



# What's in the Pipeline: New HIV Drugs, Vaccines, Microbicides, HCV and TB Treatments in Clinical Trials

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e thymidine • BI-201 • Racivir (PSI 5004) • TMC-278 • Diarylpyrimidine (DAPY) • 640385  
• Reverset (D-D4FC) • JTK-303 • UK-427 (maraviroc) • Amdoxovir • AMD-070 • Vicriviroc  
LIPO-5 • GTU-Multi-HIV • pHIS-HIV-B • rFPV-HIV-B • ADMVA • GSK Protein HIV Vaccine  
TBC-M335 (MVA) • TBC-F357 (FPV) • TBC-F349 (FPV) • LIPO-4T (LPHIV-1) • LFn-p24 • H  
G • Oligomeric gp140/MF59 • VRC-HIVDNA-009-00-VP • PolyEnv1 • ISS P-001 • EP HIV-  
• BufferGel • Lactin-V • Protected Lactobacilli in combination with BZK • Tenofovir/PMPA G  
ulose acetate/CAP) • Lime Juice • TMC120 • UC-781 • VivaGel (SPL7013 gel) • ALVAC  
Ad5 • Autologous dendritic cells pulsed w/ALVAC • Autologous dendritic cell HIV vaccination  
x • Tat vaccine • GTU-nef DNA vaccine • Interleukin-2 (IL-2) • HE2000 • Pegasys (peginter  
L-4/IL-13 trap • Serostim • Tucaresol • MDX-010 anti-CTLA4 antibody • Cyclosporine A •  
96 • HGTV43 • M87o • Vertex • VX-950 • Idenix • Valopicitabine (NM283) • JTK-003  
implant • Albuferon • Celgosivir (MBI-3253) • IC41 • INN0101 • Tarvicin • ANA971 (oral)  
floxacin, Tequin • J, TMC207 (ex R207910) • LL-3858 • M, moxifloxacin, Avelox • PA-824

# **The Tuberculosis (TB) Treatment Pipeline**

by Javid Syed

Although tuberculosis (TB) kills two million people a year—one person every 15 seconds—there have been no new drugs approved to treat TB in the last 40 years. According to the World Health Organization (WHO), the global incidence of TB disease is rising by 1% annually. This increase is concentrated in Africa and is attributable to the rise in TB infection in people with HIV. Additionally, the emergence of multidrug-resistant TB (MDR-TB) in Eastern Europe and Russia is posing a new challenge to efforts to control the disease.

TB is a disease of the poor. Ninety-five percent of those ill with TB, and 98% of those who die of TB, live in the developing world. Despite significant investment on the part of the affected countries, there is still a great need for multilateral resources and political commitment to adequately address the health-infrastructure and financing challenges of which the TB epidemic is both a product and a cause. The Global Plan to Stop TB (2001–2005) identified a resource gap of \$3.77 billion, which did not fully encompass the need for investment in new tools (including diagnostics, drugs, and vaccines), and which in any case was not fully funded (Global Partnership to Stop TB 2001).

Beyond the epidemiological and political context, there are also significant biomedical issues that new treatments need to help alleviate. Some of these concerns are:

- Length of treatment. Initial first-line therapy for uncomplicated sputum smear-positive pulmonary TB takes 6–8 months. This treatment consists of four medications taken at least three times a week for two months and followed by 4–6 months of two medications daily. The recommended first-line regimen consists of isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) (HRZE) for two months daily or thrice weekly, followed by four months of HR or six months of HE. HR is preferred since it produces fewer relapses, especially among HIV-infected persons, but due to drug interactions with many antiretroviral drugs (ARVs), its implementation remains problematic in many places (Jindani 2004; Harries 2004a).
- Drug interactions with ARVs. Rifampin, a crucial drug in first-line regimens, reduces the concentration of most ARVs, precluding its use with the non-nucleoside reverse transcriptase inhibitor (NNRTI) nevirapine or most protease inhibitors (PIs). This severely limits the ability of people coinfecting with HIV and TB, who need therapy for both conditions, to access treatment. Thus there need to be more TB drugs available that are as effective as rifampin, but that can be taken with more ARV regimens (Harries 2004b).
- Adverse events. Though TB drugs are generally well tolerated, they can have significant adverse effects and in some cases are contraindicated. Some of the more common adverse events/contraindications with first-line TB drugs include (Harries 2004b):

