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Tuberculosis pharmacotherapy: strategies to optimize patient care

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Abstract

The treatment of tuberculosis (TB) is a mature discipline, with over 60 years of clinical experience accrued across the globe. The requisite multidrug treatment of drug-susceptible TB, however, lasts six months and has never been optimized according to current standards. Multi-drug resistant tuberculosis and tuberculosis in individuals coinfectd with HIV present additional treatment challenges. This article reviews the role that existing drugs and new compounds could have in shortening or improving treatment for tuberculosis. The key to treatment shortening appears to be sterilizing activity, or the ability of drugs to kill mycobacteria that persist after the initial days of multidrug treatment.

Among existing anti-TB drugs, the rifamycins hold the greatest potential for shortening treatment and improving outcomes, in both HIV-infected and HIV-uninfected populations, without dramatic increases in toxicity. Clinical studies underway or being planned, are supported by *in vitro*, animal, and human evidence of increased sterilizing activity—without significant increases in toxicity—at elevated *daily* doses.

Fluoroquinolones also appear to have significant sterilizing activity. At least two class members are currently under evaluation for treatment shortening with different combinations of first-line drugs. However, in light of apparent rapid selection for fluoroquinolone-resistant mutants, relative frequency of serious adverse events, and a perceived need to ‘reserve’ fluoroquinolones for the treatment of drug-resistant TB, their exact role in TB treatment remains to be determined.

Other possible improvements may come from inhaled delivery or split dosing (linezolid) of anti-TB drugs for which toxicity (ethionamide) or lack of absorption (aminoglycosides and polypeptides) precludes delivery of maximally effective, oral doses, once daily. New classes of drugs with novel mechanisms of action, nitroimidazopyrans and a diarylquinoline, among others, may soon provide

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opportunities for improving treatment of drug-resistant TB and/or shortening treatment of drug-susceptible TB.

More potential options for improved TB treatment currently exist than at any other time in the last 30 years. The challenge in TB pharmacotherapy is to devise well-tolerated, efficacious, short-duration regimens that can be used successfully against drug-resistant and drug-resistant TB in a heterogeneous population of patients.

Keywords

tuberculosis; sterilizing activity; rifamycin; fluoroquinolone; new drugs

1. Introduction

The treatment of tuberculosis (TB) is a mature discipline, with over 60 years of clinical experience accrued across the globe.[1] A safe and effective standard regimen contains isoniazid, rifampin, and pyrazinamide, often with a 4th drug added to increase efficacy in case of occult drug resistance to isoniazid or rifampin. Under optimal conditions, this regimen has been reported to be effective in 90–100% of patients, with less than 3% post-treatment relapse. [2] However, few TB control programs achieve such lofty results; many struggle to reach even 80% sustained cure. Although the reasons for this are myriad, this paper will explore some of the pharmacologic avenues available to further improve TB treatment.

Medications used in the treatment of tuberculosis include both those used primarily for TB treatment and those with a broad spectrum of antimicrobial activity, which includes *M. tuberculosis*. Drugs used primarily in TB include isoniazid, pyrazinamide, and ethambutol, which most often is used as the 4th drug in initial regimens; capreomycin and its sister polypeptide, viomycin; cycloserine/terizidone; ethionamide/prothionamide; para-aminosalicylic acid; and thioacetazone, which has fallen out of favor in recent years.[3] TB drugs with other indications include the rifamycins (rifampin, rifabutin and rifapentine), the aminoglycosides (specifically streptomycin, amikacin, kanamycin, paramomycin), and the fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin). Beta-lactams (imipenem, amoxicillin-clavulanic acid), linezolid, clofazimine, clarithromycin, dapsone, and metronidazole have been used occasionally for multi-drug resistant TB (MDR-TB) but their roles are not well established at this time.

The treatment of active TB disease requires combination chemotherapy to avoid the selection of naturally occurring drug-resistant mutants. Unlike other bacterial infections, the combinations originally chosen were not based on complementary, or potentially synergistic, mechanisms of action. Rather, initial regimens were defined by what was available in the middle of the 20th century, namely, streptomycin, *para*-aminosalicylic acid, and isoniazid. As new drugs were developed, they were tested with older drugs until the current regimen of isoniazid, rifampin, and pyrazinamide (often with ethambutol as a fourth drug) was defined. Since not all possible combinations of drugs, doses, and frequencies have been tested in humans, it is quite likely that other approaches based on the currently available drugs may yield superior regimens.[4]

M. tuberculosis is a slow-growing organism. Its metabolic activity varies over time and across environments. *M. tuberculosis* is generally classified into two subpopulations: those that are metabolically active and replicating, and those that are not. Typically, successful treatment regimens contain agents that act on both subpopulations. Persisting organisms are metabolically dormant and do not actively replicate; consequently, their elimination requires

prolonged treatment duration.[5] The ability of drugs to kill these persisting mycobacteria is called *sterilizing activity*. [6]

Without continued treatment, measured in additional months, some patients may relapse with active TB disease.[7] This long duration of treatment, which is most often undertaken in resource-poor settings, is difficult for health systems to manage and often results in treatment interruption. A major focus of current efforts is to find regimens of such potency as to kill persisting organisms or prevent persisters from forming, thereby shortening treatment. An additional focus is to devise regimens of improved efficacy, increased simplicity, and reduced duration for disease caused by organisms resistant to isoniazid and rifampin (MDR-TB).

This document will focus on the question of how existing agents, and new compounds, may be used to improve standard anti-TB therapy. Shortened regimens or fewer deaths, failures or relapses would be the measure of improved standard treatment. The issue of improved MDR-TB regimens will be covered briefly, through new drugs or new formulations of existing drugs.

2. Sterilization and Shortening Treatment Duration

In combination therapy, sterilizing activity has been defined by Mitchison as, ‘the ability to kill all or virtually all of the bacilli in the lesions as rapidly as possible’ [8] and by Jindani and colleagues as the slow process of killing organisms that persist after the first two days of treatment.[6] *In vitro* models have been proposed which differentiate drug activity between logarithmic and stationary growth phases, or which measure difference in killing among three stages of persistence.[9] In animals, sterilizing activity is measured by the ability to render organs (lung, spleen) sterile. In humans, it is measured through bacteriologic response in the early part of treatment (after day 2, through 2 months) and correlated with probability of relapse. [6,8,10] Sterilizing activity is considered to be the feature most important to the length of the regimen: the greater the sterilizing activity, the shorter the regimen may be without substantial risk of relapse.[2]

Rifampin, a member of the rifamycin group, is bactericidal against *M. tuberculosis* and several other mycobacterial species, including *M. bovis* and *M. kansasii*. [11–13] It is a semisynthetic compound derived from *Amycolatopsis rifamycinica*. RIF acts on *M. tuberculosis* by inhibiting DNA-dependent RNA polymerase, blocking transcription. [11,14–16] RIF resistance results from single amino acid substitutions in the β subunit of RNA polymerase. [16] The mutations leading to this resistance occur spontaneously in about 1 in 10^8 organisms. [17] *In vitro*, subinhibitory concentrations enhance the selection of resistant organisms. Higher doses of RIF as monotherapy do not completely prevent the emergence of resistance [18]; they may, however, suppress or delay resistance. [19]

Of the first-line agents, RIF has the most potent sterilizing activity, including against semidormant *M. tuberculosis*. [20] This may be due to its rapid onset of action. [18] Dramatically improved sterilizing activity and survival were achieved in the mouse and the guinea-pig with increased RIF doses. [21,22] Studies by Verbist revealed dose-related killing of *M. tuberculosis* in mice given RIF 5 to 40 mg/kg: a 2-log increase in killing occurred when the 5 mg/kg dose was doubled. A further increase to 20 mg/kg resulted in an additional increase in killing of 1 log over the 10 mg/kg/dose. [23] These findings were confirmed in recent mouse work. [24,25]

There are similar RIF dose and concentration responses in humans. [26] At the standard dose used in TB treatment, no plateau in activity is detected with RIF at 600 mg *in vivo*. [27] This is in contrast to the standard dose of INH used in antituberculous therapy, at which the bactericidal activity of INH appears to plateau. In early bactericidal activity (EBA) studies, the sterilizing activity of RIF—as well as its dose and concentration dependence—is well

demonstrated.[6,27,28] Sirgel and colleagues revealed, in an EBA study, a linear relationship between dose (150 mg, 300 mg, 600 mg) and activity both between 0 and 2 days and between 2 and 5 days.[27] Diacon and colleagues illustrated additional dose-activity response at the higher doses tested in a recent study; the maximum dose tested was (20 mg/kg).[28] Pharmacokinetic studies have demonstrated even greater than dose-proportional increase in plasma concentrations at these elevated doses of RIF.[26,29]

A series of clinical studies evaluated a range of doses of RIF, within combination regimens, for the treatment of tuberculosis (see Table 1). One study compared two groups of patients that received 1200 mg RIF with INH and streptomycin; in one arm dosage was daily, in the other intermittent. Probability of culture conversion at one month was 72.3% in the daily group and 70.4% in the intermittent group; at two months conversion had occurred in 93.2% of the daily group and 93.6% of the intermittent group. By comparison, in a USPHS study, among patients who received 450, 600, or 750 mg of RIF within daily combination therapy, approximately 35% had converted at one month and 70% at two months. Only 60% of those receiving 450 mg of RIF, while 75% of patients who had received 750 mg of RIF/day, had converted by 2 months.[31] In an East African/British MRC trial using 450 mg of RIF in patients under 50 kg and 600 mg RIF in patients over 50 kg, results were similar to the USPHS study: at months one and two, 29% and 73% of patients respectively had negative cultures.[32] Compared to the 600 mg dose, the 1200 mg dose in humans appears to increase the frequency of culture conversion at both months 1 and 2, consistent with the mouse model results of Verbist and Nuernberger.

Although these studies demonstrated promise for higher doses of RIF to shorten treatment, several limitations stalled further evaluation of high RIF doses. First, without PZA as a companion drug in some of these studies, regimens resulted in high relapse rates. In one study, after complete treatment, which was only 3 months and did not contain PZA, relapse occurred in 11.4% of patients in the first year of follow-up.[30] It is likely that the inclusion of PZA, which was instrumental in shortening therapy to 6 months without increased disease recurrence [40,41], could reduce the probability of relapse among patients receiving a short-course regimen and high-dose RIF. Second, there was no direct, head-to-head comparison of daily administration of the current standard (600 mg) against daily administration of higher doses. Third, current reporting standards for safety and tolerability studies were not met in these early trials and potential toxicity with high-dose RIF remains a concern.

The primary toxicities attributed to RIF, hepatotoxicity and flu-like syndrome, are not likely to occur more frequently with increased daily dosing. RIF hepatotoxicity appears to be idiosyncratic.[42] Although there are some inconclusive reports of increased incidence of hepatotoxicity with RIF and INH used in combination [11,42–45], available data do not support an increase in hepatotoxicity in situations where higher doses of RIF are used.[29,34,46–48] In the last study, adverse events occurred no more frequently in the 900 mg arm, in spite of peak serum concentrations that were nearly double those in the control group. Verbist and Rollier reported transient increases in total and direct bilirubin in African patients receiving 30 mg/kg RIF (1200, 1500, 1800 mg doses) over 10 weeks; these increases did not persist and there were no additional signs or symptoms of liver toxicity in the trial, even among patients with baseline liver function abnormalities.[33] In one possible exception, Ruslami *et al.* reported recently that grades 1 and 2 hepatotoxicity occurred more frequently in patients exposed to higher-dose RIF ($p = 0.054$) while grade 3 hepatotoxicity occurred more in the lower-dose arm (no p -value reported).[26] Risk factors for hepatotoxicity with RIF include advanced age, alcohol consumption, diabetes, and concomitant hepatotoxic agents.

