400 mg/d x14d, 200 mg tiw)PaZ v. J(200 mg/d)PaZ (+ M in DR) v. HRZE	IIb	240	TB Alliance	FU to M24 ongoing, results CROI 2017 LB724	BPaMZ + BPaZ had highest BA; low AEs in 8 wks
	NC-006 STAND	NCT02342886	$4Pa_{100/200}MZ$ v. $6Pa_{100}MZ$ v. $6Pa_{200}MZ$ v. 2HRZE/4HR [DS, DR $6Pa_{200}MZ$ only]	III	284	TB Alliance	Completed early, results late 2017	
	APT	NCT02256696	12 wk: $2Pa_{200}BHZ/1Pa_{200}BH$ v. $2Pa_{200}RHZ/1Pa_{200}RH$ v. 2HRZE/1HR [DS]	II	183	JHU/UCT (Dooley/Dawson)	N=28, reopening May 2017 after Pa hold	
	NIX-TB	NCT02333799	$6JPa_{200}$/LZD (600 mg bid) [single arm, XDR]	III	200	TB Alliance	Opened Mar 2015, switch to ZeNIX Nov 2017	Interim results CROI 2017 80LB, effective, 27% AEs
	TB-PRACTECAL	NCT02589782	2 stage: 6JPaMLz v. 6JPaLzC v. 6JPaLz v. 24OBR [DR, XDR]	II/III	630	MSF Holland (Nyang'wa)	Opened Jan 2017, results Mar 2021	Belarus, South Africa, Uzbekistan
	NC-007 ZeNIX	NCT03086486	4 arms: 8 or 2 $LZD_{1200\ or\ 600}$ [double blind] + $J_{200/100}$ + Pa_{200} [DR, ≥14, HIV+/-]	III	180	TB Alliance	Opens Nov 2017, results Jan 2021	
	NC-008 SimpliciTB	n/a	4JPaMZ v. 2HRZE/4RH [DS], 6JPAMZ [DR]	III	150/150	TB Alliance	Opens 2018	
Nitroimidazoles: Delamanid - OPC-67683 - D (Otsuka)								
	Trial 204	NCT00685360	D (200 mg bid v. 100 mg bid) + OBR [DR]	II	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. 6placebo+OBR [DR]	III	511	Otsuka	Completed June 2016, results 2017	
	Trial 232	NCT01856634	18d PK: 4 peds cohorts D <25, 25, 50, 100 mg bid + OBR x 10 d [DR]	I	36	Otsuka	Opened July 2013, results 2018	Cape Town/Philippines
	Trial 233	NCT01859923	6M PK/Safety: 4 peds cohorts D <25, 25, 50, 100 mg bid + OBR x 6 mo [DR]	II	36	Otsuka	Opened Aug 2013, results 2020	Cape Town/Philippines
	MDR-END	NCT02619994	8 or 12D + $Lx_{750/1000}$ + $Lz_{600/25/+300}$ + Z v. 24OBR [DR, quinolone sensitive]	II	238	Seoul Nat. Univ. Hospital	Opened Jan 2016, results Dec 2019	
	endTB	NCT02754765	8JLzMZ v. 8JLzCLxZ v. 8JLzDLxZ v. 8DCMZ v. 24OBR [DR, quinolone sensitive]	III	750	MSF France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	A5343 DELIBERATE	NCT02583048	pK DDI QT 6J v. 6D v. 8JD + OBR [DR] [HIV-/+]	II	84	ACTG (Maartens/Dooley)	Opened Aug 2016, 51 enrolled	Results 2018
	IMPAACT 2005	n/a	PK/safety: single arm 8D + (oral)OBR [DR, 0 - 18, HIV-/+]	I/II	48	IMPAACT (Dooley)	Opens 2018, results Apr 2021	Botswana, India, South Africa, Tanzania
	A5366	n/a	8D(100 bid)+LZD(300 qd/600 qd/1200 qod) + OBR (oral) v. 6D + OBR (inj.) [DR]	IIa	240	ACTG (Benson)	Opens Q1 2018	
	A5300B / I2009B	n/a	PHOENIx LTBI: 6D v. 9H [DR contacts, age 6 and up] [HIV-/+]	III	3452	ACTG/IMPAACT	Opens Q1 2018	
Oxazolidinones: Sutezolid - PNU-100480 - U (Pfizer → Sequella + TB Alliance)								
	n/a	NCT00990990	Safety/WBA U (100, 300, 600, 1200 mg bid) x 14d, 28d +/- Z d 27-28	I	59	Pfizer	Completed	
