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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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## **Search strategy and selection criteria**

We searched reports published in English between November 1<sup>st</sup> 2014 and November 1<sup>st</sup> 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, deltapazolid 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.<sup>1</sup> 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,<sup>1-6</sup> revealing the dire need for new therapies and approaches for improving TB treatment outcomes. Many challenges remain in developing optimal TB treatment regimens.<sup>7</sup> 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 fixed-dosed 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.<sup>25</sup> 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.<sup>45</sup> Moreover, an update of this study has shown that 84.4% of the 515 patients had a bacteriologically favourable outcome.<sup>40</sup> 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.<sup>46</sup>

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.<sup>61</sup> 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  $QT \geq 450$  msec was available for 35/329 cases (10%) and  $QT \geq 500$  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.<sup>62-64</sup> 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%;<sup>65</sup> phase 2 trial 213 (339 cases), 81.4%,<sup>66</sup> and programmatic use in Latvia (19 cases), 84.2%.<sup>67</sup> Results of the compassionate use cases are encouraging, with 53/66 cases (80%) achieving sputum culture conversion.<sup>68</sup>

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.<sup>71,72</sup> There are two trials which are currently recruiting patients however results are not expected till 2020-1.<sup>73,74</sup> 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.<sup>75,76</sup>

### **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).<sup>85</sup> 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.”<sup>86</sup> 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.<sup>87</sup> PHOENIX will begin Q1 2018 as an open label study.<sup>88</sup> TB-CHAMP will enrol 1,556 children age 5 and younger at sites in South Africa.<sup>89</sup>

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.<sup>90,91</sup> 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.<sup>90,91</sup> 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.<sup>92</sup> 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.<sup>93,94</sup> 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.<sup>95</sup>

## **TB IMMUNOTHERAPEUTIC TARGETS**

### **Glucocorticoids**

Glucocorticoids and receptor agonists, such as dexamethasone and prednisone, have anti-inflammatory 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.<sup>111</sup> 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.<sup>112-113</sup> There is insufficient data on the clinical and immunological impact of PDE inhibitors and further research is required.<sup>114</sup>

## **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.<sup>115</sup> Signalling via immune checkpoints inhibit T- and B-cell function<sup>116</sup>. Checkpoint inhibitors have been successfully employed in various cancers, specifically the monoclonal antibodies nivolumab and ipilimumab, against PD-1 and CTLA-4, respectively.<sup>117</sup> Inhibition of CTLA-4 enhances immune responses without improving bacillary clearance. Polymorphisms in *CTLA-4* were linked to TB susceptibility.<sup>118</sup> Inhibition of the PD1/PD-L1 pathway enhances *Mtb*-specific responses in humans,<sup>119</sup> but not in mice.<sup>120</sup> Immune checkpoint inhibition treatment can result in development of active TB disease. This is likely due to excessive inflammation and increased focal necrosis.<sup>121</sup> Trials on the use of checkpoint inhibitors which block the PD1/PD-L1 pathway as adjunct 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.<sup>129</sup> Imatinib, a tyrosine kinase inhibitor, reduces bacterial load and lung pathology, likely by enhancing autophagy, phagosomal acidification and myeloid cell mobilization,<sup>130-131</sup> 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.<sup>132</sup> AMPK is activated by metformin, a type-2 diabetes drug,<sup>133</sup> that reduces bacterial burden and ameliorates lung pathology in mice and humans by enhancing autophagy and increasing ROS production.<sup>92</sup> 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.<sup>134</sup>

## **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.<sup>146-147</sup> There is emerging evidence that miRNAs could serve as cancer immunotherapy and could serve as therapeutic targets in TB.<sup>148-149</sup>

## **Cytokines and proteases**

TNF- $\alpha$  is essential to granuloma integrity, macrophage antimicrobial activity and ROS-mediated *Mtb* killing.<sup>150</sup> TNF- $\alpha$  can however, also trigger cell necrosis and exacerbate inflammation, thereby aggravating TB pathology.<sup>151</sup> TNF- $\alpha$  blockers and anti-TNF- $\alpha$  monoclonal antibodies, such as thalidomide and infliximab, successfully control severe TB.<sup>152</sup> On the other hand, TNF- $\alpha$  inhibition destabilizes granulomas, reactivates *Mtb* bacilli and increases the risk of TB disease.<sup>153</sup> IFN- $\gamma$  is important to protective anti-TB immunity and administration has nominal benefit in drug-sensitive,<sup>154</sup> and drug-resistant TB.<sup>155</sup>

