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.

Key messages

- Tuberculosis caused 1·67 million deaths in 2016. Drug-resistant tuberculosis is a now a major threat to global health security.
- WHO recommended treatments can only cure 50% of multidrug-resistant (MDR) tuberculosis and 30% of patients with extensively drug resistant tuberculosis. Newer, more potent drugs are required that could build a universal regimen for effectively treating and reducing the duration of drug-resistant and drug-sensitive tuberculosis.
- Concerted efforts of stakeholders, advocates, and researchers are slowly advancing the development of shorter course, more effective, safer, and better tolerated treatment regimens.
- 14 candidate drugs for drug-susceptible, drug-resistant, and latent tuberculosis are in the clinical stages of drug development.
- The new diarylquinoline (bedaquiline) and nitroimidazoles (pretomanid, delamanid) provide hope for an all-oral regimen for MDR tuberculosis.
- A range of host-directed therapies (HDTs) are being developed as adjuncts to drug treatment to hasten elimination of Mycobacterium tuberculosis infection, shorten the duration of treatment, prevent permanent lung injury, and prevent development of new drug resistance.
- Access to the new drugs and conduct of clinical trials are hampered by high costs. Development of new medicines and regimens should be twinned with funder investments to ensure that these medicines are affordable, effective, safe, and reach the people who need them.
- A substantial increase in political and funder attention is required to increase the inadequate funding portfolio for new drugs and HDTs.
specific issues regarding safety and toxicity, and drug–drug interactions. 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.11–16 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 1.13 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).14 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.15

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 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 negative with minimal pulmonary disease.16 Studies investigating the optimisation of the use of approved drugs with improved formulations and pill counts are also ongoing.17 More palatable fixed-dose combination tablets are now available for paediatric use, simplifying dosing in children weighing less than 25 kg,18 while improving drug delivery and drug adherence.19–21 Efforts are also being made to render the standard quadruple regimens less toxic. One study22 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 lung 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
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 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), 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 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.

<table>
<thead>
<tr>
<th>Target</th>
<th>Sponsors</th>
<th>Phase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline</td>
<td>Janssen, TB Alliance, NIAID, SAMRC, The Union, Unitaid, USAID</td>
<td>3</td>
<td>Conditional marketing approval</td>
</tr>
<tr>
<td>Nitromidazole</td>
<td>Otsuka, NIAID, Unitaid</td>
<td>3</td>
<td>Conditional marketing approval</td>
</tr>
<tr>
<td>Pretomanid</td>
<td>TB Alliance</td>
<td>3</td>
<td>Potent bactericidal and sterilising activity in mouse models</td>
</tr>
<tr>
<td>Oxazolidinone</td>
<td>Pfizer, then Sequella, NIAID, Medicines Patent Pool, TB Alliance</td>
<td>2a</td>
<td>Renewed commercial development, more potent and less toxic than linezolid, phase 2 trials starting in 2018</td>
</tr>
<tr>
<td>Delpazolid</td>
<td>LegoChem Biosciences</td>
<td>2</td>
<td>Results in phase 2 safety, EBA study expected later in 2018</td>
</tr>
<tr>
<td>Contezolid</td>
<td>MicroRX Pharmaceuticals</td>
<td>1</td>
<td>Potentially less toxic than linezolid</td>
</tr>
<tr>
<td>1,2-ethylene diamine</td>
<td>Sequella, PanACEA, Infectex</td>
<td>2</td>
<td>No efficacy in PanACEA phase 2 trial with high-dose rifampicin (NCT01785186), results from trial in Russia in 2018</td>
</tr>
<tr>
<td>DprE1 inhibitor</td>
<td>Nearmedic, IM4TB, BMGF</td>
<td>2</td>
<td>Benzothiazinone, synergy with bedaquiline and clofazimine</td>
</tr>
<tr>
<td>OPC-167832</td>
<td>Eli Lilly, Foundation for Neglected Disease Research, TB Alliance</td>
<td>1</td>
<td>Potential to shorten treatment for all forms of tuberculosis; phase 1 trial began August, 2017 (NCT03199339)</td>
</tr>
<tr>
<td>TBA/73/1</td>
<td>University of Munich, PanACEA</td>
<td>1</td>
<td>Benzothiazinone, synergy with rifampicin, low toxicity, no hepatic enzyme interactions</td>
</tr>
<tr>
<td>SQ109</td>
<td>Sequella, PanACEA, Infectex</td>
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</tbody>
</table>


