

# Rip Van Winkle Wakes Up: Development of Tuberculosis Treatment in the 21st Century

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The increase in drug-resistant tuberculosis and the global pandemic of human immunodeficiency virus infection–related tuberculosis threaten global tuberculosis control. There are needs for improved therapy in all aspects of tuberculosis treatment: treatment of latent infection, active drug-susceptible disease, and particularly, drug-resistant disease. Fortunately, at this time of great need, the field of tuberculosis drug development has reemerged after >30 years of inactivity. I review the specific needs for new treatment regimens, the pathways of tuberculosis drug development, and the agents that are currently in clinical development. There is renewed interest in the rifamycin class; studies in the mouse model suggest that higher doses of rifampin or rifapentine may markedly improve the treatment of drug-susceptible disease. Fluoroquinolones may allow shorter treatment durations for drug-susceptible disease, though initial phase 2B trials have shown inconsistent activity. Novel drugs, such as TMC207, OPC-67683, PA824, SQ109, and PNU-100480, may improve the treatment of drug-resistant and drug-susceptible tuberculosis.

Short-course tuberculosis (TB) treatment remains a triumph of drug development, clinical trial methodology, and public health intervention. Over a 35-year period, TB was transformed from an incurable illness associated with 50% mortality and requiring prolonged hospitalization into an infection that could be cured with 6–9 months of outpatient treatment while preventing transmission to others [1, 2]. Along the way, TB research was at the forefront of clinical trials methodology, pioneering the development of randomized trials, the science of microbial drug resistance, and the identification of treatment adherence as a key determinant of outcomes [3–5].

The regimen developed from this process, directly observed treatment, short-course (DOTS), became the basis for global TB control and led to major improvements in incidence and drug resistance in some areas of the world. A victim of its own success, TB drug development came to a virtual halt in the 1980s. The perception was that the problem of TB treatment was

solved, and all that was needed was an application of the DOTS strategy.

Events in the 1990s demonstrated the shortsightedness of this conclusion. The combination of human fallibility (inadequate attention to treatment adherence) [6] and microbial infallibility (the inevitability of resistance if combination therapy is not ensured) led to outbreaks of multidrug-resistant tuberculosis (MDR-TB) [7, 8]. The global pandemic of human immunodeficiency virus (HIV) disease led to overwhelming increases in TB incidence in settings with high burden [9]. Recent events in South Africa have shown the public health emergency that results when MDR-TB and HIV infection occur in the same setting [10].

In this time of great need, TB drug development is reemerging. New ways of using currently available drugs and the identification of new drug classes hold great promise to improve treatment. I will review the specific needs for improved treatments, the pathways of TB drug development, and the drugs currently in clinical development.

## THE NEEDS

There is a need for improvements in all aspects of TB treatment (Table 1). The effectiveness of treatment of latent TB infection is limited by poor completion rates

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**Table 1. Problems in Current Tuberculosis (TB) Treatment and Goals for TB Drug Development**

Problems in TB treatment	Goals for TB drug development
Poor completion of treatment of latent TB infection	Regimens that are much shorter than the current standard (9 months of daily isoniazid); regimens that are active when given infrequently (1–2 times per week) to foster directly observed preventive therapy
Lack of proven therapy for close contacts of patients with MDR-TB	Effective regimens of a novel drug(s) for contacts of patients with MDR-TB
Inability to easily identify TB in evolution from latency to active disease in young children and patients with HIV infection	Treatment regimens for close contacts that are potent enough to cure TB in evolution and prevent selection of drug resistance
Poor completion of treatment of active TB in some high-burden settings	Regimens that are much shorter than the current standard (6–9 months of rifampin-based therapy)
Suboptimal treatment outcomes among patients with advanced HIV disease or extensive cavitary pulmonary disease	More-potent regimens that are effective for all subgroups of patients with active TB; regimens that retain potency when administered intermittently (1–3 times per week)
Substantial toxicity associated with the standard regimen	Regimens that have a very low risk of serious toxicity (< 1%), particularly hepatotoxicity
Drug interactions between rifampin and many other drug classes, particularly antiretroviral drugs	Potent regimens that do not include rifampin
Poor outcomes, prolonged duration, and toxicity of current regimens for drug-resistant TB	Well-tolerated regimens that cure MDR-TB with <1 year of treatment
Development of resistance to new classes of drugs (eg, fluoroquinolones)	Identification of new drugs that have limited activity against other bacterial pathogens; development of coformulated regimens that prevent selective drug use
Lack of data on TB treatment among children	Assurance of the involvement of children in TB drug development; child-friendly formulations of new drugs and multidrug regimens

