

# The Tuberculosis Treatment Pipeline

*Better than Ever Is Not Good Enough*

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## Introduction

In December 2012, tuberculosis (TB) treatment reached a historic landmark with the first approval by a stringent regulatory authority of a new agent from a novel drug class in over 40 years. The U.S. Food and Drug Administration (FDA) approval of bedaquiline validates the recently revitalized global effort to develop new, better treatments for TB after decades of stagnation.

Yet the road to adequate treatment for people with TB is still a long one. First, bedaquiline has not begun to reach the up to 1 million people with drug-resistant tuberculosis who may need the drug. Delamanid, already in phase III trials, has yet to be approved by a stringent regulatory authority. As TB drugs are given in combination to prevent drug resistance, the need for improved companion drugs to truly simplify, shorten, and improve treatment for both drug-resistant TB (DR-TB) and drug-sensitive TB (DS-TB) is urgent. Yet other drugs lag even farther behind, such as the promising drug sutezolid, whose development has been thwarted by slow activity of its sponsor, Pfizer.

Faster-acting, better therapies to clear latent TB infection (LTBI) before it turns into active disease are necessary, especially for people latently infected with DR-TB, who lack evidence-based therapy to protect themselves from falling ill.

The TB drug pipeline is still scant compared to what is needed. The lack of accepted surrogate trial endpoints require phase III studies to be large, long, and expensive. Investment lags at a third of what is needed; in 2011 alone, there was nearly a US\$500 million global funding gap.<sup>1</sup>

Lack of regulatory capacity threatens the ability of countries to rapidly review new treatment options, and ensure that postmarketing studies and pharmacovigilance are carried out. Inertia and inflexibility by policy makers at national and global levels may lead to slow adoption of new treatments even after approval. Continuing stock-outs around the world jeopardize access to both new and existing drugs. These market inefficiencies, plus lack of cooperation from drug manufacturers, have contributed to high prices for second-line drugs, which are utterly unaffordable in these times of austerity.

To reach the goal of zero TB deaths, zero new TB infections, and zero TB suffering and stigma, people with TB and LTBI must receive treatment regimens effective against the infecting strain. This points to the need for rapid universal drug susceptibility testing, as discussed in the TB diagnostics chapter. Shorter, more tolerable regimens are needed for all forms of TB; in the case of DR-TB, they must also be all-oral, faster to cure, and much less toxic. TB-affected communities must play a more meaningful role in the design, implementation, and uptake of research, in line with the *Good Participatory Practice Guidelines for TB Drug Trials* released in 2012.<sup>2</sup> Countries must rapidly build regulatory capacity, and national treatment programs need to become more flexible in adopting new tools. Programs should also ensure consistent drug stocks through improved supply-chain management and procurement, while manufacturers must provide steady, safe drug supply at lower prices. People with TB need better access to existing and new treatment options, and the auxiliary care and psychosocial support necessary to make care patient-centric.

### Key Definitions and Acronyms

**TB:** tuberculosis

**DOT:** directly observed therapy

**DR-TB:** drug-resistant TB

**DS-TB:** drug-sensitive TB

**LTBI:** latent TB infection

**MDR-TB:** multidrug-resistant TB; TB resistant to at least isoniazid and rifampicin, the two most powerful TB drugs, which are used as part of the four-drug, first-line therapy

**Pre-XDR-TB:** pre-XDR-TB (see below); or MDR-TB resistant to either a second-line injectable drug (amikacin, capreomycin, or kanamycin) or a fluoroquinolone

**XDR-TB:** extensively drug-resistant TB; or MDR-TB also resistant to a fluoroquinolone and at least one injectable second-line drug

## Drugs: where are they and why can't we get them?

Challenges and inadequacies in TB research and development are mirrored on the access side by an equally frustrating host of problems. Poor estimation and consolidation of demand, inefficient ordering systems, unstable drug markets, and a lack of diversity in manufacturers have contributed to a pandemic of drug stock-outs. Drug shortages plague TB programs, consuming vast amounts of staff time, causing patients to miss doses (potentially leading to drug resistance), forcing patients to switch to inferior regimens, and requiring the use of more expensive drugs.<sup>15</sup>

With new leadership, the Global Drug Facility (GDF) is attempting to resolve some of the procedural challenges that have contributed to stock-outs. The Clinton Health Access Initiative, with support from the Bill & Melinda Gates Foundation and the U.K. Department for International Development, is working to improve demand forecasting, commodity procurement, and supply chain management in key MDR-TB treatment programs (initially, in Ethiopia, India, Lesotho, South Africa, and Swaziland), and to engage supply-side partners.

