Published in final edited form as:

Curr Opin HIV AIDS. 2013 November ; 8(6): 579–585. doi:10.1097/COH.0000000000000009.

Pipeline of drugs for related diseases: tuberculosis

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Abstract

Purpose of review—For the first time in decades, there are multiple new drugs in the pipeline for the treatment of tuberculosis (TB). In addition, existing drugs are being repurposed or optimized for TB with the goal of shortened treatment duration for drug-sensitive TB and safer, shorter treatments for multidrug-resistant (MDR) TB. In this review, the results of recent trials evaluating novel combination regimens for TB disease and latent TB infection are described.

Recent findings—High-dose rifamycins (rifampin and rifapentine) and fluoroquinolones directly observed have treatment-shortening potential when used for drug-sensitive TB disease, and a 12-dose once-weekly regimen of rifapentine along with isoniazid effectively treats latent TB. Bedaquiline, an anti-TB drug with a novel mechanism of action, and delamanid, a nitroimidazole, are entering phase 3 trials. Both improve rates of sputum culture conversion among patients with MDR-TB. Other nitroimidazoles and oxazolidinones are in Phase 2 testing, as are combinations involving multiple new chemical entities.

Summary—With the resurgence of anti-TB drug discovery efforts, we now have a modestly robust pipeline of new anti-TB drugs. Several promising new regimens involving investigational and existing drugs that may be capable of shortening treatment for drug-sensitive TB and improving management of drug-resistant TB are in late-phase clinical evaluation.

Keywords

bedaquiline; fluoroquinolone; HIV; investigational drugs; multidrug-resistant tuberculosis; nitroimidazole; oxazolidinone; rifamycin; tuberculosis

INTRODUCTION

The WHO estimates that there were over 8.7 million new cases of tuberculosis (TB) and 1.4 million deaths from TB in 2011 [1]. TB accounts for 20–25% of HIV-related deaths worldwide [2,3]. Current treatments for TB were developed over 40 years ago, and drug development for TB was moribund until recently. For the first time in decades, several drugs from multiple classes are in the pipeline for TB.

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Conflicts of interest

K.E.D. and A.H.D. report no conflict of interest. E.L.N. receives research funding from the Global Alliance for TB Drug Development and is an inventor on a patent application for combination therapy including sutezolid.

WHY DO WE NEED NEW TREATMENTS FOR TUBERCULOSIS?

Current first-line treatments for drug-sensitive TB require four drugs and 6–9 months to achieve cure without relapse. There is an urgent need for novel therapeutic strategies that can shorten the duration of TB treatment. Shorter treatment duration decreases the logistical burden and expense of extended therapy, improves adherence and helps prevent drug resistance. An anti-TB regimen that can be used safely with antiretroviral treatment (ART) without dose adjustment is particularly appealing given that patients with HIV bear a disproportionate burden of TB disease. Treatment of latent TB infection (LTBI) to prevent TB disease is not the standard of care in most settings. Even when LTBI treatment is available and offered, completion rates of a 6–9 month regimen of daily isoniazid are only 30–60% [4,5■■■].

Multidrug-resistant (MDR) TB caused by *Mycobacterium tuberculosis* resistant to isoniazid and rifampin has emerged as a worldwide epidemic with an estimated 500 000 cases in 2011. Extensively drug-resistant (XDR) TB caused by *M. tuberculosis* resistant to isoniazid, rifampin, fluoroquinolones and injectable anti-TB drugs has been found in all countries that test for it. Totally drug-resistant TB is a reality that threatens international TB control [6,7,8■■,9]. Therapeutic options for drug-resistant TB are limited by availability, acceptability and efficacy. Only one in five patients diagnosed with MDR-TB is started on treatment [10]. Current recommendations call for at least 20 months of toxic multidrug therapy, including at least 8 months of an injectable agent [11]. Treatment is successful in just 48% of patients [10].

