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# New regimens for reducing the duration of the treatment of drug-susceptible pulmonary tuberculosis

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## Abstract

Tuberculosis (TB) remains an important health problem worlwide. The structure necessary for delivering TB treatment and implementing the directly observed treatment accounts for more than two-thirds of its final cost. Furthemore, although with efficacy greater than 90%, the effectiveness of present treatment regimens ranges from 55–85%, depending on the setting, mainly due to poor adherence. Duration of treatment with the current first-line anti-TB drugs is a minimum of 6 months. Reducing the duration of the treatment from six to two months or less could result in significant increase of adherence to treatment and cost reduction. The aim of this review is to highlight potential new agents or new drug combinations that could reduce the time of treatment of drug-susceptible TB, currently under study or recently evaluated through clinical trials. We conducted a literature search in the English language for clinical studies as well as an electronic computer-assisted and manual search. The literature search was conducted on November 2010, using MEDLINE (2000–2010), EMBASE (2000–2010) and the National Institute of Health (NIH) Clinical Trials Register database (2000–2010). Most of the new agents identified as anti-TB drug candidates are still in the preclinical phases. Nitroimidazole-PA-824 and fluoroquinolones are evaluated while two first line drugs - rifampicin and rifapentine -are re-evaluated to optimize their efficacy in new ultra-short anti-TB regimens through phases II/III clinical studies. A summary of the studies are presented, with their potential to change recommendations for TB treatment in the near future.

### Keywords

tuberculosis; drugs; treatment; rifapentine; fluoroquinolones; clinical trial

## Introduction

Tuberculosis continues to be a problem of global proportions, despite more than 50 years of effective chemotherapy, preventive therapy and almost 90 years of an available vaccine, as indicated by the World Health Organization (WHO). A third of the world's people are infected with *Mycobacterium tuberculosis*, and 1.7 million die each year. HIV-related TB has emerged as an enormous challenge, causing unprecedented increases in TB incidence in areas heavily affected by a dual epidemic [WHO, 2009].

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The current standard anti-TB chemotherapy regimen recommended by WHO consists of a 2-month intensive phase with isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol, followed by a 4-month continuation phase with HR for new patients with pulmonary and extrapulmonary TB (except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy) [WHO, 2009]. Although TB treatment is usually effective, many different factors contribute to the high burden of TB around the world, such as poverty, migration, and the HIV epidemic and population growth in urban areas [WHO, 2009]. Furthermore, problems such as patients' non-compliance to 6 months of treatment, and the occurrence of drug reactions and interactions (mainly in HIV-seropositive individuals) are also important. Because of the global TB problem, a strategy called directly observed treatment, short course (DOTS) was suggested by WHO in 1994. This strategy is based on five points: i) sustained political commitment; ii) access to quality-assured sputum microscopy; iii) standardized short-course chemotherapy under proper case management conditions, including direct observation of treatment, for all cases of TB; iv) an uninterrupted supply of quality-assured drugs, and v) recording and reporting systems that allow assessment of all patient outcomes and of overall programme performance [WHO, 2009].

However, as a result of the increasing magnitude of the TB problem worldwide, as well as the impact of the HIV epidemic and the emergence of multidrug-resistant strains of *M. tuberculosis* (MDR TB), the new WHO framework for TB control in high HIV settings advocates significant expansion in the DOTS strategy [WHO, 2006]. This expansion includes intensified case finding and cure, preventive treatment for TB, and interventions aimed at preventing and treating HIV. In addition, it is well recognized that efforts must be made to develop new anti-TB regimens that shorten the treatment time for drug-susceptible cases and to improve the treatment of patients with MDR TB [O'Brien and Nunn, 2001].

Several potential anti-TB drugs are in the discovery and preclinical stages of development [Mitchison, 2006]. The preclinical stage includes chemistry and *in vitro* antimycobacterial activity studies, as well as pharmacokinetics and pharmacodinamics studies in mice, and precede clinical phases I, II, and III. In the clinical phase I study, drugs are first tested for toxicity and pharmacokinetics in human subjects.

The purpose of this review is to highlight new agents or new combinations of known agents for the treatment of drug-susceptible TB disease that are being studied or were recently evaluated through clinical study phase II (in which the drug must be proven effective and safe against human disease) and phase III licensing studies (in which the regimen is tested in large samples for the same purpose) [Mitchison, 2006].