Table 1: Development pipeline of new drugs for tuberculosis
Table 2: Ongoing and planned trials for drug-susceptible tuberculosis

<table>
<thead>
<tr>
<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>3 271 (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>2 183, 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 2015; John Hopkins University, University of Cape Town Lung Institute</td>
</tr>
<tr>
<td>TBTC 31/A5349 (NCT02410772)</td>
<td>3 2500, HIV- and HIV+ adults and children (aged ≥13 years)</td>
<td>2 months isoniazid, rifampentine (1200 mg), pyrazinamide, and ethambutol daily, and 2 months isoniazid and rifampentine (1200 mg) daily, or 2 months isoniazid, rifampicine (1200 mg), pyrazinamide, and moxifloxacin daily, and 2 months isoniazid, rifampentine (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 spottum biomarkers to predict outcomes; CDC TBTC, ACTG</td>
</tr>
<tr>
<td>SHINE (ISRCTN63570542)</td>
<td>3 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 (NCT03353527)</td>
<td>3 800, HIV- adults (aged ≥18 years)</td>
<td>2 months isoniazid, rifampicin (1200 or 1800 mg), pyrazinamide, and ethambutol daily, and 2 months isoniazid and rifampicin (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>2/3 900, 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 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 600, HIV- adults (aged ≥18 years)</td>
<td>3–4 months isoniazid, rifampicin (600 mg), pyrazinamide, and Q203 daily, or 2–3 months isoniazid, rifampicin (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/3 300, HIV- and HIV+ adults (aged ≥18 years)</td>
<td>4 months bedaquiline, pretomanid, moxifloxacin, pyrazinamide vs standard 6 month therapy</td>
<td>Opened 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 pyrazinamide 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-TB²⁵ 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-resistant 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.²⁶ Concerns over QT prolongation have led to new studies to investigate the phenomenon. 1602 patients from the OFLOTUB cohort (NCT00216385)²⁷ 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
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. 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. 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. A retrospective study 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.