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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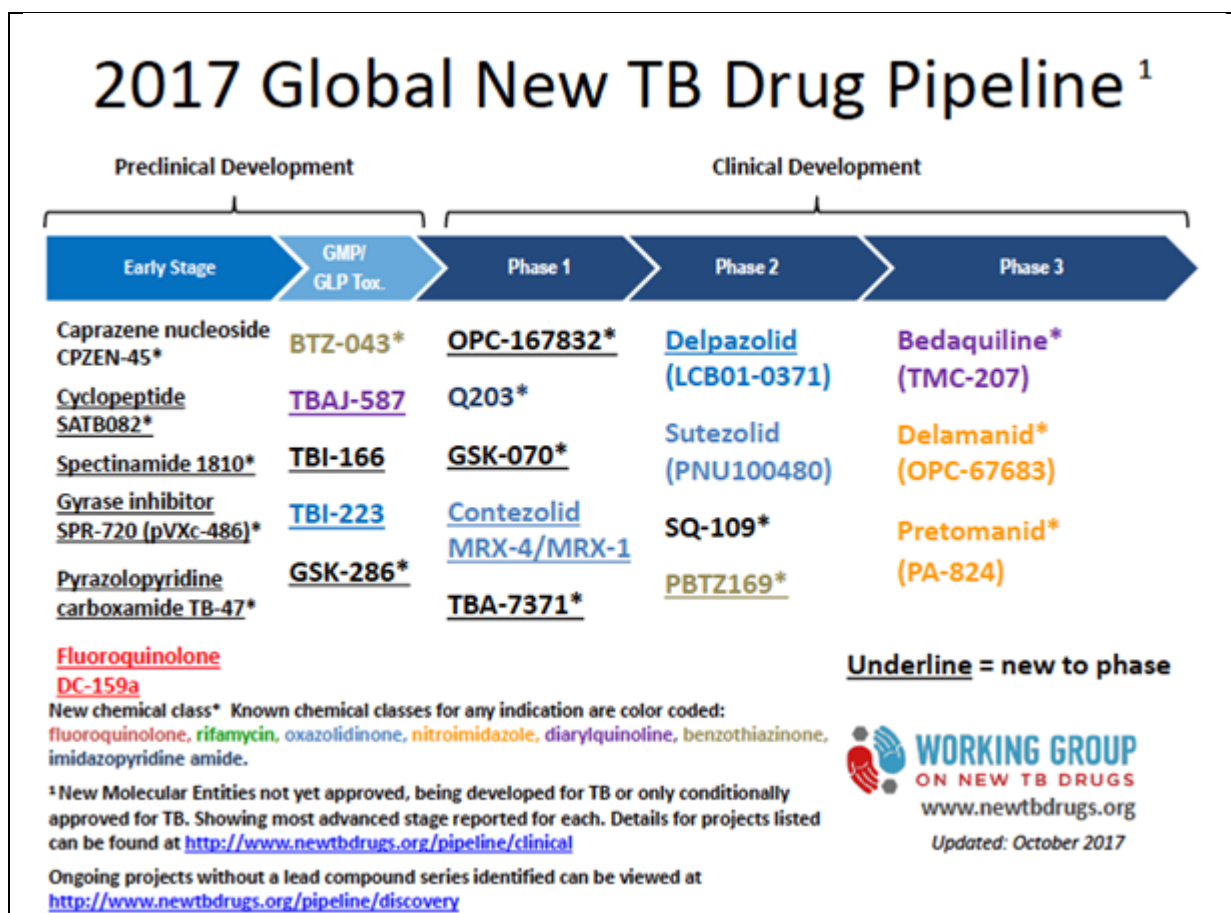


