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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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...
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.
early introduction of antiretroviral therapy (ART) has been shown to reduce the incidence of HIV-associated 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].

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).
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

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**Table 2 The clinical development phases**

<table>
<thead>
<tr>
<th>Phase I trials</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II trials</td>
<td>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).</td>
</tr>
<tr>
<td>Phase III trials</td>
<td>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.</td>
</tr>
<tr>
<td>Phase IV trials</td>
<td>Postmarketing studies to delineate additional information, including the drug’s risks, benefits, and optimal use in populations.</td>
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elimination of *M. tuberculosis* from 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-oxazole 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.

**Ethylendiamines (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
The authors wish to thank Dr Zhenkun Ma and Dr Omar Vandal for their help in collecting information on new drugs for TB.

A.V. works with a TB clinical trials group that sometimes collaborates with pharmaceutical manufacturers. He reports no financial conflicts.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 287–289).

6 This is the first ever done systematic review and meta-analysis of treatment regimens for active TB, investigating the effect of duration and intermittency of rifampin use on TB treatment outcomes. This analysis found that TB treatment outcomes were significantly worse with shorter duration of rifampin, or with initial drug resistance to isoniazid, streptomycin, or both. Treatment outcomes were similar with all intermittent schedules evaluated, but there was insufficient evidence to support administration of treatment twice weekly throughout therapy.
8 The new WHO treatment guidelines have some important changes compared with former ones. Most important is that the 8-month ethambutol-containing regimen has been abandoned in view of the higher rates of failures and relapses seen in meta-analyses. Other changes include more restricted recommendations for the use of intermittent regimens, use of ‘retreatment’ regimen and indications for appropriate use of MDR-TB treatment, and daily intensive phase for joint treatment of TB and HIV. All previously treated patients should have culture and DST prior to start of treatment.
Infectious diseases


This is the first report investigating evidence on the use of the WHO recommended ‘retreatment’ regimen for patients with a history of previous treatment or documented isoniazid monoresistance. This review found that there were few published studies to support the use of the current standardized retreatment regimen. A pooled analysis of 33 trials in 1907 patients with mono-resistance to isoniazid showed that a longer duration of rifampin, use of streptomycin, daily therapy initially, and treatment with a higher number of effective drugs was associated with lower failure, relapse, and acquired drug resistance rates.


These new guidelines present some important innovations in the management of MDR-TB and XDR-TB, especially in patients with dual HIV–TB infection. The guidelines, first, stress the use of rapid DST in all HIV-infected patients who are smear-positive and quick enrolment on treatment in order to avoid the high mortality associated with untreated MDR-TB; second, it introduces the use of DST for second-line drugs for XDR-TB case finding; third, it strongly recommends to introduce outpatient models of care, preferably community-based, with a patient-centered approach; and fourth, it emphasizes infection control, especially in congregate settings, with detailed guidance.


This is the first systematic review of treatment outcomes among patients with MDR-TB that analysed the effect of differences in treatment regimen design, study methodology, and patient population. This study showed that successful outcome was related to treatment duration (at least 18 months) and use of directly observed therapy (DOT) throughout treatment.


This is the first systematic review and meta-analysis of treatment outcome in MDR-TB patients published in 2009. Results were about the same as the above review. In addition, authors identified several factors associated with poor outcomes (male sex, alcohol abuse, low BMI, smear positivity at diagnosis, fluoroquinolone resistance, and presence of an XDR resistance pattern). Factors associated with successful outcome were surgical intervention, absence of previous treatment, and fluoroquinolone use.


19 Lawn SD, Gail-Bekker L, Miller R. Immune reconstitution disease associated with successful outcome were surgical intervention, absence of previous treatment, and fluoroquinolone use.


This is the report of a consensus meeting in which case definitions for paradoxical TB-associated IRS, ART-associated TB, and unmasking TB-associated IRS were developed for standard use in high-income and resource-limited settings.


This cohort study suggested that efavirenz-based ART could be used in conjunction with rifampicin-based therapy in HIV patients coinfected with TB with similar efficacy as in HIV patients without TB, whereas virological outcomes were inferior when nevirapine-based ART was commenced while taking antituberculosis treatment.