## Methods

We conducted a literature search for clinical studies that evaluated new drugs or new combinations of known drugs for the treatment of drug-susceptible TB disease. In addition to conducting electronic computer-assisted and manual searches, we scanned the bibliographies of all retrieved articles as well as review articles in the English language. The literature search was conducted on November 2010 using MEDLINE (2000–2010), EMBASE (2000–2010) and the National Institute of Health (NIH) Clinical Trials Register database (2000–2010). Using the medical subject headings (MeSH), the search terms "tuberculosis" and "drug therapy" were combined using the boolean operator 'AND'. With these terms, we used the highly sensitive filters "clinical trial" and "review." On the site for NIH Clinical Trials, we sought the term "tuberculosis treatment". Many drugs identified as anti-TB drug candidates are in the preclinical phase or are on clinical trial phase I (nitroimidazoles OPC-67683 and diarylquinoline-TMC207) or are being tested for MDR TB

(ethylenediamine-SQ109 and pyrrole-LL-3858). At present, nitroimidazole PA-824 and fluoroquinolones are being evaluated while first-line TB drugs rifampin/rifapentine are being re-evaluated to optimize their efficacy with the aim of shortening the duration of treatment of drug-susceptible TB through clinical studies phases II or III.

## Results and Discussion

### Nitroimidazole-PA-824

The nitroimidazoles are a novel class of drugs for TB treatment. Currently the nitroimidazo-oxazine PA-824, is in phase II of clinical development beng evaluated for drug-susceptible pulmonary TB. [Stover et al., 2000] In 2002, PA-824 and its analogs were outlicensed to the Global Alliance for TB Drug Development (TB Alliance), granting a worldwide exclusive license to develop them for TB [Ginsberg, 2008].

**Preclinical study of activity of PA-824 against M. tuberculosis—**The reported *in vitro* potency against *M. tuberculosis* H37Rv of PA-824 was 0.13 μg/mL and 0.15 - 0.3 μg/mL. [Stover et al., 2000; Manjunatha et al., 2006] There are some characteristics of PA-824 suggesting a potential to shortening the treatment duration. It shows significant bactericidal activity against nonreplicating mycobacteria and “persistent” bacilli are believed to be nonreplicating or slowly replicating organisms. [Lenaerts et al, 2005]. PA-824 demonstrated bactericidal efficacy equivalent to isoniazid during the intensive phase of TB as well as activity in the continuation phase of treatment similar to that of rifampicin plus isoniazid, in mouse model, confirming the hypothesis that PA-824 migth be effective against “persistent” mycobacteria [Tyagi et al., 2005]. In the mouse infection model, PA-824 in combination with moxifloxacin (Moxi) and pyrazinamide (Z) cleared lungs of bacilli more rapidly than the standard regimen of RHZ [Nuermberger et al., 2008]. PA-824 appears to have no significant interactions with the cytochrome P450 enzyme system, is orally bioavailable and has pharmacokinetic properties consistent with once daily dosing.

**Clinical experience with PA-824 for tuberculosis treatment—**PA-824 is now being evaluated for safety, tolerability, pharmacokinetic properties, and efficacy in drug-sensitive, sputum-smear-positive, adult, pulmonary TB patients. A phase IIa proof of concept study was recently completed in South Africa. PA-824 demonstrated increases that were dose linear but less than dose proportional in serum concentrations in doses from 200 –1,000 mg daily. Dosing of 1,200 mg gave no additional exposure compared to 1,000 mg daily. The mean daily CFU fall under standard treatment was 0.148 (+/− 0.055), consistent with that found in previous studies. PA-824 appeared safe and well tolerated; the incidence of adverse events potentially related to PA-824 appeared to be dose-related. It was concluded that PA-824 demonstrated bactericidal activity over the dose range of 200 – 1,200 mg daily forr 14 days. As maximum efficacy was unexpectedly achieved at the lowest dose tested, the activity of lower dosages should probably be explored in future studies [Diacon et al., 2010].