In the meantime, drug-supply problems continue to crop up, increasingly so even in better-resourced countries such as the United States: in the past year alone, the CDC's *Morbidity and Mortality Weekly Report* has published articles on isoniazid- and second-line injectable shortages (as well as on shortages of Tubersol, an important product for TB diagnosis).<sup>4,5,6,7</sup> The FDA has also reported shortages of injectable rifampicin.<sup>8</sup> TAG has been working with key public, private, and community partners to better understand and address the causes of these issues.

To learn more, see <http://www.treatmentactiongroup.org/tagline/2012/fall/future-tb-united-states-going-or-growing>.

To view the videos or the meeting report from the January 2013 consultation on TB drug shortages, see <http://www.treatmentactiongroup.org/tb/advocacy/silent-crisis-tuberculosis-drug-shortages-united-states>.

## Special populations: TB and people who use drugs, alcohol, methadone, or buprenorphine, or who have HIV or viral hepatitis

A recent review showed that the linkages between TB and injection drug use, alcohol consumption, HIV, hepatitis B, hepatitis C and incarceration are strong, and pose challenges for patients and care providers.<sup>8a</sup> These linkages are further complicated by drug interactions among TB, HIV, and hepatitis medicines, and—though too little research has been done—among TB medicines and methadone or buprenorphine. These special populations are more likely to have heart and liver conditions, and many TB drugs, particularly those for DR-TB, pose a safety concern with heart and liver toxicities.

Programmatic efforts to comprehensively care for people are also inadequate: treatment, if it occurs at all, too often exists in a silo. The majority of people with HIV are not screened for TB, and only 40 percent of TB patients have a documented HIV test result.<sup>9</sup> Data on TB testing among people with hepatitis B or C are unavailable. Despite presenting an opportunity for entry into other health services, drug and alcohol treatment programs rarely screen for, let alone treat, TB. This vertical approach to addressing disease and substance use leaves people with TB or other comorbidities undiagnosed and untreated. Even those who do manage to obtain full but independent diagnoses and treatment have uncoordinated care, losing more time in health care visits, incurring greater costs, and becoming more vulnerable to potential harm from unmanaged drug interactions.

More research is urgently needed about the safety and suitability of TB drugs and regimens in these populations. On the programmatic side, integration of services is essential for patients to access timely diagnostic and comprehensive care, and to manage any drug interactions. The criminalization of drug use poses a number of barriers to rapid diagnosis and effective treatment, and to receiving humane and compassionate care.

More information is available in the recently released *TB Advocacy Guide for People Who Use Drugs* from the Joint United Nations Programme on HIV/AIDS, the World Health Organization (WHO), HIT (a U.K.-based harm reduction organization), and the International Network of People who Use Drugs. Available at: [http://www.stoptb.org/wg/tb\\_hiv/assets/documents/TBHIV\\_Advocacy\\_Guide.pdf](http://www.stoptb.org/wg/tb_hiv/assets/documents/TBHIV_Advocacy_Guide.pdf).

## Clinical trials science

Conducting TB clinical trials is challenging. The inefficient traditional paradigm of testing one new drug at a time for a disease that requires combination therapy is, fortunately, being overhauled, with several new combination trials for both DS- and DR-TB ongoing from the TB Alliance, and proposed studies from other groups pending. Adaptive designs that include multiple arms, some of which are dropped if they do not meet predetermined criteria after interim analyses have the potential to make TB drug development more efficient. For more information, see <http://www.treatmentactiongroup.org/tagline/2013/spring/necessary-transformation>.

Yet without accurate surrogate endpoints, TB trials will remain lengthy and large as required by the relatively rare endpoints of cure and relapse. Waiting for lengthy phase III data (or even phase IIb data with long follow-up times) for approval delays and potentially discourages the development of new treatments. A recent article posits that a better approach may involve pursuing adaptive licensing based

on two-month sputum culture conversion to shorten registration timelines, with a thorough global outcomes registry confirming safety and effectiveness.<sup>10</sup> However, an open-label registry would not provide sufficient information on safety and efficacy. Longer-term randomized studies with clinical endpoints are still required to change practice and will be required by the WHO to provide an evidence base for new regimens. Certainly, given the complexity, length, and expense of conducting TB clinical trials, along with the great need for new TB treatments, a better way is needed. More research into biomarkers and potential endpoints is critical, as is innovation and cooperation from researchers (and flexibility from regulators) to make TB drug development more efficient.

