Tuberculosis remains the world’s leading cause of death from an infectious disease, responsible for an estimated 1·67 million deaths annually. WHO estimated 600 000 cases of rifampicin-resistant tuberculosis in 2016—of which 490 000 were multidrug resistant (MDR), with less than 50% survival after receiving recommended treatment regimens. Concerted efforts of stakeholders, advocates, and researchers are advancing further development of shorter course, more effective, safer, and better tolerated treatment regimens. We review the developmental pipeline and landscape of new and repurposed tuberculosis drugs, treatment regimens, and host-directed therapies (HDTs) for drug-sensitive and drug-resistant tuberculosis. 14 candidate drugs for drug-susceptible, drug-resistant, and latent tuberculosis are in clinical stages of drug development; nine are novel in phase 1 and 2 trials, and three new drugs are in advanced stages of development for MDR tuberculosis. Specific updates are provided on clinical trials of bedaquiline, delamanid, pretomanid, and other licensed or repurposed drugs that are undergoing investigation, including trials aimed at shortening duration of tuberculosis treatment, improving treatment outcomes and patient adherence, and reducing toxic effects. Ongoing clinical trials for shortening tuberculosis treatment duration, improving treatment outcomes in MDR tuberculosis, and preventing disease in people with latent tuberculosis infection are reviewed. A range of HDTs and immune-based treatments are under investigation as adjunctive therapy for shortening duration of therapy, preventing permanent lung injury, and improving treatment outcomes of MDR tuberculosis. We discuss the HDT development pipeline, ongoing clinical trials, and translational research efforts for adjunct tuberculosis treatment.

Introduction
In 2016, there were an estimated 10·4 million cases of tuberculosis with 1·67 million deaths, making tuberculosis the ninth leading cause of death worldwide.1 The 2017 WHO Global Tuberculosis Report estimated 490 000 cases of multidrug-resistant (MDR) tuberculosis, with less than 50% survival in patients who received recommended WHO treatment regimens.4 The Report reveals the dire need for new therapies and approaches for improving tuberculosis treatment delivery and management outcomes. Many challenges remain in developing optimal tuberculosis treatment regimens.2 Concerted efforts of stakeholders, advocates, and researchers are advancing the further development of shorter course, more effective, safer, and better tolerated treatment regimens. Only three novel drugs are in advanced stages of development for MDR tuberculosis, and nine are being assessed in phase 1 and 2 trials. In addition to new drugs, an array of immune-based treatments and host-directed therapies are under development aimed at eliminating Mycobacterium tuberculosis infection, shortening the duration of treatment, preventing permanent lung injury, and preventing development of new drug resistance. This Series paper provides updates on advances and progress in the development pipeline of new and repurposed tuberculosis drugs and host-directed therapies, addressing the unmet needs of treatment management for patients with tuberculosis (panel 1). In this Series paper we review ongoing clinical trials for shortening tuberculosis treatment, improving treatment outcomes in MDR tuberculosis, and preventing disease in people with latent tuberculosis infection. We also discuss tuberculosis drug resistance, treatment regimens, and host-directed therapies.
Specific issues regarding safety and toxicity, and drug–drug interactions.1–4 The organisations TB Alliance and WHO Stop TB Partnership provide more information about research and treatment of tuberculosis around the world.

Progress in the development of new drugs and treatment regimens

In the past 5 years, development of several new and repurposed antituberculosis drugs has accelerated with the approval of the first new antituberculosis drug in 35 years.1–4 The advent of diarylquinoline and the nitroimidazoles provides hope for an oral pan-tuberculosis regimen, based on potent specific drugs for which resistance is weak or non-existent. The line-up of the tuberculosis drug development pipeline, as of December, 2017, is shown in the figure. The class of drugs, their mechanisms of action, trial phase, and relevant sponsors are presented in table 1.5 PBTZ169 is now in phase 2 early bactericidal activity trials. A new compound, Q203, was assessed in a phase 1 trial completed in 2017, and TBA7371 entered a phase 1 trial in 2017. SQ109 appears to be sterilising in vitro but should not be used with rifampicin, which substantially reduces its levels. Interim results from a double-blind placebo-controlled trial in Russia, in patients with MDR tuberculosis, showed that at 24 weeks 80% of patients receiving SQ109 plus optimised background regimen were sputum negative compared with 61% patients receiving placebo plus regimen (p=0.048).16 However, with these advances there have also been some setbacks. Sutezolid yielded promising phase 2 trial results, but some stage 1 studies needed to be repeated because of licensing issues. AZD5847 and TBA–354 showed no activity in phase 1 studies and are associated with neurotoxicity.17

14 candidate drugs for drug-susceptible, MDR, and latent tuberculosis are in the clinical stages of drug development; nine are novel, and three have been approved (appendix).

Drug-susceptible tuberculosis

Treatments for patients with drug-susceptible tuberculosis last at least 6 months, requiring the patient to take on average ten pills a day during the intensive phase. WHO recommends treatment for drug-susceptible tuberculosis with an initial 2-month intensive phase (isoniazid, rifampicin, pyrazinamide, and ethambutol daily), continued by dual therapy isoniazid and rifampicin with an initial 2-month intensive phase (isoniazid, rifampicin, pyrazinamide, and ethambutol daily), continued by dual therapy isoniazid and rifampicin for the last 4 months. The whole course of treatment for the disease is around US$20, and treatment success in programmatic conditions is approximately 85%. Apart from the efficacy and economic value, the regimen is lengthy, hepatotoxic, and not well tolerated by a substantial proportion of patients prescribed the medication. 4-month standard regimens are, so far, only recommended by the American Thoracic Society for patients who are sputum smear and culture positive at shortening and simplifying regimens for drug-susceptible tuberculosis and improving management, including increasing patient adherence.18

Studies investigating the optimisation of the use of approved drugs with improved formulations and pill counts are also ongoing.19 More palatable fixed-dose combination tablets are now available for paediatric use, simplifying dosing in children weighing less than 25 kg,20 while improving drug delivery and drug adherence.21,22 Efforts are also being made to render the standard quadruple regimens less toxic. One study23 showed that liver toxicity was reduced when methionine

Panel 1: Unmet needs of tuberculosis treatment

A potent and cheap pan-tuberculosis treatment regimen that is well tolerated and can treat both drug-susceptible and drug-resistant disease without cumulative toxic drug effects or increased relapse rates

- Treatment regimens that can improve survival rates in patients with drug-resistant tuberculosis and with Mycobacterium tuberculosis–HIV coinfection

- A treatment regimen that is of short duration with minimal side-effects and low pill burden to improve patient acceptance and adherence, and reduce loss to follow-up and treatment failure

- Nearly 50% of patients treated for pulmonary tuberculosis develop long-term lung damage and functional disability (chronic cough, breathlessness, impaired lung function, and reduced longevity, despite treatment success); new strategies are required to prevent, manage, and perhaps reverse the loss in lung function

- Improved treatments for latent M tuberculosis infections due to drug-resistant strains

- Adjunct host-directed therapies with tuberculosis drug treatment to minimise or prevent long-term injury and long-term functional impairment

- Improved biomarkers to predict response to treatment, risk of relapse, assure cure, and accelerate drug development

- Better supply chain and delivery of drugs to the patients that need them—as of 2017, very few patients with drug-resistant tuberculosis have access to effective treatment

- Increased funder investments into development and assessment of new drugs, host-directed therapies, and biomarkers

Figure: Global new tuberculosis drug development pipeline

Adapted from Stop TB Partnership’s Working Group on New TB Drugs (October, 2017) with permission.27

*New chemical class. GMP=good manufacturing practice. †New to phase. GLP tox=good laboratory practice toxidology studies.