### Fluoroquinolones

The fluoroquinolones are a class of fluorine compounds with potent antibacterial activity that have been used against bacterial infections since the 1980s. Newer fluoroquinolones including ciprofloxacin, ofloxacin, levofloxacin and moxifloxacin have shown improvements in antibacterial activity variety of different types of bacteria and serum half-life [Silva et al., 2003]. The fluoroquinolones are also active against most strains of *M. tuberculosis* [Gosling et al., 2003; Rodriguez et al., 2001]. Gatifloxacin is not included as a case-control study reported an increased risk for both hypoglycemia (adjusted odds ratio 4.3; 95% CI 2.9–6.3) and hyperglycemia (adjusted OR 16.7;95% CI 10.4–26.8) with its use [Park-Wyllie et al., 2006].

**Preclinical study of activity of fluoroquinolones against *M. tuberculosis*—**In general, the mechanism of action of fluoroquinolones against microorganisms is inhibition of the bacterial enzymes, DNA gyrase (topoisomerase II) and topoisomerase IV. DNA gyrase is involved in DNA replication, transcription, and reparation, and topoisomerase IV is responsible for the decatenation that allows separation into two daughter cells at the end of the replication round [Silva et al., 2003]. A study evaluating ofloxacin demonstrated that the MIC of 0.63–1.25 mg/l was favorable for 92% (147 of 159) of clinical sputumisolates of *M. tuberculosis*, including 95 isolates susceptible to all drugs, 31 isolates resistant to HS, 27 isolates resistant to RHS, and 6 isolates resistant to R [Yew et al., 1990]. A study evaluating 55 strains of *M. tuberculosis* from patients who had not been treated previously with any anti-TB regimen showed that moxifloxacin and levofloxacin had greater activity against *M. tuberculosis* than ofloxacin and ciprofloxacin [Rodriguez et al., 2001]. The MIC for moxifloxacin ranged from 0.12 - 0.5 μg/ml for *M. tuberculosis* clinical isolates (susceptible or resistant to HS, HR, and S). A study using the proportion method in 7H10 agar determined the MICs for 19 strains of *M. tuberculosis* to moxifloxacin, ciprofloxacin, levofloxacin, and sparfloxacin, and concluded that moxifloxacin was the most active of the drugs tested [Gillespie and Billington, 1999]. In another study, the activity of moxifloxacin was tested against 86 *M. tuberculosis* strains, including 13 resistant and 4 MDR TB strains, and all but two strains were susceptible to moxifloxacin at 0.5 μg/ml [Tortoli et al., 2004]. Ji et al. [1998] evaluated the *in vitro* activities of moxifloxacin, clinafloxacin, and sparfloxacin, and the $MIC_{90}$ for sparfloxacin and for moxifloxacin were similar to and slightly lower than that for clinafloxacin. In infected mice treated six times weekly over 4 weeks with various drug dosages beginning one day after infection, moxifloxacin was the most active of the fluoroquinolones tested [Ji et al., 1998].

Miyazaki et al. [1999] evaluated moxifloxacin and isoniazid in 5-week-old mice infected with the CDC1551 strain of *M. tuberculosis* and concluded that the drug had activity comparable to isoniazid, as well as a possible added effect from the two drugs combined. The regimen of 2 weeks of daily RHZM followed by 5.5 months of once-weekly rifapentine (P) plus HM gave results comparable to those achieved with standard treatment (2RHZ/4RH) [Lounis et al., 2001].

A 6-month treatment study was conducted in a murine model to evaluate the sterilizing activity with different regimens [Nuermberger et al., 2004a]. Treatment with RMZ resulted in a 2.5-log greater reduction in CFU counts relative to RHZ at 2 months ($p < 0.001$). After 3 months of RMZ/RM, only 2 of 5 mice had positive lung cultures, with only 1 CFU per mouse. In contrast, 6/6 mice given RHZ/RH were still culture-positive at 4 months. These data suggest that the combination RMZ has greater sterilizing activity than the standard regimen and may be able to shorten the duration of therapy for human TB by 2 months or more.