## Latent TB Infection

With an estimated one-third of the human population infected with *Mycobacterium tuberculosis* (the bacterium that causes active TB disease), the need for short, affordable treatment of latent TB infection (LTBI) is urgent.

**Table 1. Latent Tuberculosis Infection Studies as of May 2013**

Study/Regimen	Status	Population	Sponsor(s)
<b>PREVENT TB</b> (TBTC Study 26, A5259) Once-weekly rifapentine + isoniazid for 12 weeks (directly observed)	Completed	Persons with LTBI and high risk of progression (close contacts, recent converters, fibrosis on chest X-ray) including children and people with HIV	TBTC/ ACTG
<b>A5279</b> Daily rifapentine + isoniazid for 1 month	Enrolling	People with HIV with positive skin test/IGRA or living in high TB prevalence regions	ACTG
<b>iAdhere</b> (TBTC Study 33) Self-administered once-weekly rifapentine + isoniazid for 12 weeks	Enrolling	Adults with LTBI	TBTC
<b>P4v9</b> 4 months of self-administered daily rifampicin	Enrolling	Children with LTBI, including HIV-positive children	CIHR
<b>A5300</b> To be determined	In discussion	Close contacts of individuals with MDR-TB	ACTG

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases

CIHR: Canadian Institutes of Health Research

IGRA: Interferon gamma release assay – QuantiFERON-TB Gold In-Tube or T-SPOT TB test

TBTC: U.S. Centers for Disease Control and Prevention’s Tuberculosis Trials Consortium

In 2011, following research from the CDC's Tuberculosis Trials Consortium (TBTC), the U.S. Centers for Disease Control and Prevention (CDC) recommended a new three-month regimen of once-weekly isoniazid and rifapentine administered as directly observed therapy (DOT).<sup>11</sup> Cure was similar with this new regimen of 12 treatment doses compared with nine months of daily isoniazid. Programmatically, the 12-week, 12-dose regimen would save substantial patient costs compared with the nine-month daily isoniazid standard. Further studies in people with HIV and in children published this year further demonstrate the regimen's safety.<sup>12,13,14</sup>

The TBTC is now conducting the iAdhere study to see if this regimen can work as well when given as self-administered therapy (SAT)—with and without SMS reminders—as when given by DOT. However, rifapentine costs much more than isoniazid alone.<sup>15</sup> Sanofi is developing a fixed-dose combination of isoniazid and rifapentine to reduce the current high pill burden of the regimen, and will file with the FDA for a latent indication once this is complete. Unfortunately, however, despite receiving substantial public support for the development of its compound, Sanofi has yet to commit to lowering the drug price to make it affordable in either low- or high-incidence settings.

Study A5279 by the AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)—funded by the U.S. National Institute of Allergy and Infectious Diseases (NIAID)—is evaluating whether rifapentine and isoniazid can be given in a super-short course treatment for LTBI in 3,000 people coinfecting with HIV.<sup>16</sup> This study is looking at daily administration of the two drugs for just one month. Results are expected in 2015–16.

The Canadian Institutes of Health Research and McGill University are conducting a study to determine the safety and tolerability of a four-month, once-daily rifampicin regimen in children to prevent active disease. Already recommended for adults, this regimen is readily accessible and is shorter than the current standard of care for children, which is nine months of isoniazid. The study is enrolling newborns to children 17 years of age; results should be available in 2016.<sup>17</sup>

While these regimens are promising, treatment-shortening options not based on rifamycins are desirable. Both rifapentine and rifampicin interact with a number of anti-HIV drugs, such as protease inhibitors (e.g., ritonavir), non-nucleoside reverse transcriptase inhibitors (e.g., nevirapine, efavirenz) and integrase inhibitors (e.g., raltegravir), complicating treatment in people coinfecting with HIV who are on antiretroviral therapy (ART).<sup>18</sup>