The flu-like syndrome is hypothesized to be immunologic in nature: an extended interval between the doses may induce hypersensitivity while daily dosing permits tolerance.[49]

Martinez and colleagues suggest that the increased frequency of flu-like syndrome in intermittent treatment is due to 'an antibody excess relative to the antigen level in the drug-free days.' [50] The flu-like syndrome has been described predominantly in situations where elevated doses are highly intermittent (once or twice-weekly), either by design, or because of patient non-adherence to treatment.[1,11,38,39,51,52] In at least one study, frequency of 'flu-like' syndrome was higher in patients who received RIF (900–1800 mg) only once weekly when compared to patients who received it twice-weekly.[37] Even then, these reactions may not warrant regimen changes [35] and typically do not occur until after three months of treatment. If the sterilizing and shortening effects of high-dose RIF can be realized in 8 weeks or less, then existing data do not support increased frequency of these reactions.[27,31,53–55]

GI irritation is a common reaction to the four-drug combination used for TB. Some of this likely is due to RIF. It is, however, difficult to single out one drug in many instances. Although it is possible that GI irritation could be aggravated with higher doses of RIF, anecdotal evidence available to date does not support this hypothesis. In six patients not responding to standard doses of antituberculous therapy, RIF doses were raised from 600 mg to 900 mg, and in one patient, to 1500 mg. Although three patients were alcoholics and one was HIV-infected, all responded to therapy and no adverse effects or poor outcomes were experienced.[56] Kimerling and colleagues reported a similar experience with patients in whom RIF doses were raised in response to low serum concentrations of RIF on standard therapy. At least one patient ultimately received RIF at 1800 mg/day with no reported adverse events.[57]

More severe effects, including thrombocytopenia, hemolytic anemia, and acute renal failure, also may occur, and these require permanent discontinuation of RIF.[11,43,45] These reactions appear to be immunologically related, as they are associated with the presence of RIF-dependent IgM or IgG antibodies. RIF has variable effects on cellular and humoral immunity. Suppression of *in vitro* lymphocyte responses in cells collected from TB patients has been reported but clinically evident immunosuppression has not been demonstrated.[11,58] No evidence of increased frequency of these events with higher daily doses of RIF has been reported.[31]

RIF has also been used at higher doses for other mycobacterial indications and for a wide range of non-mycobacterial infections. These experiences support the contention that the vast majority of RIF's adverse effects are idiosyncratic, and not dose related. With intermittent treatment for leprosy (usually at 900 mg) flu-like syndrome may be reported [59] but generally resolves spontaneously. RIF is also used commonly at 900 mg for 45–60 days to treat brucellosis. In combination with doxycycline, RIF has 'the most favorable efficacy/safety ratio' among the recommended regimens [60] and was not associated with more adverse events than two other regimens in a multicenter trial.[60] RIF (20 mg/kg/day for 7 days) was used in an outbreak of resistant *Streptococcus pneumoniae* at a day care in the US without any reports of adverse events.[61] In staphylococcal infections of orthopedic implants, daily RIF (900 mg) was used in combination for 6 months with no treatment-related side effects reported.[62] RIF (1200 mg) was administered for 21 days in a patient with *Legionella jordanis* without any reported problem.[63] Lastly, in a randomized placebo-controlled trial, RIF was used at 1200 mg daily for 4 weeks to treat cutaneous leishmaniasis. The authors report that there were no elevations in liver function tests 'or other side effects' during therapy.[64]

RIF is a profound inducer of CYP3A4 and other hepatic P450 enzymes.[11,65,66] However, RIF is not a substrate for these enzymes, so other agents, such as HIV protease inhibitors, do not affect RIF's clearance.[11,44,67] Extensive lists of drugs affected by the co-administration of RIF have been published.[65,66,68] A simple rule of thumb is that most hepatically-metabolized drugs will have shorter half-lives in the presence of RIF, especially if they are

substrates for CYP3A4, and to a lesser degree, 2C9, 2C19, and 2D6. Enzyme activity and the pharmacodynamic effects of the affected drug generally return to baseline levels within 2 weeks after discontinuing RIF therapy.[65,66,68]

Importantly, the companion therapeutic agents for first-line TB therapy, INH, PZA, and EMB, are not substrates for RIF drug interactions. There do not appear to be any clinically significant drug interactions among these four drugs.[68–72] Reduced plasma concentrations of moxifloxacin or gatifloxacin (addressed below as agents with treatment-shortening potential) with coadministered rifampin have, however, been observed.[73–75] Since the potential for changes in the pharmacokinetics of companion drugs when given with higher doses of RIF has not been entirely ruled out, the effect of the increased RIF dose on their concentrations will need to be determined.

In summary, previous work supports the hypothesis that high-dose RIF, given daily in the two-month intensive phase, improves sterilizing activity over standard doses. Reports on thousands of patients exposed to daily RIF doses, ranging from 900–1800 mg, offer strong evidence that this effect can be achieved without a significant increase in adverse events. Nearly 40 years after the first clinical studies of high-dose RIF in humans for TB, interest persists in exploring the potential for increased *daily* doses of RIF—a widely available, inexpensive first-line anti-TB drug—to enhance sterilizing activity, shorten treatment therapy, and improve treatment outcomes for TB patients.[28,30,53,60,76,77] A large Phase II trial of high-dose RIF in combination therapy could examine the hypothesis that an increase in RIF dose size would result in enhanced sterilization, without additional adverse effects.[25,31] This possibility represents the most direct method for improving outcomes, and shortening TB treatment, with the existing first-line drugs.

3. Rifapentine (RPNT)

RPNT is the cyclopentyl derivative of rifampin, with the same mechanism of action and a similar overall toxicity profile.[11,78–81] RPNT has a long plasma half-life (14–18 h compared to 2–3 h for RIF), although its $t_{1/2}$ is shorter than that of RBN.[11,67] RPNT is more slowly absorbed than RIF or RBN (T_{max} about 5 h), and its C_{max} of 8–30 $\mu\text{g/mL}$ is somewhat higher than RIF's when both are dosed at 600 mg.[67,82,83]

There is significant interest in identifying the dose, dosing frequency, and companion drugs to optimize the activity of RPNT. Like RIF and RBN, RPNT shows concentration-dependent killing.[11] Also like RIF, RPNT-containing regimens that include MOXI and exclude INH appear to be more active in the mouse model. A murine study, which examined equivalent doses of RIF & RPNT in a multidrug regimen, revealed substantially greater antimicrobial activity with RPNT.[4] Clinical studies show that the toxicity of RIF and RPNT are very similar [84] and RPNT has been shown to be safe in humans at doses up to 1200 mg.

Although the approved dose of RPNT is 600 mg once weekly, planned and ongoing trials are examining higher doses or increased frequency of dosing. For example, USPHS TB trial 29 will compare the antimicrobial activity and safety of a standard daily rifampin-based regimen to that of an experimental rifapentine-based regimen (approximately 10 mg/kg/day). This trial represents one step in the process of optimizing dose and dosing frequency. The Phase III RIFAQUIN study, which began enrolling patients in mid-2008, is designed to evaluate whether RPNT- and moxifloxacin- containing regimens can shorten treatment and reduce frequency of acquisition of rifamycin mono-resistance. Intervention regimens contain RIF (600 mg), moxifloxacin, ethambutol, and PZA in a daily two-month intensive phase. The continuation phases contain either RPNT (900 mg) administered twice-weekly for two months or RPNT (1200 mg) administered once weekly for one month. Other clinical studies, which would take advantage of RPNT's desirable PK properties, are currently in the design stage.

RPNT is very similar to RIF with respect to drug interactions and adverse effects. RPNT is about 85% as potent as RIF in inducing CYP3A.[65,66,68] Therefore, RPNT does not offer any advantage in sparing the drug interactions, unlike RBN, which is significantly less potent as an enzyme inducer. However, because RPNT (like RIF) is not a substrate for CYP enzymes, it is not the object of drug interactions, as is RBN.

In summary, given the demonstrated activity of RPNT in the mouse model, along with its extended half-life and sterilizing ability, treatment with RPNT has the potential to improve and shorten TB therapy. Examinations of RPNT with moxifloxacin are underway. The benefit of matching drug PK profiles is more apparent as the dosing interval increases; most active drugs should prevent emergence of moxifloxacin during daily therapy. RPNT, moreover, may prevent emergence of moxifloxacin resistance during intermittent regimens.

4. Rifabutin (RBN)

RBN retains RIF's clinical activity against *M. tuberculosis*. [85–87] RBN's primary advantage in the treatment of TB is its reduced induction of hepatic metabolism, roughly 40% of that seen with RIF.[66,67] This allows for combinations of TB and anti-HIV drugs that are not possible with RIF-containing regimens.[88,89]

Recent clinical trials clearly show that poor absorption of rifabutin is associated with failure, relapse, and the emergence of rifamycin resistance.[90] Given that a range of RBN doses is recommended in HIV-positive patients, depending on co-administered drugs, a case can be made for monitoring of RBN drug concentrations or therapeutic drug monitoring (TDM). [91]

RBN induces the metabolic enzyme CYP3A. Most drug interactions that involve RIF also involve RBN but to a lesser degree (about 40%). [11,65–67] Induction of metabolic enzymes, particularly CYP3A, is the reason for most interactions. Like RIF, RBN also induces CYP1A2, CYP2D6, the Phase II enzymes glucuronosyltransferase and sulfotransferase, and the efflux transporter P-glycoprotein.[65–67] After stopping RBN, enzyme activity returns to baseline levels in about 2 weeks.[65–67]

In addition to induction, RBN is also metabolized by CYP3A. As a result, the macrolide antibiotics, azole antifungal drugs, and the HIV-1 protease inhibitors have complex bidirectional interactions with RBN.[65–67,89,92] The CYP3A-inducing effect of RBN results in decreased concentrations of the macrolides and protease-inhibitors, sometimes to levels that substantially decrease their antimicrobial activity.[66,68] Conversely, as CYP3A inhibitors, the macrolides (except azithromycin) and protease inhibitors increase the concentrations of RBN and 25-O-desacetyl RBN, and can cause RBN toxicity.[65,66,68] The enzyme inducer efavirenz requires the use of increased doses of RBN, typically 600 mg.[1,11,89,91]

RBN differs somewhat from RIF and RPNT in its adverse effect profile. RBN can show concentration-related toxicity, most often when administered with CYP3A4 inhibitors. These inhibitors increase RBN concentrations and dramatically increase 25-O-desacetyl RBN concentrations, leading to arthralgias, anterior uveitis, skin discoloration, and leucopenia.[11, 43]

Various treatment studies of HIV-infected TB patients, designed to overcome these complex drug interactions, are underway. Because it is nearly impossible to predict drug concentrations in patients receiving 3 or more interacting drugs, TDM is a reasonable tool to apply in such situations. Blood samples can be collected at 3–4 h and 7 h post dose to assess the peak concentration, and to detect delayed absorption.[93–95]

The primary advantage of RBN is its usefulness in TB patients also receiving antiretroviral therapy; the challenge for clinicians using RBN, however, is the selection of the correct dose. Guidelines are a reasonable starting point but they remain severely limited. This has recently been demonstrated in the use of the recommended doses of RBN for patients concurrently treated with lopinavir-ritonavir.[96] All five patients studied had RBN serum concentrations lower than those shown previously to be associated with treatment failure, relapse, and the emergence of rifamycin resistance.[96] Given that too much RBN (and metabolite) leads to toxicity, and too little leads to clinical failure and drug resistance, we recommend TDM for rifabutin in order to minimize toxicity and maximize good outcomes.