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. 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. A systematic review 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 on bedaquiline after temporary interruption. A retrospective study of 428 patients with MDR tuberculosis, treated under programmatic conditions with bedaquiline, from across 15 countries, suggested that the risk of QT prolongation appears to be less than initially envisaged. At the end of treatment, sputum smear conversion was observed in 126 (90%) of 140 patients and culture conversion in 191 (92%) of 208 patients. 25 (6%) of 428 patients discontinued the drug because of adverse events, with one death related to non-bedaquiline-related arrhythmia. Importantly, a
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 delamanid (200 mg daily) plus OBR vs 6 months placebo plus OBR was confirmed.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otsuka Trial 213  (NCT01424670)</td>
<td>3</td>
<td>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>
</tr>
<tr>
<td>STREAM Stage 1 (ISRCTN78372190)</td>
<td>3</td>
<td>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>
</tr>
<tr>
<td>NC-005 (NCT02193776)</td>
<td>2b</td>
<td>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>
</tr>
<tr>
<td>OPTI-Q (NCT01918397)</td>
<td>2</td>
<td>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>
</tr>
<tr>
<td>NC-006 STAND (NCT02342886)</td>
<td>3</td>
<td>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>
</tr>
<tr>
<td>NIX-TB (NCT02333799)</td>
<td>3</td>
<td>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 twice daily), single arm study</td>
</tr>
<tr>
<td>NEtX-5001 (NCT02454205)</td>
<td>2/3</td>
<td>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>
</tr>
<tr>
<td>MOR-END (NCT02619994)</td>
<td>2</td>
<td>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>
</tr>
<tr>
<td>STREAM Stage 2 (NCT02409290)</td>
<td>3</td>
<td>2155, HIV- and HIV + adults (aged ≥18 years)</td>
<td>9 months moxifloxacin, clofazimine, ethambutol, pyrazinamide daily, with initial 2 months isoniazid, kanamycin, prophthionamide daily, or 9 months bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide daily, with initial 2 months isoniazid (high dose), prothionamide (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>
</tr>
<tr>
<td>Janssen C211 (NCT02354014)</td>
<td>2</td>
<td>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>
</tr>
<tr>
<td>ACTG A5343 DELIBERATE (NCT02583048)</td>
<td>2</td>
<td>84, HIV- and HIV + adults (aged ≥18 years)</td>
<td>Pharmacokinetics, QTC 6 months bedaquiline daily plus OBR, or 6 months delamanid daily plus OBR, or 6 months bedaquiline and delamanid daily plus OBR</td>
</tr>
<tr>
<td>endTB (NCT02754765)</td>
<td>3</td>
<td>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, pyrazinamide daily vs local regimen</td>
</tr>
<tr>
<td>TB-PRACTECAL (NCT02583972)</td>
<td>2/3</td>
<td>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>
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(Table 3 continues on next page)
delamanid in children older than 6 years is under investigation through several studies: the Otsuka Trial 233 (NCT01859923) is a 6-month pharmacokinetic and safety study in all paediatric weight groups, and results are expected in 2020; results of the Otsuka Trial 232, (NCT01856634) with 18-day pharmacokinetic and safety in different groups aged 0–17 years, are due out in 2018.42,43

Results of the first phase 3 trial studying the use of delamanid for treatment of MDR tuberculosis (Otsuka Trial 213, NCT01424670) were presented at the 48th Union World Conference on Lung Health in October, 2017 (Guadalajara, Mexico). The primary endpoint was time to sputum culture conversion over the first 6 months of delamanid plus optimised background regimen versus placebo and optimised background regimen. Patients in the delamanid group had a more rapid culture conversion of 6–13 days than the placebo group, with a non-significant p value for efficacy of 0·056. The proportions of patients who had favourable treatment outcomes at 24 months were similar in both groups. Importantly, adverse events did not increase significantly in the delamanid group. Moreover, delamanid reduced the development of fluoroquinolone resistance (NCT01424670). Despite the disappointing results, delamanid is a specific antituberculosis medication with an excellent safety profile, making it a useful companion drug 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 study 44 A5343 DELIBERATE includes three groups—delamanid, bedaquiline, and a combination of the two in a shorter regimen of 24 weeks—and seeks to understand whether the combination is safe and to compare the mean changes from baseline (averaged over 8–24 weeks) in QTcF when delamanid and bedaquiline are given in combination to the mean change seen when each drug is given alone.

**Pre tom anid**

Pretomanid, a nitroimidazole developed by the TB Alliance, is being considered as a potential component for a pan-tuberculosis regimen for both drug-susceptible and MDR tuberculosis. The drug is being assessed in several trials for drug-susceptible and drug-resistant tuberculosis (NC-005, NC-006 STAND, NiX-TB, TB-PRACTECAL, NC-007 ZeNIX, NC-008 SimpliciTB). Of particular note, the NC-005 trial (NCT01498419) is studying a combination of bedaquiline, pretomanid, and pyrazinamide for 8 weeks in patients with drug-susceptible tuberculosis, with a separate group for patients with drug-resistant tuberculosis with the addition of moxifloxacin to the regimen. The bedaquiline, pretomanid, and pyrazinamide combination had greater antimycobacterial activity than the standard quadruple regimen.45 This combination was exquisitely bactericidal: sputum was converted in 78%–96% of patients receiving bedaquiline, pretomanid, and pyrazinamide with moxifloxacin at 8 weeks of treatment.
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 SimplicitTB 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 discolouration, a common side-effect of clofazimine. A sizeable programmatic study in Brazil used clofazimine 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 combination of amoxicillin plus clavulanic acid (which protects meropenem or carbapenem from β-lactamases) reduce the appeal of carbapenems. Faropenem (an oral penem) showed little activity in a phase 2b trial despite promising hollow fibre studies. This result might be due to the low oral bioavailability of faropenem sodium. Future development of oral penem or carbapenem formulations could offer another solution to the need for a pan-tuberculosis regimen. Similarly, another β-lactam, ceftazidime, combined with the new β-lactamase inhibitor avibactam, has shown encouraging preclinical results. The *M tuberculosis* class A β-lactamase is potently inhibited by avibactam, rendering ceftazidime active against mycobacteria.