**NOTE.** MDR, multidrug-resistant.

of the standard regimen (9 months of daily isoniazid) [11, 12] and lack of effectiveness for patients infected with drug-resistant isolates. In addition, the expansion of treatment of latent TB to contacts at high risk who have HIV coinfection and/or are young children is limited by the difficulty of identifying those patients in the process of evolving from initial infection to active disease (ie, TB-in-evolution). Treatment programs are understandably concerned about the risk of undertreating TB-in-evolution and, thereby, selecting for drug resistance. Better tests for TB-in-evolution would be valuable, but a simpler solution may be the identification of treatment regimens of sufficient potency to cure those patients with evolving TB.

**Drug-susceptible TB.** Despite the moniker of short-course treatment, retaining patients in a treatment program for 6 months can be difficult, particularly in settings in which HIV infection-related TB is overwhelming the capacity of TB-control programs. Furthermore, recent studies and meta-analyses have shown that the standard regimen does not perform well in key patient subgroups, particularly patients with advanced HIV disease [13] and those with extensive cavitary pulmonary involvement [14–16]. The optimal treatment for such patients is uncertain; some treatment guidelines suggest prolonging therapy to 8–9 months [17], but doing so creates complexity for local programs. The identification of shorter and more potent regimens would facilitate completion of therapy, allow an expansion in the ability to supervise that therapy, and allow use of a standard regimen for all patients.

Current regimens for active TB have a concerning risk of serious toxicity, particularly hepatotoxicity [18, 19]. The TB

field has become overly accustomed with a 2%–5% risk of hepatotoxicity; in other areas of medical therapy, such as diabetes treatment, such a risk would lead to drug withdrawal. In addition, current regimens frequently cause nausea, vomiting, and rash [18]—adverse effects that are seldom life-threatening but that certainly complicate treatment. Therefore, the identification of regimens with reduced risks of both serious toxicity and common bothersome adverse effects is a key goal for drug development.

Rifampin, the key drug in current TB treatment regimens, probably has more clinically significant interactions than any other drug in the pharmacopoeia [20]. Particularly problematic, because of the intersections between TB and the global pandemics of HIV infection and diabetes mellitus, are the interactions between rifampin and some antiretroviral drugs [21, 22] and oral antidiabetic drugs [23, 24].

**Drug-resistant TB.** Even in well-established treatment programs, 20%–30% of patients with MDR-TB experience therapy failure [8]. The treatment duration required to achieve even these suboptimal treatment outcomes (18–24 months) greatly limits the number of patients who can be treated. Furthermore, the poor tolerability of current second- and third-line drugs limits treatment completion and program expansion. Although less publicized than MDR-TB, treatment outcomes among patients infected with isolates having lesser degrees of drug resistance (isoniazid resistance with or without resistance to drugs other than rifampin) are suboptimal. Treatment failure among patients infected with isoniazid-resistant isolates is one of the key sources of new MDR-TB cases. Thus, there is a great need

for the identification of more effective and better tolerated regimens for treatment of drug-resistant TB.