As MDR-TB is by definition resistant to isoniazid and rifampicin—closely related to rifapentine—existing and novel treatment options for LTBI are unlikely to work among those latently infected with MDR-TB (though some evidence suggests isoniazid

can prevent active disease in some instances, possibly due to mixed infection).<sup>19</sup> The millions of contacts of people with MDR-TB around the world desperately need an option to prevent their infection from progressing into active disease, which is lengthy, costly, and very difficult to treat. The ACTG is planning a study of novel LTBI treatment in close contacts of people with MDR-TB. The ACTG originally proposed a study of bedaquiline in close contacts of people with MDR-TB. However, risks and benefits of treating LTBI differ from those of treating active MDR-TB, and bedaquiline may not yet be proved safe enough to give to people without active disease. Current work in mice to identify the best drug or regimen for treating drug-resistant LTBI will inform the final study design.<sup>20</sup>

While researchers wait for new drugs to study, and programs wait for rifapentine to become affordable, isoniazid preventive therapy (IPT) continues to be an essential and effective treatment for LTBI. A systematic review assessing the effect of LTBI therapy on the risk for isoniazid-resistant TB did not find a statistically significant increased risk for resistance in those who had taken IPT; it is assumed that those given preventive therapy have undergone a diagnostic screen to rule out active disease.<sup>21</sup>

A recent paper modeling the effect of community-wide IPT points to its potential to drive increases in drug resistance at the population level.<sup>22</sup> While these results are from theoretical modeling exercises, and while human studies have shown that IPT does not increase DR-TB, it would be ideal if LTBI therapy involved different drugs than treatment for active disease. Until more drugs enter the pipeline and this becomes feasible, IPT will remain an important tool for preventing disease. Early diagnosis and appropriate treatment of all active TB disease will reduce transmission of infection.

## Active TB

**Table 2. Classes of Drugs with Antituberculosis Activity in Clinical Studies**

Class	Drug(s)	Mechanism of Action
Diarylquinoline	<b>bedaquiline</b>	interferes with how bacterial cells make energy by targeting the proton pump adenosine triphosphate synthase <sup>23</sup>
Ethylenediamine	<b>SQ109</b>	disrupts bacterial cell-wall construction by disturbing the assembly of mycolic acids, possibly by targeting the MmpL3 protein; <sup>24</sup> in vitro activity has yet to be confirmed in humans
Fluoroquinolone	gatifloxacin, levofloxacin, moxifloxacin, ofloxacin	disrupts bacterial replication by inhibiting the DNA gyrase enzyme, thus preventing bacterial DNA from unwinding and duplicating <sup>25</sup>
Nitroimidazole	<b>delamanid, PA-824, TBA354</b> (preclinical)	destabilizes the bacterial cell membrane by blocking the synthesis of mycolic acids; <sup>26</sup> poisons the bacterial cell by releasing nitric oxide when metabolized <sup>27</sup>
Oxazolidinone	<b>AZD5847, linezolid, sutezolid, tedizolid</b> (for MRSA)	blocks protein synthesis (translation) by inhibiting the initiation step at the ribosome <sup>28</sup>
Rifamycin	rifabutin, rifampicin, rifapentine	blocks messenger RNA synthesis (transcription) by inhibiting the bacterial DNA-dependent RNA polymerase <sup>29</sup>
Riminophenazine	clofazimine	unclear, but it appears that the bacterium's ineffective attempts to metabolize drug lead to cycle (redox cycle), which generates toxic reactive oxygen species within the bacteria; may target the bacterium's outer membrane by inhibiting the bacterial respiratory chain and ion transporters <sup>30</sup>

Note: Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds.