1 Caprane nucleoside
2 CIP52N–45
3 Cyclapcptide SAT1082
4 Spectinamide 1810
5 Gyrane inhibitor
6 Pyrazolopyridine carboxamide TBB–47
7 D-359
8 Oxazolidinone
9 Nitroimidazoline
10 Benzothiazinone
11 Diarylquinoline
12 Imidazopyridine amide
13 Rifamycin
14 Fluoroquinoline

Preclinical development

Early stage

Caprane nucleoside
CIP52N–45
Cyclapcptide SAT1082
Spectinamide 1810
Gyrane inhibitor
Pyrazolopyridine carboxamide TBB–47
DC–359

Clinical development

Preclinical development

Early stage

Caprane nucleoside
CIP52N–45
Cyclapcptide SAT1082
Spectinamide 1810
Gyrane inhibitor
Pyrazolopyridine carboxamide TBB–47
DC–359

Preclinical development

Early stage

Caprane nucleoside
CIP52N–45
Cyclapcptide SAT1082
Spectinamide 1810
Gyrane inhibitor
Pyrazolopyridine carboxamide TBB–47
DC–359

Clinical development

Phase 1

IBTZ 043
Q203
Delpazolid (LCBO-0371)
Bedaquiline (TMC-207)
Sutezolid (PN100480)
SQ109
PBTZ169
Rifapentine

Phase 2

OPC-16/8372
Q203†
GSK070†
Contezolid MRX-46/219
TBA7371†

Phase 3

Bedaquiline (TMC-207)
Sutezolid (PN100480)
Drotamid (OPC-6/7683)
Pretomanid (PA-842)

Table 1: Candidate drugs and their development status

Adapted from Stop TB Partnership’s Working Group on New TB Drugs (October, 2017) with permission.27

*New chemical class. GMP=good manufacturing practice. †New to phase.
and vitamin B complex were added to the standard regimen.

Research on rifampicin, which was introduced in the 1970s, is centred on determining the therapeutic window and assessing higher doses, which can achieve greater potency than lower doses. A phase 2 trial\(^a\) showed that 20 mg/kg of rifampicin did not increase efficacy when compared with 10 mg/kg of rifampicin and 15 mg/kg of rifampicin together with isoniazid, ethambutol, and pyrazinamide. The PanACEA trial (NCT01785186),\(^a\) the first multiarm multistage (MAMS) study of tuberculosis treatment, investigated 20 mg/kg and 35 mg/kg doses of rifampicin against a standard 10 mg/kg dose in patients with drug-susceptible tuberculosis. The 35 mg/kg dose was safe and the 35 mg/kg group had faster 8-week culture conversion times than both the 20 and 10 mg/kg groups, which might lead to shorter treatment durations. The addition of SQ109 or moxiﬂoxacin did not achieve superiority over the standard quadruple regimen.

The RIFASHORT (NCT02581527) and NC-006 STAND (NCT02342886) trials are focused on shortening the standard tuberculosis regimen, assessing the efficacy of high-dose rifampicin and an entirely new regimen. Rifapentine is being tested at a flat dose of 1200 mg daily in the Tuberculosis Trials Consortium (TBTC) Study 31/A5349; the phase 3 study will recruit 2500 patients

<table>
<thead>
<tr>
<th>Target</th>
<th>Sponsors</th>
<th>Phase</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Diaryquinoline</td>
<td>ATP synthase</td>
<td>Janssen, TB Alliance, NIAID, SAMRC, The Union, Unitaid, USAID</td>
<td>3</td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td>Delamanid</td>
<td>Cell wall synthesis and cell respiration</td>
<td>Otsuka, NIAID, Unitaid</td>
</tr>
<tr>
<td></td>
<td>Pretomanid</td>
<td>Cell wall synthesis and cell respiration</td>
<td>TB Alliance</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>Sutezolid</td>
<td>Protein synthesis (23s ribosome)</td>
<td>Pfizer, then Sequella, NIAID, Medicines Patent Pool, TB Alliance</td>
</tr>
<tr>
<td></td>
<td>Delpazolid</td>
<td>Protein synthesis (23s ribosome)</td>
<td>LegoChem Biosciences</td>
</tr>
<tr>
<td></td>
<td>Contezolid</td>
<td>Protein synthesis (23s ribosome)</td>
<td>MicoRX Pharmaceuticals</td>
</tr>
<tr>
<td>1,2-ethylene diamine</td>
<td>SQ109</td>
<td>Cell wall synthesis (MmpL3)</td>
<td>Sequella, PanACEA, Infectex</td>
</tr>
<tr>
<td>DprE1 inhibitor</td>
<td>PBTZ169</td>
<td>Cell wall synthesis</td>
<td>Nearmedic, IM4TB, BMGF</td>
</tr>
<tr>
<td></td>
<td>OPC-167832</td>
<td>Cell wall synthesis</td>
<td>Otsuka, BMGF</td>
</tr>
<tr>
<td></td>
<td>TBA7371</td>
<td>Cell wall synthesis</td>
<td>Eli Lilly, Foundation for Neglected Disease Research, TB Alliance</td>
</tr>
<tr>
<td></td>
<td>BTZ 043</td>
<td>Cell wall synthesis</td>
<td>University of Munich, PanACEA</td>
</tr>
<tr>
<td>Imidazopyridine</td>
<td>Q203</td>
<td>Cytochrome QcrB and cell respiration</td>
<td>Querient, Infectex, PanACEA</td>
</tr>
<tr>
<td>Riminophenazine</td>
<td>TBI-166</td>
<td>Ion transport and cell respiration</td>
<td>Institute of Materia Medica, TB Alliance</td>
</tr>
<tr>
<td>Oxaborole</td>
<td>GSK070, GSK 3016656</td>
<td>Protein synthesis (leucyl-tRNA synthetase)</td>
<td>GlaxoSmithKline</td>
</tr>
</tbody>
</table>

Ongoing and planned trials for drug-susceptible tuberculosis patients ≥50 kg and 450 mg for patients <50 kg) daily. CDC TBTC=Centers for Disease Control and Prevention Tuberculosis Trials Consortium. ACTG=AIDS Clinical Trials Group. MAMS=multiarm multistage trial.