	n/a	NCT01225640	2 wk EBA + WBA U (600 mg bid v. 1200 mg qd) v. HRZE	EBA	59	Pfizer	Results IAS 2012 THLBB02, PLOS Apr 2014	1200 mg qd > 600 mg bid, ↑ LFTs
	A5288	n/a	2-stage dose-range open label: UHRZ v. UHTZ v. HRZE [DS only] [HIV-/+]	II	182	ACTG (Luetkemeyer)	On hold (Sep 2016)	
Oxazolidinones: Linezolid - LZD - Lz (Pfizer)								
	J-1310-026-523	NCT01994460	LZD (600 mg/d, 2 wk v 4 wk) + 2HRZ/4HR v. 2HRZE/4RH [DS only] [HIV-]	III	429	Seoul Nat. Univ. Hospital	Opened Jan 2014, results end 2016	
	LIN-CL001	NCT02279875	2 wk EBA/Safety LZD (1200 qd, 600 bid, 800 qd, 300 bid, 300 qd) [DS only]	EBA	113	TB Alliance	Opened Nov 2014, results Feb 2017	New dose strategies tested in study extension
	NIX-TB	NCT02333799	$6BPa_{200}$/LZD (600 mg bid) [single arm, XDR]	III	200	TB Alliance	Opened Mar 2015, switch to ZeNIX Nov 2017	Interim results CROI 2017 80LB, effective, 27% AEs
	NExT-5001	NCT02454205	6-8LzJLxZ(H or Eth or Ter) v. 6-8KMZ(Eth or Ter)/16-18MZ(Eth or Ter) [DR]	II/III	300	UCT/Stellenbosch (Dheda)	Opened Oct 2015, results Jan 2019	
	MDR-END	NCT02619994	8 or 12D + $Lx_{750/1000}$ + $Lz_{600/25/+300}$ + Z v. 24OBR [DR, quinolone sensitive]	II	238	Seoul Nat. Univ. Hospital	Opened Jan 2016, results Dec 2019	
	TB-PRACTECAL	NCT02589782	2 stage: 6JPaMLz v. 6JPaLzC v. 6JPaLz v. 24OBR [DR, XDR]	II/III	630	MSF Holland (Nyang'wa)	Opened Jan 2017, results Mar 2021	Belarus, South Africa, Uzbekistan
	endTB	NCT02754765	8JLzMZ v. 8JLzCLxZ v. 8JLzDLxZ v. 8DCMZ v. 24OBR [DR, quinolone sensitive]	III	750	MSF France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	A5366	n/a	8D(100 bid)+LZD(300 qd/600 qd/1200 qod) + OBR (oral) v. 6D + OBR (inj.) [DR]	IIa	240	ACTG (Benson)	Opens Q1 2018	
	NC-007 ZeNIX	NCT03086486	4 arms: 8 or 2 $LZD_{1200\ or\ 600}$ [double blind] + $J_{200/100}$ + Pa_{200} [DR, ≥14, HIV+/-]	III	180	TB Alliance	Opens Nov 2017, results Jan 2021	
Oxazolidinones: Delpazolid - LCB01-0371 - DZD - Dz (LegoChem)								
	LCB01-0371-16-2-01	NCT02836483	2 wk EBA Dz (800 mg qd v. 800 mg bid v. 400 mg bid) [DS only]	EBA	64	LegoChem Biosciences	Opened Dec 2016, results Q1 2018	
Iminophenazines: Clofazimine - Lamprene - CFZ - C (Novartis)								
	NC-003	NCT01691534	2 wk EBA JPaZ, JPaZC, JPaC, JZC, Z, C	EBA	105	TB Alliance	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: 6JPaMLz v. 6JPaLzC v. 6JPaLz v. 24OBR [DR, XDR]	II/III	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]	III	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]	II/III	380	Novartis	Trial suspended 2017	Lithuania/Latvia/Russia/Peru/Philippines/RSA/Thailnd
	endTB	NCT02754765	8JLzMZ v. 8JLzCLxZ v. 8JLzDLxZ v. 8DCMZ v. 24OBR [DR, quinolone sensitive]	III	750	MSF France/Harvard	Opened Dec 2016, results Sep 2020	Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru
	A5362 Clo-FAST	n/a	2 stage: ($4C_{50}$ v. $4C_{100}$ v. 4placebo) + 4HRZE / 2placebo v. 2placebo v. 2HR	IIc	400	ACTG (Metcalfe)	Opens Q1 2018, follow up to M18	