This meta-analysis of the published studies on compliance, toxicity, and cost effectiveness of the two strategies suggests that the 4-month rifampin therapy is associated with improved compliance, safety, and cost compared with 9-month isoniazid.


This study gives a good review and update of the tools for identification of persons with LTBI and of the potential preventive treatment regimens to be used in various populations the most at risk of developing disease.


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48 Hu Y, Coates AR, Mitchison DA. Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of Mycobacterium tuberculosis. Anti-


This phase IIb trial measured the rate of decline of viable colony counts in the intensive phase of treatment, using various combinations of drugs including fluoroquinolones (ofloxacin, gatifloxacin, and moxifloxacin) substituted for ethambutol in the standard WHO recommended 6-month regimen. This study applied new modelling techniques for best estimation of fall in counts in unit time for each patient with each regimen, thus allowing reliable comparison of sterilizing activities of each of the tested regimens. It also measured the activity of each regimen on sputum culture conversion at 2 months, as well as on time to sputum culture conversion.


This study investigated the effect of substituting moxifloxacin for ethambutol in the first 2 months of treatment of sputum smear-positive pulmonary TB and found a superior activity of the moxifloxacin-containing regimen in terms of speed of sputum culture conversion.


These two studies [52,53] investigated the effect of substituting moxifloxacin for ethambutol or isoniazid in the first 2 months of treatment of sputum smear-positive pulmonary TB. Neither found a superior activity of the moxifloxacin-containing regimen in terms of speed of sputum culture conversion. In contrast to the Durban [50] and Rio [51] studies, these two trials were multicenter trials and did not standardize laboratory methods.


This is the first report of a phase II trial carried out with a new chemical entity purposely developed to treat TB. This trial used the original design of testing for microbiological efficacy when added to an optimized background therapy in patients with MDR-TB [see also Barry CE 3rd, Unorthodox approach to the development of a new antibacterial therapy. N Engl J Med 2009; 360: 2466–2467].

58 Stover CK, Warrener P, VanDerWantr DR, et al. A small-molecule nitroimi-

59 Singh R, Manjunatha U, Boshoff HJ, et al. PA-824 kills nonreplicating Myco-

60 Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a nitro-dihydro-

61 Ginsberg AM, Laurenzi MW, Rouse DJ, et al. Safety, tolerability, and phar-


64 Migliori GB, Eker B, Richardson MD, et al. A retrospective TBNET assess-
ment of linezolid safety, tolerability and efficacy in multidrug-resistant tuber-

65 Schecter GF, Scott C, True L, et al. Linezolid in the treatment of multidrug-


67 Cynamon MH, Klempes SP, Sharpe CA, Chase S. Activities of several novel oxazolidinones against Mycobacterium tuberculosis in a murine model. Anti-


69 Williams KN, Brickner SJ, Stover CK, et al. Addition of PNU-100480 to first-
line drugs shortens the time needed to cure murine tuberculosis. Am J Respir Crit Care Med 2009; 180:371–376.


72 Showalter HD, Dennis WA. A roadmap for drug discovery and its translation to small molecule agents in clinical development for tuberculosis treatment. Tuberculosis (Edinb) 2008; 88 (Suppl 1):S3–S17. This remarkable review describes the key stages of drug discovery and early development, including target identification and validation, assay development and screening, confirmed hits to leads, lead optimization, and progressing develop-
ment candidates to an investigational new drug filing, and provides particular examples of this process in the development of small-molecule treatments for TB.

73 Nunn AJ, Phillips PP, Gillespie SH. Design issues in pivotal drug trials for drug-

With the increasing number of new products being advanced through preclinical and clinical development, the whole issue of clinical trial design to evaluate safety and efficacy has to be reevaluated. This review describes very clearly the points to be addressed when developing phase III trials for drug-susceptible TB with new drugs, regimens, or both.

74 Sacks LV, Behmam RE. Developing new drugs for the treatment of drug-

Simplifying and shortening treatment for drug-sensitive TB and providing new treatment options for drug-resistant TB constitute two principal goals in the development of novel drugs for TB. This study describes a new approach of investigating efficacy of novel treatments in the setting of drug-resistant disease.