# New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes

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**Purpose of review**
The aim is to review briefly the problems related to treatment of drug-susceptible and drug-resistant tuberculosis (TB), describe recent advances in the development of new drugs and new regimens, and discuss implications for control programmes.

**Recent findings**
Encouraging advances in TB drug research and development have been made since the turn of the century, resulting in a large number of new products introduced into the global portfolio.

**Summary**
Currently, nine compounds at least have advanced to clinical development, including four existing drugs redeveloped for TB indication and five new chemical entities. Present clinical trials are testing new combinations of drugs for a shortened treatment of drug-susceptible TB (<6 months duration) or the safety and efficacy of new drugs in addition to an optimized background therapy for the treatment of multidrug-resistant TB. There are at least 34 compounds or projects in the discovery and preclinical stages, including eight compounds in preclinical development. This increasing development of single compounds underscores the needs for a novel approach to test for optimal drug combinations that would be proposed for treatment of TB in all its forms, and the necessary collaboration of pharmaceutical companies, academia, research institutions, donors, and regulatory authorities.

**Keywords**
drug development, drug-resistant tuberculosis, drug-susceptible tuberculosis, multidrug therapy

## Introduction

Current treatment of tuberculosis (TB) is based on drugs that are more than 40 years old. Despite a demonstrated high efficacy in clinical trials [1], standardized short-course chemotherapy (SCC) of active drug-susceptible TB requires direct supervision to assure good adherence and prevent drug resistance [2]. Drugs that are active against resistant forms of TB are less potent, more toxic, and need to be taken for a long time (≥18 months). The recent emergence of virtually untreatable extensively drug-resistant TB (XDR-TB) poses a new threat to TB control worldwide. Furthermore, effective treatment of TB in persons coinfected with HIV is complicated due to drug–drug interactions. Shorter and simpler regimens that are safe, well tolerated, effective against drug-susceptible and drug-resistant TB, appropriate for joint HIV–TB treatment, and amenable to routine programmatic conditions are needed urgently. In the present paper, we review the problems related to current treatment of TB and its variants, and discuss recent advances in the development of new drugs and new regimens for the treatment of drug-susceptible and drug-resistant TB.

## The current treatment of tuberculosis

The current treatment of drug-susceptible TB is the result of a comprehensive series of trials conducted over 20 years by the British Medical Research Council [1] that has led to the definition of a 6-month four-drug regimen.

### Treatment of drug-susceptible tuberculosis in newly detected patients

The 6-month regimen includes rifampin, isoniazid, pyrazinamide, and ethambutol given daily or intermittently for two months, followed by rifampin and isoniazid for four months (Table 1). Treatment-limiting side effects vary [3], but most are not severe. Treatment regimens that are intermittent, or use rifampin during the intensive phase of treatment, offer some practical advantages, but their