As new potent drug classes are identified, it will be critical to prevent the development of resistance. One way to do this is to develop coformulated regimens that prevent selective drug use, as has been done for the artemisinin derivatives for the treatment of *Plasmodium falciparum* malaria. Another way to prevent development of resistance to new TB drugs is to prioritize the agents that have minimal activity against common bacterial pathogens. For example, fluoroquinolones are being evaluated for the treatment of drug-susceptible TB. However, the usefulness of fluoroquinolones in TB treatment will be curtailed by resistance [25–27], driven in part by the use of this drug class for other common infections [28]. Conversely, widespread use of fluoroquinolones for TB treatment is likely to hasten the development of problematic drug resistance in other pathogens for which this drug class plays a key role in treatment [29].

Finally, one of the key shortcomings of TB drug development efforts in the 20th century was the virtual exclusion of children. As a result of this omission, there are fundamental uncertainties about the treatment of the estimated 1,000,000 children who develop active TB each year [30, 31] and an inexcusable lack of child-friendly drug formulations. Children must be included in current TB drug development efforts to ensure that improvements in therapy are applicable to all patients [32].

## OVERVIEW OF CURRENT TB DRUG DEVELOPMENT STRATEGIES

There are currently more drugs in development for TB treatment than at any time in the past 40 years. I will only review the drugs that are currently in human trials; additional new agents are in preclinical development. Before reviewing each drug class, it is useful to review the kinds of studies that are part of TB drug development.

The most important preclinical step in the evaluation of a new agent is an evaluation of its activity in the mouse model of TB treatment. Measures of *in vitro* drug activity do not necessarily correlate with sterilizing activity (ie, the ability to kill the relatively dormant bacilli that survive the initial weeks of TB treatment) [33]. The mouse model has been quite successful in identifying the activity of individual drug and drug combinations [34].

**Phase 1 and phase 2 studies.** After an agent has been shown to be effective in the mouse model and has satisfactory preclinical safety, phase 1 studies of safety, tolerability, and pharmacokinetics can be done. The first use of a new agent in patients with TB is usually an evaluation of its activity as monotherapy in the first 1–2 weeks of TB treatment. Sputum samples are collected daily for quantitative culture on solid media, thus allowing an analysis of the activity of the new agents on the

basis of sputum mycobacterial load (often termed early bactericidal activity) [35]. Activity during the first 2 days of monotherapy correlates with the ability of a drug to prevent selection of drug resistance [35]; activity during days 2–14 of monotherapy may correlate with sterilizing activity [36, 37]. Monotherapy studies show activity in humans and evaluate a range of possible doses.

Phase 2B studies evaluate the effect of a new drug in the context of multidrug therapy. The most common end point of phase 2B studies is sputum culture status after 2 months of therapy. In the large series of studies by the British Medical Research Council, differences in 2-month culture status correlated with the sterilizing activity of regimens [38]. The difference in 2-month culture status resulting from a new drug predicts the likelihood that it will allow for shortening the duration of treatment.

Despite its long history in TB drug development, 2-month culture status is a problematic end point. As a dichotomous end point at a single time, 2-month culture status requires relatively large sample sizes (75–225 patients per arm, depending on assumptions). Therefore, there is great interest in identifying more efficient end points for phase 2B studies. Changes in quantitative culture results over the first 2 months of therapy offer such an end point, because quantitative culture of sputum has a broad range ( $1 \times 10^8$  to  $\leq 1$  colonies/mL) [39]. Time to detection of growth in broth culture systems is another promising end point that assesses the quantity and metabolic state of bacilli in sputum [40, 41]. This technique may be more easily standardized across study sites, compared with quantitative culture on solid media. Changes in time to detection correlate with treatment failure [42].

**Phase 3 trials.** Phase 3 TB trials assess treatment failure (continued positive culture results during treatment) and recurrent (or relapsed) TB (positive culture results after treatment completion). Of patients with drug-susceptible TB, only 2%–5% experience therapy failure or relapse. Therefore, the most common phase 3 trial design for a new agent for drug-susceptible TB is to evaluate whether its addition will allow shortening of treatment duration while retaining this low risk of treatment failure or relapse. Such trials use a noninferiority design. Depending on the desired statistical power, a noninferiority trial for shortening treatment duration will require 500–900 patients per arm, followed up for 18–30 months.