PIPELINE OF DRUGS FOR TUBERCULOSIS

In 1993, WHO declared TB a global emergency. In the face of rising rates of TB disease and drug resistance and limited treatment options, pharmaceutical companies and private/public partnerships responded to the challenge. The development pipeline remains thin, but for the first time in decades, multiple drugs are in development for TB (Table 1). In the discovery pipeline are several lead compounds with familiar mechanisms of action (e.g. RNA polymerase inhibitors, fatty acid synthase inhibitors, gyrase inhibitors, pyrazinamide analogues), but there are also compounds with unique mechanisms of action that exhibit little or no cross-resistance with existing TB drugs, such as drugs targeting enzymes involved in energy production for *M. tuberculosis* [12]. Some discovery efforts are directed towards designing next-generation drugs that retain potent anti-TB activity but have fewer undesirable attributes, such as water-soluble analogues of clofazimine that are less likely to cause skin discoloration or oxazolidinones with reduced mitochondrial toxicity and, perhaps, reduced risk of dose-limiting neuropathy compared with linezolid.

Several new chemical entities have progressed to clinical evaluation, including nitroimidazoles (delamanid, PA-824 and TBA-354), oxazolidinones (sutezolid and AZD5847), the ATP synthase inhibitor, bedaquiline and an ethambutol analogue, SQ109. Bedaquiline was registered with the Food and Drug Administration in 2012 after expedited review and is available for treatment of MDR-TB in some settings. Efforts to optimize rifamycin antibiotics (rifampin and rifapentine) or repurpose drugs with good anti-TB

activity (moxifloxacin) are ongoing and these drugs are considered part of the TB drug pipeline.

Evaluation of TB drugs is complex for several reasons. First, each drug in first-line treatment is thought to play a different role (e.g. isoniazid rapidly reduces bacterial burden by killing rapidly dividing bacilli, rifampin kills semi-dormant persister bacilli that cause relapse if they are not eradicated, pyrazinamide kills a subset of bacilli in acidic environments and ethambutol protects companion drugs against resistance). It is, thus, challenging to determine the optimal way to incorporate new drugs into TB regimens. Second, current biomarkers of TB treatment response based on sputum microbiology in Phase 2 trials do not enable confident dose and regimen selection. Finally, for novel regimens containing two or more new drugs, it may be difficult to tease out the individual contributions of each drug. The typical series of clinical efficacy experiments starts with a Phase 2A early bactericidal activity (EBA) study, in which patients with sputum smear-positive TB are administered the experimental drug as monotherapy for 7 – 14 days, and the rate of change in quantity of *M. tuberculosis* in sputum is measured. Provided the results demonstrate evidence of activity, they may be used for selecting a dose to take forward either into a multi-drug EBA study or into an 8-week Phase 2B trial intended to assess the safety, tolerability and efficacy of one or more new regimens. The phase 3 trial follows, with an endpoint of cure without relapse that requires follow-up for at least 1 year after treatment completion [13].

RIFAMYCINS

Rifamycin antibiotics have unique sterilizing activity against *M. tuberculosis*. The clinical consequence of bacterial resistance to rifampin is a need to prolong treatment from 6 months to at least double the duration of treatment. Data from animal models and clinical trials indicate that rifamycins have dose-dependent activity that is not optimized at current doses [14–16]. Now, more than 40 years after the introduction of rifampin, a maximal tolerated dose 2-week EBA study is underway. Doses up to 35 mg/kg have been well tolerated in small cohorts of patients, and these doses are being tested in an 8-week trial [17]. Rifapentine, a rifamycin with a lower mean inhibitory concentration against *M. tuberculosis* and a longer half-life, is currently approved for once-daily or twice-weekly administration. After daily dosing of rifapentine was shown to shorten the duration of treatment needed to prevent relapse in mice [18], this strategy was studied in clinical trials. Rifapentine at a dose of 10 mg/kg daily failed to demonstrate better efficacy when substituted for the same dose of rifampin in the context of multidrug TB treatment using 2-month culture conversion as an endpoint [19]. However, in a recently completed clinical trial of doses of 10–20 mg/kg daily, rifapentine clearly out-performed rifampin dosed at the conventional 10 mg/kg, with 2-month culture conversion of 100% at the highest dose, a result never before seen in a TB trial [20]. A Phase 3 treatment shortening trial with high-dose rifapentine is planned.