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 rifampin-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 (10 mg/kg to a maximum of 600 mg a day), 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 quinolone 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.77 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, in the first 2 months. 65% people achieved culture 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 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 16.77 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.78

**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.79 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.80

Table 4 summarises ongoing and planned trials investigating chemoprophylaxis for individuals exposed to drug-susceptible and drug-resistant tuberculosis that are underway or will open soon.

**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.81 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.81 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.82 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.84-86 Translational studies incorporating novel technologies, such as tissue-embedded microchips and ex-vivo three-dimensional culture models, are underway for studying HDTs for further preclinical and translational research HDT strategies see appendix).
Ongoing and planned trials for the treatment of latent tuberculosis infection

Table 4: Phase Study population Study groups Notes

**Drug-susceptible infection**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<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)</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>
</tbody>
</table>

**Drug-resistant infection**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Study population</th>
<th>Study groups</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>V-QUIN MDR (ACTRN12616000215426)</td>
<td>3</td>
<td>2006, HIV- and HIV+ adults and children (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>3456, 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 1200JB 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 9 months isoniazid (300 mg daily)</td>
</tr>
</tbody>
</table>

**Immunotherapeutic targets**

**Small molecule drugs**

Glucocorticoids and receptor agonists, such as dexamethasone and prednisone, have anti-inflammatory properties. Earlier studies 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.

Biological mechanisms underlying disparate outcomes could be related to glucocorticoid contribution to mycobacterial survival, but this theory requires further investigation. Larger ongoing trials will provide 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 lipoygenase (5-LOX) to generate leukotrienes. Selective COX-2 inhibitors decrease unproductive inflammation and improve survival in murine tuberculosis by direct antimycobacterial activity. However, COX-2 inhibition is also associated with cell necrosis, which favours in-vitro and in-vivo M tuberculosis survival. 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. 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. Therefore, dinoprostone (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 activities and might reduce risk of tuberculosis. Statin use by people newly
N-acetylcysteine
- N-acetylcysteine plus rifampicin, isoniazid, pyrazinamide, and ethambutol to exert simultaneous antibacterial and antioxidative (tissue-protective) effects in patients with active pulmonary tuberculosis.

Azithromycin
- Adjunctive HDT with standard or MDR tuberculosis regimens to treat pulmonary tuberculosis—for reducing overt inflammation in patients’ lungs (and potentially systemic inflammation also).

Everolimus, auranofin, colecalciferol (INN on Martindale) are colocalised when referring to its use as a drug use colecalciferol, but when referring to the natural occurrence within the body, use 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 tuberculosis.

Mycobacterium indicus pranii
- Used as an immunomodulatory treatment to induce beneficial effects in patients with pulmonary tuberculosis following antibacterial therapy.

Colecalciferol
- Used as a supplement to help resolve inflammation or to induce productive intracellular defence mechanisms—ie, antimicrobial peptide production; multiple colecalciferol doses are assessed.

Dexamethasone
- Adjunctive corticosteroid used as an anti-inflammatory drug to resolve cytokine storm and tissue destruction in patients with tuberculosis, including tuberculous meningitis.