There is increasing interest in using MDR-TB treatment to evaluate new drugs that have novel mechanisms of action [43]. As mentioned above, current treatment for MDR-TB is suboptimal. Therefore, the added activity of a new drug will be more easily detected in the context of MDR-TB treatment than in the treatment of drug-susceptible TB. Once limited to a few specialized centers, MDR-TB treatment has now expanded to a number of programs in countries with a high burden, thus

providing access to relatively large numbers of patients. Finally, the antiretroviral drug development field has shown how a flexible trial design in which patients are treated with individualized regimens with or without the new drug can provide a rigorous evaluation of the safety and tolerability of a novel agent [44, 45].

Treatment of drug-resistant TB may become the preferred pathway to initial drug approval for novel agents, as treatment of drug-resistant HIV infection was the path to licensure of the last 5 antiretroviral drugs approved in the United States. The appropriate end point for a pivotal study of a new agent in the treatment of drug-resistant TB is conversion of sputum culture results to negative (perhaps by 6 months of treatment) or death, because this is the definition of treatment failure. After more effective therapy has been identified, subsequent studies may then evaluate the effect of that new regimen on the duration of therapy required to cure drug-resistant TB, and such studies will probably use a noninferiority design. A key limiting factor for all of these types of studies is the lack of study sites, particularly in settings with a high burden, that are prepared to do high-quality clinical trials.

## DRUGS CURRENTLY IN CLINICAL DEVELOPMENT

**Enhanced rifamycins.** Despite its use in TB treatment for >30 years, there is increasing evidence that the current rifampin dose is suboptimal. The 600-mg (~10-mg/kg) dose of rifampin was chosen on the basis of a single randomized trial [46] and the finding that higher doses of rifampin were not well tolerated when given once or twice a week [47, 48]. The mouse model has shown that rifampin has increasing sterilizing activity with higher doses; indeed, the current dose appears to be at the low end of the activity curve [49]. Furthermore, reanalysis of older studies suggests that higher doses of rifampin (900–1200 mg/day) may be well tolerated when given daily [50, 51]. Finally, an initial nonrandomized study suggests that rifampin's activity is markedly increased at 1200 mg [52]. As a result, phase 2B trials are being designed to evaluate the activity and tolerability of high-dose daily rifampin.

Rifapentine was initially studied in once-weekly regimens because of its long half-life (~15 h). However, in this context, its activity was marginal [14, 53]. However, recent mouse model studies have shown that more frequently administered rifapentine is ~4 times as active as rifampin [54] and can cure murine TB in 10–12 weeks [54, 55]. In humans, there is a dose-response curve for rifapentine monotherapy [56], and higher doses appear to be well tolerated [57]. A phase 2B trial by the Tuberculosis Trials Consortium is currently comparing rifampin with rifapentine (dose of ~10 mg/kg for both); the trial is expected to be completed by mid-2010.

The promise of enhanced rifamycins is that this strategy

should be applicable to all important patient subgroups, including children and reproductive-age women. The limitations of this strategy are that it will not help with MDR-TB and that rifapentine has a drug interaction profile similar to that of rifampin, making it problematic during antiretroviral therapy. More work needs to be done with rifabutin (a drug that avoids many of the drug interactions of rifampin), but it is doubtful that rifabutin will be the basis of shortening of treatment durations (because higher doses do not appear to be well tolerated).