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-006 STAND (NCT02342886)</td>
<td>3</td>
<td>271 (of original target of 1200), HIV- and HIV+ adults (aged ≥18 years)</td>
<td>4 months pretomanid (100 mg twice daily or 200 mg once daily), moxifloxacin, pyrazinamide daily, or 6 months pretomanid (100 mg twice daily), moxifloxacin, pyrazinamide daily, or 6 months pretomanid (200 mg once daily), moxifloxacin, pyrazinamide daily vs standard 6 month therapy</td>
<td>Opened February 2015 (paused October 2016–May 2017); accrual not resumed, results March 2018; TB Alliance</td>
</tr>
<tr>
<td>APT (NCT02256696)</td>
<td>2</td>
<td>183, HIV- adults (aged ≥18 years)</td>
<td>2 months pretomanid, rifabutin, isoniazid, pyrazinamide daily, and 1 month pretomanid, rifabutin, isoniazid daily, or 2 months pretomanid, rifampicin, isoniazid, pyrazinamide daily, and 1 month pretomanid, rifampicin, isoniazid daily vs 2 months isoniazid, rifampicin, pyrazinamide, ethambutol daily, and 1 month isoniazid, rifampicin daily</td>
<td>Opened April, 2015 (paused October, 2016–May, 2017), results 2019; John Hopkins University, University of Cape Town Lung Institute</td>
</tr>
<tr>
<td>TBTC 31/A5349 (NCT02410772)</td>
<td>3</td>
<td>2500, HIV– adults and children (aged ≥13 years)</td>
<td>2 months isoniazid, rifampetine (1200 mg), pyrazinamide, and ethambutol daily, and 2 months isoniazid and rifapetine (1200 mg) daily, or 2 months isoniazid, rifapetine (1200 mg), pyrazinamide, and moxifloxacin daily, and 2 months isoniazid, rifapetine (1200 mg), and moxifloxacin daily vs standard 6 month therapy</td>
<td>Opened January, 2016; accrual to close at the end of 2018; results 2020; substudies include interactions of rifapentine and efavirenz, intensive pharmacokinetics and pharmacodynamics of rifapentine, and sputum biomarkers to predict outcomes; CDC TBTC, ACTG</td>
</tr>
<tr>
<td>SHINE (ISRCTN63579542)</td>
<td>3</td>
<td>1200, HIV- and HIV+ children (aged &lt;16 years) with minimal disease</td>
<td>2 months isoniazid, rifampicin (600 mg), pyrazinamide, and (in some) ethambutol daily, and 2 months isoniazid and rifampicin (600 mg) daily vs standard 6 month therapy</td>
<td>Opened third quarter of 2016, results 2020; treatment shortening strategy trial for children with minimal tuberculosis; India, Uganda, South Africa, and Zambia; BMRC</td>
</tr>
<tr>
<td>RIFASHORT (NCT02353527)</td>
<td>3</td>
<td>800, HIV– adults (aged ≥18 years)</td>
<td>2 months isoniazid, rifampicin (1200 or 1800 mg), pyrazinamide, and ethambutol daily, and 2 months isoniazid and rifapentine (1200 or 1800 mg) daily vs standard 6 month therapy</td>
<td>Opened February, 2012; results January, 2020; St George’s London, INTERTB</td>
</tr>
<tr>
<td>TRUNCATE-TB</td>
<td>2/3</td>
<td>900, HIV- and HIV+ adults (aged ≥18 years)</td>
<td>2 months various new regimens vs standard 6 month therapy</td>
<td>Opened late 2017, results 2021; MAMS adaptive trial design; Thailand, Indonesia, Philippines, and Singapore; BMRC, NUS</td>
</tr>
<tr>
<td>HIGHRIF 1 Extension (NCT01392911)</td>
<td>2</td>
<td>30, HIV- adults (aged ≥18 years)</td>
<td>EBA safety, tolerability, pharmacokinetics study: 14 days rifapentine 50 mg/kg (3000 mg) daily</td>
<td>Opened September, 2017, results mid-2018; PanACEA</td>
</tr>
<tr>
<td>STEP</td>
<td>2c</td>
<td>600, HIV- adults (aged ≥18 years)</td>
<td>3-4 months isoniazid, rifampicin (600 mg), pyrazinamide, and Q203 daily, or 2-3 months isoniazid, rifapentine (high dose), pyrazinamide (high dose), and Q203 daily vs standard 6 month therapy</td>
<td>Opens mid-2018, results 2021, adaptive trial design, examining new treatment backbones; PanACEA</td>
</tr>
<tr>
<td>NC-008 SimpliciTub (NCT03338621)</td>
<td>2c/3</td>
<td>300, HIV- and HIV+ adults (aged ≥18 years)</td>
<td>4 months bedaquiline, pretomanid, moxifloxacin, pyrazinamide vs standard 6 month therapy</td>
<td>Opens August, 2018, results 2022; TB Alliance</td>
</tr>
</tbody>
</table>

Standard 6 month therapy is 2 months isoniazid, rifampicin (600 mg for patients ≥50 kg and 450 mg for patients <50 kg), pyrazinamide, ethambutol daily, and 4 months isoniazid and rifampicin (600 mg for patients ≥50 kg and 450 mg for patients <50 kg) daily. CDC TBTC=Centers for Disease Control and Prevention Tuberculosis Trials Consortium. ACTG=AIDS Clinical Trials Group. MAMS=multiarm multistage trial. BMRC=British Medical Research Council. NUS=National University of Singapore. EBA=early bactericidal activity. PanACEA=Pan African Consortium for the Evaluation of Antituberculosis Antibiotics.

Table 2: Ongoing and planned trials for drug-susceptible tuberculosis without HIV and those living with HIV with CD4 count above 100 cells per μL. The first experimental group includes rifapentine and isoniazid for 4 months, with ethambutol and isoniazid for the first 2 months. The second experimental group replaces ethambutol with 4 months of moxifloxacin. The control group is the standard 6-month therapy. The TRUNCATE-TB⁷ is a phase 2c open-label MAMS trial assessing the treatment of drug-susceptible tuberculosis in just 2 months, administering high-dose rifampicin, bedaquiline, delamanid, and linezolid in different combinations over five experimental groups. Treatment is extended to 12 weeks if study participants are still symptomatic or smear positive at week 8. Moxifloxacin is often used as a substitute for isoniazid or ethambutol in patients with mono- or poliresistant tuberculosis, or in patients with intolerability or contraindications (or both); however, moxifloxacin did not show potency in shortening regimens. Concomitant rifampicin reduces concentration of moxifloxacin in the blood by up to 31%, so higher doses of moxifloxacin might be required.²⁹ Concerns over QT prolongation have led to new studies to investigate the phenomenon. 1602 patients from the OFLOTUB cohort (NCT00216385)³⁰ to investigate the phenomenon. 1602 patients from the OFLOTUB cohort (NCT00216385)³⁰ who had received quinolone-containing regimens contributed to the analysis of Fridericia’s formula (QTcF) by treatment group in an extensive survey of QT prolongation. Neither a standard 6-month nor a 4-month gatifloxacin-based regimen seemed to carry a sizeable risk of QT prolongation in patients with newly diagnosed pulmonary tuberculosis. Gatifloxacin, a component of the Bangladesh regimen, is no longer on the WHO
essential drug list due to concerns over dysglycaemia, and it has been replaced in the shorter drug regimen by moxifloxacin, a drug which is known to prolong QTc. 36

Drug-resistant tuberculosis

The taxonomy of antituberculosis drugs and their combinations is undergoing a rapid transformation as a result of new clinical trials data and meta-analyses.37,38 The updated classification of new antituberculosis drugs by WHO (panel 2) guides physicians in constructing an effective drug-resistant treatment regimen that is patient specific, based on a minimum of four active drugs.33 The regimen recommends two core drugs (a later-generation fluoroquinolone and an injectable aminoglycoside), and then the addition of other core drugs (eg, ethionamide or prothionamide, cycloserine or terizidone, linezolid, and clofazimine); if further drugs are required because of resistance or intolerance, then non-core drugs such as bedaquiline (especially if the patient is quinolone resistant) or delamanid should be added (combination of these two drugs is not recommended). Non-core drugs, such as para-aminosalicylic acid, carbapenems with clavulanate are reserved for patients with extensively drug-resistant (XDR) tuberculosis, with few therapeutic options. Pyrazinamide and ethambutol might be added, but they should not be counted as active drugs in the regimen.33,34 A retrospective study35 showed that the use of rifabutin was associated with improved treatment outcomes compared with no rifabutin treatment in patients with MDR tuberculosis. At least 20 new drugs are estimated to be required in phase 1 and 2 trials to ensure that a few progress to phase 3 assessment. With research investment being at its lowest amount since 2008, more resources are urgently required.36

Table 3 summarises the ongoing drug trials aimed at shortening and simplifying regimens for drug-resistant tuberculosis. Three drugs are in phase 3: bedaquiline, delamanid, and pretomanid, of which delamanid and pretomanid are nitroimidazoles and unlikely to be used together. Nine candidates are in phase 1 and 2 studies; five of the drugs are from two classes (oxazolidinones and DprE1 inhibitors). Sutezolid and delpazolid are two newer generation oxazolidinones in early clinical trials that are anticipated to be just as effective as linezolid, but less toxic.