**Table 1 Antituberculosis agents for treatment of drug-susceptible and drug-resistant tuberculosis**

| Group | Drugs | Characteristics |
| --- | --- | --- |
| Group 1 | First-line oral agents − isoniazid, rifampicin, ethambutol, and pyrazinamide | The most potent and best tolerated agents to be used in combined 6-month chemotherapy − each should be used if there is laboratory evidence and clinical history to suggest that it is effective. For patients with strains resistant to low concentrations of isoniazid but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (when isoniazid is used in this manner, it is considered a Group 5 drug; see below). |
| | New generation rifamycins − rifabutin and rifapentine | Rifabutin is used in place of rifampin under certain conditions such as treatment of TB in HIV patients on protease inhibitors. Rifapentine, a long-acting rifamycin, recommended by CDC for once-weekly continuation phase in low-risk, HIV-negative TB patients is presently in trials for treatment shortening, using higher or daily dosing. These two newer generation rifamycins have high cross-resistance to rifampin. |
| Group 2 | Injectable agents − kanamycin, amikacin, capreomycin, and streptomycin | All patients with MDR-TB should receive a Group 2 injectable agent if susceptibility is documented or suspected. Use of kanamycin or amikacin should be preferred, given the high rates of streptomycin resistance in drug-resistant TB patients and the fact that both these agents are low cost, have less toxicity than streptomycin, and have been used extensively for the treatment of drug-resistant TB throughout the world. |
| Group 3 | Fluoroquinolones − moxifloxacin, gatifloxacin, levofloxacin, and ofloxacin | All patients with MDR-TB should receive a Group 3 medication if the strain is susceptible or if the agent is thought to have efficacy. Currently, the most potent available fluoroquinolones in descending order based on in-vitro activity and animal studies are: moxifloxacin = gatifloxacin > levofloxacin > ofloxacin. If gatifloxacin is used, patients should undergo close monitoring and follow-up due to reports of severe dysglycaemia. |
| Group 4 | Oral bacteriostatic second-line agents − thioamides (ethionamide and prothionamide), cycloserine, terizidone, and *p*-aminosalicylic acid | Group 4 medications are added based on estimated susceptibility, drug history, efficacy, side-effect profile, and cost. |
| Group 5 | Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients) − clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, high-dose isoniazid[a], and clarithromycin | Group 5 drugs are not recommended by WHO for routine use in drug-resistant TB treatment because their contribution to the efficacy of multidrug regimens is unclear. Although they have demonstrated some activity *in vitro* or in animal models, there is little or no evidence of their efficacy in humans for the treatment of drug-resistant TB. However, they can be used in patients in whom adequate regimens are impossible to design with the medicines from Groups 1 to 4 in consultation with an expert in the treatment of drug-resistant TB. |

CDC, Centers for Disease Control; MDR, multidrug resistant; TB, tuberculosis.
[a] High-dose isoniazid is defined as 16−20 mg/kg per day.

efficacy has been challenged in comparison with the 6-month regimen, including rifampin throughout [4]. In a systematic review of regimens in previously untreated patients with bacteriologically confirmed pulmonary TB, regimens utilizing rifampin for the first 2 months only had significantly higher rates of failure, relapse, and acquired drug resistance than regimens that used rifampin for 6 months [5••]. There was little difference in efficacy between daily or thrice-weekly schedules of treatment, but there was insufficient evidence to support administration of twice-weekly treatment throughout therapy. As a result, the WHO now recommends the universal use of the 6-month rifampin throughout SCC regimen for the treatment of drug-susceptible TB, given under strict supervision [6••].

**Treatment of tuberculosis in patients previously treated, with monoresistance to isoniazid, or both**
A single 8-month 'retreatment' regimen (including isoniazid, rifampin, and ethambutol, with pyrazinamide added for the first 3 months and streptomycin added for the first 2 months − 2SHRZE/1HRZE/5HRE) was earlier recommended for patients with a history of prior treatment of TB [7] and is still commonly used worldwide

[8]. This regimen was initially designed for resource-poor settings with low prevalence of initial drug resistance, and for patients previously treated with a regimen that included rifampin administered only for the first 2 months of therapy. This regimen was considered adequate for patients with resistance to a single drug other than rifampin (e.g. isoniazid). However, it has been criticized [9] because of poor results in settings of high initial drug resistance [8,10] or when rifampin is used throughout the initial phase [11]. Importantly, no randomized trial of the 8-month retreatment regimen has ever been conducted [12**]. A meta-analysis [12**] of studies of rifampin-containing regimens in patients with monoresistance to isoniazid showed that longer duration of rifampin, use of streptomycin, daily therapy initially, and treatment with a greater number of effective drugs were associated with lower rates of failure, relapse, and acquired drug resistance. This reinforces the need to expand access to drug sensitivity testing (DST) and to develop an evidence base for treatment recommendations in previously treated patients (of note, the standard 8-month 'retreatment' regimen may still be used in patients who relapse or return after default but not in those who fail treatment [7]).