MRSA: Methicillin-resistant *Staphylococcus aureus*



Table 3. Recently Completed Clinical Studies for Active Tuberculosis

Study/Regimen	Stage	Indication	Sponsor
<b>OFLOTUB</b> 4 months of gatifloxacin, isoniazid, pyrazinamide, rifampicin	Phase III	DS-TB	WHO-TDR, IRD
<b>REMOxTB</b> 4 months of moxifloxacin substituting isoniazid or ethambutol, plus pyrazinamide and rifampicin	Phase III	DS-TB	TB Alliance, Bayer, University College London, University of St Andrews, MRC-UK, EDCTP
<b>RIFAQUIN</b> ethambutol, moxifloxacin, pyrazinamide, rifampicin in intensive phase, rifapentine in continuation phase for treatment-shortening and intermittent dosing	Phase III	DS-TB	INTERTB
<b>HR2 or HIGHRIF</b> rifampicin 10, 15, 20 mg/kg daily, ethambutol, isoniazid, and pyrazinamide	Phase IIb (2-month)	DS-TB	PanACEA, EDCTP
<b>Linezolid to treat XDR-TB</b> delayed or immediate start of linezolid at 600 mg for 4 months or till culture conversion, then 600 mg or 300 mg for $\geq 18$ additional months, plus individualized background regimen	Phase IIb	XDR-TB	NIAID
<b>NC-002</b> moxifloxacin, <b>PA-824</b> , pyrazinamide	Phase IIb (2-month)	DS/DR-TB	TB Alliance
<b>RIFATOX</b> rifampicin 900 mg and 1,200 mg daily for first 4 months of standard 6-month regimen	Phase IIb	DS-TB	INTERTB
<b>RioMAR</b> isoniazid, rifapentine, pyrazinamide, moxifloxacin	Phase IIb (2-month)	DS-TB	Johns Hopkins University, TBTC
<b>TBTC Study 29</b> rifapentine 10 mg/kg, isoniazid, ethambutol, pyrazinamide 5 times/week	Phase IIb (2-month)	DS-TB	TBTC
<b>TBTC Study 29X</b> rifapentine 10, 15, 20 mg/kg daily, isoniazid, ethambutol, pyrazinamide in the intensive phase	Phase IIb (2-month)	DS-TB	TBTC

Study/Regimen	Stage	Indication	Sponsor
<b>B1171003</b> sutezolid 600 mg twice daily vs. <b>sutezolid</b> 1,200 mg daily vs. isoniazid, rifampicin, ethambutol, pyrazinamide	Phase IIa (2-week EBA study)	DS/DR-TB	Pfizer
<b>HR1</b> rifampicin 10, 20, 25, 30, or 35 mg/kg daily as monotherapy and with ethambutol, isoniazid, and pyrazinamide	Phase IIa (2-week EBA study)	DS-TB	PanACEA, EDCTP
<b>NC-003</b> <b>bedaquiline</b> , clofazimine, <b>PA-824</b> , pyrazinamide in various combinations	Phase IIa (2-week EBA study)	DS/DR-TB	TB Alliance

Note: Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds.

DR-TB: Drug-resistant TB DS-TB: Drug-sensitive TB EBA: Early bactericidal activity

EDCTP: European and Developing Countries Clinical Trials Partnership

INTERTB: International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis

IRD: Institut de recherche pour le développement

MRC-UK: British Medical Research Council

NIAID: U.S. National Institute of Allergy and Infectious Diseases

PanACEA: Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics

TBTC: U.S. Centers for Disease Control and Prevention Tuberculosis Trials Consortium

WHO-TDR: World Health Organization–based Special Programme for Research and Training in Tropical Diseases

## NOVEL COMPOUNDS

### AZD5847

AstraZeneca’s AZD5847 is an oxazolidinone. AZD5847—like sutezolid, described below—has promise as it is in the same class as Pfizer’s linezolid, which is effective in treating drug-resistant TB, but comes with damaging side effects including vision loss, painful damage to the peripheral nervous system, and anemia.<sup>31</sup> AZD5847 has appeared well tolerated in the very short, small trials that have been conducted. The main effects were nonserious gastrointestinal events and reductions in white blood cells (important in immune functioning) and red blood cell counts (which can lead to anemia).<sup>32,33,34</sup>

AZD5847 moved into a phase IIa clinical trial in the fall of 2012. This two-week early bactericidal activity (EBA) study compares four different dosing schedules of AZD5847 (500 mg orally once daily, 500 mg orally twice daily, 1,200 mg orally once daily, or 800 mg orally twice daily) with a control arm of the standard four-drug, first-line therapy.<sup>35</sup> The study is currently enrolling; results are expected in the first half of 2014.<sup>36</sup> AstraZeneca's investments in developing AZD5847 made it the third-largest private funder of TB research and development in 2011.<sup>37</sup> AstraZeneca has been notably reticent when approached by community groups seeking discussions; it is time for the company to engage with research advocates and representatives from TB-affected communities in a meaningful way.