For LTBI, a 12-dose regimen of rifapentine along with isoniazid given once weekly via directly observed therapy (DOT) was recently demonstrated to be noninferior to 9months of daily isoniazid [5]. Although the latter study was conducted only in settings in which TB incidence is low to moderate, it still represents a significant advance for LTBI treatment. Studies of the durability and efficacy of this regimen in settings in which re-exposure to TB

is common are needed. Drug interaction trials to determine antiretroviral concentrations when rifapentine is given once-weekly are in progress.

FLUOROQUINOLONES

Fluoroquinolones, notably moxifloxacin, have potent bactericidal activity against *M. tuberculosis*, and studies in the mouse model suggest that substitution of moxifloxacin for ethambutol or isoniazid may enable reduction of treatment duration [21]. Clinical trials in which moxifloxacin was substituted for ethambutol or isoniazid demonstrated at best a modest reduction in time to sputum culture conversion [22–24]. Results are eagerly awaited from the Phase 3 OFLOTUB trial evaluating a 4-month regimen in which gatifloxacin was substituted for ethambutol and given throughout the 4-month treatment. In the Phase 3 RIFAQUIN trial, a 4-month treatment arm—2 months of daily moxifloxacin, rifampin, pyrazinamide and ethambutol followed by 2 months of twice-weekly moxifloxacin and rifapentine (15 mg/kg)—was inferior to 6 months of the first-line regimen on the basis of unfavourable status after treatment completion (17 vs. 5%, respectively), primarily due to relapses [25]. Another recent Phase 3 trial in which moxifloxacin and gatifloxacin were substituted for ethambutol in the thrice-weekly regimen used in India was stopped early after finding a higher rate of unfavourable response for the 4-month fluoroquinolone arms (15 and 11%, respectively) compared with the 6-month standard therapy arm (6%) [26]. Finally, the Phase 3 REMoxTB trial evaluating two daily 4-month treatments (moxifloxacin substituted for ethambutol or moxifloxacin substituted for isoniazid) is complete; results are expected in 2014.

DIARYLQUINOLINES

Bedaquiline inhibits ATP synthase, the proton pump of *M. tuberculosis*, a novel mechanism of action [12,27]. Experiments in mouse models suggest that bedaquiline has sterilizing activity on par with rifampin and synergistic activity with firstline and investigational TB drugs [28,29]. When added to second-line drugs to treat MDR-TB, bedaquiline improved 2-month sputum culture conversion (48 vs. 9% with the standard regimen) [30]. When added for 6 months second-line treatment, bedaquiline improved long-term culture conversion and reduced the emergence of additional resistance [31]. In December 2012, bedaquiline was licensed by the FDA for use among patients with MDR-TB or XDR-TB, but the label bears a black box warning of drug-related QT prolongation and higher mortality in the bedaquiline group than in the placebo group (9/79 vs. 2/81) in the controlled Phase 2 trial [32]. Death occurred on average more than 1 year after drug discontinuation, many deaths were due to TB, and mortality in the control arm was uncharacteristically low, but the difference in mortality remains unexplained. Guidelines for use of bedaquiline issued by WHO suggest that it should be used with caution after an informed consent process [33]. Safety data from the Phase 3 trial in MDR-TB are eagerly awaited. Of note, bedaquiline is currently added to second-line treatment rather than substituted for MDR-TB drugs, so toxicities of second-line drugs are not avoided. Combining multiple new chemical entities in a regimen may be a better approach to improving MDR-TB treatment [29]; this strategy is being tested in a Phase 2 EBA study. When bedaquiline is given with TB drugs that prolong the QT interval such as moxifloxacin or clofazimine, there is an additive effect. In addition,

bedaquiline is a substrate of CYP3A, so interactions with drugs that induce or inhibit CYP3A, such as rifampin or efavirenz, must be considered.