Bedaquiline

Bedaquiline (a diarylquinoline inhibiting ATP synthase), delamanid, and pretomanid are being investigated in some novel trials that are assessing their use as single drugs and in combination. By October, 2017, an estimated 12 194 patients had received bedaquiline.37 The WHO caution on the potential toxic effects of bedaquiline originated from the observation of ten unexpected late deaths in the bedaquiline group of the C208 phase 2b trial.38 A systematic review39 of published results from 1293 patients treated with bedaquiline reported that QTc was greater than 450 ms for 35 (11%) of 329 people, and greater than 500 ms for 42 (3%) of 1293 people. In 44 (3%) of 1293 people, bedaquiline was stopped because of adverse events. In eight (1%) of 857 people, bedaquiline was discontinued specifically because of QT prolongation. Of these eight participants, two were restarted non-bedaquiline-related arrhythmia. Importantly, a

Panel 2: WHO categorisation of second-line antituberculosis drugs recommended for treatment of rifampicin-resistant and multidrug-resistant tuberculosis33

Group A: fluoroquinolones
- Levofoxacin
- Moxifloxacin
- Gatifloxacin

Group B: second-line injectable drugs
- Amikacin
- Capreomycin
- Kanamycin
- Streptomycin*

Group C: other core second-line drugs
- Ethionamide or prothionamid
- Cycloserine or terizidone
- Linezolid
- Clofazimine

Group D: add-on drugs (not part of the core multidrug-resistant 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†

*Caution: streptomycin is frequently resistant and unlikely to be active against drug-resistant tuberculosis. †Thioacetazone can give serious adverse events. HIV-negative status needed before administering thioacetazone. Not to be administered to people who are HIV-positive.
significant clinical interaction appears to occur between rifamycins and bedaquiline, leading to a reduction in concentration of bedaquiline in the blood. As a result, the combined use of these two drugs are restricted in their use to treat drug-sensitive tuberculosis.

**Delamanid**

By October, 2017, 976 patients had received delamanid, made available by Otsuka, for a compassionate use programme that used approval processes of the European Respiratory Society–WHO Tuberculosis Consilium, Médecins Sans Frontières (MSF), and others. The Otsuka proprietary delamanid studies yielded consistent favourable outcomes (eg, sputum smear and conversion): phase 2 trial 204, 143 (74%) of 192 people; phase 3 trial 213, 276 (81%) of 339 people; and programmatic use in Latvia, 17 (84%) of 19 people. Results of these compassionate use programmes are encouraging, with 53 (80%) of 66 patients achieving sputum culture conversion. The efficacy and safety of the use of

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
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<tr>
<td>Otsuka Trial 213 (NCT01424450)</td>
<td>3 511, HIV- adults (aged ≥18 years)</td>
<td>2 months delamanid (100 mg twice daily) and 4 months delamanid (200 mg daily) plus OBR vs 6 months placebo plus OBR</td>
<td>Opened September 2011, completed June, 2016, preliminary findings presented at IUATLD October, 2017, confirm efficacy with less toxicity, results mid-2018; Otsuka at IUATLD October, 2017, results mid-2018; IUATLD, BMRC, USAID</td>
</tr>
<tr>
<td>STREAM Stage 1 (ISRCTN/832190)</td>
<td>3 424, HIV- and HIV + adults (aged ≥18 years)</td>
<td>4 months daily moxifloxacin, clofazimine, pyrazinamide, ethambutol, isoniazid (high dose), kanamycin (daily for 3 months, then 3 times per week), prothionamide, and 5 months of moxifloxacin, clofazimine, pyrazinamide, ethambutol daily</td>
<td>Opened 2012, closed to accrual June, 2015, preliminary findings presented at IUATLD October, 2017, results mid-2018; IUATLD, BMRC, USAID</td>
</tr>
<tr>
<td>NC-005 (NCT02193776)</td>
<td>2b 60, HIV- adults (aged ≥18 years)</td>
<td>Serial sputum culture counts: 8 weeks bedaquiline (200 mg daily), pretomanid (200 mg daily), moxifloxacin, pyrazinamide, single arm study with long follow-up</td>
<td>Opened November, 2014, preliminary findings presented at CROI, 2017, results mid-2018; TB Alliance</td>
</tr>
<tr>
<td>OPTI-Q (NCT01918397)</td>
<td>2 100, HIV- and HIV + adults (aged ≥18 years)</td>
<td>6 months levofloxacin (14, 17, or 20 mg/kg/d) plus OBR vs 6 months levofloxacin (11 mg/kg/d) plus OBR</td>
<td>Opened January, 2015, results mid-2018; South Africa, Peru; NIAID, Boston University, CDC TBTC</td>
</tr>
<tr>
<td>NC-006 STAND (NCT02342886)</td>
<td>3 13 (of original target of 300), HIV- and HIV+ children (aged ≥14 years)</td>
<td>6 months pretomanid (200 mg), moxifloxacin, pyrazinamide daily, single arm study</td>
<td>Opened February, 2015, paused October, 2016–May, 2017, accrual not resumed, results March, 2018; TB Alliance</td>
</tr>
<tr>
<td>NIX-TB (NCT02333799)</td>
<td>3 109 (of original target of 300), HIV- and HIV + adults (aged ≥18 years)</td>
<td>6 months bedaquiline (200 mg daily for 2 weeks then 200 mg three times weekly), pretomanid (200 mg daily), linezolid (600 mg daily for 2 months), single arm study</td>
<td>Opened March, 2015, preliminary findings presented at CROI, 2017, accrual closed November, 2012, with opening of NC-007 XeNIX trial; TB Alliance</td>
</tr>
<tr>
<td>NExt-5001 (NCT02454205)</td>
<td>2/3 300, HIV- and HIV + adults (aged ≥18 years)</td>
<td>6–9 months bedaquiline, linezolid, levofloxacin, pyrazinamide, and either high-dose isoniazid or ethionamide or terizidone daily (all oral) vs 6–8 months kanamycin, moxifloxacin, pyrazinamide, ethionamide, terizidone daily, and 16–18 months moxifloxacin</td>
<td>Opened October, 2015, results January, 2019; University of Cape Town</td>
</tr>
<tr>
<td>MOR-END (NCT02019994)</td>
<td>2 238, HIV- and HIV + adults (aged ≥18 years)</td>
<td>9 or 12 months delamanid, levofloxacin (750 or 1000 mg), linezolid (600 mg daily for 2 months, 300 mg daily thereafter) vs local regimen</td>
<td>Opened January, 2016, results December, 2019; Korea</td>
</tr>
<tr>
<td>STREAM Stage 2 (NCT02403930)</td>
<td>3 2155, HIV- and HIV + adults (aged ≥18 years)</td>
<td>9 months moxifloxacin, clofazimine, ethambutol, pyrazinamide daily, with initial 2 months isoniazid, kanamycin, prothionamide daily, or 9 months bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose), pyrazinamide daily (all oral), or 6 months bedaquiline, clofazimine, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose) and kanamycin vs 20–24 month local regimen</td>
<td>Opened April, 2016, results April, 2021; IUATLD, BMRC, USAID; TB Alliance</td>
</tr>
<tr>
<td>Janssen C211 (NCT02354014)</td>
<td>2 60, HIV- adults (aged ≥18 years)</td>
<td>Pharmacokinetics, safety, dose-range 6 months bedaquiline (daily for 2 weeks, then 3 times a week) plus OBR, single arm study</td>
<td>Opened May, 2016, results March 2021, India, Philippines, Russia, South Africa, Janssen</td>
</tr>
<tr>
<td>ACTG65343 DELIBERATE (NCT0253048)</td>
<td>2 84, HIV- and HIV + adults (aged ≥18 years)</td>
<td>Pharmacokinetics, QTC 6 months bedaquiline daily plus OBR, or 6 months bedaquiline daily plus OBR, or 6 months bedaquiline and delamanid daily plus OBR</td>
<td>Opened August, 2016, results 2019; ACTG</td>
</tr>
<tr>
<td>endTB (NCT02754765)</td>
<td>3 750, HIV- and HIV + adults (aged ≥18 years)</td>
<td>9 months bedaquiline, linezolid, moxifloxacin, pyrazinamide daily, or 9 months of bedaquiline, linezolid, clofazimine, levofloxacin, pyrazinamide daily, or 9 months of delamanid, linezolid, clofazimine, levofloxacin, pyrazinamide daily, or 9 months of delamanid, linezolid, clofazimine, levofloxacin, pyrazinamide daily vs local regimen</td>
<td>Opened December, 2016, results September, 2020; Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, MSF, Partners in Health</td>
</tr>
<tr>
<td>TB-PRACTECAL (NCT02538972)</td>
<td>2/3 630, HIV- and HIV + adults (aged ≥18 years)</td>
<td>6 months bedaquiline, pretomanid, moxifloxacin, linezolid daily, or 6 months bedaquiline, pretomanid, linezolid, clofazimine daily, or 6 months bedaquiline, pretomanid, linezolid daily (all oral) vs local regimen</td>
<td>Opened January, 2017, results March, 2021; Belarus, South Africa, Uzbekistan; MSF</td>
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</table>