All of the rifamycins remain key to successful TB treatment. For each, one can argue that the dose has yet to be optimized. For rifampin and rifapentine, there is no established maximum dose. Since these drugs are extremely potent against drug-susceptible TB and in the case of RIF widely available, we argue that immediate research efforts should focus on the rifamycins and the impact of increasing dose on treatment outcomes.

5. Fluoroquinolones (FQ)

Fluoroquinolones have been found to be active against *M. tuberculosis*. Ciprofloxacin (CIP), ofloxacin (OFL) are the least active, while levofloxacin (LEVO, the optical S-(-) isomer of the racemic mixture OFL), gatifloxacin (GATI), and moxifloxacin (MOXI) are the most.[97–100] FQs are bactericidal against *M. tuberculosis*, with MBC/MIC ratios generally between 2 and 4.[101,102] The fluoroquinolones inhibit DNA gyrase.[102,103] Point mutations in DNA gyrase lead to resistance, and cross-resistance among these drugs is common.[102,104]

After the rifamycins, the fluoroquinolones represent the next most potent class of drugs currently available to treat TB. Like the rifamycins, they appear to have concentration-dependent activity, and the most effective doses against TB remain unknown. Unlike rifampin and rifapentine, however, large escalations in the doses may not be possible. Adverse events may include prolongation of the QT interval [105], dysglycemia [106], severe dermatologic conditions, and tendon rupture.[107,108] For most fluoroquinolones, intracellular concentrations exceed those in the plasma [103], and this might be desirable for addressing a portion of the mycobacterial population.

5.1 Recent Quinolone Advances against TB

Recent studies have provided additional insight into the use of fluoroquinolones for TB; the focus has been on regimen shortening with newer members of the class (GATI and MOXI). First, in the mouse model, substituting MOXI for INH seems to enhance the regimen, leading to more rapid sterilization.[109] Isoniazid has been described as antagonizing the sterilizing activity of the RIF-PZA combination in the mouse model.[110] Mouse models have also demonstrated that escalation of rifamycin dose, in conjunction with moxifloxacin, can further accelerate sterilization.[4]

The promising sterilizing activity appears to be a common characteristic among all later-generation fluoroquinolones; EBA studies have made important contributions to the evidence for the potential for late-generation fluoroquinolones to shorten standard treatment. Several studies established the strong activity of MOXI, when compared to INH; Pletz and colleagues established that 400 mg of MOXI, dosed daily, resulted in a log decrease in colony-forming units of 0.209 compared to INH at 0.273.[111] One EBA study showed comparable activity across GATI 400 mg, MOXI 400 mg, and LEVO 1000 mg, with the latter being slightly more active, at that elevated dose.[112] This represents a substantial improvement over the earlier fluoroquinolones (CIPRO and OFLOX).[98,113,114]

Several Phase II trials have examined the potential for these later-generation fluoroquinolones to shorten treatment. USPHS trial 27 compared MOXI to EMB to test for long-term safety, as did a second trial in Brazil.[115] Study 28 compared INH to MOXI, with the standard companions drugs: RIF, PZA and EMB.[116] In another Phase II trial, GATI has been substituted for EMB.[117] Bacteriologic end points in all these trials have included frequency of culture conversion at two months; the target difference in end points has been roughly 13%, thought to correspond to potential for shortening treatment.[118] Although the magnitude of increase in culture conversion was variable among the studies, they have all yielded results suggestive of an accelerated time to culture conversion or increased frequency of conversion at one month.

A Phase III, open-label non-inferiority trial of the GATI-containing regimen is currently underway (Oflo tub). This trial compares a 4-month regimen, substituting GATI for EMB, to the standard 6-month regimen; results are likely to be available in 2009. Another Phase III, placebo-controlled, non-inferiority trial (REMOX) has recently begun with the objective of examining the shortening potential of MOXI in two intervention arms; in one, it replaces ethambutol and, in the other, isoniazid. Both intervention arms have a two-month intensive phase and a two-month continuation phase. The continuation phase in the intervention arms contains MOXI and rifampin, with or without isoniazid.

In spite of these substantial efforts, concerns have been raised about using fluoroquinolones for shortening treatment. These reservations include the apparent, relative ease with which fluoroquinolone resistance emerges in mycobacterial populations.[119] FQ resistance is disturbingly common among MDR-TB isolates in some places: resistance to CIPRO and OFLO was detected among more than 50% of clinical isolates from patients with MDR-TB in the Philippines [120] Reports of emergence of resistance among other pathogenic organisms (e.g., *Streptococcus pneumonia*) exposed to fluoroquinolones through TB treatment [121] present further cause for concern. As do the serious adverse events occasionally associated with the class. This is particularly salient for GATI: in 2006, the rights for its manufacture were released and production was ceased in the US.[122] Although the Oflo tub study will yield additional safety data on GATI in young, otherwise healthy, carefully screened patients, significant regulatory hurdles to its study have emerged.[123] In addition, regimens for MDR-TB treatment increasingly rely on fluoroquinolones and widespread use in first-line therapy would likely 'burn' them for use in treatment of resistant disease. Lastly, fluoroquinolones have also been considered for prophylaxis among latently infected contacts of MDR-TB patients. Fluoroquinolones clearly hold great promise for improved TB treatment; their exact dosing and role, however, have yet to be determined.

6. Linezolid

Linezolid is an oxazolidinone antibiotic designed to treat Gram-positive bacterial infections. It also has considerable *in vitro* activity against *M. tuberculosis*, with MIC(90) values on the order of 0.5 to 1.0 mcg/mL.[124] These MIC values are similar to those reported with Gram-positive organisms.[125] Linezolid has excellent oral bioavailability, producing serum concentrations on par with intravenous administration.[126] Linezolid is neither a substrate for nor an inducer or inhibitor of cytochrome P450 enzymes.[127] Its inhibition of monoamine oxidase is weak and reversible.[128] Because of the threat of MDR- and XDR-TB and the lack of agents available to meet this challenge, interest in linezolid as a possible TB drug has increased. Anecdotal data have been presented at international conferences, small series have been published [129], and recently, an EBA trial has been completed. In the latter study, linezolid appeared to have relatively weak EBA.[130]

Although linezolid generally is well tolerated in the short-term, long-term use, such as is required to treat TB, presents several challenges. Linezolid is known to be associated with myelosuppression when used for several weeks, and this effect appears to be linked, at least to some extent, to AUC. Linezolid exposure can result in anemia, leucopenia, pancytopenia, and thrombocytopenia.[131] Anemia, peripheral neuropathy, and optic neuropathy have also been reported in small case series of TB patients receiving linezolid within multidrug regimens. [132–134] One potential alternative is to reduce the frequency of dosing of linezolid from twice daily to once daily. The rationale here is that, unlike Gram-positive organisms that multiply every 30 min, TB is a much slower-growing organism, doubling roughly every 18 h. Although such adjustments may reduce the incidence of myelosuppression, the frequency of peripheral and optic neuropathies may not be affected.[134] Optic neuropathies generally appear to be reversible upon discontinuation of linezolid, while peripheral neuropathy may persist when the drug is stopped. The TBTC is cautiously planning a feasibility study of linezolid in the treatment of MDR-TB (LiMiT). Pfizer (the company that manufactures linezolid) has reportedly undertaken an effort to optimize the oxazolidinone class for *M. tuberculosis*. This effort is still in the preclinical stage.

7. Drug Delivery

In some cases, medications that might otherwise be considered early for initial TB treatment are limited in their applications due to drug intolerance or adverse side effects. Capreomycin and ethionamide are two such examples. When tolerated, the medications can be effective components of an MDR-TB regimen. Treatment benefits, however, must be weighed against the possibility of non-adherence or treatment failure secondary to intolerance. Treatment of the growing burden of drug-resistant TB will, for the foreseeable future, rely on these and other drugs which have serious delivery limitations. Even as new drugs become available, optimized use of existing, companion drugs will be essential to protect the new agents and improve treatment outcomes.

Capreomycin is a daily intramuscular (IM) injection, a potentially painful route of administration for which proper treatment adherence can be difficult.[1] Ethionamide, although in oral formulation, can produce significant GI distress.[1] These medications, and others like them, have sparked renewed interest in the development of alternative delivery systems for the treatment of TB.[135–137]

Capreomycin is a polypeptide antibiotic, specifically indicated for the treatment of MDR-TB. [1,97] Capreomycin is a recent drug target for the development of an inhaled delivery system for TB treatment.[138] To date, efficacy of capreomycin formulations delivered by aerosol have only been evaluated in the guinea-pig model with animals receiving aerosolized capreomycin showing a significantly reduced bacterial burden in the lungs compared to untreated controls.[139] How these results will translate into humans is unknown, especially in patients with fibrotic lesions with severely compromised blood supply. The potential advantages of an inhaled system for capreomycin include avoidance of painful, intramuscular injections, direct administration of drug to the site of disease, and the minimization of plasma-concentration dependent side effects; an additional benefit could be enhanced delivery to damaged tissue, otherwise not reached by blood. The eventual goal is to develop an inhaled capreomycin, which will help improve adherence, improve outcomes, and possibly shorten treatment duration.

Ethionamide, a thioamide, was first synthesized in 1956.[1,140] ETA shares structural features with INH and its mechanism of action involves disrupting mycolic acid synthesis [141,142], allowing it to be active against extra- and intracellular mycobacteria. However, ethionamide is a singularly unpleasant drug to take and effective serum concentrations can be difficult to

achieve through oral administration.[143] The MBC/MIC ratios are 2–4, making concentrations necessary for bactericidal activity beyond the range of clinically achievable concentrations for most patients.[144] As such, it is perhaps the weakest of the TB drugs and tends to be reserved for cases when there are no other options. Consideration of all these factors makes the development of an inhaled delivery system for ETA an attractive proposition. Experience with ETA does not differ significantly from the historical difficulties of administering oral asthma medications in the 1960s. At serum concentrations necessary to achieve a desired therapeutic effect, toxicity becomes much more likely and in many cases intolerable for the patient. It is worth noting that it is generally easier to deliver drug to the bronchi (where asthma drugs act) than to the alveoli or cavitary lesions. These challenges notwithstanding, direct drug administration via inhalation may provide a route of delivery to help circumvent toxicities associated with oral dosing.

Specifically in the case of pulmonary TB, inhaled therapy may not only limit toxicity, it may reduce dosing frequency, minimize drug interactions, and simplify treatment through co-formulated medications. If a single drug can be administered by inhalation, then co-formulated inhaled products may ultimately appear on the horizon.

8. New Uses for Older Drugs

With renewed focus on improving the efficacy and shortening the duration of tuberculosis treatment, considerations of treatment combinations other than the current standard regimen of rifampin, isoniazid, pyrazinamide, and ethambutol (RIPE) are warranted. Although new drugs may eventually change the gold standard of TB treatment, older medications currently used only as second-line treatments may be the most accessible solution to improved first-line TB treatment. In addition to ethionamide and capreomycin, cycloserine, aminoglycosides, PAS, and the fluoroquinolones are the foundation of treatment of MDR-TB. Aside from fluoroquinolones and streptomycin (an aminoglycoside), these drugs have yet to be tested in randomized controlled trials as first-line treatment combinations. Given the unique mechanisms of action of these medications when compared to standard RIPE therapy, it is possible their use could shorten treatment and improve outcomes when used as adjuvant therapy or in completely novel treatment combinations.

9. New Drugs (Updates)

Recent years have seen the emergence of new chemicals that may become entirely novel TB drugs.[145–154] Although hopes are high, the road to achieving an approved and marketed drug is a long and difficult one, and considerable attrition should be expected along the way. [155]

The diarylquinoline R207910 (now known as TMC207) is distantly related chemically to the malaria drug chloroquine.[156] The target of TMC207 is the proton pump of adenosine triphosphate (ATP) synthase.[156] It is equally active against drug-sensitive and drug-resistant strains of *M. tuberculosis*, with an MIC of about 0.03 mcg/mL; it is also active against many other types of mycobacteria. Its activity appears to be time-dependent.