NITROIMIDAZOLES

Two investigational nitroimidazoles, delamanid and PA-824, are in Phase 2 or 3 clinical trials. These antibiotics not only inhibit cell wall (mycolate) synthesis but also have less specific activity [34]. PA-824, for example, is metabolized by *M. tuberculosis* into reactive nitrogen species that poison its respiratory apparatus. This mechanism of action is thought to contribute to its activity against nonreplicating persisters [35]. In mice and guinea pigs, a rifamycin-sparing combination of PA-824, moxifloxacin and pyrazinamide had similar or better activity than standard TB treatment [36,37]. In mice, delamanid shortened treatment duration needed for cure when used with first-line TB drugs [38].

In a Phase 2 trial of delamanid among patients with MDR-TB receiving background treatment, sputum culture conversion after 2 months of treatment was 45% in the 100mg twice-daily group, 42% in the 200mg twice-daily group and 29% among those receiving placebo [39]. Among participants who subsequently enrolled in a nonrandomized 24-month observational study, mortality was 1% among those patients who received delamanid for at least 6 months and 8% among those receiving delamanid for 2 months or less [40]. On 25 July 2013, the European Medicines Agency refused marketing authorization for delamanid for treatment of MDR-TB, stating that data from the 2-month randomized controlled trial (RCT) along with the nonrandomized longer duration trial were insufficient to demonstrate its effectiveness if used for 6 months for MDR-TB treatment [41].

PA-824 has demonstrated EBA at least as great as that of delamanid [42,43]. In a 2-week combination EBA study, PA-824 and moxifloxacin along with pyrazinamide outperformed standard first-line TB treatment [44], and this combination is now being tested in a Phase 2B clinical trial with PA-824 given at doses of 100 or 200mg daily. Metronidazole, a candidate for ‘repurposing’ for TB treatment, was tested in a 2-month clinical trial among patients with MDR-TB, but the trial had to be stopped early because of high rates of peripheral neuropathy (50 vs. 12% in the placebo arm) [45].

OXAZOLIDINONES

Sutezolid is a new oxazolidinone protein synthesis inhibitor in Phase 2 development. Sutezolid is more potent than linezolid against *M. tuberculosis in vitro*. At clinically relevant exposures, sutezolid also may have a lower potential for mitochondrial toxicity [46,47]. Sutezolid is also more potent than linezolid against TB in mice [48], in which it contributes activity to several novel bedaquiline-containing regimens. In multiple ascending dose studies in humans, doses up to 1200mg daily for 28 days were well tolerated with no haematologic or neurologic safety signals [49]. In a 2-week EBA study of sutezolid 600mg twice daily vs. 1200mg once daily, both doses demonstrated bactericidal activity. Asymptomatic elevations in transaminases were seen in seven out of 50 patients [50]. In July 2013, global rights to clinical development of sutezolid were acquired by Sequella; further clinical development plans for this drug are not publicly available [51]. AZD5847 is another oxazolidinone in

clinical development. A 14-day EBA trial is currently enrolling with results expected in mid-2014.

Multiple case series and meta-analyses suggest that linezolid, an already-marketed drug, significantly improves treatment outcomes among patients with XDR-TB. In a clinical trial among 41 patients with chronic XDR-TB, adding linezolid as a single drug to an ineffective regimen resulted in a remarkable 87% culture conversion by 6 months of treatment [52]. Acquired resistance was seen but was rare and occurred late in therapy, suggesting that linezolid has a high barrier to resistance. Adverse events were common and included myelosuppression, optic neuropathy and peripheral neuropathy.

ETHYLENEDIAMINES

SQ109 is an ethylenediamine with structural similarities to ethambutol but a distinct mechanism of action, disruption of cell wall assembly [53]. In-vitro studies suggest additive effects when combined with rifamycins, bedaquiline and sutezolid [54–56]. In mice, substitution of SQ109 for ethambutol increased the bactericidal effect [57]. However, in a 14-day EBA study, SQ109 at doses of 150 or 300mg had no detectable bactericidal activity. SQ109 is being tested for a longer duration as part of combination TB treatment for MDR-TB in Russia and drug-sensitive TB at African trial sites.