Another 6-month treatment study was designed to determine the shortest duration of therapy needed with RMZ to successfully prevent relapse [Nuermberger et al., 2004b]. Mice received either the standard regimen of 2RHZ+4RH or experimental regimens of 2RMZ+3RM, 1RMZ+4RM, or 5RMZ. Four months of therapy with any of the RMZ-based regimens resulted in complete sterilization in all mice, whereas 4 months of therapy with the standard RHZ-based regimen resulted in a relapse rate of 42%. These data suggest that the use of RMZ-based regimens may permit the duration of therapy to be shortened by at least 2 months. These animal model studies suggest that moxifloxacin has potent sterilizing activity and that the combination of M with other two drugs with potent sterilizing activity such as R and H may allow TB treatment to be shortened with no increase in the risk of relapse rates.

**Clinical experience with fluoroquinolones for tuberculosis treatment—**Early-phase studies of ciprofloxacin (Cipro) demonstrated bactericidal activity against *M. tuberculosis* in humans [Kennedy et al., 1993a; 1993b; 1996]. However, TB patients treated with RHCipro remained culture positive for *M. tuberculosis* for a longer period of time than patients treated with the standard four-drug regimen, and there was a trend toward a higher relapse rate among TB patients receiving RHCipro, suggesting a lower sterilizing ability than with the standard regimen [Kennedy et al., 1993b]. Another study evaluated the efficacy of ofloxacin 300 mg (in 10 patients) or 800 mg (in 10 patients) with second-line accompanying drugs, for 9 months - 1 year, in TB patients with multiple resistant *M. tuberculosis* strains [Yew et al., 1990]. Five and 8 patients of the ofloxacin 300-mg group and the 800-mg group, respectively, achieved culture conversion. All patients tolerated the drugs well. Patients in the ofloxacin 800-mg group had more rapid sputum culture conversion than those in the group taking ofloxacin 300 mg once daily.

In 2001, a study evaluating the efficacy and safety of an ofloxacin-based regimen for treating TB in patients with underlying chronic liver disease was published [Saigal et al., 2001]. Thirty-one patients were randomly assigned to one of two regimens: 15 to a regimen including RHE for 2 months, followed by RH for a further 7 months; 16 to a regimen of HZE and ofloxacin (O) for 2 months, followed by HEO for a further 10 months. Treatment response was achieved in all patients who completed therapy. Four (26%) patients on the RHE regimen developed hepatotoxicity, compared to none on the HZEO regimen ($P = 0.043$). The authors conclude that in TB patients who have underlying chronic liver disease, an ofloxacin-based anti-TB regimen without R is as effective as a regimen including R, and the combination regimen HR is more hepatotoxic than the combination OZ. Data from a different study that evaluated TB regimens of 4 and 5 months' duration (including RHZO) provided the suggestion that ofloxacin can be used to shorten the duration of the TB treatment. Patients treated daily with 3RHZO, followed by RH twice a week during 1 or 2 months, had cure rates of 92–98% [Tuberculosis Research Centre, 2002]. One limitation of this study is that a standard control anti-TB regimen was not included for comparative evaluation.

In practice, fluoroquinolones are often one of the two first agents used in constructing a regimen for treatment of MDR TB. Fluoroquinolones are known to be active against *M. tuberculosis*, although their exact role has not yet been determined [Singla et al., 2001; Yew et al., 2000]. A randomized trial evaluating the effect of levofloxacin on 2-month culture conversion rates among HIV-infected patients did not find a statistically significant difference at 8 weeks of therapy [El-Sadr et al., 1998]. However, culture conversion rates were unusually high in this trial (97% by 2 months), decreasing the ability to detect a difference due to levofloxacin.

Therefore, the results of one multicenter study and previous smaller controlled trials are consistent in showing that the addition of a fluoroquinolone to current standard therapy has some sterilizing activity (negative cultures at earlier time points) but does not have a significant effect on the 2-month sputum culture. Earlier differences in sputum conversion might be important for treatment shortening, and therefore, despite the failure of the studies to show enhanced 2-month culture conversion, fluoroquinolone antibiotics may still allow significant shortening of the treatment of drug-susceptible tuberculosis. Trials compared moxifloxacin to ethambutol, the best tolerated of the first-line antituberculosis drugs. Nausea, a side effect previously associated with the fluoroquinolones, was more common among patients treated with moxifloxacin but seldom resulted in drug discontinuation. These data add to the growing and favorable experience with prolonged use of fluoroquinolones in the treatment of MDR TB and *Chlamydia pneumoniae* [Yew et al., 2000; Valerio et al., 2003; Cannon et al., 2005]. These and other studies suggested that moxifloxacin has an

acceptable safety profile that would allow it to be used in future phase III studies of treatment of drug-susceptible tuberculosis [Iannini et al, 2001; Frothingham 2001].