$C_{\max}$ of TMC207 in TB patients receiving monotherapy was approximately 5 mcg/mL (of which over 99% is bound to serum protein) 6 h after a 400 mg dose, with plasma concentrations of approximately 2 mcg/mL 24 h after the dose.[157] Plasma concentrations of TMC207 are significantly reduced by concurrent use of RIF, so modifications of combination regimens might include higher doses of TMC207, or the substitution of RBN for RIF.

Initial mouse work with TMC207, RPNT, and pyrazinamide once weekly demonstrated rapid sterilization of the lungs when compared to the standard regimen, administered 5 days/week

for 8 weeks.[158] In mouse studies, TMC207 concentrates within tissues, in particular, the lungs.[156] The substitution of INH, RIF, or PZA by TMC207 in the mouse model produced superior results compared to the reference regimen. Sterilization in lungs or spleen was seen as early as 2 months after initiation of treatment with TMC207.[156] Recent mouse work suggests that TMC207 results in earlier detectable activity in the intensive phase and more complete sterilization in the continuation phase than INH, RIF, or MOXI.[159] In contrast, TMC207 in humans showed little EBA at the 2 lower doses (25 and 100 mg daily), while the 400 mg dose was active, albeit less so and later than the comparators (RIF 600 mg and INH 300 mg daily).[157] It has not yet been elucidated what causes the delayed onset of activity in humans, and whether 'extended EBA' monotherapy for 14 days or longer would reveal more equivalent activity. To date, serious adverse reactions have not been reported with TMC207, including after 2 months of treatment in combination with second-line drugs in MDR-TB patients in South Africa. The Phase IIB (stage 1) clinical trial of TMC207 plus a standardized background regimen demonstrated significant improvement in sterilization of cultures over 2 months when compared to the standardized regimen plus placebo (47.5% vs 8.7% treated [$p = 0.003$]).[160] A 6-month Phase IIB trial is enrolling at the time of this writing; results are expected in mid-2010. Recent mouse work also supports its potential to improve MDR-TB treatment: in mice that received 6 months of Amikacin, ETA, MOXI, and PZA, TMC207 reduced relapse from 11/19 to 5/18.[161] Since TMC207 lacks cross-resistance with any antituberculous agent, including the fluoroquinolones, its potential contribution to the treatment of resistant TB remains encouraging. Further development of the drug for DS-TB indications will require resolution of the documented interaction with RIF.

PA-824 is a nitroimidazopyran, a chemical cousin of metronidazole, and it is being advanced through clinical development by the Global Alliance for TB Drug Development.[145,146,162,163] PA-824 has an MIC of 0.015–0.25 mcg/mL, which is similar to that of isoniazid.[164] Like metronidazole, it is proposed that PA-824 is a prodrug, which is activated inside of mycobacteria, resulting in the disruption of mycolic acid synthesis and protein synthesis in a dose-dependent manner.[163] Possible effects upon DNA, analogous to metronidazole, are being studied. PA-824's active form has a reduced aromatic nitro group.[163] Unlike TMC207, PA-824 appears to be active against only the *M. tuberculosis* complex, without more generalized antimycobacterial activity. PA-824 is active against both replicating and non-growing *M. tuberculosis*, and cross-resistance with other TB drug classes has not been demonstrated.[163] It appears to be active against susceptible as well as MDR-TB.

In the mouse model, PA-824 shows dose-dependent activity against TB, and the minimal bactericidal dose is approximately 100 mg/kg in the mouse model. PA-824 has a murine elimination half-life of about 13 h, with C_{max} concentrations varying with dose. These data, generated using oral suspensions of the drug, suggest pharmacokinetic nonlinearities that require further study. Animal tissues show extensive uptake of PA-824, with tissue concentrations 3 to 8-fold higher than in the plasma. Recent studies have revealed that high doses may result in ocular and male reproductive toxicity in the animal model.[165]

PA-824 is not a substrate for cytochrome P450 enzymes, so many combinations, without interaction, are possible. A range of results on the contribution of PA-824 to regimens has emerged from the mouse model. First, it appeared that PA-824 may not add significantly to the current standard regimen, since combinations that included RIF were not improved by its addition.[166] Yet, the combination of PA-824, PZA, and MOXI resulted in a very potent regimen for MDR-TB.[167] Most recently, although PA-824 was found to be active against MDR-TB and XDR-TB in a mouse model, its effect was less than that of other drugs studied (OPC-67683, RIF, and INH) on lung sterilization in an intra-tracheal model of DS-TB and on mean survival days in DS-TB and XDR-TB models.[168]

Optimization of the oral formulation of PA-824 may be necessary due to its lipophilic nature. [169] In healthy volunteers and in TB patients, the drug demonstrated dose-linear but less than dose-proportional, increases in C_{max} and AUC when administered in doses that ranged from 200 to 1000 mg daily; the highest dose, 1200 mg daily, resulted in no additional increase. An extended EBA study, during which drug was administered over 14 days, and at a range of doses—200 to 1200 mg—revealed activity at all doses. Subsequent studies will examine lower doses.[165]

Another chemical related to metronidazole, OPC-67683 is a newly synthesized nitro-dihydroimidazo-oxazole from Otsuka Pharmaceutical Company (Tokyo, Japan).[145,146, 170] The compound has an MIC against *M. tuberculosis* between 0.006 to 0.024 mcg/mL and has shown promising activity in the mouse model.[170] OPC-67683 is also a prodrug, activated inside of mycobacteria, resulting in the disruption of mycolic acid synthesis. *In vitro*, it appears that even brief exposure may kill *M. tuberculosis* residing with THP1 cells.[170] OPC-67683, administered orally, also shows a dose-dependent response against TB in the mouse model, and potent activity when combined with RIF and PZA. As noted above, OPC-67683 was recently found to extend mean survival in mice infected with XDR-TB and DS-TB at all doses examined and in comparison to PA-824. Moreover, at high doses (5 mg/kg/day), OPC-67683 had demonstrated efficacy in lungs, spleen and liver.[168]

OPC-67683 is not a substrate for cytochrome P450 enzymes, so many types of drug interactions may be avoided. The potential for interactions that might affect oral absorption, such as those affecting P-glycoprotein, have yet to be described. In the mouse model, OPC-67683 at a dose of 2.5 mg/kg displayed a C_{max} of approximately 0.3 mcg/mL, a T_{max} of 6 h, and an elimination half-life of 7.6 h. OPC-67683 is in clinical Phase II testing for MDR-TB.[171]

A pyrrole derivative, LL3858, is currently in development for tuberculosis by Lupin Limited (Mumbai, India).[145,146] It appears to be active *in vitro* and in animal models against TB. Currently, there are no publications on PubMed regarding this compound, so apparently no data have been subjected to peer review so far. Other pyrrole derivatives are at earlier stages of development.[172]

SQ109 was derived from ethambutol but appears to have a unique mechanism of action against the mycobacterial cell wall.[145,146] It has an MIC against *M. tuberculosis* of 0.16 to 0.63 mcg/mL and appears to be bactericidal.[146,173] Early animal model data show that SQ-109 was effective as delivered orally in mice, exhibiting C_{max} values less than 0.2 mcg/mL and a half-life about 5 h.[163,173,174] This drug demonstrates enhanced activity, compared to ethambutol, when combined with standard first-line drugs in the mouse.[175] Consequently, it has entered clinical Phase I testing [174] and will be included in Phase II treatment-shortening trials beginning in 2009. Recent mouse work suggests that SQ109 has a synergistic effect on the activity of TMC207, decreasing its MIC by 75%.[176] This finding supports the possible introduction of SQ109 into DR-TB treatment.[177] Five agents, which boast new mechanisms of action, no cross-resistance with extant drugs, and activity against resistant organisms, are currently in clinical testing.

Although the probability that one or more of these new agents will be approved for TB treatment remains slim, the prospects for improved treatment of drug-resistant TB are considerably brighter than ever before. If TMC207 could be paired with one of the nitroimidazoles and one or two of the existing second-line drugs, DR-TB treatment could potentially be shortened, simplified (i.e., delivered intermittently), rendered less toxic, and/or, more effective.

10. Conclusions

More potential options for improved TB treatment currently exist than at any other time in the last 30 years. Options range from integration of completely new agents, with new mechanisms of action and a very narrow spectrum of activity (e.g., OPC-67683, PA-824), to confirmation of clinical efficacy of antimicrobials developed for other indications and already used for TB (e.g., fluoroquinolones, linezolid), to different drug dosing or unique formulations for medications already being used in TB treatment (e.g., rifamycins, inhaled capreomycin).

The challenge in TB pharmacotherapy is to devise well-tolerated, efficacious, short-duration regimens that can be used in a heterogeneous population of TB patients: children, pregnant women, diabetics, substance abusers, and those receiving antiretroviral therapy for HIV disease. Also critical to the future of TB control is the development of regimens effective against TB caused by strains of *M. tuberculosis* resistant to isoniazid and rifampin, as well as to fluoroquinolones and aminoglycosides/polypeptides (XDR-TB).

11. Expert Opinion

In this paper, we review a wide range of therapeutic strategies that might be employed to stem the rising tide of TB in the world. Over the past several decades, TB treatment and policy have relied largely on a single, standardized regimen. The consensus was that this approach had the greatest potential for reducing the global burden of TB and that additional effort should be devoted to implementation of the proper logistics to ensure delivery of treatment over a period of 6 months.

Missing from this approach was an acknowledgement that, although clinical trials had demonstrated cure in more than 95% of patients receiving regimens comprising isoniazid, rifampin, pyrazinamide, and ethambutol, most countries struggled to cure 80%. Further, many HIV-infected TB patients were not adequately treated with a 6-month regimen, and treatment was extended to 9 months for such patients. In resource-poor nations, 9-month regimens significantly tax an already overburdened healthcare system. Finally, the emergence of MDR- and XDR-TB—which are not effectively treated by the standard TB regimen—has made the search for new TB drugs imperative.

Against this background, several potential strategies have emerged for improving TB treatment. These can broadly be divided into treatments that use current TB drugs, those that use existing drugs, off-label for TB, and those that will incorporate TB drugs in development. While awaiting the advent of these new agents—which is unlikely in the near future—we advocate a strong commitment to the first two approaches. In particular, optimizing the doses of rifampin and its cyclopentyl derivative, rifapentine, holds the greatest promise for ensuring better outcomes with the current first-line treatment over the course of 6 months. High-dose rifampin or rifapentine also may permit shorter therapy, perhaps 4 months or less. Mouse model data are very encouraging in this regard, and several clinical trials are about to begin. In the near term, this approach may maximize the benefit of treatment to those who harbor fully drug-susceptible TB.

Reformulation of ‘old’ TB drugs might extend their usefulness. In particular, capreomycin is an injectable polypeptide used for MDR-TB. The requirement for intramuscular or intravenous injection poses several logistical challenges around the globe. Experiments in guinea-pigs suggest that capreomycin might effectively be delivered by inhalation. A simple, disposable inhalation device might preclude the use of needles, reduce burden on healthcare workers, and improve patient acceptance while simultaneously reducing the risk of spread of blood-borne pathogens. Ethionamide, an extremely unpleasant drug to consume orally, also might be used as an inhaled agent. Here, it might supplement a reduced oral dose, or replace oral dosing

altogether. If successful, this could dramatically reduce the current high frequency of gastrointestinal intolerance caused by ethionamide.