NEW TREATMENTS FOR TUBERCULOSIS: THE IMPACT OF HIV COINFECTION

Recent randomized clinical trials have demonstrated that there is a mortality benefit to initiation of ART prior to completion of TB therapy among patients with TB/HIV coinfection; beginning ART early in TB treatment is particularly beneficial for patients with CD4 cell counts less than 50 cells/ μ l [58–61]. Compatibility with commonly-used ART regimens is, thus, highly desirable for new TB drugs. Consideration must be given to metabolic drug interactions as well as overlapping toxicities of TB and HIV drugs [62,63]. It is essential that patients with HIV participate in trials of experimental TB regimens [64,65], given that risk of TB relapse and acquired resistance differs among patients with and without HIV, and we need treatments at doses that are effective for all.

CONCLUSION

Multiple novel drugs are in the pipeline for treatment of TB. New combinations involving investigational compounds and repurposed or dose-optimized existing drugs are being evaluated with the ultimate goal of short, well tolerated drug combinations that can be used safely with ART. Although the number of combinations available for testing is considerable, a more robust pipeline involving new drug classes is sorely needed, particularly for treatment of drug-resistant TB.

Acknowledgments

Authors on this manuscript acknowledge the support of the following grants: NIH grants K23AI080842 (K.E.D.) and R01AI090820 (E.L.N.).

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KEY POINTS

- For the first time in over 40 years, multiple new agents including some with novel mechanisms of action are in clinical development for TB. In mice, many of the new drugs show potential for shortening of treatment duration, but these results need confirmation in humans.
- A pathway for the evaluation of novel anti-TB drugs now exists from the laboratory to studies in murine models, studies of early bactericidal activity over 14 days as monotherapy or as combinations in patients, followed by 2-month trials to evaluate sputum culture negativity, then confirmatory Phase 3 studies.
- The coming year will bring results from a variety of Phase 2 and 3 trials, which could reveal new regimens capable of shortening the duration of treatment for drug-susceptible TB and improving the management of drug-resistant TB.
- Results from ongoing Phase 3 trials should provide critical insights into the value of new clinical biomarkers of treatment response based on sputum microbiology and the extent to which new and existing preclinical efficacy models predict results in patients.
- Drug–drug interactions amongst anti-TB drugs and between anti-TB drugs and antiretrovirals will require careful study to optimize the use of new anti-TB drugs.

Table 1

Investigational or existing drugs in Phase 2 or 3 clinical development for the treatment of tuberculosis disease

Drug	Class	Mechanism(s) of action	Target
Rifapentine	Rifamycin	Inhibition of RNA synthesis	DNA-dependent RNA polymerase
High-dose rifampin	Rifamycin	Inhibition of RNA synthesis	DNA-dependent RNA polymerase
Moxifloxacin	Fluoroquinolone	Inhibition of DNA synthesis	DNA gyrase
Bedaquiline	Diarylquinoline	Inhibition of ATP synthesis	F1F0 proton ATP synthase
PA-824	Nitroimidazo-oxazine	Inhibition of cell wall lipid synthesis, inhibition of protein synthesis, indirect effects of nitric oxide generation (?)	Unknown
Delamanid	Nitroimidazo-oxazole	Inhibition of cell wall lipid synthesis, inhibition of protein synthesis, indirect effects of nitric oxide generation (?)	Unknown
SQ109	Diethylamine	Inhibition of cell wall synthesis	Unknown
Linezolid	Oxazolidinone	Inhibition of protein synthesis	Ribosomal initiation complex
Sutezolid	Oxazolidinone	Inhibition of protein synthesis	Ribosomal initiation complex
AZD5847	Oxazolidinone	Inhibition of protein synthesis	Ribosomal initiation complex