The early bactericidal activity (EBA) of moxifloxacin for the treatment of pulmonary TB is excellent. In one EBA study, after 5 days of monotherapy with either moxifloxacin or isoniazid, the EBA for moxifloxacin was 0.275 $\log_{10}$ cfu/mL of sputum per day, and the EBA for isoniazid was 0.209 [Pletz et al. 2004]. Johnson et al. [2006] assessed the decline in bacilli during the first two days (days 0–2) and during days 2–7 of monotherapy in adults with untreated newly diagnosed pulmonary TB; 10 patients per drug arm were studied. The EBA (0–2) of isoniazid (0.67 $\log_{10}$cfu/ml/d) was greater than that of moxifloxacin (0.33 $\log_{10}$cfu/ml/d) but the extended mean EBA (2–7) for moxifloxacin (0.17 $\log_{10}$cfu/ml/d) was greater than that for isoniazid (0.08 $\log_{10}$cfu/ml/d). Valerio et al. [2003] conducted an observational study of the tolerability of moxifloxacin, given for 6 months in combination with isoniazid and rifampin, for treatment of active TB in individuals not eligible for standard TB treatment. In the moxifloxacin treated patients, results of chemical analyses, which included complete blood counts and comprehensive metabolic panels, did not change over the 6-month treatment course. Information about adverse events was not reported.

Three phase II studies have been conducted recently studying the effect of moxifloxacin in place of either ethambutol or isoniazid during the first 2 months of treatment for newly diagnosed adult, pulmonary TB. A multicenter study conducted by the U.S. CDC TB Trials Consortium (TBTC study 27) evaluated moxifloxacin versus ethambutol. In this study the moxifloxacin arm did not have an effect on 2-month sputum culture status but did result in a higher frequency of negative cultures at earlier time points among patients with smear-positive pulmonary TB [Burman et al., 2006]. A single center randomized double-blind trial also comparing the regimen RHZMoxifloxacin with the standard regimen RHZEthambutol in Rio de Janeiro (Brazil) was recently published and showed a different result. This study demonstrated that moxifloxacin-containing regimen increased the 2-month sputum conversion rate by 17% ($p = 0.02$) [Conde et al., 2009]. A new multicenter phase II study conducted by the U.S. CDC TB Trials Consortium (TBTC study 28) was recently published [Dorman et al., 2009]. This international randomized double-blind trial compared the safety and antimicrobial activity of a moxifloxacin-containing regimen in which isoniazid has been replaced by moxifloxacin in the intensive phase of treatment of pulmonary TB. The study design was based on animal model studies in which moxifloxacin was used in place of isoniazid and all animals were culture negative by 3 months of treatment, and treatment could be shortened to 4 months [Nuermberger et al., 2004a; 2004b]. Data analysis suggested that moxifloxacin substitution for isoniazid during the first 2 months of TB treatment had no significant effect on 2-month sputum conversion rates.

These phase II clinical trials suggest that the introduction of fluoroquinolones in the intensive phase of TB treatment could potentially lead to a shortening of treatment duration. Phase III clinical trials using gatifloxacin instead of ethambutol (the OFLOTUB Consortion, involving WHO-TDR, the Europian Commission, among others) or moxifloxacin in place of either isoniazid or ethambutol (led by the British Medical Council, University College London and others) are under way.

## Rifapentine

### Preclinical Studies of Activity of Rifapentine Against *M. tuberculosis*—

Rifamycins (rifampin, rifabutin, and rifapentine) have concentration-dependent activity against *M. tuberculosis* and rifapentine is a rifamycin derivative with excellent activity against *M. tuberculosis*. For rifapentine, the minimum inhibitory concentration $(MIC)_{50}$ and $MIC_{90}$ are one- to two-fold dilutions lower than those of rifampin (for the 7H10 agar system, rifapentine's $MIC_{50}$ and $MIC_{90}$ are 0.125 and 0.25, compared with 0.5 and 1.0 for

rifampin) [Bemer-Melchior et al., 2000]. In addition, rifapentine's half-life ($t_{1/2}$) is five times longer than that of rifampin (14–18 hours vs. 2–5 hours). Rifapentine's low MIC and long half-life make it an attractive candidate for use in intermittently dosed (ie less frequently than daily) TB treatment regimens [McDonald et al. 1982; Cohn et al. 1990]. Rifapentine, at a dose of 600 mg twice-weekly, was approved by the Federal Drug Administration (FDA) in June 1998 for the treatment of pulmonary TB.