### **Bedaquiline (brand name: Sirturo; formerly known as TMC207)**

Bedaquiline made history in late 2012, when the FDA granted it accelerated approval as part of combination therapy for MDR-TB. A diarylquinoline, bedaquiline is the first new drug from a new class of drugs to be approved in over 40 years. Bedaquiline is being developed for DR-TB by Janssen Infectious Diseases BVBA (a subsidiary of Johnson & Johnson formerly known as Tibotec), and for DS-TB by the TB Alliance.

FDA approval was based on data from two phase II studies of 440 people with DR-TB. These studies found that bedaquiline, when given with existing MDR-TB drugs, was extremely effective against TB. For example, in study C208 when a five-drug background regimen was administered with six months of bedaquiline or a placebo, 79 percent of those randomized to receive bedaquiline achieved culture conversion, versus 58 percent of those who received background regimen alone. Median time to conversion in the bedaquiline arm was 12 weeks versus 18 weeks for those in the placebo arm.<sup>38</sup>

Janssen's data were encouraging regarding bedaquiline's efficacy, but less so for its safety. Most drugs used to treat MDR-TB have serious side effects—bedaquiline's include moderate QT prolongation (a disturbance in the heart's electrical activity that could potentially lead to serious and even fatal rhythm disturbances) and elevated aminotransferase levels (increased liver enzymes in the blood, indicating potential liver damage).

The drug's long terminal half-life of about five and a half months means it lingers in tissues for a long time. This may mean longer exposures to bedaquiline's side effects. As bedaquiline remains in the body long after treatment ends and other TB drugs have cleared, if a patient had not yet cleared all bacteria and achieved cure, there is potential for resistance to bedaquiline to develop.<sup>39</sup> However, since it was taken for only six months over a background of therapy lasting 18 to 24 months, this has not been observed in the studies conducted to date.

One study found excess mortality in the bedaquiline arm: 13 percent (10/79) of patients who took bedaquiline and other drugs died, versus only two percent (2/81) in the placebo arm ( $P = 0.017$ ). Drawing conclusions from these data is difficult, given that the overall number of people taking the drugs was small. There was no common cause of death other than TB (five of 10 deaths) among those who died in the bedaquiline arm, and all but one death occurred after bedaquiline administration ceased.<sup>40</sup> The mortality rate in the control arm was lower than expected in a population with DR-TB. Nevertheless, this increased mortality requires further investigation of bedaquiline's safety; it will be essential to monitor mortality not only during, but for at least six months after bedaquiline administration.

Because of safety and drug interaction issues, the FDA urged caution when using bedaquiline with clofazimine and fluoroquinolones, as all cause QT prolongation. Based on available data, bedaquiline should not be used with rifampicin or rifapentine.<sup>41,42</sup> The TB Alliance and NIAID recently completed a drug-drug interaction study with a single dose of bedaquiline added to rifabutin or rifampicin; pending results will further inform whether bedaquiline and rifamycins can be used safely together.<sup>43</sup> As delamanid also causes QT prolongation and is far along in the development pipeline, research is urgently needed to determine if it can be combined safely with bedaquiline—the National Institutes of Health (NIH) is arranging for this research, but the process is moving slowly.<sup>44</sup>

Bedaquiline interacts with anti-HIV protease and non-nucleoside reverse transcriptase inhibitors such as efavirenz (used globally in first-line HIV therapy) and lopinavir/ritonavir (used in second-line therapy), and should not be taken with the antifungal ketoconazole for more than two weeks, as both cause QT prolongation.<sup>45,46,47</sup> Bedaquiline may cause liver or heart damage, so more research is necessary to see if it is safe for people who use alcohol, methadone or buprenorphine, or other drugs, or have hepatitis B or C.