### Treatment of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis

Combinations of first and second-line drugs are used for the treatment of multidrug-resistant TB (MDR-TB) and XDR-TB based on the results of DST [13*] (Table 1). Current regimens for MDR-TB and XDR-TB are, however, complicated due to long duration, high toxicity, poor tolerance, and high cost, resulting in poor outcomes [8,14]. In a recent meta-analysis [15*] of 33 studies, the overall treatment success rate (proportion of patients who were cured or completed treatment) was only 62% [95% confidence interval (CI) 58–67], with a nonstatistically significant 10% difference in treatment success between studies of individualized (64%, 95% CI 59–68) and standardized treatment regimens (54%, 95% CI 43–68). In another meta-analysis [16*] of 36 studies, 62% (95% CI 57–67) of patients had successful outcomes, whereas 13% (95% CI 9–11) defaulted, 11% (95% CI 9–13) died, and 2% (95% CI 1–4) were transferred out. Reported mortality among patients with HIV infection is particularly high [14,17]. Simpler, safer, and more effective treatments for MDR-TB are, therefore, an urgent priority [18].

### Treatment of tuberculosis–HIV coinfection

Early introduction of antiretroviral therapy (ART) has been shown to reduce the incidence of HIV-associated TB [19]. Although the optimal time to start ART in HIV-infected TB patients has not yet been defined [20], most recent WHO guidelines recommend starting ART as soon as possible after diagnosis of TB, regardless of CD4 lymphocyte count [21]. The two main difficulties

in combining these drugs derive from (i) potentially severe drug–drug interactions between rifampin and selected ART drugs (particularly the protease inhibitors) and (ii) the emergence of the immune reconstitution inflammatory syndrome (IRIS) characterized by a worsening clinical picture or the appearance of new TB lesions [19,22,23*]. Drug interactions arise because rifampin is a potent inducer of the hepatic cytochrome CYP450 enzyme system that reduces the plasma concentration of coadministered drugs metabolized through this pathway. Recent studies [24*,25] suggest, however, that efavirenz-based regimens are compatible with rifampin-based TB therapy, whereas standard twice-daily doses of nevirapine may provide acceptable (though slightly inferior) efficacy and safety in patients with contraindications to efavirenz. The situation is more complex for coinfected patients treated with ART regimens containing protease inhibitors, as their concentrations are decreased by concomitant use of rifampin [26]. Because of its lower effect on protease inhibitor concentrations, rifabutin has been proposed as an alternative to rifampin, and studies are currently underway to define a safe and effective standardized dosing approach when combined with protease inhibitors [27,28].

### Treatment of latent tuberculosis infection

The objective of latent tuberculosis infection (LTBI) treatment is to prevent the development of TB disease in high-risk populations such as contacts of infectious patients or TB-infected HIV-positive patients. Isoniazid monotherapy reduces the risk of TB in contacts of infectious TB patients by at least 60% over 2 years when taken for 6–9 months [29–31]. A 4-month daily rifampin regimen may result in better compliance and fewer adverse events than combined rifampin regimens or the 6–9-month isoniazid regimen [32–34,35*]. In HIV-positive individuals, isoniazid monotherapy has been shown to reduce the risk of TB by about 60% (95% CI 51–81), with a greater benefit among tuberculin skin test-positive individuals (62%) than among people with a negative test (17%) [36]. In this population, however, diagnosis of LTBI and exclusion of active TB are difficult, especially in resource-poor, high-prevalence settings [37*].

## Recent advances in clinical development

After 40 years of neglect, encouraging advances have been made in TB drug research and development, resulting in a large number of new projects introduced into the global portfolio. Currently, there are at least nine compounds in clinical development: two in phase III, four in phase II, and three in phase I trials (Stop TB Partnership Working Group on New TB Drugs 2009) (Table 2). Among these, four are existing drugs redeveloped for a TB indication and five are new chemical entities (Fig. 1).

**Table 2 The clinical development phases**

| | |
|---|---|
| Phase I trials | Initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness; may include healthy participants or patients. |
| Phase II trials | Controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks. This phase can also be used to establish dose ranges and dose–response relationships. Phase IIa addresses dose and dose–response with limited numbers of participants (typically 30–50), whereas phase IIb engages risks and efficacy with larger numbers of participants (typically 200–500). |
| Phase III trials | Expanded controlled and uncontrolled trials conducted after preliminary evidence suggesting effectiveness of the drug has been obtained, that are intended to gather additional information to evaluate the overall benefit–risk relationship of the drug and provide adequate basis for physician labeling based on established short and long-term safety and efficacy of the drug. |
| Phase IV trials | Postmarketing studies to delineate additional information, including the drug's risks, benefits, and optimal use in populations. |

Source: http://clinicaltrials.gov/ct2/info/ from ClinicalTrials.gov 2009.