(Table 3 continues on next page)
Although WHO does not recommend this combination, bedaquiline in combination might well be tolerated. Delamanid has few drug–drug interactions and might be useful in patients who are co-infected with HIV, and who have a higher risk of developing resistance. Delamanid has an excellent safety profile, making it a useful companion to other drugs in a regimen and useful for reducing the development of resistance. Delamanid has few drug–drug interactions and might be useful in patients who are co-infected with HIV, and who have a higher risk of being unresponsive to treatment than those with tuberculosis alone.

Reports indicate that treatment with delamanid and bedaquiline in combination might well be tolerated. Although WHO does not recommend this combination because of concerns that bedaquiline and delamanid, which both prolong QT, would have potential detrimental effects in patients, it recognises that physicians might require guidance and has provided recommendations, including active safety drug monitoring, which itself might assist more rapid phase 4 safety data collection. Two trials (NCT02583048, NCT02754765) will study the co-administration of these two drugs. The AIDS Clinical Trials Group study51 A5343 DELIBERATE includes three administration of these two drugs. The AIDS Clinical Trials Group study51 A5343 DELIBERATE includes three trials (NCT02583048, NCT02754765) will study the co-administration of these two drugs. The AIDS Clinical Trials Group study51 A5343 DELIBERATE includes three

### Table 3: Ongoing and planned treatment trials for drug-resistant tuberculosis

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPAACT P1108 (NCT0141060)</td>
<td>2 72, HIV- and HIV+ children (aged ≤18 years)</td>
<td>Pharmacokinetics, safety, dose-range 6 months bedaquiline (daily for 2 weeks, then 3 times a week) plus OBR, single arm study</td>
<td>Opened June, 2017, results June, 2020, Haiti, India, South Africa; IMPAACT</td>
</tr>
<tr>
<td>NC-007 ZeNiX (NCT03084886)</td>
<td>3 180, HIV- and HIV+ adults and children (aged ≥14 years)</td>
<td>2 or 6 months linezolid (600 or 1200 mg daily, double-blinded), bedaquiline (200 mg daily for 2 weeks, then 100 mg daily), and pretomanid (200 mg daily)</td>
<td>Opened November, 2017, results January, 2021</td>
</tr>
<tr>
<td>IMPAACT 2005 (NCT03141060)</td>
<td>1/2 40, HIV- and HIV+ children (aged ≤18 years)</td>
<td>Pharmacokinetics, safety 6 months delamanid (100 mg twice daily) plus OBR, single arm study</td>
<td>Opened January, 2018, results April, 2021, Botswana, India, South Africa, Tanzania; IMPAACT</td>
</tr>
<tr>
<td>ACTG A5356</td>
<td>2a 240, HIV- and HIV+ adults (aged ≥18 years)</td>
<td>6 months delamanid (100 mg twice daily), linezolid (300 or 600 mg daily or 1200 mg every other day) plus OBR (oral) vs 6 months delamanid (100 mg twice daily) plus OBR (injectable)</td>
<td>Opens August, 2018; ACTG</td>
</tr>
<tr>
<td>NC-008 SimpliciTB (NCT03358621)</td>
<td>3 150, HIV- and HIV+ adults (aged ≥18 years)</td>
<td>6 months bedaquiline, pretomanid, moxifloxacin, pyrazinamide daily, single arm study</td>
<td>Opens August, 2018, results March 2022; TB Alliance</td>
</tr>
</tbody>
</table>

depending on whether the *M tuberculosis* strain was susceptible to the drugs in the regimen. Clearance was also up to three-times faster than the comparison group on standard quadruple therapy. Regimens with bedaquiline, pretomanid, and pyrazinamide, along with moxifloxacin, reduce pill burden and might be potent enough to reduce treatment duration to 3 months in total. The regimen of bedaquiline, pretomanid, and pyrazinamide with moxifloxacin could be advantageous for patients with MDR tuberculosis by offering a shorter injectable-free regimen that might be able to treat the majority of patients. The NC-008 SimpliciTB study (NCT03338621) will investigate a 4-month regimen of bedaquiline, pretomanid, and pyrazinamide with moxifloxacin in patients with drug-susceptible tuberculosis versus standard isoniazid, rifampicin, pyrazinamide, and ethambutol plus this combination for 6 months in patients with MDR tuberculosis.

### Repurposed drugs

The antileprosy drug clofazimine has shown sterilising and treatment-shortening potential. A new rimino-phenazine, TBI-166, has entered phase 1 trials (table 1) and will hopefully not produce skin discoloration, a common side-effect of clofazimine. A sizeable programmatic study in Brazil used clofazimin in a standardised 2006 MDR tuberculosis regimen, replacing pyrazinamide. 1446 patients were treated with clofazimine-containing regimens and 1096 with pyrazinamide-containing regimens. The clofazimine-containing regimen was found to have similar success to the pyrazinamide-containing regimen, but more patients in the clofazimine group responded to treatment and fewer were lost to follow-up. Bedaquiline and clofazimine have been shown to have cross-resistance with the mutation in Rv0678, leading to increased removal of these drugs by the MmpL5 efflux pump.