Nitazoxanide
- Tested in clinical trials for early antimycobacterial activity; however, nitazoxanide might also exert its effects via autophagy, as shown in a preclinical study.

Nydutil Resae
- Heat-killed Mycobacterium manesensis to induce generation of memory regulatory T cells as a mechanism of avoiding overt tuberculosis-associated inflammation; safety study in children; given as a probiotic capsule.

Recombinant human interleukin-2
- Given subcutaneously to patients with MDR tuberculosis as adjunct to standard chemotherapy for modulating T-cell activity.

GX-70
- Safety study of DNA vaccine combining genes encoding Mycobacterium tuberculosis antigens as well as the human Flt3 ligand for immunomodulation in patients with tuberculosis who did not respond to treatment or experienced disease relapse.

Etoricoxib with or without H56 IC31
- Etoricoxib is a COX2 inhibitor, and can increase the production of the anti-inflammatory lipid mediator prostaglandin E₂; combination of etoricoxib and H56 IC31 (subunit vaccine with adjuvant) is expected to reduce non-specific inflammation while inducing targeted antibacterial immune responses; assessed in patients with MDR tuberculosis.

Table 5: HDTs in tuberculosis—ongoing clinical trials

<table>
<thead>
<tr>
<th>Description</th>
<th>Notes</th>
<th>Trial number</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-acetylcysteine</td>
<td>N-acetylcysteine plus rifampicin, isoniazid, pyrazinamide, and ethambutol to exert simultaneous antibacterial and antioxidative (tissue-protective) effects in patients with active pulmonary tuberculosis.</td>
<td>Phase 2, Brazil</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Adjunctive HDT with standard or MDR tuberculosis regimens to treat pulmonary tuberculosis—for reducing overt inflammation in patients’ lungs (and potentially systemic inflammation also).</td>
<td>Phase 2, Netherlands</td>
</tr>
<tr>
<td>Everolimus, auranofin, colecalciferol (INN on Martindale) are colocalised when referring to its use as a drug use colecalciferol, but when referring to the natural occurrence within the body, use vitamin D₃, or CC-11050)</td>
<td>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 tuberculosis.</td>
<td>Phase 2, South Africa</td>
</tr>
<tr>
<td>Mycobacterium indicus pranii</td>
<td>Used as an immunomodulatory treatment to induce beneficial effects in patients with pulmonary tuberculosis following antibacterial therapy.</td>
<td>Phase 3, India</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>Used as a supplement to help resolve inflammation or to induce productive intracellular defence mechanisms—ie, antimicrobial peptide production; multiple colecalciferol doses are assessed.</td>
<td>Several intermediate to advanced clinical trials (phases 2–4), South Africa, India, UK</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Adjunctive corticosteroid used as an anti-inflammatory drug to resolve cytokine storm and tissue destruction in patients with tuberculosis, including tuberculous meningitis.</td>
<td>2 phase 3 trials, Vietnam and Indonesia</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>Tested in clinical trials for early antimycobacterial activity; however, nitazoxanide might also exert its effects via autophagy, as shown in a preclinical study.</td>
<td>Phase 2, Haiti</td>
</tr>
<tr>
<td>Nydutil Resae</td>
<td>Heat-killed Mycobacterium manesensis to induce generation of memory regulatory T cells as a mechanism of avoiding overt tuberculosis-associated inflammation; safety study in children; given as a probiotic capsule.</td>
<td>Phase 1, Spain</td>
</tr>
<tr>
<td>Recombinant human interleukin-2</td>
<td>Given subcutaneously to patients with MDR tuberculosis as adjunct to standard chemotherapy for modulating T-cell activity.</td>
<td>Phase 2/3, China</td>
</tr>
<tr>
<td>GX-70</td>
<td>Safety study of DNA vaccine combining genes encoding Mycobacterium tuberculosis antigens as well as the human Flt3 ligand for immunomodulation in patients with tuberculosis who did not respond to treatment or experienced disease relapse.</td>
<td>Phase 1, Korea</td>
</tr>
<tr>
<td>Etoricoxib with or without H56 IC31</td>
<td>Etoricoxib is a COX2 inhibitor, and can increase the production of the anti-inflammatory lipid mediator prostaglandin E₂; combination of etoricoxib and H56 IC31 (subunit vaccine with adjuvant) is expected to reduce non-specific inflammation while inducing targeted antibacterial immune responses; assessed in patients with MDR tuberculosis.</td>
<td>Phase 1, Norway</td>
</tr>
</tbody>
</table>