Ethylene diamines: SQ-109 - Q (Sequella)								
	SQ109-01	NCT01218217	EBA Q (75 v. 150 v. 300 mg qd) ± R	EBA	90	EDCTP/PanACEA	Completed 2012, JAC Jan 2015	Safe/tolerable, no QT signal, 2C19 induction
	MAM8-TB-01	NCT01785186	~~$HR_{50}ZE$ v. $HRZQ$ v. $HR_{50}ZQ$~~ v. $HR_{50}ZM$ v. HRZE	II	372	EDCTP/PanACEA	Completed Q1 2015, results CROI 2015 95LB	$HRZQ + HR_{50}ZQ$ arms dropped Mar 2014
	n/a	n/a	8Q + OBR v. OBR [DR]	IIb/III	140	Infectex/Sequella	Results 2017 (7 sites Russia)	Safe/tolerable, 80% 6M SCxC v. 61% controls
Imidazopyridines: Q203 - Telacebec (Qurient)								
	n/a	n/a	PK, safety, dose range: single + multiple doses [healthy volunteers]	I	?	Infectex/Qurient	Opened March 2016, results pending	
	Q203-TB-PI-US001	n/a	PK, safety, dose range: single doses [healthy volunteers]	Ia	56	Qurient US	Opened Aug 2015, completed Feb 2016	
	Q203-TB-PI-US002	NCT02858973	PK, safety, dose range: multiple doses [healthy volunteers, placebo, blinded]	Ib	24	Qurient US	Opened August 2016, results end 2017	
	STEP	n/a	Optimized dose R and Z + arm with Q203 v. 2HRZE/4RH [DS]	II c	600	EDCTP/PANACEA/Qurient	Opens Q1 2018	Univ. of Munich
3,4 Carbostyril Derivative: OPC-167832 (Otsuka)								
	n/a	n/a	PK, safety, dose range, EBA studies	HI	?	Otsuka	4 studies to open Oct 2016 through 2017	
Benzothiazinones (DprE1 inhibitor): PBTZ169 (Nearmedic Plus LLC)								
	PBTZ169-Z00-C01-1	NCT03036163	PK, safety, dose range healthy volunteers	I	35	Nearmedic Plus	Opened Jan 2016, results Nov 2016	
	PBTZ169	n/a	EBA [DR]	II	?	Nearmedic Plus	Opens late 2017	14 sites Russia
Beta-lactams/Carbapenems: Faropenem - F_{AC} (with amoxicillin/clavulanate), Meropenem - M_{AC} (with amoxicillin/clavulanate)								
	TASK-001	NCT02349841	2 wk EBA: M (2 gm IV tid) + AC tid v. F (600 mg po tid) + AC tid v. HRZE	EBA	46	Task (Diacon)/GSK	Opened Sep 2014, results CPTR Apr 2016	$Meropenem_{AC}$ showed EBA, F_{AC} low exposures
	Faropenem-TB	NCT02381470	6d EBA: F (400 mg po tid) + AC (600/125 mg po tid) v. H_{300} v. Z (2 gm) [DS]	EBA	28	NUH Singapore (Paton)	Opens July 2017, results Mar 2018	Philipines, Singapore
Thiazolides: Nitazoxanide - NTZ - N (Romark)								
	NTZ001	NCT02684240	2 wk EBA: N (1000 mg bid) + HRZE v. HRZE [DS, HIV-]	EBA	30	Cornell/GHESKIO (Pape)	Opened Feb 2016, results late 2017	Haiti
2 Month Treatment Shortening Strategies [DS]								
	TRUNCATE-TB	n/a	MAM8 2(multiple new regimens) v. 2HRZE/4HR	II/III	900	MRC/UCL (Paton/Philips)	Opens Q1 2017, results 2019	Thailand, Indonesia, Philipines, Singapore
4 Month Treatment Shortening Strategies [Minimal DS < 16 yrs]								
	SHINE	ISRCTN63579542	2HRZ(E)/2HR v. 2HRZE/4HR [DS, < 16 yrs, minimal disease, HIV-/+]	III	1200	MRC/UCL/DFID (Gibb)	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[37]