Meta-analyses and systematic reviews of the use of carbapenems (ertapenem, imipenem, meropenem) for treatment of MDR and XDR tuberculosis on the basis of clinical necessity indicate a role for their use in tuberculosis treatment. They appear very active with excellent tolerability and safety records. However, the absence of an active oral formulation and the need for the MmpL5 efflux pump. Linezolid, an oxazolidinone, has shown antimycobacterial efficacy and is included in many drug trial regimens. Its toxicity profile has restricted its use beyond drug-resistant tuberculosis. In-vitro model dose-ranging studies have identified optimal linezolid doses for use in combination therapy, maximising bactericidal activity, while avoiding toxic effects. Ongoing pharmacokinetic and pharmacodynamic studies are clarifying many dosing issues associated with new or repurposed drugs.

### Newer regimens for drug-resistant tuberculosis

**Injectable-free regimens**

Newer treatment regimens for MDR tuberculosis are focused on assessment of injectable-free regimens to reduce the substantial toxic effects (ototoxicity and nephrotoxicity), simplify the logistics of administration of injectable drugs, and improve patient adherence. The NeXT trial (NCT02454205) compares a new, all oral 6–9 month regimen of bedaquiline, linezolid, levofloxacin, and pyrazinamide, with either high-dose isoniazid or ethionamide or terizidone daily, with the standard WHO treatment regimen of 21–24 months, in patients with MDR tuberculosis.

### Shorter treatment regimens

A standardised Bangladesh regimen (high-dose gatifloxacin, clofazimine, ethambutol, and pyrazinamide supplemented by prothionamide, kanamycin, and double-dose isoniazid during the 4-month intensive phase) cured 181 (87·9%, 95% CI 82·7–91·6) of 206 people, with no relapses. A further study reported a bacteriologically favourable outcome in 435 (84%) of 515 people. WHO, in 2016, subsequently recommended a shorter, standardised 9–12-month regimen for people with pulmonary MDR or rifampicin-resistant tuberculosis susceptible to aminoglycosides and fluoroquinolones. Exclusion criteria include pregnancy, extrapulmonary cases, and patients who underwent previous treatment with second-line drugs. The 4–6-month intensive phase includes moxifloxacin, an injectable (amikacin or kanamycin), ethionamide or prothionamide, clofazimine, high-dose isoniazid or ethambutol, and pyrazinamide, and the 5-month continuation phase includes moxifloxacin, clofazimine, ethambutol, and pyrazinamide. The only difference between the Bangladesh regimen and the WHO shorter regimen is the substitution of gatifloxacin for moxifloxacin. A meta-analysis reported the effectiveness of this regimen for treating MDR tuberculosis, although quinoline resistance was associated with unsuccessful treatment and relapse (odds ratio 46, 95% CI 8–273). Several research centres have attempted to foresee what effect the shorter regimen would have in their setting—a subject that is much debated.

The phase 3 STREAM Stage 1 trial assessed the 2011 WHO standard MDR tuberculosis regimen (20–24 months), and compared it with the current WHO MDR tuberculosis
regimen (9 months). Although interim results suggest the more recent regimen is not non-inferior, it might be a good option for selected patients because treatment success was achieved in 78.1% of participants with the regimen compared with 80.6% in the individualised 20–24-month regimen. Severe adverse events were similar in both groups, although a higher frequency of cardiac conduction disorders was observed in patients who received the shorter 9-month regimen. A phase 3 STREAM Stage 2 trial (NCT02409290) is establishing whether bedaquiline could play a part in a shorter regimen, by comparing 6-month and 9-month all-oral bedaquiline-containing regimens against the locally used WHO-approved MDR tuberculosis regimen, and the 18-month WHO MDR tuberculosis regimen—results are expected in 2021.

The NiX-TB trial (NCT02333799) assessed a 6-month regimen of bedaquiline, pretomanid, and linezolid (600 mg twice daily). For situations in which a patient does not culture convert by month 4, the regimen is prolonged (600 mg twice daily). For situations in which a patient does not culture convert by week 8 and 100% by week 16.77 In November, whereas early mortality was reported in four participants, relapse-free cure to date was 26 (87%) of 30 participants, follow-up. The proportion of patients who have achieved a 6-month treatment course, with 31 reaching 6-month enrolment in the study, 70 of whom had completed the to 9 months. As of October, 2017, 109 participants were not culture convert by month 4, the regimen is prolonged against the locally used WHO-approved MDR tuberculosis regimen, and the 18-month WHO MDR tuberculosis regimen—results are expected in 2021.

The NiX-TB trial (NCT02333799) assessed a 6-month regimen of bedaquiline, pretomanid, and linezolid (600 mg twice daily). For situations in which a patient does not culture convert by month 4, the regimen is prolonged to 9 months. As of October, 2017, 109 participants were enrolled in the study, 70 of whom had completed the 6-month treatment course, with 31 reaching 6-month follow-up. The proportion of patients who have achieved a relapse-free cure to date was 26 (87%) of 30 participants, whereas early mortality was reported in four participants in the first 2 months. 65% people achieved culture conversion by week 8 and 100% by week 16. In November, 2017, NiX-TB rolled over into the new NC-007 ZeNiX trial (NCT0258972), which includes a dose-ranging study for linezolid. The TB-PRACTECAL (NCT02589782) is an adaptive-design study assessing culture conversion at week 8, outcome, and safety of a short regimen (6 months) versus the WHO-recommended MDR tuberculosis regimen (locally used and accepted), including bedaquiline, pretomanid, and linezolid, with or without moxifloxacin or clofazimine, to treat adults with MDR or XDR tuberculosis. The endTB is an MSF and UNITAID study (NCT02754765) that aims to develop one to three priority regimens for the treatment of MDR and XDR tuberculosis and to increase access to bedaquiline and delamanid. The study is a phase 3 trial comparing five experimental groups with a standard-of-care control, which may include delamanid or bedaquiline. High rates of culture conversion at 6 months and low culture reversion rates at 12 months are preliminary findings.76

**Advances and progress in host-directed therapies**

Effective host immunity prevents *M tuberculosis* from causing disease in most individuals. Waning host defence leads to increased susceptibility to disease and poor treatment outcomes as illustrated by *M tuberculosis* and HIV co-infection. Augmentation of beneficial immune responses might serve as useful adjunct therapy to tuberculosis drug-treatment regimens.84 Host-directed therapy (HDT) approaches (table 5) are now a focus for use as adjunct treatment options for MDR tuberculosis, for shortening treatment duration, limiting immunopathology by modulating aberrant *M tuberculosis*-induced immune responses, and improving treatment outcomes.85 Immunotherapy is revolutionising cancer treatment, and similar host pathways operational in tuberculosis are being investigated. Three main approaches are being taken forward for HDT as adjunct therapy for tuberculosis treatment: amplification of host immunity, modulation of inflammation to reduce lung tissue destruction, and killing or containment of *M tuberculosis*.

Small-molecule drugs and enzymes that have therapeutic value in metabolic diseases are being investigated for their usefulness as HDTs. Metformin has been shown to augment immune effector function and reduce *M tuberculosis* burden in preclinical tuberculosis models.86 Other HDTs being assessed are commonly used over-the-counter drugs that are safe and cheap, such as aspirin, indomethacin, as well as vitamins and biological compounds—eg, flavonoids and stilbenoids. Therapeutic antibodies targeting cell surface molecules of *M tuberculosis*-infected cells, or molecules that neutralise circulating proteins detrimental to protective immunity, are being developed as HDT options for use as adjuncts with antituberculosis treatment regimens. Exosomes released by T and B lymphocytes might enhance anti-*M tuberculosis* immune reactivity. MHC-peptide complexes, micro RNA, and fragments of DNA, as well as apoptosis inducers such as Fas ligand, could play an overall part in immunomodulation.84,85 Translational studies incorporating novel technologies, such as tissue-embedded microchips and ex-vivo three-dimensional culture models, are underway for studying HDTs88 (for further preclinical and translational research HDT strategies see appendix).