<b>Drug</b>	<b>Adverse Event/Contraindication</b>
Isoniazid	Peripheral neuropathy
Pyrazinamide	Hepatitis
Rifampin	Hepatitis, GI reactions
Streptomycin	Contraindicated during pregnancy
Thiacetazone	Severe skin rash among HIV+ (not recommended)

- Need for drugs effective against MDR-TB. MDR-TB is any strain of TB that is resistant to the bactericidal effects of rifampin (R) and isoniazid (H). According to Médecins Sans Frontières (Doctors without Borders), approximately 250,000–400,000 new cases of MDR-TB each year globally are added to 500,000 or more ongoing cases (MSF 2005). In parts of the Baltic States, Russian Federation, Ukraine, and Central Asia, TB patients are ten times more likely to have MDR-TB. In the Tomsk Oblast of Russia, MDR cases have risen to nearly 14% of TB cases (WHO 2004). A significant proportion of the TB cases in this region are among injecting drug users (IDUs) who are also at significant risk for HCV and HIV coinfections; there is, therefore, an urgent need for a new TB treatment that has low liver toxicity.
- Pediatric TB. In 2004, the global burden of pediatric TB was estimated to be ten percent of total TB cases. This accounted for 1.5 million new cases and 130,000 deaths. Pediatric TB is often smear-negative (even among HIV-negative children), and it is therefore often under diagnosed, and untreated. There is an urgent need to improve pediatric access to TB treatment and to develop TB drugs, including fixed-dose combinations (FDCs), which are safe and effective among children (Chauhan 2004).

To address these urgent, emerging challenges for TB control, there has been recent unprecedented activity in the arena of TB drug development. Agencies such as WHO, the Global Fund for HIV, TB, and Malaria, and the Gates Foundation have galvanized multilateral support and initiated public-private partnerships to increase resources to combat this disease of poverty. One result of these actions is that after a lull of 40 years, six new drugs for TB are currently in clinical trials. At least three other potentially exciting compounds are in preclinical studies. These compounds are products of research and development undertaken by pharmaceutical companies and public-private collaborations funded through philanthropic foundations. One leader championing the cause of TB drug development is the nonprofit Global Alliance for TB Drug Development, which is supported by the Gates and Rockefeller Foundations. The Global Alliance has catalyzed a new focus and leadership for TB treatments by initiating public-private partnerships among stakeholders doing basic science and clinical trials.

The Draft Strategic Plan of the New Drugs Working Group for the Global Plan to Stop TB-II includes the following drugs that are currently or imminently scheduled for clinical trials (New Drugs Working Group Draft for Global Plan II April 2005). All the compounds in this unprecedented TB drug pipeline have been endorsed by the Global Alliance and are being screened to ensure that they can be taken with ARVs, manufactured inexpensively for use in developing countries, and used with other TB drug regimens, ideally to shorten and simplify the duration of TB treatment and address MDR-TB (New Drugs Working Group 2005).