Existing drugs without a TB indication, such as moxifloxacin, gatifloxacin, and levofloxacin, can potentially improve treatment of drug-susceptible and drug-resistant TB. In drug-susceptible TB, they might substitute for current first-line agents such as isoniazid or ethambutol, thus increasing the potency of the regimen. As with high-dose rifamycins, inclusion of fluoroquinolones might increase the probability of cure over the course of 6 months. Additionally, they may permit shorter regimens, at least in selected patients. Several trials have been completed, and others are ongoing. Second, the fluoroquinolones increasingly are used as primary agents in the treatment of MDR-TB. Their inclusion in the treatment regimens has been associated with improved cure rates relative to regimens without fluoroquinolones; potential for shortening these lengthy regimens with later-generation fluoroquinolones is also real.

In the context of improved treatment for DR-TB, linezolid may also have a role. Although fairly potent against TB *in vitro*, long-term linezolid exposure has been associated with myelosuppression and peripheral and optic neuropathies. These toxicities, along with linezolid's relatively high price, have limited the broad use of linezolid as a TB drug; tolerance for these disadvantages, however, may be higher among patients with MDR-TB and XDR-TB who have fewer treatment options.

Finally, a host of new agents has been discovered, and several drug discovery programs continue to search for others. The most advanced clinical development efforts are focused on MDR- and XDR-TB. Currently, only relative weak regimens are available for disease caused by these resistant strains of TB, and treatment often lasts 2 years or more and cures approximately 70% of patients. If successful, the new agents might improve probability of cure and/or reduce the duration of treatment for MDR- and XDR-TB. Further, in combination with selected first-line agents, the new TB drugs might be able to produce extremely short course regimens, further revolutionizing the treatment of TB.

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References

1. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis. *Am J Respir Crit Care Med* 2003;167:603–62. [PubMed: 12588714]
- 2**. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *Int J Tuberc Lung Dis* 1999;3(10 Suppl 2):S231–79. [PubMed: 10529902]Excellent, concise review of the history of antituberculosis chemotherapy
- 3**. Peloquin, CA. Clinical pharmacology of the anti-tuberculosis drugs. In: Davies, PDO., editor. *Clinical Tuberculosis*. Vol. 3. London, England: Arnold Publishers; 2003. p. 171-90.Excellent, comprehensive review
4. Rosenthal IM, Zhang M, Williams KN, et al. Daily dosing of rifapentine cures tuberculosis in three months or less in the murine model. *PLoS Med* 2007;4(12):e344. [PubMed: 18092886]
5. Lenaerts AJ, Hoff D, Aly S, et al. Location of persisting mycobacteria in a guinea pig model of tuberculosis revealed by R207910. *Antimicrob Agents Chemother* 2007;51(9):3338–45. [PubMed: 17517834]
- 6**. Jindani A, Dore CJ, Mitchison DA. Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. *Am J Respir Crit Care Med* 2003;167(10):1348–54. [PubMed: 12519740]

Establishes current standard for distinguishing between early bactericidal and sterilizing activity in humans

7. Aquinas M. Short-course therapy for tuberculosis. *Drugs* 1982;24(2):118–32. [PubMed: 6749471]
8. Mitchison DA. The action of antituberculosis drugs in short-course chemotherapy. *Tubercle* 1985;66(3):219–25. [PubMed: 3931319]
- 9*. Mitchison DA, Coates AR. Predictive in vitro models of the sterilizing activity of anti-tuberculosis drugs. *Curr Pharm Design* 2004;10(26):3285–95. Important advance in model to measure sterilizing activity
10. Davies GR, Khoo SH, Aarons LJ. Optimal sampling strategies for early pharmacodynamic measures in tuberculosis. *J Antimicrob Chemother* 2006;58(3):594–600. [PubMed: 16857690]
11. Peloquin, CA.; Vernon, A. Antimycobacterial Agents: Rifamycins for Mycobacterial Infections. In: Yu, VL.; Edwards, G.; McKinnon, PS.; Peloquin, C.; Morse, GD., editors. *Antimicrobial Chemotherapy and Vaccines, Antimicrobial Agents*. Vol. 2. Vol. II. Pittsburgh, PA: ESun Technologies; 2005. p. 383-402.
12. Heifets LB. Antimycobacterial drugs. *Sem Respir Infect* 1994;9(2):84–103.
13. Hobby GL. Summation of experimental studies on the action of rifampin. *Chest* 1972;61(6):550–4. [PubMed: 4624277]
14. Verbist L. Mode of action of antituberculous drugs (Part I). *Medicon Intl* 1974;3:11–23.
15. Verbist L. Mode of action of antituberculous drugs (Part II). *Medicon Intl* 1974;3:3–17.
16. Somoskovi A, Parsons LM, Salfinger M. The molecular basis of resistance to isoniazid, rifampin, and pyrazinamide in *Mycobacterium tuberculosis*. *Resp Res* 2001;2(3):164–8.
17. Blanchard JS. Molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. *Annu Rev Biochem* 1996;65:215–39. [PubMed: 8811179]
18. Trnka, L.; Mison, P.; Bartmann, K.; Otten, H. Experimental evaluation of efficacy. In: Bartmann, K., editor. *Antituberculosis Drugs*. Berlin: Springer-Verlag; 1988. p. 31-232.
- 19*. Gumbo T, Louie A, Deziel MR, et al. Concentration-dependent *Mycobacterium tuberculosis* killing and prevention of resistance by rifampin. *Antimicrob Agents Chemother* 2007;51(11):3781–8. [PubMed: 17724157] Novel approach to evaluating drug activity
- 20*. Dickinson JM, Mitchison DA. Experimental models to explain the high sterilizing activity of rifampin in the chemotherapy of tuberculosis. *Am Rev Respir Dis* 1981;123(4 Pt 1):367–71. [PubMed: 6784622] Important, early piece to elucidate mechanism of RIF's sterilizing activity
21. Verbist L, Gyselen A. Antituberculous Activity of Rifampin In Vitro and In Vivo and the Concentrations Attained in Human Blood. *Am Rev Respir Dis* 1968;12(986):923–32. [PubMed: 4972215]
22. Dickinson JM, Mitchison DA. Suitability of rifampicin for intermittent administration in the treatment of tuberculosis. *Tubercle* 1970;51(1):82–94. [PubMed: 4992976]
23. Verbist L. Rifampicin activity “in vitro” and in established tuberculosis in mice. *Acta Tuberc Pneumol Belg* 1969;60(3):397–412. [PubMed: 4984420]
24. Nuermberger, E.; Rosenthal, I.; Zhang, M., et al. Does Autoinduction of Rifamycin Metabolism Affect the Efficacy of TB Chemotherapy?. *Proceedings of the American Thoracic Society International Conference*; San Francisco, CA. 2007. p. A971
25. Jayaram R, Gaonkar S, Kaur P, et al. Pharmacokinetics-pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. *Antimicrob Agents Chemother* 2003;47(7):2118–24. [PubMed: 12821456]
- 26*. Ruslami R, Nijland HM, Alisjahbana B, et al. Pharmacokinetics and tolerability of a higher rifampin dose versus the standard dose in pulmonary tuberculosis patients. *Antimicrob Agents Chemother* 2007;51(7):2546–51. [PubMed: 17452486] Current human evidence to support increase in RIF dose
27. Sirgel FA, Fourie PB, Donald PR, et al. The early bactericidal activities of rifampin and rifapentine in pulmonary tuberculosis. *Am J Respir Crit Care Med* 2005;172(1):128–35. [PubMed: 15805182]
- 28*. Diacon AH, Patientia RF, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrob Agents Chemother* 2007;51(8):2994–6. [PubMed: 17517849] Current human evidence to support increase in RIF dose

29. Decroix G, Kreis B, Sors C, et al. [Comparison between regimes of rifampicin-isoniazid administered daily and administered twice a week (initial results of a comparative study conducted in 4 medical services of the Parisian region)]. *Rev Tuberc Pneumol* 1969;33(6):751–68.
- 30*. Kreis B, Pretet S, Birenbaum J, et al. Two Three-Month Treatment Regimens for Pulmonary TB. *Bull Int Un Tuberc* 1976;51:71–5. [PubMed: 1030315] Sentinel study of high-dose RIF in humans
31. Long MW, Snider DE Jr, Farer LS. U.S. Public Health Service Cooperative trial of three rifampin-isoniazid regimens in treatment of pulmonary tuberculosis. *Am Rev Respir Dis* 1979;119(6):879–94. [PubMed: 110184]
32. East African/British Medical Research Council. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. *Lancet* 1972;1(7760):1079–85. [PubMed: 4112569]
33. Verbist L, Rollier F. Pharmacological study of rifampicin after repeated high dosage during intermittent combined therapy. II. Bilirubin levels and other biochemical determinations. *Respir Int Rev Thorac Dis* 1971;28(Suppl):17–28.
34. Decroix G, Kreis B, Sors C, et al. [Comparative study of the treatment of pulmonary tuberculosis by a combination of rifampicin and isoniazid administered daily and twice weekly for a year]. *Rev Tuberc Pneumol* 1971;35(1):39–54.
35. A comparative study of daily followed by twice or once weekly regimens of ethambutol and rifampicin in retreatment of patients with pulmonary tuberculosis. The results at 1 year. A cooperative tuberculosis chemotherapy study in Poland. *Tubercle* 1975;56(1):1–26. [PubMed: 1096388]
36. A comparative study of daily followed by twice or once weekly regimens of ethambutol and rifampicin in retreatment of patients with pulmonary tuberculosis: Second Report. *Tubercle* 1976;57:105–13. [PubMed: 822547]
37. Hong Kong Tuberculosis Treatment Services, Brompton Hospital, British Medical Research Council. A controlled trial of daily and intermittent rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis: results up to 30 months. *Tubercle* 1975;56(3):179–89. [PubMed: 766340]
38. Dutt AK, Moers D, Stead WW. Undesirable side effects of isoniazid and rifampin in largely twice-weekly short-course chemotherapy for tuberculosis. *Am Rev Respir Dis* 1983;128(3):419–24. [PubMed: 6614636]
39. Poole G, Stradling P, Worlledge S. Potentially serious side effects of high-dose twice-weekly rifampicin. *Brit Med J* 1971;3(5770):343–7. [PubMed: 5314737]
40. Controlled clinical trial of four 6-month regimens of chemotherapy for pulmonary tuberculosis. Second report. Second East African/British Medical Research Council Study. *Am Rev Respir Dis* 1976;114(3):471–5. [PubMed: 788570]
41. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle* 1979;60(4):201–10. [PubMed: 396701]
42. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med* 2006;174(8):935–52. [PubMed: 17021358]
43. McEvoy, GK.; Snow, EK.; Kester, L., editors. AHFS Drug Information 2006. Bethesda, MD: American Society of Health-System Pharmacists; 2006.
44. Peloquin, CA. Antituberculosis drugs: pharmacokinetics. In: Heifets, LB., editor. *Drug-Susceptibility in the chemotherapy of Mycobacterial infections*. Boca Raton, FL: CRC Press; 1991. p. 89-122.
45. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1982;23(1–2):56–74. [PubMed: 6459920]
46. Pande JN, Singh SP, Khilnani GC, et al. Risk factors for hepatotoxicity from antituberculosis drugs: a case-control study. *Thorax* 1996;51(2):132–6. [PubMed: 8711642]
47. Sarma GR, Immanuel C, Kailasam S, et al. Rifampin-induced release of hydrazine from isoniazid. A possible cause of hepatitis during treatment of tuberculosis with regimens containing isoniazid and rifampin. *Am Rev Respir Dis* 1986;133(6):1072–5. [PubMed: 3717759]
48. Steele MA, Burk RF, DesPrez RM. Toxic hepatitis with isoniazid and rifampin. A meta-analysis *Chest* 1991;99(2):465–71.