HDTs=host-direct therapies. MDR=multidrug resistant.

Diacid with type 2 diabetes did, however, not prevent development of tuberculosis. Everimibe, a cholesterol absorption inhibitor, reduced M tuberculosis survival in cells from individuals with diabetes (appendix). As adjunctive therapy in murine tuberculosis, statins limit tumour necrosis factor (TNF) α production, and reducing macrophage activation. 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, are being repurposed as HDTs for tuberculosis treatment in preclinical murine models. Imatinib reduces M tuberculosis bacterial load and lung pathology, probably through the enhancement of autophagy, phagosomal acidification, and myeloid cell mobilisation. 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...
of cellular energy, T-cell differentiation, and development of memory.\textsuperscript{11} Metformin reduces bacterial burden and ameliorates lung pathology in mice and human beings by enhancing autophagy and increasing production of reactive oxygen species.\textsuperscript{63,112} The use of metformin as adjunctive treatment, however, did not improve sterilising activity and tuberculosis relapse in patients with diabetes who also had tuberculosis.\textsuperscript{113} 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.

**Immuno-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.\textsuperscript{114} Signalling via immune checkpoints inhibits T-cell and B-cell function\textsuperscript{115} and in tuberculosis, these immune regulatory checkpoints are perturbed and linked to T-cell exhaustion.\textsuperscript{116} Inhibition of CTLA4 enhances immune responses in murine tuberculosis, albeit without improving bacillary clearance.\textsuperscript{117} CTLA4 polymorphisms are linked to tuberculosis susceptibility in several population groups.\textsuperscript{118} Inhibition of the PD1–PD-ligand1 pathway enhances *M tuberculosis*-specific responses in human peripheral blood mononuclear cells.\textsuperscript{119} However, case reports caution that ICIs can result in the development of active tuberculosis, probably due to excessive inflammation and increased focal necrosis.\textsuperscript{119} 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\textsuperscript{120} and its use as adjunct HDT treatment has yielded varying outcomes. Although some trials showed enhanced clinical and radiographic improvement, host immune activation,\textsuperscript{121} and accelerated time to sputum conversion,\textsuperscript{122} other studies have not.\textsuperscript{123} 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 immuno-modulatory potential and in-vitro antimycobacterial capabilities.\textsuperscript{124} 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.\textsuperscript{125} 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.\textsuperscript{126} 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).\textsuperscript{127}

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.\textsuperscript{128,129} Mesenchymal stromal cells (MSCs) have immuno-modulatory and antibacterial properties\textsuperscript{130} that improve peripheral blood immune responses and lung pathology in human and murine tuberculosis.\textsuperscript{131,132} The effects of MSCs at local sites of disease require definition.\textsuperscript{132} 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,\textsuperscript{133–135} and harbour *M tuberculosis*. Ongoing clinical trials targeting MDSC in cancer,\textsuperscript{136–139} and preclinical evidence from the tuberculosis mouse model with denileukin diftitox, 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.\textsuperscript{140,141} Evidence is
emerging that suggests miRNAs could serve as cancer immunotherapy. Fundamental research, including the functional role of several miRNAs—e.g., 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.30,10,16

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 destabilizes 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 shown variable efficacy and nominal benefit in drug-sensitive14 and drug-resistant tuberculosis.14 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, ND, 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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