**Table 1. TB Drugs Currently in Clinical Trials**

Drug Name(s)	Drug Class	Sponsor(s)	Phase/Status/Comments
G, gatifloxacin, Tequin®	Fluoroquinolone	Bristol-Myers Squibb	Approved/marketed for some bacterial infections; status for TB unclear; may permit intermittent therapy (thrice weekly) and have activity against MDR-TB.
J, TMC207 (ex R207910)	Diarylquinoline	Tibotec/J&J	Phase I underway (dose-ranging studies); once-weekly dosing; may enable shortened duration of TB treatment; phase II discussions underway. Unique bactericidal mechanism; potential as MDR-TB treatment.
LL-3858	Pyrrole	Lupin Laboratories	India-based R&D manufacturer of cephalosporins, rifampin, etc.; has marketing offices in Maryland; unresponsive to queries for information.
M, moxifloxacin, Avelox®	Fluoroquinolone	Bayer	Marketed in 100+ countries for some bacterial infections; shown to reduce time for sterilization of TB-infected lungs and therefore has potential for shortening treatment time.
		Bayer/TBTC	Phase II underway for initial phase TB treatment (HRZM vs. HRZE; TBTC-27)
		Bayer/TBTC	Phase II in planning for use in the continuation phase of TB treatment (TBTC-28)
		Bayer/Global Alliance	Discussions underway between Bayer and Global Alliance regarding FDA IND (investigational new drug) application for M as TB drug.
PA-824	Nitroimidazopyran	Global Alliance for TB Drug Development	Active against active and static TB bacilli. Similar to R and H in sterilizing ability. Bactericidal activity against MDR-TB.
Proprietary Compound	Unknown	Otsuka Pharmaceuticals	Mystery compound from Japanese company; Otsuka not willing to share any information currently; compound is in clinical testing and information is to be released in September 2005 at the Interscience Conference on Antimicrobial Agents and Chemotherapy (IAAAC) in New Orleans, USA.

**Diarylquinoline TMC207 (J) (previously R207910)**

This compound, TMC207, or J, is owned by Johnson & Johnson (J&J) and is being developed at its research subsidiary Tibotec. Tibotec scientists discovered J by screening their chemical libraries for compounds with anti-mycobacterial properties. The compound has many characteristics that make it an attractive TB drug candidate, including low molecular weight, high potency against drug-sensitive and drug-resistant TB strains, very long half-life (permitting once-weekly dosing), and low potential for drug interactions.

**Mechanism:** TMC207, or J, is among the Diarylquinoline (DARQ) class of compounds, which have a very specific and previously unknown anti-mycobacterial mechanism. It is postulated that J inhibits the proton pump of the *M. tuberculosis* adenosine triphosphate (ATP) synthase that is the main source of fuel for *M. tuberculosis* (Andries 2004).

**Reduction of treatment burden:** Studies in mice show that J has a long half-life (43.7–64.0 hours in plasma and 28.1–92.0 hours in tissue) and a low minimum inhibitory concentration (MIC). The bactericidal activity of the drug seems to be time-dependent, not concentration-dependent. Due to its ability to penetrate and stay concentrated in tissue for long periods of time, J holds the promise of being active against latent TB infection as well as active TB disease. Its long half-life, low MIC, and bactericidal potency also give J the potential to reduce the duration and the pill burden of TB treatment. In mice, a single dose had bactericidal potency for about eight days. When used as monotherapy, a single dose of J was at least as potent as the triple combination of rifampin (R), isoniazid (H), and pyrazinamide (Z) and was more active than R alone. Due to potential for resistance development, however, J will not be used as monotherapy, but only in combination with the other current TB drugs. When it was substituted for one of three current TB medications (R, H, or Z), the J-containing regimens performed significantly better—they were as effective in one month as RHZ was in two months. In particular, the JHZ and RJZ combinations cleared the lungs of TB in all the mice after two months. These promising murine data need to be replicated in humans (Andries 2004).

**Utility against MDR-TB and TB/HIV coinfections:** Because of its unique mechanism, J is active *in vitro* against TB organisms resistant to isoniazid (H), rifampin (R), streptomycin (S), ethambutol (E), pyrazinamide (Z), and moxifloxacin (M). Furthermore, it has no cross-resistance with current anti-TB medications (Andries 2004). J can also be used in conjunction with antiretroviral drugs, and unlike rifampin, it doesn't accelerate their metabolism (Ibid.)