- 49*. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *The J Antimicrob Chemother* 1977;3(2):115–32. Comprehensive review of adverse events thought to be associated with RIF, including pathophysiology
50. Martinez E, Collazos J, Mayo J. Hypersensitivity reactions to rifampin. Pathogenetic mechanisms, clinical manifestations, management strategies, and review of the anaphylactic-like reactions. *Medicine* 1999;78(6):361–9. [PubMed: 10575418]
51. Aquinas M, Allan WG, Horsfall PA, et al. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *Brit Med J* 1972;1(5803):765–71. [PubMed: 4259217]
52. Grosset J, Leventis S. Adverse effects of rifampin. *Rev Infect Dis* 1983;5(Suppl 3):S440–50. [PubMed: 6356277]
53. Peloquin C. What is the ‘right’ dose of rifampin? *Int J Tuberc Lung Dis* 2003;7(1):3–5. [PubMed: 12701829]
- 54**. Mitchison DA. Antimicrobial therapy of tuberculosis: justification for currently recommended treatment regimens. *Sem Respir Crit Care Med* 2004;25(3):307–15. Excellent review of historical evidence for current treatment and indication of knowledge gaps
55. Boman G, Ringberger VA. Binding of Rifampicin by Human Plasma Proteins. *Eur J Clin Pharmacol* 1974;7:369–73. [PubMed: 4138537]
56. Mehta JB, Shantaveerapa H, Byrd RP Jr, et al. Utility of rifampin blood levels in the treatment and follow-up of active pulmonary tuberculosis in patients who were slow to respond to routine directly observed therapy. *Chest* 2001;120(5):1520–4. [PubMed: 11713129]
57. Kimerling ME, Phillips P, Patterson P, et al. Low serum antimycobacterial drug levels in non-HIV-infected tuberculosis patients. *Chest* 1998;113(5):1178–83. [PubMed: 9596291]
58. Humber DP, Nsanzumuhire H, Aluoch JA, et al. Controlled double-blind study of the effect of rifampin on humoral and cellular immune responses in patients with pulmonary tuberculosis and in tuberculosis contacts. *Am Rev Respir Dis* 1980;122(3):425–36. [PubMed: 7416618]
59. Dhar S, Kaur I, Sharma VK, Kumar B. “Flu” syndrome due to rifampin; experience with four cases”. *Int J Lepr Other Mycobact Dis* 1995;63(1):92–4. [PubMed: 7730725]
60. Bertrand A. Antibiotic treatment of brucellosis. *Presse Med* 1994;25(2324):1128–31. [PubMed: 7971834]
61. Reichler MR, Allphin AA, Breiman RF, et al. The spread of multiply resistant *Streptococcus pneumoniae* at a day care center in Ohio. *J Infect Dis* 1992;166(6):1346–53. [PubMed: 1431252]
62. Drancourt M, Stein A, Argenson JN, et al. Oral treatment of *Staphylococcus* spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. *J Antimicrob Chemother* 1997;39(2):235–40. [PubMed: 9069545]
63. Baty V, Hoen B, Schuhmacher H, et al. *Legionella jordanis* pneumonia unresponsive to fluoroquinolones in a non-immunocompromised host. *Scand J Infect Dis* 1997;29(3):319–20. [PubMed: 9255901]
64. Kochar DK, Aseri S, Sharma BV, et al. The role of rifampicin in the management of cutaneous leishmaniasis. *Q J Med* 2000;93(11):733–7.
65. Namdar, R.; Ebert, SC.; Peloquin, CA. Drugs for Tuberculosis. In: Piscitelli, SC.; Rodvold, KA., editors. *Drug Interactions in Infectious Diseases*. Vol. 2. Totowa, NJ: Humana Press; 2006. p. 191–214.
66. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis* 1999;28(3):419–29. [PubMed: 10194057] quiz 30
67. Burman WJ, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin Pharmacokinet* 2001;40(5):327–41. [PubMed: 11432536]
68. Grange JM, Winstanley PA, Davies PD. Clinically significant drug interactions with antituberculosis agents. *Drug Safety* 1994;11(4):242–51. [PubMed: 7848544]
69. Yew WW. Clinically significant interactions with drugs used in the treatment of tuberculosis. *Drug Safety* 2002;25(2):111–33. [PubMed: 11888353]
70. Israili ZH, Rogers CM, el-Attar H. Pharmacokinetics of antituberculosis drugs in patients. *J Clin Pharmacol* 1987;27(1):78–83. [PubMed: 3680559]

71. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984;9(6):511–44. [PubMed: 6391781]
72. Jain A, Mehta VL, Kulshrestha S. Effect of pyrazinamide on rifampicin kinetics in patients with tuberculosis. *Tuber Lung Dis* 1993;74(2):87–90. [PubMed: 8324212]
- 73*. Weiner M, Burman W, Luo CC, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother* 2007;51(8):2861–6. [PubMed: 17517835] Establishes impact of RIF on MOXI concentrations in humans
74. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007;45(8):1001–7. [PubMed: 17879915]
75. McIlleron H, Norman J, Kanyok TP, et al. Elevated gatifloxacin and reduced rifampicin concentrations in a single-dose interaction study amongst healthy volunteers. *J Antimicrob Chemother* 2007;60(6):1398–401. [PubMed: 17951604]
76. Acocella G, Bertrand A, Beytout J, et al. Comparison of three different regimens in the treatment of acute brucellosis: a multicenter multinational study. *J Antimicrob Chemother* 1989;23(3):433–9. [PubMed: 2732125]
- 77*. Ruslami R, Nijland H, Aarnoutse R, et al. Evaluation of high- versus standard-dose rifampin in Indonesian patients with pulmonary tuberculosis. *Antimicrob Agents Chemother* 2006;50(2):822–3. [PubMed: 16436757] Current human evidence to support increase in RIF dose
78. Chan SL, Yew WW, Porter JHD, et al. Comparison of Chinese and Western rifapentines and improvement of bioavailability by prior taking of various meals. *Int J Antimicrob Agents* 1994;3:267–74. [PubMed: 18611569]
79. Acocella G. Clinical pharmacokinetics of rifampicin. *Clin Pharmacokinet* 1978;3(2):108–27. [PubMed: 346286]
80. Tam CM, Chan SL, Lam CW, et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. *Am J Respir Crit Care Med* 1998;157(6 Pt 1):1726–33. [PubMed: 9620898]
81. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet* 2002;360(9332):528–34. [PubMed: 12241657]
82. Keung A, Reith K, Eller MG, et al. Enzyme induction observed in healthy volunteers after repeated administration of rifapentine and its lack of effect on steady-state rifapentine pharmacokinetics: part I. *Int J Tuberc Lung Dis* 1999;3(5):426–36. [PubMed: 10331733]
83. Keung A, Eller MG, McKenzie KA, Weir SJ. Single and multiple dose pharmacokinetics of rifapentine in man: part II. *Int J Tuberc Lung Dis* 1999;3(5):437–44. [PubMed: 10331734]
84. Weiner M, Bock N, Peloquin CA, et al. Pharmacokinetics of rifapentine at 600, 900, and 1,200 mg during once-weekly tuberculosis therapy. *Am J Respir Crit Care Med* 2004;169(11):1191–7. [PubMed: 14962821]
85. Heifets LB, Iseman MD. Determination of in vitro susceptibility of mycobacteria to ansamycin. *Am Rev Respir Dis* 1985;132(3):710–1. [PubMed: 3929660]
86. Schwander S, Rusch-Gerdes S, Mateega A, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. A single-blind randomized evaluation in Ugandan patients with HIV-1 infection and pulmonary tuberculosis. *Tuber Lung Dis* 1995;76(3):210–8. [PubMed: 7548903]
87. McGregor MM, Olliaro P, Wolmarans L, et al. Efficacy and safety of rifabutin in the treatment of patients with newly diagnosed pulmonary tuberculosis. *Am J Respir Crit Care Med* 1996;154(5):1462–7. [PubMed: 8912765]
88. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001;164(1):7–12. [PubMed: 11435232]
89. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. *MMWR Morb Mortal Wkly Rep* 2000;49:185–9. [PubMed: 11795500]

90. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clin Infect Dis* 2005;40(10):1481–91. [PubMed: 15844071]
91. Centers for Disease Control and Prevention. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2008. [Last accessed 3 June 2008]. Available at: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm/
92. Narang PK, Lewis RC, Bianchine JR. Rifabutin absorption in humans: relative bioavailability and food effect. *Clin Pharmacol Ther* 1992;52(4):335–41. [PubMed: 1330396]
93. Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. *Drugs* 2002;62(15):2169–83. [PubMed: 12381217]
94. Peloquin CA. Pharmacological issues in the treatment of tuberculosis. *Ann NY Acad Sci* 2001;953:157–64. [PubMed: 11795409]
95. Peloquin CA. Tuberculosis drug serum levels. *Clin Infect Dis* 2001;33(4):584–5. [PubMed: 11462203]
96. Boulanger, C.; Peloquin, C.; Hollender, E., et al. PK analysis of rifabutin given with lopinavir/ritonavir to persons co-infected with TB and HIV [abstract]. 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Sydney, Australia. 2007.
97. Heifets, LB. Drug susceptibility tests in the management of chemotherapy of tuberculosis. In: Heifets, LB., editor. *Drug Susceptibility in the Chemotherapy of Mycobacterial Infections*. Boca Raton, FL: CRC Press; 1991. p. 89-122.
98. Berning SE. The role of fluoroquinolones in tuberculosis today. *Drugs* 2001;61(1):9–18. [PubMed: 11217874]
99. Alvarez-Freites EJ, Carter JL, Cynamon MH. In Vitro and In Vivo Activities of Gatifloxacin against *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2002;46(4):1022–5. [PubMed: 11897584]
100. Lounis N, Bentoucha A, Truffot-Pernot C, et al. Effectiveness of once-weekly rifapentine and moxifloxacin regimens against *Mycobacterium tuberculosis* in mice. *Antimicrob Agents Chemother* 2001;45(12):3482–6. [PubMed: 11709328]
101. Rastogi N, Goh KS. In Vitro Activity of the New Difluorinated Quinolone Sparfloxacin (AT-4140) against *Mycobacterium tuberculosis* Compared with Activities of Ofloxacin and Ciprofloxacin. *Antimicrob Agents Chemother* 1991;35(9):1993–36.
102. Garcia-Rodriguez JA, Gomez Garcia AC. In-vitro activities of quinolones against mycobacteria. *J Antimicrob Chemother* 1993;32(6):797–808. [PubMed: 8144420]
103. Davis, SL.; Neuhauser, MM.; McKinnon, PS. Quinolones. In: Yu, VL.; Edwards, G.; McKinnon, PS.; Peloquin, C.; Morse, GD., editors. *Antimicrobial Chemotherapy and Vaccines, Antimicrobial Agents*. Vol. 2. Vol. II. Pittsburgh, PA: ESun Technologies; 2005. p. 337-66.
104. Peloquin, CA.; Auclair, B. Pharmacology of the second-line antituberculosis drugs. In: Portaels, F.; Bastian, I., editors. *Multidrug-resistant tuberculosis*. Dordrecht, The Netherlands: Kluwer Academic Publications; 2000. p. 163-74.
105. Tsikouris JP, Peeters MJ, Cox CD, et al. Effects of three fluoroquinolones on QT analysis after standard treatment courses. *Ann Noninvasive Electrocardiol* 2006 Jan;11(1):52–6. [PubMed: 16472283]
- 106*. Park-Wyllie LY, Juurlink DN, Kopp A, et al. Outpatient gatifloxacin therapy and dysglycemia in older adults. *New Engl J Med* 2006;354(13):1352–61. [PubMed: 16510739]Presents evidence of rare but serious dysglycemia in elderly patients receiving GATI
107. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007;41(11):1859–66. [PubMed: 17911203]
108. Sode J, Obel N, Hallas J, Lassen A. Use of fluoroquinolone and risk of Achilles tendon rupture: a population-based cohort study. *Eur J Clin Pharmacol* 2007;63(5):499–503. [PubMed: 17334751]
109. Nuermberger EL, Yoshimatsu T, Tyagi S, et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. *Am J Respir Crit Care Med* 2004;169(3):421–6. [PubMed: 14578218]