## Clinical (re-)development of existing drugs

A number of known drugs are being currently investigated for their contribution in simplification or improvement of the current TB drug regimen. These include rifamycins and fluoroquinolones.

### Rifamycins (rifampin and rifapentine)

Rifampin, used at 10 mg/kg, is the cornerstone of first-line therapy against TB. Higher doses have recently been shown to have higher bactericidal activity [38], and clinical trials assessing the potential use of high-dose rifampin to shorten TB treatment will begin soon. Because of its greater potency against *Mycobacterium tuberculosis* and its longer half-life compared with rifampin, rifapentine is an attractive candidate for shortening or simplifying therapy [39]. In an earlier phase III trial using a once-weekly rifapentine and isoniazid in the continuation phase of treatment, efficacy was suboptimal, especially in HIV-infected patients who were at increased risk of relapse with acquired rifamycin resistance [40,41]. Recent studies [42,43] in the mouse model suggested that a regimen of daily rifapentine, pyrazinamide, and either isoniazid or moxifloxacin could dramatically shorten the duration of treatment. Phase II trials are underway to evaluate the ability of rifapentine given 5 or 7 days a week to shorten the treatment.

### Fluoroquinolones

Fluoroquinolones are broad-spectrum antimicrobial agents that have shown potent activity against *M. tuberculosis* *in vitro* and *in vivo*. They are used as second-line drugs in MDR-TB treatment [44,45]. Two newer methoxyfluoroquinolones, gatifloxacin and moxifloxacin, have demonstrated more potent in-vitro activity against *M. tuberculosis* than the older compounds, ofloxacin and ciprofloxacin [46–49]. In a phase II trial in South Africa, the rates of

**Figure 1 Compounds that are currently in preclinical or clinical development for the treatment of active tuberculosis**
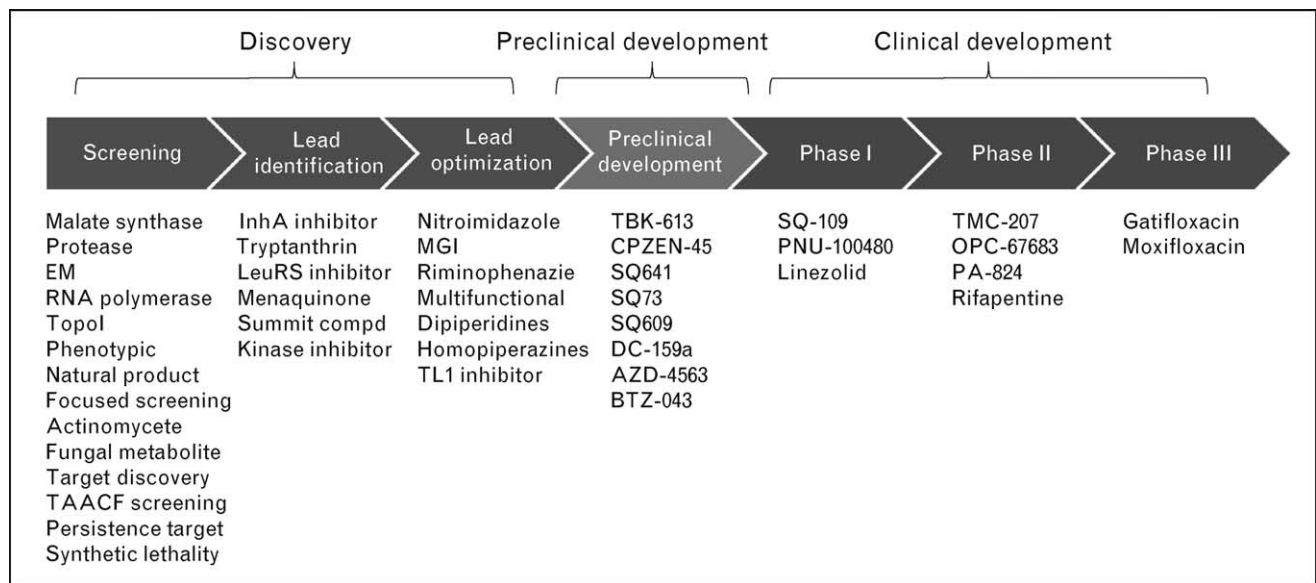