**Adverse effects:** Single ascending dose (SAD) and 14-day multiple ascending dose (MAD) studies in healthy human males were orally presented at the 16th TB Trials Consortium (TBTC) meeting in San Diego on 20 May 2005. J was well absorbed after a single oral dose and has an effective half-life of 24 hours. No severe adverse effects were observed. The treatment duration needed for sterilization, as well as the most effective drug combinations, are as yet unknown in mice and humans (McNeeley 2005).

**Needed studies:** Studies in TB patients have not yet begun. More research on the pharmacokinetics of the compound is needed to develop a safety profile in women, children, and individuals coinfecting with HIV or HCV and TB. Studies that will provide more information about the sterilizing duration of the drug and its potential to prevent recurrence of TB still need to be conducted.

## **Fluoroquinolones**

The fluoroquinolone (FQ) compounds are a class of synthetic antibiotic derived from nalidixic acid, with a broad spectrum of activity. This family includes ciprofloxacin and a variety of related compounds, two of which are in the current TB pipeline. FQs are well absorbed orally, and have good tissue penetration and relatively long duration of activity. Quinolones are “broad-spectrum antibacterial agents that block DNA replication and kill bacterial cells” (Drlica 2004). Some newer

fluoroquinolones are effective against nondividing bacteria as well; they do not have cross-resistance to other classes of TB drugs. Several fluoroquinolones have been studied for their antimycobacterial activities (Pletz 2004; Gradelski 2002).

During the 1990s, two C-8-methoxy fluoroquinolones (moxifloxacin and gatifloxacin) were developed commercially for use against gram-positive pathogens... Moxifloxacin and gatifloxacin also had exceptional activity with *M. tuberculosis* if assessed by a mutant selection criterion. However, when examined for activity in cultured cells or in animal models, the C-8-methoxy compounds were not lethal enough to be spectacular anti-tuberculosis agents. Thus, successful use of fluoroquinolones with tuberculosis will probably require finding appropriate combination therapies (Drlica 2004).

### **Gatifloxacin (G)**

Gatifloxacin is a broad-spectrum fluoroquinolone antibiotic that is marketed in the U.S. by Bristol-Myers Squibb as Tequin. It is used to treat a number of bacterial infections and is usually taken at 400 mg once daily (Bristol-Myers Squibb 2004).

**Mechanism:** An *in vitro* study looking at the bactericidal action of gatifloxacin (G) by itself and in combination with isoniazid (H) or rifampin (R) showed that G added limited bactericidal activity for the first two days, but not thereafter. The hypothesis is that G is active against the occasionally dividing bacteria, but that in the static, persisting bacilli it does not contribute any sterilizing activity to that of the other drugs (Paramasivan 2005).

**Reduction of treatment burden:** The failure of G to add to the sterilization activity of H or R suggests that it will not reduce treatment time. Gatifloxacin is active against intramacrophage *M. tuberculosis* when used with certain combinations of antituberculosis drugs (R, H, and Z). Gatifloxacin's activity against intramacrophage bacilli in combination with antituberculosis drug implies that with the right additional drugs, G can produce effective suppression of TB (Sato 2003). Another study looking at the use of G in combination with ethionamide (ETA) with or without pyrazinamide (Z) in mice showed that G, ETA, and Z was the most effective combination to sterilize the lungs and prevent relapse. When treated with G and ETA at 5 days/week doses of 300 mg/kg and 25 mg/kg of body weight, respectively, the mice lungs were completely sterilized in 12 weeks; however, there was relapse during the eight-week subsequent observation period. When Z was added to ETA and G at 450 mg/kg for 5 days/week for 12 weeks, the murine lungs remained free of live mycobacteria during eight weeks of follow-up observation. For the lower dose regimen of G at 300 mg/kg plus ETA at 75 mg/kg, the twice-weekly regimen was as effective as the daily regimen. These data suggest the possibility of using this regimen in intermittent therapy, thus potentially reducing treatment burden (Cynamon 2003).