In murine models, intermittent rifapentine-containing regimens have been effective for the treatment of TB: Daniel et al [2000] used a murine model of active TB to evaluate the activity of once weekly rifapentine (10 mg/kg/dose) during the continuation phase of TB treatment. Mice were treated with 2 months of RHZ, then were treated either with 4 months of daily rifampin plus isoniazid (RH) or 4 months of once-weekly rifapentine (10 mg/kg/dose) plus isoniazid (PH). The regimens were equally effective. Thus, murine studies indicate that rifapentine administered daily during combination intensive phase treatment has potent antimycobacterial activity that is associated with ability to achieve durable cure without relapse after approximately 3 months of total treatment.

**Clinical Experience with Rifapentine for Tuberculosis Treatment—**Rifapentine (Priftin), at a dose of 600 mg twice-weekly, was used in a clinical trial sponsored by the industry, comparing 2 months of daily isoniazid, rifampin, pyrazinamide, plus ethambutol (HRZE) followed by 4 months of twice weekly HR, with 2 months of daily HZE plus twice weekly rifapentine (600 mg/kg/dose) followed by 4 months of once weekly HP. The percentage of patients converting their sputum culture to negative was slightly higher in the rifapentine group (87%, 248/286) compared with the standard rifampin group (80%, 226/283). However, the proportion of patients with relapsed TB during 24-month follow-up was higher in the rifapentine group (12%, 29/248) than in the standard rifampin group (7%, 15/226). Benator et al. [2002] did a randomized, prospective study further evaluated the role of rifapentine in continuation phase therapy of pulmonary TB. After completion of two months of standard intensive phase TB treatment, patients were randomized to receive either once weekly rifapentine (600 mg, approximately 10 mg/kg/dose) plus isoniazid, or twice weekly rifampin (600 mg/dose) plus isoniazid. Crude rates of treatment failure or relapse were 46/502 (9.2%) in the rifapentine group, and 28/502 (5.6%) in the rifampin group (relative risk 1.64, 95% CI 1.04–2.58, p=0.04). Subsequent early bactericidal activity (EBA) studies of rifapentine in pulmonary TB patients indicate that 600 mg is not the optimal rifapentine dose. Sirgel et al. [2000] demonstrated that the maximum effect for rifapentine was obtained at a dose of 900 to 1200 mg (15–20 mg/kg). Bock et al. [2002] evaluated the tolerability of higher doses of rifapentine given once weekly in combination with isoniazid during the continuation phase of pulmonary TB treatment. Tit was concluded that rifapentine 900 mg given on a once weekly schedule was well-tolerated, and that a 1200 mg dose once weekly deserves further study. Thus, rifapentine shows promise for treatment of TB, especially with doses greater than the currently approved rifapentine dose of 600 mg twice weekly.

## Conclusions

Along with the socioeconomic and host factors that underlie the serious global burden of TB, a fundamental problem that hinders more effective TB control is the ability of *M. tuberculosis* to persist in the host and to develop drug resistance, often because of poor adherence to lengthy therapy. Within a rational and well-funded infrastructure for conducting multinational large clinical trials, the importance of the development of new sterilizing drugs that target persistent bacteria and shorten TB therapy must be intensely promoted by the medical and TB patient advocacy communities. Public sector sources, research-funding agencies, and development agencies based in the United States, the United

Kingdom and the European Union are currently the world's major funders of TB research. Significant investment is needed in basic research in order to assure that the current pipeline of promising new TB drugs is explored fully and replenished continuously. Also, greater investment in clinical trials infrastructure is needed to support this type of product development in settings of high TB case burden but with limited economic resources Donors, funders, and developing countries need to create better mechanisms to track and report spending on research, including basic and applied TB research and development, and need to raise a combination of both financial and political capital for these efforts.

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