**Updates on tuberculosis drugs for latent infection**

Clinicians and patients have long desired shorter, more tolerable, and safer alternatives for treatment of latent tuberculosis infection than standard daily isoniazid for 9 months or more. In 2011, the phase 3 TBTC Study 26 (NCT00164450), undertaken in 7731 participants, showed non-inferiority of weekly rifapentine and isoniazid (given for 3 months) when compared with 9 months of daily isoniazid.77 Rifapentine is still unavailable in most countries worldwide. To date, no data are available from phase 3 trials of eradication of latent infection due to drug-resistant *M tuberculosis*, though two trials are underway assessing 6 months of daily levofloxacin versus placebo, and a large trial will soon begin assessing 6 months of daily delamanid versus 9 months of daily isoniazid, in adults and children. Drug-resistant latent tuberculosis infection is a high priority for the control of the growing drug-resistant tuberculosis threat.89
Table 4: Ongoing and planned trials for the treatment of latent tuberculosis infection

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-susceptible infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS279 (NCT01404312)</td>
<td>3</td>
<td>3000, HIV+ adults (aged ≥18 years)</td>
<td>1 month isoniazid (300 mg) and rifapentine (600 mg) daily vs 9 months isoniazid (300 mg) daily</td>
</tr>
<tr>
<td>CORTIS, CORTIS-HR (NCT02735590)</td>
<td>3</td>
<td>3200, HIV– adults (aged ≥18 years) and 860 HIV+ adults (aged ≥18 years), stratified by risk of active tuberculosis by activation transcripts</td>
<td>12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly vs no intervention</td>
</tr>
<tr>
<td>WHIP3TB (NCT02980016)</td>
<td>3</td>
<td>4000, HIV– and HIV+ adults (aged ≥18 years)</td>
<td>12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly in year 1, or 12 doses isoniazid (900 mg) and rifapentine (900 mg) weekly in years 1 and 2 vs 6 months isoniazid (300 mg) daily in year 1</td>
</tr>
<tr>
<td>IMPAACT 2001 (NCT02651259)</td>
<td>1/2</td>
<td>82, HIV– and HIV+ pregnant or lactating women (aged ≥18 years)</td>
<td>Pharmacokinetics, safety: 12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly</td>
</tr>
<tr>
<td>TBTC Study 35</td>
<td>2</td>
<td>80, HIV– and HIV+ children (aged &lt;12 years)</td>
<td>Pharmacokinetics, safety: 12 doses weekly rifapentine (25–35 mg/kg) plus isoniazid (10–15 mg/kg) in children aged &lt;2, 2–5, and 6–12 years</td>
</tr>
<tr>
<td>Drug-resistant infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-QUIN MDR (ACTRN12616000215426)</td>
<td>3</td>
<td>2006, HIV– and HIV+ adults (aged ≥15 years)</td>
<td>6 months levofloxacin (250, 500, or 750 mg) vs placebo (blinded, cluster randomised)</td>
</tr>
<tr>
<td>TB-CHAMP (ISRCTN92634082)</td>
<td>3</td>
<td>1556, HIV– and HIV+ children (aged ≥5 years)</td>
<td>6 months levofloxacin (15–20 mg/kg daily) vs placebo (blinded, cluster randomised)</td>
</tr>
<tr>
<td>ACTG A5300B/IMPAACT 1230JB PHOENix</td>
<td>3</td>
<td>3452, HIV– and HIV+ adults and children (aged ≥6 years)</td>
<td>6 months delamanid (maximum 200 mg once daily) vs placebo (blinded, cluster randomised)</td>
</tr>
</tbody>
</table>

CDC TBTC=Centers for Disease Control and Prevention Tuberculosis Trials Consortium. IMPAACT=International Maternal Pediatric Adolescent AIDS Clinical Trials Network. NHMRC=Australia National Health and Medical Research Council. BMRC=British Medical Research Council. ACTG=AIDS Clinical Trials Group.

Table 4: Ongoing and planned trials for the treatment of latent tuberculosis infection

Immunotherapeutic targets

Small molecule drugs

Glucocorticoids and receptor agonists, such as dexamethasone and prednisone, have anti-inflammatory properties.87 Earlier studies88–90 have shown survival benefits and faster radiological response linked to adjunct corticosteroid treatment in pulmonary tuberculosis, tuberculosis–immune reconstitution inflammatory syndrome, and other forms, including tuberculosis pericarditis, pleurisy, and meningitis. Improved lung pathology and reduced bacillary burden has, however, only been reported for pulmonary tuberculosis during early disease.91 Biological mechanisms underlying only been reported for pulmonary tuberculosis during early disease.91 Biological mechanisms underlying disparate outcomes could be related to glucocorticoid contribution to mycobacterial survival, but this theory requires further investigation.92 Larger ongoing trials wixwax further evidence regarding the durable improvement of pulmonary and disseminated tuberculosis, irrespective of HIV, to present a case for glucocorticoids as HDT in tuberculosis (table 5).

Eicosanoids are generated by metabolism of arachidonic acid by cyclooxygenase (COX) to generate prostaglandins, and by lipoxygenase (5-LOX) to generate leukotriene.93 Selective COX-2 inhibitors decrease unproductive inflammation and improve survival in murine tuberculosis by direct antimycobacterial activity.94,95 However, COX-2 inhibition is also associated with cell necrosis, which favours in-vitro and in-vivo M tuberculosis survival.96 Zileuton, a 5-LOX inhibitor, approved for use in asthma, increases prostaglandin E2 (PGE2) and inhibits leukotrienes to limit type 1 interferon-mediated lung pathology, and it improves survival of M tuberculosis-infected mice.97 The eicosanoid pathway thus represents a complex target for tuberculosis HDTs since the effect appears to be dependent on the stage of M tuberculosis disease.98 Therefore, dinoprost (ie, prostaglandin E2) administration or zileuton might be an appealing HDT strategy during early infection given their enhancement of phagocyte-mediated immunity. However, considering its impairment of type-1 T-helper immunity, prostaglandin E2 inhibition might show an effect at later stages of disease. Information about the timing and benefit of eicosanoid modulators as HDT will be available from an ongoing clinical trial in Norway, which is assessing the therapeutic effect of adding etoricoxib as an adjunct to tuberculosis treatment (table 5).

In addition to lipid-lowering properties, statins possess potent anti-inflammatory activities99 and might reduce risk of tuberculosis.100 Statin use by people newly
diagnosed with type 2 diabetes did, however, not prevent development of tuberculosis.\textsuperscript{106} Ezetimibe, a cholesterol absorption inhibitor, reduced \textit{M tuberculosis} survival in cells from individuals with diabetes (appendix). As adjunctive therapy in murine tuberculosis, statins may limit tumour necrosis factor (TNF) α production, and reducing macrophage activation.\textsuperscript{30,37} An interventional trial recruiting in South Africa is investigating the phosphodiesterase 4 inhibitor CC–11050, as HDT in conjunction with the full tuberculosis regimen. Similarly, CC–3052 delivered promising results in a tuberculosis model in mice (appendix).