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)

D1

- Pyrazinamide
- Ethambutol
- High-dose isoniazid

D2

- Bedaquiline
- Delamanid

D3

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

*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 phase (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:

	However, nitazoxanide may also exert its effects via autophagy, as shown in the preclinical study by Gupta *et al*., 2016		NCT02684240
Nyaditum Resae®	Heat-killed *Mycobacterium manresesis* 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	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			
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]

	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 *Mtb* 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 *Mtb*. 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 *Mtb*-infected cells and bacterial reservoirs in the host	Vγ2Vδ2 TCR+ T cells (gamma-delta) were adoptively transferred to nonhuman primates infected with *Mtb*, 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 *Mtb* infection, IL-6 overproduction in advanced TB	Preclinical evidence that mice challenged with virulent *Mtb* 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	Ezetimibe is 2-azetidinone cholesterol absorption inhibitor that has deleterious effects on the intracellular life cycle of *Mtb*, and can augment anti-TB drug therapy	Ezetimibe was shown to reduce the growth of intracellular *Mtb* 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]
Aroylated phenylenediamines	As potent pharmacological	APDs were shown to	[15]

(APDs)	inducers of antimicrobial peptides i.e. LL-37, APDs can be crucial in the intracellular control of *Mtb* 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 *Mtb* by potentiating T-cell activity	Administration of tin protoporphyrin IX, an HO-1 inhibitor together with anti-TB drugs to *Mtb*-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 *Mtb* 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 *Mtb* 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 co-localisation of	[19]

		Microtubule-associated proteins 1A/1B light chain 3, which is involved in autophagolysosome formation, with *Mtb* 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 *Mtb* 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 *Mtb*-infected host cells	Preclinical evidence in a mouse model of TB showed that administration of ATRA, vitamin D3 and αGalCer lead to enhance anti-mycobacterial 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 *Mtb* 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 hyper-inflammation or mycobacterial persistence can augment standard TB drug treatment	Various genetic targets, including genes that allow *Mtb* 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 *Mtb*, in conjunction with standard drug therapy	Preclinical evidence of augmenting Myd88-dependent immune activation in *T. gondii* (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 (*Mtb* 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 *Mtb* antigen recognition	TCRs that can recognise a broad range of *Mtb* epitope can be used in developing T-cell products for infusion into patients	TCRVβ sequences from 22 individuals with LTBI analysed using grouping of lymphocyte interactions by paratope hotspots (GLIPH), leading to identification of motifs that allow for binding to shared antigenic ligands	[28]

FOR TABLE 4 ABOVE AS SUPPLEMENTAL ONLINE APPENDIX

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