110. Grosset J, Truffot-Pernot C, Lacroix C, Ji B. Antagonism between isoniazid and the combination pyrazinamide-rifampin against tuberculosis infection in mice. *Antimicrob Agents Chemother* 1992;36(3):548–51. [PubMed: 1622164]
111. Pletz MW, De Roux A, Roth A, et al. Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. *Antimicrob Agents Chemother* 2004;48(3):780–2. [PubMed: 14982764]
- 112*. Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2006;10(6):605–12. [PubMed: 16776446] Demonstrates potential advantage in activity with high-dose LEVO
113. Tomioka H, Sato K, Kajitani H, et al. Comparative antimicrobial activities of the newly synthesized quinolone WQ-3034, levofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis* and *Mycobacterium avium* complex. *Antimicrob Agents Chemother* 2000;44(2):283–6. [PubMed: 10639351]
114. Vacher S, Pellegrin JL, Leblanc F, et al. Comparative antimycobacterial activities of ofloxacin, ciprofloxacin and grepafloxacin. *J Antimicrob Chemother* 1999;44(5):647–52. [PubMed: 10552981]
115. Chaisson, RE.; Efron, A.; Ram, M., et al. A randomized, placebo-controlled trial of moxifloxacin versus ethambutol in the initial phase of tuberculosis therapy in Brazil. Abstract L-736-A. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, IL. 2007.
116. Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med* 2006;174(3):331–8. [PubMed: 16675781]
- 117*. Rustomjee R, Lienhardt C, Kanyok T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2008;12(2):128–38. [PubMed: 18230244] Demonstrates possibility of using continuous measure—serial quantitative cultures—as measure of sterilizing activity, with substantially reduced sample size
118. British Thoracic Association. A controlled trial of six months chemotherapy in pulmonary tuberculosis. First Report: results during chemotherapy. *British Thoracic Association Brit J Dis Chest* 1981;75(2):141–53.
119. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. *Lancet Infect Dis* 2003;3(7):432–42. [PubMed: 12837348]
120. Grimaldo ER, Tupasi TE, Rivera AB, et al. Increased resistance to ciprofloxacin and ofloxacin in multidrug-resistant mycobacterium tuberculosis isolates from patients seen at a tertiary hospital in the Philippines. *Int J Tuberc Lung Dis* 2001;5(6):546–50. [PubMed: 11409582]
121. von Gottberg A, Klugman KP, Cohen C, et al. Emergence of levofloxacin-non-susceptible *Streptococcus pneumoniae* and treatment for multidrug-resistant tuberculosis in children in South Africa: a cohort observational surveillance study. *Lancet* 2008;371(9618):1108–13. [PubMed: 18359074]
122. Zvonar R. Gatifloxacin-induced dysglycemia. *Am J Health Syst Pharm* 2006;63(21):2087–92. [PubMed: 17057046]
123. Department of Health and Human Services/Food and Drug Administration. Determination That TEQUIN (Gatifloxacin) Was Withdrawn From Sale for Reasons of Safety or Effectiveness. Federal Register September 9, 2008:52357–8
124. Rodriguez JC, Ruiz M, Lopez M, Royo G. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis*. *Int J Antimicrob Agents* 2002;20(6):464–7. [PubMed: 12458143]
125. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. *J Antimicrob Chemother* 2003;51(Suppl 2):ii9–16. [PubMed: 12730138]
126. Moellering RC. Linezolid: the first oxazolidinone antimicrobial. *Ann Intern Med* 2003;138(2):135–42. [PubMed: 12529096]
127. Wienkers, LC.; Wynalda, MA.; Feenstra, KL., et al. In vitro metabolism of linezolid (PNU-100766): lack of induction or inhibition of cytochrome P450 enzymes and studies on the mechanism of formation of the major human metabolite, PNU-142586. Program and Abstracts of the Thirty-Ninth

- Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco, CA. Abstract 11, p. 3. American Society for Microbiology, Washington, DC 1999.
128. Antal EJ, Hendershot PE, Batts DH, et al. Linezolid, a novel oxazolidinone antibiotic: assessment of monoamine oxidase inhibition using pressor response to oral tyramine. *J Clin Pharmacol* 2001;41(5):552–62. [PubMed: 11361052]
 129. Ntziora F, Falagas ME. Linezolid for the treatment of patients with [corrected] mycobacterial infections [corrected] a systematic review. *Int J Tuberc Lung Dis* 2007;11(6):606–11. [PubMed: 17519090]
 - 130*. Dietze R, Hadad DJ, McGee B, et al. Early and extended early bactericidal activity of linezolid in pulmonary tuberculosis. *Am J Respir Crit Care Med* 2008;178(11):1180–5. [PubMed: 18787216] Demonstrates poor EBA of linezolid
 131. French G. Safety and tolerability of linezolid. *J Antimicrob Chemother* 2003;51(Suppl 2):ii45–53. [PubMed: 12730142]
 132. Fortun J, Martin-Davila P, Navas E, et al. Linezolid for the treatment of multidrug-resistant tuberculosis. *J Antimicrob Chemother* 2005;56(1):180–5. [PubMed: 15911549]
 133. von der Lippe B, Sandven P, Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB)--a report of ten cases. *J Infection* 2006;52(2):92–6.
 134. Park IN, Hong SB, Oh YM, et al. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. *J Antimicrob Chemother* 2006;58(3):701–4. [PubMed: 16857689]
 135. Rastogi R, Sultana Y, Ali A, Aqil M. Particulate and vesicular drug carriers in the management of tuberculosis. *Curr Drug Deliv* 2006;3(1):121–8. [PubMed: 16472101]
 136. Pandey R, Khuller GK. Solid lipid particle-based inhalable sustained drug delivery system against experimental tuberculosis. *Tuberculosis (Edinburgh, Scotland)* 2005;85(4):227–34.
 137. Pandey R, Sharma A, Zahoor A, et al. Poly (DL-lactide-co-glycolide) nanoparticle-based inhalable sustained drug delivery system for experimental tuberculosis. *J Antimicrob Chemother* 2003;52(6):981–6. [PubMed: 14613962]
 138. Garcia-Contreras L, Fiegel J, Telko MJ, et al. Inhaled large porous particles of capreomycin for treatment of tuberculosis in a guinea pig model. *Antimicrob Agents Chemother* 2007;51(8):2830–6. [PubMed: 17517845]
 139. Fiegel J, Garcia-Contreras L, Thomas M, et al. Preparation and in vivo evaluation of a dry powder for inhalation of capreomycin. *Pharm Res* 2008;25(4):805–11. [PubMed: 17657592]
 140. Namdar, R.; Peloquin, C. Ethionamide. In: Yu, VL.; Edwards, G.; McKinnon, PS.; Peloquin, C.; Morse, GD., editors. *Antimicrobial Chemotherapy and Vaccines, Antimicrobial Agents*. Vol. 2. Vol. II. Pittsburgh, PA: ESun Technologies; 2005. p. 533–8.
 141. Morlock GP, Metchock B, Sikes D, et al. ethA, inhA, and katG loci of ethionamide-resistant clinical *Mycobacterium tuberculosis* isolates. *Antimicrob Agents Chemother* 2003;47(12):3799–805. [PubMed: 14638486]
 142. Winder FG, Collins PB, Whelan D. Effects of ethionamide and isoxyl on mycolic acid synthesis in *Mycobacterium tuberculosis* BCG. *J Gen Microbiol* 1971;66(3):379–80. [PubMed: 4999216]
 143. Somner AR, Brace AA. Late results of treatment of chronic drug-resistant pulmonary tuberculosis. *Brit Med J* 1966;26:775–8. [PubMed: 5910108]
 144. Zhu M, Namdar R, Stambaugh JJ, et al. Population pharmacokinetics of ethionamide in patients with tuberculosis. *Tuberculosis (Edinburgh, Scotland)* 2002;82(2–3):91–6.
 - 145*. Spigelman M, Gillespie S. Tuberculosis drug development pipeline: progress and hope. *Lancet* 2006;18(3679514):945–7. [PubMed: 16546546]Excellent review of current drug development efforts
 146. O'Brien RJ, Spigelman M. New drugs for tuberculosis: current status and future prospects. *Clin Chest Med* 2005;26(2):327–40. vii. [PubMed: 15837114]
 147. Khasnobis S, Escuyer VE, Chatterjee D. Emerging therapeutic targets in tuberculosis: post-genomic era. *Expert Opin Ther Targets* 2002;6(1):21–40. [PubMed: 11901479]
 148. Biava M, Porretta GC, Deidda D, Pompei R. New trends in development of antimycobacterial compounds. *Infect Disord Drug Targets* 2006;6(2):159–72. [PubMed: 16789877]

149. Tomioka H. Current status of some antituberculosis drugs and the development of new antituberculous agents with special reference to their in vitro and in vivo antimicrobial activities. *Curr Pharm Design* 2006;12(31):4047–70.
150. Janin YL. Antituberculosis drugs: ten years of research. *Bioorga Med Chem* 2007;15(7):2479–513.
151. Stop, TB. New technologies for tuberculosis control: A framework for their adoption, introduction and implementation. Geneva: World Health Organization; 2007. Partnership.
152. Casenghi, M. Development of new drugs for TB chemotherapy: Analysis of the current drug pipeline. Geneva: Medecins San Frontieres, Campaign for Access to Essential Medicines; 2006.
153. Hudson, A.; Imamura, T.; Gutteridge, W., et al. The current anti-TB drug research and development pipeline. Geneva: Special Programme for Research and Training in Tropical Diseases, World Health Organization; 2003.
154. Tomioka H, Tatano Y, Yasumoto K, Shimizu T. Recent advances in antituberculous drug development and novel drug targets. *Expert Rev Respir Med* 2008;2(4):455–71.
- 155*. Glickman SW, Rasiel EB, Hamilton CD, et al. Medicine. A portfolio model of drug development for tuberculosis. *Science (New York, NY)* 2006;311(5765):1246–7. Describes low probability of short-term success with compounds currently in drug pipeline
- 156*. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science (New York, NY)* 2005;307(5707):223–7. Breakthrough of new compound, with new mechanism of action, with activity limited to mycobacteria
- 157*. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. *Antimicrob Agents Chemother* 2008;52(8):2831–5. [PubMed: 18505852] Confirms limitations of EBA for studying activity of new drugs, while demonstrating activity of TMC207
- 158[. Veziris N, Ibrahim M, Lounis N, et al. A Once-weekly R207910-containing Regimen Exceeds Activity of the Standard Daily Regimen in Murine Tuberculosis. *Am J Respir Crit Care Med*. 2008Epub ahead of print]
159. Ibrahim, M.; Truffot-Pernot, C.; Andries, K., et al. Early and Late Bactericidal Activity of R207910 (TMC207) in Murine Tuberculosis. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting; Washington, D.C. October 25–28, 2008;
160. Diacon, AH.; Pym, A.; Grobusch, M., et al. Interim Analysis of a Double-Blind, Placebo-Controlled Study with TMC207 in Patients with Multi-Drug Resistant (MDR) Tuberculosis. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting; Washington, D.C. October 25–28, 2008;
161. Ibrahim, M.; Truffot-Pernot, C.; Andries, K., et al. Sterilizing Activity of a Second Line Regimen Including R207910 (TMC207) in Murine Tuberculosis. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting; Washington, D.C. October 25–28, 2008;
162. Stover KC, Warrenner P, VanDevanter DR, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* 2000;405:962–6. [PubMed: 10879539]
163. Pa-824. Tuberculosis (Edinburgh, Scotland) 2008;88(2):134–6.
164. Lenaerts AJ, Gruppo V, Marietta KS, et al. Preclinical testing of the nitroimidazopyran PA-824 for activity against *Mycobacterium tuberculosis* in a series of in vitro and in vivo models. *Antimicrob Agents Chemother* 2005;49(6):2294–301. [PubMed: 15917524]
165. Ginsberg, A.; Diacon, A.; Dawson, R., et al. Extended Early Bactericidal Activity (EBA) of PA-824, a Novel Drug for Tuberculosis Treatment. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting; Washington, D.C. October 25–28, 2008;
166. Nuermberger E, Rosenthal I, Tyagi S, et al. Combination chemotherapy with the nitroimidazopyran PA-824 and first-line drugs in a murine model of tuberculosis. *Antimicrob Agents Chemother* 2006;50(8):2621–5. [PubMed: 16870750]
- 167*. Nuermberger E, Tyagi S, Tasneen R, et al. Powerful bactericidal and sterilizing activity of a regimen containing PA-824, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. *Antimicrob*