**Fluoroquinolones.** Potent fluoroquinolone antibiotics (levofloxacin, moxifloxacin, and gatifloxacin) are quite active in the mouse model, resulting in the ability to shorten treatment to 4 months. These drugs are also quite active as monotherapy in humans [37, 58]. Moxifloxacin and gatifloxacin have had variable results in phase 2B studies, with 2 trials showing significant activity [39, 59] and 2 other trials showing little activity [60, 61]. Difference in microbiological techniques has been suggested as an explanation for this difference in results [59], although the lack of consistency is still concerning. Furthermore, fluoroquinolones have inherent disadvantages (Table 2); particularly, the risks of adverse effects do not allow use during pregnancy and limit use among young children. Phase 3 trials are under way to determine whether gatifloxacin or moxifloxacin can support shortening TB treatment to 4 months.

**TMC207.** TMC207 is a novel drug that inhibits a mycobacterial ATP-synthase enzyme, with potent activity against *Mycobacterium tuberculosis* isolates, regardless of resistance to current agents [62]. Of note, TMC207 has little activity against common bacterial pathogens [62] and almost no activity against eukaryotic mitochondrial ATP-synthase [63]. As monotherapy, TMC207 was more active in the mouse model than conventional multidrug therapy, and regimens of TMC207 with current drugs produced complete sterilization by 2 months of treatment [62]. Serum concentrations of TMC207 are reduced by 50% when given with rifampin, although TMC207 remained potent in rifampin-containing regimens in the mouse model [64]. In humans, TMC207 had moderate activity during a study of 1-week monotherapy [65] and appeared to be highly potent and well tolerated in the initial analysis of a pivotal randomized trial of treatment of patients with MDR-TB [66].

Although many questions about TMC207 remain (implications of its long serum half-life, long-term safety, and tolerability), it is likely that the drug will markedly improve the treatment of drug-resistant TB and may be useful in the treatment of close contacts of patients with infectious MDR-TB. Despite the interaction with rifampin, TMC207 may also support treatment shortening for patients with drug-susceptible TB.

**PA824 and OPC-67683.** PA824 and OPC-67683 are nitro-furanylamides that have potent activity against *M. tuberculosis*

**Table 2. Drugs Currently in Development to Improve Tuberculosis (TB) Treatment**

Drug	Mechanism of action	Activity in the mouse model of TB treatment	Clinical stage of development	Possible advantages	Limitations and/or cautions
High-dose rifampin	Inhibition of mycobacterial RNA-polymerase (rpoB gene)	May support shortening of treatment to 4 months	Enhanced activity demonstrated in monotherapy (EBA); phase 2B trials in development	Global system in place for manufacture and distribution; should be applicable to children and pregnant women	No activity against MDR-TB; drug interactions
Higher-dose and more frequently administered rifapentine	Inhibition of mycobacterial RNA-polymerase (rpoB gene)	Shortening of treatment to 3 months	Large trial under way of once-weekly therapy (with isoniazid) for latent TB infection; enhanced activity shown in monotherapy (EBA); initial phase 2B trial underway	Substantially greater potency than rifampin in the mouse model; should be applicable to children and pregnant women; age-specific dosing available (to age 2 years)	No activity against MDR-TB; drug interactions are likely to be similar to those of rifampin
Fluoroquinolones	Inhibition of mycobacterial DNA gyrase	Shortening of treatment to 4 months; active in models of MDR-TB treatment	Activity demonstrated as monotherapy (EBA); variable activity in phase 2B trials; phase 3 trials under way	Proven capacity for manufacture	Increasing rates of resistance in <i>Mycobacterium tuberculosis</i> in some parts of the world; uncertainties about safety during pregnancy and in children
TMC207	Inhibition of mycobacterial ATP-synthetase	Shortening of treatment to 3 months; marked improvement in treatment of MDR-TB	Activity demonstrated in monotherapy (EBA) and in the initial stage of a pivotal trial in MDR-TB	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes	Very long tissue half-life raises concerns for toxicities; drug resistance; CYP3A4 metabolized; susceptible to interactions with rifampin and antiretroviral drugs
OPC67683	Inhibition of mycobacterial cell wall synthesis	Shortening of treatment to 3 months; marked improvement in treatment of MDR-TB	Activity shown in monotherapy (EBA); phase 2B dose-ranging trial under way	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes; low likelihood of having drug-drug interactions	Early in development, so data needed on dose, adverse effects, etc.
PA-824	Inhibition of mycobacterial cell wall synthesis	Treatment shortening to 3 months, marked improvement in treatment of MDR-TB	Activity demonstrated in monotherapy (EBA)	No cross-resistance with current drugs—may markedly improve MDR-TB treatment outcomes Low likelihood of having drug-drug interactions	Early in development, so data needed on dose, side effects, etc.
SQ-109	Inhibition of mycobacterial cell wall synthesis	May support shortening of treatment, but has not been rigorously evaluated in the standard model	Phase 1 studies of tolerability and pharmacokinetics among healthy volunteers under way	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes; low likelihood of having drug-drug interactions	Very early in development, so data needed on dose, adverse effects, etc.
PNU 100480	Inhibition of mycobacterial protein synthesis	Shortening of treatment to 3 months	Phase 1 studies of tolerability and pharmacokinetics among healthy volunteers under way	No cross-resistance with current drugs; may markedly improve MDR-TB treatment outcomes	Very early in development, so data needed on dose, adverse effects, etc.; possibility of toxicities similar to linezolid