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Figure 1

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.pipelinerreport.org/sites/default/files/2017%20Pipeline%20Report%20Final.pdf>)

<b>Drug</b>	<b>Class</b>	<b>Target</b>	<b>Sponsor(s)</b>	<b>Phase</b>	<b>Notes</b>
<b>bedaquiline</b>	diarylquinolone	ATP synthase	Janssen, TB Alliance, NIAID, AMRC, The Union, Unitaid, USAID	III	Conditional marketing approval
<b>delamanid</b>	nitroimidazole	Inhibit cell wall synthesis and cell respiration	Otsuka, NIAID, Unitaid	III	Conditional marketing approval
<b>pretomanid</b>	nitroimidazole	Inhibit cell wall synthesis and cell respiration	TB Alliance	III	
<b>sutezolid</b>	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.
<b>SQ109</b>	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.
<b>PBTZ169</b>	DprE1 inhibitor	Inhibit cell wall synthesis	Nearmedic, iM4TB, BMGF	II	synergies with bedaquiline and clofazimine
<b>delpazolid LCB01-0371</b>	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.
<b>Q203</b>	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.
<b>TBI-166</b>	rimenophenzine	Outer membrane, bacterial respiratory chain and ion transporters	Institute of Materia Medica, TB Alliance	I	
<b>OPC-167832</b>	DprE1 inhibitor	Inhibit cell wall synthesis	Otsuka, BMGF	I	Co-developed with delamanid

<b>GSK 070, GSK 3036656</b>	oxaborole	Protein synthesis Leucyl-tRNA Synthetase	GlaxoSmithKline	I	
<b>TBA7371</b>	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 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)**

**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
<i>A. Clinical development phase (for TB)</i>			
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
<i>Mycobacterium w</i>	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 <i>et al.</i> , 2016		NCT02684240
Nyaditum Resae <sup>®</sup>	Heat-killed <i>Mycobacterium manresensis</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	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>B. Developmental pipeline- Basic/translational research phase</b>			
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	<sup>1</sup>
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	<sup>2</sup>

	in the granuloma	concomitant with reduced regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)	
Gefitinib	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	<sup>3</sup>
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	<sup>4</sup>
V $\gamma$ 2V $\delta$ 2 T-cell therapy	Adoptive transfer of gamma delta T cells for eradication of <i>Mtb</i> -infected cells and bacterial reservoirs in the host	V $\gamma$ 2V $\delta$ 2 TCR+ T cells (gamma-delta) were adoptively transferred to nonhuman primates infected with <i>Mtb</i> , resulting in heavily reduced bacterial dissemination	<sup>5</sup>
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	<sup>6</sup>
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	<sup>7-11</sup>

	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	<sup>12,13</sup>
Ezetimibe	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	<sup>14</sup>
Aroylated phenylenediamines	As potent pharmacological	APDs were shown to	<sup>15</sup>

(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	<sup>16</sup>
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	<sup>17</sup>
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	<sup>18</sup>
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- $\alpha$ production. Loperamide also increased the co-localisation of	<sup>19</sup>

		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	<sup>20</sup>
All-trans retinoic acid (ATRA), 1,25(OH) <sub>2</sub> -vitamin D <sub>3</sub> , and $\alpha$ -galactosylceramide ( $\alpha$ GalCer)	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 D <sub>3</sub> and $\alpha$ GalCer lead to enhance anti-mycobacterial activity, reduced relapse rates as well as increased TNF- $\alpha$ production in the lungs	<sup>21</sup>
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	<sup>22</sup>
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	<sup>23</sup>

	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 <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	<sup>24</sup>
<i>Toxoplasma gondii</i> 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	<sup>25</sup>
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- $\gamma$ responses to CMV/EBV antigens were indicative of extended survival	<sup>26</sup>
<i>Mtb</i> /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	<sup>27</sup>

CD4+ TCR motifs for shared <i>Mtb</i> antigen recognition	TCRs that can recognise a broad range of <i>Mtb</i> epitope can be used in developing T-cell products for infusion into patients	TCRV $\beta$ 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
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#### FOR TABLE 4 ABOVE AS SUPPLEMENTAL ONLINE APPENDIX

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