Agents Chemother 2008;52(4):1522–4. [PubMed: 18285479] Demonstration of potential regimen, containing a new drug, which is currently in human trials, and its marked, potent activity against *M. tuberculosis* in the murine model

168. Doi, N.; Disratthakit, A. Characterization of In Vivo Activity of Novel Anti-TB Drug Candidates OPC-67683 and PA-824 in Murine TB Models. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting; Washington, D.C. October 25–28, 2008;
169. Laurenzi, M. Nitroimidazo-oxazine PA-824. The Second Annual Open Forum on Key Issues in TB Drug Development; London, UK. 2006.
170. Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006;3(11):e466. [PubMed: 17132069]
171. Hittel, N. Nitroduhydro-imidazooxazole derivative OPC-67683. The Second Annual Open Forum on Key Issues in TB Drug Development; London, UK. 2006.
172. Biava M, Porretta GC, Poce G, et al. Antimycobacterial agents. Novel diarylpyrrole derivatives of BM212 endowed with high activity toward Mycobacterium tuberculosis and low cytotoxicity. J Med Chem 2006;49(16):4946–52. [PubMed: 16884306]
173. Jia L, Noker PE, Coward L, et al. Interspecies pharmacokinetics and in vitro metabolism of SQ109. Brit J Pharmacol 2006;147(5):476–85. [PubMed: 16432511]
174. Chen P, Gearhart J, Protopopova M, et al. Synergistic interactions of SQ109, a new ethylene diamine, with front-line antitubercular drugs in vitro. The J Antimicrob Chemother 2006;58(2):332–7.
175. Nikonenko BV, Protopopova M, Samala R, et al. Drug therapy of experimental tuberculosis (TB): improved outcome by combining SQ109, a new diamine antibiotic, with existing TB drugs. Antimicrob Agents Chemother 2007;51(4):1563–5. [PubMed: 17242141]
176. Reddy, VM.; Einck, L.; Andries, K.; Nacy, CA. The New Antitubercular Drugs SQ109 and TMC207 Act Synergistically In Vitro to Kill *M. tuberculosis*. 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) and the Infectious Diseases Society of America (IDSA) 46th Annual Meeting; Washington, D.C. October 25–28, 2008;
177. Nacy, C. Diamine SQ109. The Second Annual Open Forum on Key Issues in TB Drug Development; London, UK. 2006.

Table 1
Summary of safety, tolerability, and efficacy findings from clinical studies of high-dose RIF

Authors, year (reference)	Summary of Design	N*	% Convert 1 month	% Convert 2 months	% failure/relapse or combined failure & relapse	Adverse Events
Decroix, Kreis, Sors et al, 1969 [29]	RIF (900 mg) + H (750 mg) twice weekly	32	44	75		none
	RIF (600 mg) + H (450 mg) daily	38	39	70		2 elevated LFT; 1 erythema
	H (900 mg) + SM (1 g) +					
Kreis, Pretet, Birenbaum et al, 1976 [30] ¹	RIF 1200 mg (daily)	44	72.3	93.6	11.4	none reported
	RIF 1200 mg (every 2 days)	47	70.4	93.2	14.9	
	I: H (300 mg) daily +					leucopenia, hepatotoxicity, arthritis, anemia (no significant difference among groups)
Long, Snider, Farer et al (USPHS), 1979 [31] ^{2,3}	RIF (450 mg) daily, 20 weeks	167	24	60	22.4/3.1	6.2%
	RIF (600 mg) daily, 20 weeks	324	35	70	9.1/0.6	6.8%
	RIF (750 mg) daily, 20 weeks	331	33	75	9.4/0	5.7%
E. Africa/BMRC, 1972 [32] ⁴	C: H (300 mg) + EMB (15 mg/kg)					
	Daily SM (1 g) + H (300 mg), 6 months +	80	20	49	10/15	4% had drugs interrupted/terminated; 3 (0.05%) had RIF interrupted/terminated
	RIF (10 mg/kg), 6 months	82	29	73	9/1	4%
Verbist & Rollier, 1971 [33]	PZA (2 g), 6 months	73	29	64	10/6	6%
	THZ (150 mg), 6 months	66	17	46	8/16	9%
	SM, 8 weeks; THZ (150 mg), 18 months, daily	68	18	56	8/0	8%
Decroix, Kreis, Sors et al, 1971 [34] ⁵	RIF 30 mg/kg (1200, 1500, 1800 mg) +					transient increases in bilirubin only; renal monitoring, no AEs
	H (15 mg/kg)	53				
	EMB (100 mg/kg)	43				
	RIF (600 mg) + H (450 mg) daily	47	37	71	0	2% changed due to AEs

Authors, year (reference)	Summary of Design	N*	Outcomes		% failure/ relapse or combined failure & relapse	Adverse Events
			% Convert 1 month	% Convert 2 months		
Cooperative TB Chemotherapy Study, Poland, 1975 [35] ⁶	RIF (900 mg) + H (750 mg) twice weekly	50	44	74	0	1% changed due to AEs
	I: RIF (600 mg) + EMB (25 mg/kg) daily 12 weeks	247	25	60		overall 12%; self-limiting increase in LFTs, asymptomatic. No permanent drug withdrawals.
	C: RIF (1200 mg) + EMB (50 mg/kg)					
	once weekly, 12 months	123			2/6.7	29% systemic, 3% hepatic; rx withdrawn in 10%
	twice weekly, 12 months	124			4/0.6	24% systemic, 2% hepatic; rx withdrawn in 10%
Cooperative TB Chemotherapy Study, Poland, 1976 [36] ^{6,7}	I: RIF (600 mg) + EMB (25 mg/kg) daily, 12 weeks					
	C: RIF (600 mg) + EMB (50 mg/kg)				NA/6.7	
	once weekly, 12 months	38			5/8	10% AEs; 2% treatment changed
	twice weekly, 12 months	40			5/5	3% AEs; 0% treatment changed
	C: RIF (1200 mg) + EMB (50 mg/kg)				2.9/0.6	
	once weekly, 12 months	35			4.6/0	33% AEs; 9% treatment changed
	twice weekly, 12 months	30				
	once weekly, 18 months	70			3.4/4	27% AEs; 19% treatment changed
	twice weekly, 18 months					
	once weekly, 24 months	68			2/0	26% AEs; 20% treatment changed
Hong Kong TB Treatment Services, 1975 [37] H-Resistant, previously treated w/H, SM and/or PAS; adverse reactions evaluated up to 18 months ⁸	I: EMB (15 mg/kg) + RIF (450 mg), daily, 2 months					
	C: EMB (25 mg/kg) + RIF (450 mg), daily, 16 months	42			2/0	11% of 47 (0 flu-like)
	C: EMB (25 mg/kg) + RIF (450 mg), daily, 10 months	39			3/0	Excluded (not followed for 18 months)

Authors, year (reference)	Summary of Design	N*	Outcomes		% failure/ relapse or combined failure & relapse	Adverse Events
			% Convert 1 month	% Convert 2 months		
Dutt, Moers, Stead, 1983 [38] ⁹ ; elderly patients	C: RIF (>20 mg/kg) + EMB (90 mg/kg) once weekly , 16 months	62			13	48% of 77 (40% flu-like)
	RIF (>20 mg/kg) + EMB (45 mg/kg) twice weekly , 18 months	84			21	32% of 68 (22% flu-like)
	RIF (>20 mg/kg) + EMB (90 mg/kg) once weekly , 18 months	53			19	61% of 72 (50% flu-like)
	I: Ethio (>10 mg/kg) + PZA (>30 mg/kg) + CS (0.5 g) daily, 6 months	68			19/0	54% of 57 (0 flu-like)
	C: Ethio (>10 mg/kg) + PZA (>30 mg/kg), daily, 12 months					
Ruslami, Nijland, Alisjabbana et al, 2007 [26] ¹⁰	I: RIF (600 mg) + H (300 mg), daily , 1 month;	586		71	2.9/1.7	mean age of those experiencing AEs older than treatment population 6% major (hepatitis, blood disorders); 0 flu-syndrome
	C: RIF (600 mg) + H (900 mg) twice weekly (8 months)					4.7% major (hepatitis, blood disorders); 1.5% flu syndrome
	I: H (300 mg) daily + PZA (1500 mg) + EMB (750 mg) +					
	C: H (900) thrice weekly , 3 months +					
	RIF (450 mg, 9.5 [1.4] mg/kg)	24			8	hepatotoxicity, grades 1 & 2: 20%; grade 3: 12%
Poole, Stradling, Worlledge, 1971 [39]	RIF (600 mg, 12.9 [1.7] mg/kg)	23			4	hepatotoxicity, grades 1 & 2: 46%; grade 3: 4%
	I: SM (0.75 g) + H (300 mg) + RIF (600 mg), daily , 3 months	37		89		22% discontinued RIF: flu-like (16%); thrombocytopenia (6%)
	C: H (900) + RIF (1200 mg), twice weekly , 15 months					transient renal failure (1 patient)
		*	Different numbers of subjects were used across analyses within studies. When possible, the N reported is the number of participants included in analysis of the first endpoint.			
		1	Failure=reappearance of bacilli and radiologic shadiness			
Phase of Treatment		2	Failure= not culture converted on HR before 20 weeks. Also, after 20 weeks, while on HE: culture-positive, clinical non response, or prolongation of HE			
I=Intensive	SM=streptomycin	3	Includes AEs in HE continuation phase.			

Authors, year (reference)	Summary of Design	N*	Outcomes			Adverse Events
			% Convert 1 month	% Convert 2 months	% failure/relapse or combined failure & relapse	
C=Continuation	THZ=thiacetazone	4	Failure= ≥ 1 positive cultures in last 3 months of treatment.			
	RIF=rifampin/rifampicin	5	Failure= ≥ 1 positive (>+) culture in the last 6 months of treatment.			
	H=isoniazid	6	Failure= ≥ 2 positive cultures (≥ 6 results) at 44, 48, & 52 weeks, or in final 3 months of treatment.			
	EMB=ethambutol	7	This paper was the second report of the same study described in ref. 36. The design & results, specifically the randomization groups, were presented differently in the 2 reports. Moreover, although the 18-month and 24-month groups were split for dosing frequency (once or twice weekly), because no difference was detected, all results were aggregated by the study authors.			
	Ethio=ethionamide	8	Failure= ≥ 2 positive cultures (among 6) at 16, 17, & 18 months			
	CS=cycloserine	9	Failure= no bacteriologic conversion after 5–6 months of treatment			
		10	Failure=Smear-positive at month 5 or later.			