**NOTE.** MDR, multidrug-resistant.

isolates regardless of susceptibility to current TB drugs [67, 68]. Similar to isoniazid, both drugs have to be activated in the mycobacterial cell, and both inhibit mycobacterial wall synthesis, although in a manner distinct from isoniazid. There is substantial cross-resistance between these 2 agents, implying that they have a similar if not identical mechanism(s) of action [69]. Both agents have activity in the mouse model, although OPC-67683 may be more potent [68]. When added to rifampin and pyrazinamide, either PA824 or OPC67683 allows short-

ening of TB treatment in the mouse model to 3–4 months [68, 70].

Both drugs have completed phase 1 evaluation in humans [71]. Despite initial concerns about possible nephrotoxicity with PA824, a subsequent study showed that the drug inhibits excretion of creatinine but does not affect the glomerular filtration rate [72]. Both drugs have measurable activity as monotherapy in humans, although these reports are only available in preliminary form at present. Assuming adequate bioavaila-

bility and safety, the nitrofuranylamides may be potent drugs for the treatment of drug-resistant and drug-susceptible TB.

**SQ109.** SQ109 is a congener of ethambutol, but it retains activity against ethambutol-resistant strains [73]. The drug is synergistic with isoniazid and rifampin [74], although the therapeutic relevance of this finding remains to be shown. In the mouse model, SQ109 adds to the activity of standard first-line drugs [75]. SQ109 is currently being evaluated in phase 1 studies involving healthy volunteers.

**PNU-100480.** The oxazolidinones have activity against *M. tuberculosis* [76, 77], leading to the use of linezolid as a third-line agent for MDR-TB. However, adverse effects associated with extended linezolid therapy—peripheral neuropathy and bone marrow suppression [78, 79]—will preclude its widespread use. A related oxazolidinone, PNU-100480, has substantially greater activity than linezolid in the mouse model [76, 80]. Addition of PNU-100480 to standard drugs results in a 2-log reduction in bacillary load, suggesting that this drug has potent sterilizing activity [81]. PNU-100480 is currently being evaluated in phase 1 studies.

## SUMMARY

This is a time of great need in TB therapeutics, but it is also a time of great opportunities. With the promising new drugs outlined above and sustained global commitment, it is likely that there will be major improvements in TB treatment over the next decade. The first major improvement will probably be in the treatment of MDR-TB, but improvements in the treatment of drug-susceptible and latent TB are also likely. Progress will require a coordinated effort of industry and publicly funded groups, more so than in drug development of antiretroviral drugs. Finally, we must ensure that children benefit from this round of TB drug development.

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