Produced by the Working Group on New Drugs of the Stop TB Partnership.

elimination of *M. tuberculosis* from serial sputum cultures collected over the first 2 months of treatment were more rapid when gatifloxacin or moxifloxacin, but not ofloxacin, were substituted for ethambutol in the intensive phase of therapy [50•]. Three other phase IIb trials investigated the effect of moxifloxacin, substituted either for ethambutol or isoniazid during the intensive phase of treatment, on culture conversion at 2 months; one found a dramatic effect on 2-month sputum conversion [51•], whereas the other two showed limited or no effect [52,53•]. Both compounds are presently in phase III trials evaluating their potential for shortening therapy of drug-susceptible TB when substituted for ethambutol or isoniazid in a 4-month regimen [54].

### New drugs in clinical development

Much progress has been done in drug development over the past decade. Here, we present the compounds that are presently in clinical development phases.

#### Diarylquinolines (TMC-207)

TMC-207, a novel ATP synthase inhibitor developed by Tibotec BVBA, Mechelen, Belgium, is highly potent against both drug-susceptible and drug-resistant strains of *M. tuberculosis* [55]. In a 7-day early bactericidal activity (EBA) study [56], TMC-207 at a dose of 400 mg daily demonstrated late (5–7 days) bactericidal activity similar to that of isoniazid or rifampin. The safety and efficacy of TMC-207 is being evaluated in a phase IIb placebo-controlled, double-blind, randomized trial in newly diagnosed MDR-TB patients, in which either the investigational drug or placebo is added to an optimized background regimen. Results in the initial group of 50 patients showed that the TMC-207 arm achieved a significantly higher rate of sputum culture conversion at 2 months (48% in the TMC arm vs. 9% in the placebo arm) [57••]. The second stage of the study is now evaluating microbiological outcomes at 6 months in 200 patients.

#### Nitroimidazoles (PA-824 and OPC-67683)

Nitroimidazoles belong to a novel class of antimycobacterial agents that are active against drug-susceptible and drug-resistant organisms [58]. They show similar activity against both replicating and nonreplicating organisms, which suggests a potential to shorten the therapy [59]. Two nitroimidazoles are currently in clinical development. The first, OPC-67683, developed by Otsuka Pharmaceutical Co. Ltd. (Tokyo, Japan), is a member of the nitroimidazo-oxazole subclass [60]; it is currently being evaluated in a phase II trial for the treatment of MDR-TB. The second, PA-824, a member of the nitroimidazo-oxazine subclass, is being developed by the TB Alliance New York City, New York, USA, and has shown good safety and tolerability in adult pulmonary TB patients in South Africa when given once daily for 7 days [61].

#### Oxazolidinones (linezolid and PNU-100480)

As a class, oxazolidinones possess a broad spectrum of antibiotic activity, encompassing anaerobic and Gram-positive aerobic bacteria, as well as mycobacteria [62]. Linezolid, the only approved drug in the class, has modest in-vitro activity against *M. tuberculosis*. Although used off-label in combination regimens for the treatment of MDR-TB, its efficacy is unclear. Modest EBA against *M. tuberculosis* was reported in patients with cavitary pulmonary TB during the first 2 days of administration, but the effect waned thereafter [63]. A retrospective assessment in four European countries did not show objective advantages of adding linezolid 600 mg daily to individualized multidrug regimen for treatment of MDR-TB/XDR-TB patients due to severe side effects [64]. A retrospective review [65] in the United States, however, reported more positive findings. A reduced dose of 300 mg might retain efficacy while causing fewer side effects [66]. Linezolid 600 mg is presently being tested in a phase IIa trial for treatment of XDR-TB in the Republic of Korea, and the 300 mg dose is under investigation in a phase IIa MDR-TB pilot trial in South Africa.