**Utility against MDR-TB and TB/HIV coinfections:** As the above data show, gatifloxacin can be active in regimens without H or R. The combination of G, ETA, and Z could therefore potentially be useful against isoniazid- (H) and rifampin- (R) resistant TB. It is also anticipated that G will work well with ARVs (Cynamon 2003).

**Adverse effects:** None of the studies spoke of the any side effects specific to the treatment of TB; however, in general, fluoroquinolones can cause CNS toxicity. Gatifloxacin has been associated with increases in insulin levels among diabetics. Caution should be used when taking G along with antacids, heart rhythm disturbance medications, or with mineral supplements containing zinc, magnesium, or iron. Gatifloxacin has not been shown to be safe or effective in children younger than 18 or in pregnant or lactating women (Bristol-Myers Squibb 2004).

**Needed studies:** Studies are needed to more clearly define the use of G in combination with current TB therapy and to define its safety. The optimal dose and combination regimen for TB need to be understood better. The validity of the assumption that early sterilization of lungs is a predictor of relapse inhibition also needs to be studied.

### **Moxifloxacin (M)**

Moxifloxacin (M) may be the most promising of the fluoroquinolones being tested against *M. tuberculosis* (Gillespie 1999). It is made by Bayer and marketed as Avelox (moxifloxacin hydrochloride) in over 100 countries for the treatment of a variety of bacterial infections. It is most often given as a single oral 400 mg dose once daily (Bayer 2004).

The bactericidal potential of M at 25 mg/kg six times a week was equivalent to isoniazid (H) (Ji 1998). A study in mice replicated this apparent equivalence between M and H monotherapy and also showed that the combination of M and H together is much stronger than each alone (Miyazaki 1999). M showed early bactericidal activity comparable to isoniazid and rifampin in human subjects (Pletz 2004; Gosling 2003).

**Mechanism:** M is a broad-spectrum antibiotic, active against gram-negative, gram-positive, and anaerobic bacteria. It has a mechanism that is distinct from H in that it affects bacteria by binding to the DNA gyrase and topoisomerase IV, which are involved in bacterial replication. Compared to some other fluoroquinolones, it has a lower minimum inhibitory concentration (MIC) and a half-life that is equivalent to other fluoroquinolones. Unlike some other effective fluoroquinolones, M is not phototoxic (Ji 1998).

**Reduction of treatment burden:** Two studies in mice showed that using M along with already approved anti-TB drugs can lead to faster sterilization of the lungs. In mice, a combination of M along with rifampin (R) and pyrazinamide (Z) was shown to eradicate *M. tuberculosis* from the lungs by up to 2 months earlier compared to the standard regimen of isoniazid (H) with R and Z. Another study showed that adding M to a rifapentine and H regimen was more effective than adding streptomycin in clearing the lungs. Due to its sterilizing effect against slow or intermittent replicating bacteria, M in combination with other drugs seems promising for the continuation phase of TB treatment and to potentially shorten therapy (Lounis 2001). Some data from a yet unpublished study in mice that Jacques Grosset presented during the May 2005 TBTC meeting showed that four months of M with R and Z was as effective as six months of the standard regimen of RHZ/RH. In another study, TBTC Study 27 conducted by the CDC-funded TB Trials Consortium, unpublished data from a randomized, blinded comparison of HRZM vs. HRZE showed that the M-containing regimen led to faster sputum and culture-conversion, with no difference by dosing frequency (five versus three days weekly). However the study also showed

that there was a marked difference between African study participants and North American participants in the rates of two-month culture-conversion (60% vs. 85%; surprisingly, this difference was not affected by HIV status) (Burman 2005).