Cancer drugs, such as tyrosine kinase inhibitors,\textsuperscript{108} are being repurposed as HDTs for tuberculosis treatment in preclinical murine models. Imatinib reduces \textit{M tuberculosis} bacterial load and lung pathology, probably through the enhancement of autophagy, phagosomal acidification, and myeloid cell mobilisation.\textsuperscript{90,109} Imatinib is being assessed for its safety and immunogenicity in a phase 1 trial. The tyrosine kinase inhibitor gefitinib and janus kinase inhibitor tofacitinib, also yield similar findings to imatinib and warrant prospective clinical trial investigations (appendix).

Metformin, a drug used for type 2 diabetes, activates AMP-activated protein kinase, which regulates the amount...
Search strategy and selection criteria


of cellular energy, T-cell differentiation, and development of memory. Metformin reduces bacterial burden and ameliorates lung pathology in mice and human beings by enhancing autophagy and increasing production of reactive oxygen species. The use of metformin as adjunctive treatment, however, did not improve sterilising activity and tuberculosis relapse in patients with diabetes who also had tuberculosis. The surge in cellular and immune-metabolism research will yield several new HDT candidates, which will require careful assessment in preclinical models before being tested in human beings. Several factors require investigation before introducing metformin to tuberculosis treatment regimens, including pharmacokinetics and drug–drug interactions in the context of HIV.

Immune-modulatory biologics

Immune checkpoint inhibitors (ICIs), such as monoclonal antibodies nivolumab (acts against programmed death [PD] I) and ipilimumab (acts against cytotoxic T-lymphocyte–associated antigen 4 [CTLA4]), have been successfully used for treatment of various cancers. Signalling via immune checkpoints inhibits T-cell and B-cell function and in tuberculosis, these immune regulatory checkpoints are perturbed and linked to T-cell exhaustion. Inhibition of CTLA4 enhances immune responses in murine tuberculosis, albeit without improving bacillary clearance. CTLA4 polymorphisms are linked to tuberculosis susceptibility in several population groups. Inhibition of the PD1–PD-ligand1 pathway enhances M tuberculosis-specific responses in human peripheral blood mononuclear cells. However, case reports caution that ICIs can result in the development of active tuberculosis, probably due to excessive inflammation and increased focal necrosis. The use of ICIs, which block the PD1–PD-L1 pathway, as adjunct HDTs with tuberculosis therapy, should be viewed in light of such potential deleterious consequences. This treatment will require further assessment with regards to method, dose, and timing in animal models that closely reflect human lung pathology.

Vitamin D3 deficiency is a risk factor for development of tuberculosis and its use as adjunct HDT treatment has yielded varying outcomes. Although some trials showed enhanced clinical and radiographic improvement, host immune activation, and accelerated time to sputum conversion, other studies have not. Ongoing trials (table 5) take into consideration several variables, such as differing concentrations of baseline serum vitamin D3, dietary intake, and therapeutic dosage of colecalciferol.

Vitamin A might have host immunomodulatory potential and in-vitro antimycobacterial capabilities. In one study, vitamin A deficiency was associated with risk of incident tuberculosis in household contacts, and co-supplementation of retinol with zinc improved tuberculosis treatment outcomes. However, this result has not been supported by other studies. The difference in results might be due to different methods of determining vitamin A status, which requires measurements of serum retinol concentrations. In a murine model of tuberculosis the active derivative of vitamin A, all-transretinoic acid, has shown potential for decreasing in-vitro M tuberculosis burden and reducing relapse rates (appendix).

Cellular therapy has shown promise in the cancer field, and it is being extrapolated for use as adjunct therapy for individuals with drug-resistant tuberculosis. Mesenchymal stromal cells (MSCs) have immunomodulatory and antibacterial properties that improve peripheral blood immune responses and lung pathology in human and murine tuberculosis. The effects of MSCs at local sites of disease require definition. Modulation of immune regulatory cells, with low-dose cyclophosphamide chemotherapy, can reduce circulating regulatory T cells and might allow for effective cellular immune responses to be established. In murine tuberculosis, T-cell adoptive transfer in the lungs did not substantially accelerate mycobacterial clearance, although gamma delta (γδ) T-cell transfer resulted in reduced bacterial dissemination in non-human primates (appendix). Further studies are required of interventional T-cell therapy as an HDT, for treating tuberculosis. Myeloid-derived suppressor cells (MDSCs) are increased in human and murine tuberculosis, display T-cell immunosuppressive properties, and harbour M tuberculosis. Ongoing clinical trials targeting MDSC in cancer and preclinical evidence from the tuberculosis mouse model with denuleukin difluto, suggest MDSCs as a focus for investigations (appendix).

Micro RNA (miRNAs) are small non-coding RNAs that regulate gene expression and can affect host immunity to M tuberculosis infection through modulation of inflammation, TNFa, interleukin-6, chemokines, and stimulation of macrophage polarisation. Evidence is
emerging that suggests miRNAs could serve as cancer immunotherapy. Fundamental research, including the functional role of several miRNAs—eg, miRNA-223, miRNA-21, and miRNA 29—and their relationship to cavity tuberculosis, should be expanded to establish their value as potential therapeutic targets in tuberculosis.14,15

Although TNFα is essential to granuloma formation, macrophage antimicrobial activity, and killing of *M tuberculosis* mediated by reactive oxygen species,10 TNFα can also trigger cell necrosis and exacerbate inflammation, paradoxically exacerbating pathology.14 TNFα inhibition destabilises granulomas, reactivates *M tuberculosis* bacilli in patients with latent *M tuberculosis* infection, and increases the risk of tuberculosis progression. Therefore, drugs that block TNFα require assessment as adjunctive HDT.14,15 Cytokine supplementation with interferon gamma has paradoxically exaggerated pathology.143 TNFα inhibition can also trigger cell necrosis and exacerbate inflammation, and block TNFα require assessment as adjunctive HDT.144,145 These studies underscore the complexity of the use of cytokines as HDTs. Trials investigating recombinant interleukin-2 treatment in patients with drug-resistant tuberculosis are ongoing (table 5).

Future HDT research

Although several HDTs show promise in preclinical studies, further research is required to assess the effect of HDTs on key immune functions during different phases of *M tuberculosis* infection and disease. The timing of specific HDTs might be crucial since proinflammatory and anti-inflammatory immune mechanisms have important roles during different stages of tuberculosis. The use of companion biomarker studies (ie, circulating cytokines), expression of cell-surface molecules (immune checkpoints, chemokine receptors, signalling molecules), existing pharmacological data, and safety and efficacy profiles based on previous clinical studies in other modalities (ie, cancer, autoimmune diseases), will help select the most promising HDT strategies for clinical investigation in tuberculosis. Assessment of new HDTs in trials should be undertaken in different geographical and clinical settings, and they should include safety, kinetic studies, mechanisms of action, disease severity, and impact studies.

Conclusions

Steady progress is being made in the development of new and repurposed tuberculosis drugs, treatment trials, and HDTs. Several new or repurposed drugs are being studied for improved management of drug-susceptible and MDR tuberculosis. A range of candidate HDTs and immune-based treatments are being investigated as adjunct therapy. Development of tuberculosis drugs and HDTs, and access to them, is hampered by inadequate funding. Another big challenge is ensuring that these treatments are affordable, effective, safe, and reach the people who need them.

Contributors

AZ initiated the idea. AZ, ST, MJV, MR, GW, NdP, and MJM developed the first, subsequent, and final drafts of the manuscript. All authors contributed to sections relevant to their expertise, and helped refine the text and content.

Declaration of interests

We declare no competing interests.

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