PNU-100480 is a close analogue of linezolid developed by Pfizer, New York City, New York, USA, that demonstrated slightly better activity *in vitro* [67]. Recent mouse model studies [68,69] showed marked improvement of bactericidal activity when added to current first-line TB drugs or used in combination with moxifloxacin and pyrazinamide. These findings suggest that PNU-100480 has the potential to significantly shorten therapy for both drug-susceptible and drug-resistant TB. This compound is currently in phase I trials.

#### Ethylenediamines (SQ-109)

SQ-109 is a derivative of ethambutol that appears to have a different mechanism of action [70]. The substitution of SQ-109 for ethambutol in the standard regimen demonstrated increased efficacy in the mouse model [71]. A phase I single-dose study has been completed and a phase I dose-escalation study is underway.

### New drugs in preclinical development

Development of new drugs is a complex, lengthy, and expensive process, involving a series of stages (discovery, lead identification, and lead optimization), ultimately leading into preclinical development [72••]. Each of these early stages has a substantial rate of attrition. There are today at least 34 compounds or projects in the discovery and preclinical stages, including eight compounds in preclinical development, seven projects in lead optimization, six in lead identification, and 14 in the high-throughput screening stage of discovery (Fig. 1).

## The programmatic implications

A unique series of critical challenges must be faced in the development of new drugs for TB. First, as the 6-month standard regimen has 95% efficacy under trial conditions, the most appropriate design to test the efficacy of new drugs/regimens for drug-susceptible TB is one of non-inferiority. This requires the recruitment of a large number of patients who must be followed closely for a long period of time (usually 12–24 months after treatment) in order to detect trial endpoints (failure and relapse) reliably [73••]; such trials are thus lengthy and expensive, typically costing tens of millions of dollars. A second challenge is the need for combination therapy in order to inhibit the growth of various mycobacterial populations and prevent the development of drug resistance. If, for selection of a proper combination, new drugs were added to, or substituted into, the current regimen one at a time, it would take 20–30 years to develop a new regimen that contains three to four new drugs [54]. This has led drug developers to select the use of superiority trial designs in MDR-TB patients, that entail testing the new drug against placebo, in conjunction with an optimized background therapy determined according to patients' treatment experience and DST results [74•]. This approach requires much smaller sample sizes than noninferiority trials, and allows an equal distribution of key potential confounding factors between study arms. This, however, may have labelling implications, as if a drug receives provisional licensing as an addition to an optimized regimen for MDR-TB, its role in the treatment of drug-susceptible TB and the selection of appropriate companion drugs remain to be established. Furthermore, given that misuse of a new compound may induce rapid emergence of drug resistance, a programmatically essential question arises concerning the strategy for introduction of a new compound into the public and private sectors. This issue should be addressed early in the process of drug development, ideally before new drugs are marketed. This highlights the difficulty of translating the initial regulatory approval of a new drug into subsequent recommendations for combination treatment regimens. It also underscores the need for an innovative approach to identify optimal new drug combinations that would involve pharmaceutical companies, academia, research institutions, donors, and regulatory authorities.

## Conclusion

TB continues to be one of the greatest challenges in global health. Current therapeutic agents against TB are life-saving for many patients, but cannot overcome increasing new challenges, including the creation and dissemination of MDR-TB/XDR-TB and the need for simultaneous treatment of TB and HIV. Recent advances in TB drug research and development are encouraging, with nine compounds already in the clinical development pipeline, including five new chemical entities specifically developed against TB. However, this slender pipeline is not likely to be sufficient. New drugs are needed that have strong, synergistic and complementary activities against various *M. tuberculosis* subpopulations in order to shorten TB treatment, be effective against MDR-TB/XDR-TB, and be easily administered in conjunction with ART. Furthermore, from a programmatic standpoint, it is imperative to test new combinations of new and old drugs in order to avoid misuse of the new compounds and prevent emergence of novel resistance. This calls for the development of a broader drug pipeline and a new paradigm for the identification of novel TB drug combinations. It requires the wide involvement of all relevant parties (industry, academia, drug regulatory agencies, and international policy-making agencies) who must collaborate effectively to deliver optimal future therapies for TB.

## Acknowledgements

## References and recommended reading

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