**Utility against MDR-TB and TB/HIV coinfections:** M might be very useful against MDR-TB since it has no cross-resistance to other antituberculosis drug classes. An *in vitro* pharmacodynamic infection model that simulated drug decline similar to those seen in humans suggested that doses of 400, 600, and 800 mg/day of M would suppress drug resistance in TB by 59%, 86%, and 93%, respectively (Gumbo 2004). When tested against 86 strains of *M. tuberculosis*, including 13 resistant and 4 multidrug-resistant ones, M was effective against all strains but two at 0.5 mcg/ml. The other two, both of which were MDR strains, were suppressed at minimum inhibitory concentration (MIC) of 2 and greater than 4 mcg/ml (Tortoli 2004). M plus ethionamide (ETH) showed more activity than M alone in mice infected with MDR-TB (Pletz 2004; Fattorini 2003).

When compared with the standard third-line regimen of ofloxacin (OFX), ethionamide (ETA), amikacin, and pyrazinamide (Z), nine months of M, ethionamide, amikacin, and Z was found to be as effective as six months of the standard third-line regimen. Thus, though it doesn't shorten the treatment, M does broaden the treatment options for MDR-TB (Veziris 2003).

M can be used with current ARVs, as it is a broad-spectrum antibiotic class that is already being prescribed commonly, and no drug interactions have been mentioned.

**Adverse effects:** M has CNS side effects and drug interactions with other FQs. Only small studies in TB patients have been done so far, and few AEs have been reported. Moxifloxacin has not been shown to be safe or effective in children younger than 18 or in pregnant or lactating women (Bayer 2004).

**Needed studies:** There is a need to better understand the pharmacokinetics of M, and to explain the potential ethnic or geographical differences in the two-month TB culture-conversion rates suggested in TBTC study 27. Moxifloxacin, like gatifloxacin, needs to have its safety and activity determined in children under 18 and in pregnant and lactating women. Finally, the role of M in combination therapy for TB, including initial intensive and continuation-phase regimens, and for treatment of MDR-TB and in combination with ARVs needs to be defined in well-conducted randomized and operational research studies.

### **Nitroimidazopyran PA-824**

Since being identified in 1995 at PathoGenesis, this drug has had many proprietors. First Chiron Corporation acquired the compound and then the Global Alliance For TB Drug Development obtained worldwide rights to it and its derivatives from Chiron with Chiron's commitment to make the drug available for TB without royalty in countries where TB is endemic. *In vitro* and in murine models it is shown to be effective against MDR TB, and actively and slow growing *M. tuberculosis*.

**Mechanism:** PA-824 kills *M. tuberculosis* bacilli by inhibiting the synthesis of protein and cell wall lipids (Stover 2000). It has specific bactericidal effect against *M. tuberculosis* complex. In mice, it has a minimum bactericidal dose (MBD) of 100 mg/kg/day. When used at MBD by itself, PA-824

was bactericidal during initial therapy phase at a level comparable to an equipotent dose of isoniazid in humans (Tyagi 2005). It was even shown to be effective against MDR strains and TB bacilli grown under oxygen depletion showing potential bactericidal impact in latent state TB bacilli (Lenaerts 2005). Its sterilization effects rival those of R and H. PA-824 at a single oral dose of 25 and 100 mg/kg reached high levels in the lungs and spleen. Regular dosing over 14 days showed PA-824 was at higher levels in target tissues than in plasma and that the plasma concentration is dose dependent (Global Alliance 2004).

**Reduction of treatment burden:** In continuation phase PA-824 has been seen to target bacilli that had persisted despite a two-month intensive treatment phase of R, H, Z. There are no clear data that show the potential for PA-824 for shortening TB treatment. However, its effectiveness against active and static TB bacilli shows promise for its use in initial and continuing phases of TB treatment (Tyagi 2005).

**Utility against MDR-TB and TB/HIV coinfections:** PA-824 in combination with isoniazid prevents selection of TB mutants resistant to isoniazid (Tyagi 2005). Unlike current TB drugs, it has shown high bactericidal activity against all MDR-TB isolates as well as potential for activity against latent TB. There is no cause to suspect that PA-824 cannot be used with HIV medications as there was no significant inhibition of cytochrome P450 isozymes (Global Alliance 2004).

**Adverse effects:** The adverse effects profile of PA-824 has not yet been evaluated in humans.

**Needed studies:** Studies are needed to define PA-824's utility in TB treatment during the initial and continuation phase for drug-susceptible TB infections, and its best use in combination for MDR-TB. Clinical trials are needed to define its adverse effects profile, its sterilization effect, and its effect on TB culture conversion and on preventing relapse. Since it seems active against MDR-TB, its use needs to be defined in hepatitis C virus (HCV) and HIV coinfecting TB patients.

### **Otsuka Pharmaceuticals and Lupin Laboratory Compounds**

Two additional drugs are also currently being tested in the clinic: a proprietary compound of Otsuka Pharmaceuticals, and pyrrole LL-3858 of Lupin Laboratories. Currently, there is no significant information publicly available about these compounds.

### **Conclusions**

As the above pipeline shows, it is an exciting time for TB drug development. There is the promise of therapies that may shorten treatment duration of drug-susceptible TB, as well as increase treatment options for MDR-TB. The novel mechanism of activity and long half-life of TMC207, or J, has promise for not only reducing treatment burden, but also providing a powerful tool against TB that is resistant to current TB drugs. The sterilizing effects of M and G have the potential to reduce time to culture-conversion, thereby reducing the transmission and potential for relapse.

Much work remains to be done, however, before these drugs can be adopted into standard regimens. This work includes better understanding drug dosage and drug interactions, and developing a safety profile for these drugs. New trial designs need to be devised as well as rapid,

well-designed, well-controlled studies for these drugs to make a difference in reducing the world's TB and TB/HIV epidemics in the near future. Researchers, study sponsors, and regulatory agencies including the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) need to agree on study designs that can quickly validate these new TB drugs while also defining their side effects and potential interactions with ARVs and other commonly used drugs. FDA should consider utilizing accelerated approval mechanisms for TB drugs that fill unmet needs in TB control.

TAG is concerned that there is insufficient infrastructure worldwide to rapidly validate these new TB drugs and scale up their use in a variety of settings where they will be needed. The only well-established multicenter network capable of carrying out clinical trials of new TB drugs, the CDC-funded TB Trials Consortium (TBTC), receives just \$9.2 million in funds annually and will experience a budget cut of \$800,000 due to reduced federal support for the CDC. Though in its recent trials the TBTC has added well-performing and highly productive international sites in Brazil, South Africa, and Uganda, TBTC is mainly centered in North America, where TB case rates are still falling. There is an urgent need to further expand the TBTC significantly to enhance its capacity to carry out the larger, longer, phase III studies that will soon be needed to validate the efficacy of the new anti-TB drugs. Much broader support is also needed from the National Institutes of Health (NIH) for clinical trials of new TB drugs. Other consortia approaches like the new European and Developing Country Clinical Trials Program (EDCTP) are also needed and require funding well in excess of its current budget of \$400 million for 5 years (2003–2008) for HIV, TB, and malaria. The U.K. Department for International Development (DFID) could also provide significant new support along with other developed and developing countries. Additionally, the human resources and insights of affected communities and people with TB are still untapped. Their leadership is vital to further TB treatment and advocacy and will also be needed to make TB trials a success.

Based on the current prediction of resources, the draft plan of the New Drugs Working Group for the Global Plan to Stop TB II anticipates that the first new TB drugs will be available by 2010 at the earliest. Dramatically scaled-up funding for clinical trials of new TB drugs will be a prerequisite for achieving success. High-level political will and significant resources must be mobilized to accelerate these developments lest the unconscionable deaths of two million people continue unabated year after year.

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