To address safety questions, confirm its efficacy, determine its optimal use, and comply with the conditions of FDA approval, Janssen is about to begin a phase III trial of bedaquiline and a patient registry of all those who receive the drug in the United States. The phase III trial will involve 600 subjects with sputum smear-positive pulmonary MDR-TB, including pre-XDR-TB. Participants in the first arm will receive nine months of bedaquiline and a background regimen (six months of prothionamide, high-dose isoniazid, levofloxacin, ethambutol, clofazimine, and pyrazinamide, with four months of kanamycin; followed by three months of levofloxacin, ethambutol, clofazimine, and pyrazinamide). Those in the control arm will receive placebo and the background regimen. Participants from the first two arms whose treatment failed will have access to rollover arms, where they will receive an individualized salvage regimen.<sup>48</sup>

People with HIV will be included in the study, but only if their viral load levels are below 400 copies/mL and their CD4 counts are above 250 cells/mm<sup>3</sup> at screening; participants cannot be on anti-HIV medicines other than triple nucleoside reverse transcriptase inhibitor-, nevirapine-, or lopinavir/ritonavir-based regimens.<sup>49</sup>

The primary endpoint will be the proportion of subjects with a favorable treatment outcome (i.e., two consecutive negative cultures 25 days apart or no signs or symptoms of active TB if no sputum can be produced) at 15 months for those in the first two arms, representing six months of treatment-free follow-up—this is a traditional endpoint for efficacy. The final analysis will look at the proportion of favorable outcomes at 21 months, or one year of treatment-free follow-up.<sup>50</sup> Janssen is looking into increasing community engagement at identified phase III trial sites. A strong community engagement program could benefit the required study's enrollment, which may be challenged by parallel marketing approvals in trial-site countries. Individuals may be reluctant to participate in a phase III trial if a drug is on the market; community outreach and education about the importance of research may help with recruitment and retention.

The FDA required Janssen to create a patient registry for all bedaquiline-treated patients in the United States to assess the incidence of serious adverse events including death.<sup>51</sup> This assessment must be completed and submitted to the FDA by 2019.

The IMPAACT network is currently completing protocol design for study 1108, a pharmacokinetic and safety study of bedaquiline in children with MDR-TB, which will begin by placing the oldest children (12–18 years) on an adult formulation of bedaquiline. All younger cohorts (6–12 years, 2–6 years, 6 months–2 years, 0–6 months) will be placed on a pediatric formulation currently in development by Janssen, sequentially from oldest to youngest, once adequate data from the preceding cohort are available. Enrollment is anticipated to start in the first quarter of 2014. The study plans to first enroll HIV-negative children in each age cohort, then enroll similar numbers of HIV-positive children in the oldest cohort, all with proven or presumed MDR-TB. A separate HIV-coinfection trial for the younger age groups is under discussion.<sup>52</sup>

Bedaquiline's potential to help shorten MDR-TB treatment or to replace existing, inferior drugs has not yet been verified, though it is plausible given evidence of the drug's ability to reduce time-to-culture conversion.<sup>53</sup> Janssen will pursue additional studies of interest in collaboration with others in the TB community. Some proposed treatment-shortening studies include ACTG 5319 (called the MDR-Additive Regimens Varying Experimental Layouts or MARVEL study), which plans to use bedaquiline as a backbone in various combinations with other new and existing drugs to determine optimal regimens. The recently completed NC-003 study tests bedaquiline with

various combinations of clofazimine, PA-824, and pyrazinamide to assess its safety and efficacy with these drugs. The TB Alliance's proposed NiX-TB open-label study involves bedaquiline given only with other new drugs—PA-824 and an oxazolidinone—to patients with pre-XDR/XDR-TB. Given the limited site capacity for conducting MDR-TB trials, the TB research community needs to come together to develop the most efficient path forward for testing bedaquiline and other new drugs to determine optimal combinations.

### **Bedaquiline Approval and the Evolving Regulatory Landscape**

As the first new TB drug from a new drug class to be approved by the FDA in over 40 years, and with filings in China, Europe, Russia, South Africa, and Thailand and more planned, bedaquiline is a wake-up call for regulators across the world to develop their capacity to review new drugs for TB. Janssen's laudable compassionate use program (which provides pre-approval access to the drug for individual patients in critical condition under select circumstances) has stimulated regulatory authorities in countries where these patients live, who must approve the importation of the drug.

Regulators are generally not equipped to rapidly convene a group of experts who can provide knowledgeable feedback on new TB drugs, as they have not been required to do so for over 40 years. Bureaucracy and financial and human resource constraints tend to slow down drug review processes, particularly in the countries most affected by TB. Countries must both scale up their capacity to rapidly review new drug applications and implement adequate systems for holding drug sponsors accountable postapproval. Particularly as bedaquiline and new drugs are approved under accelerated mechanisms with only phase II data, regulators must ensure their ability to enforce post-marketing surveillance and the sponsor's completion of required studies.

TB programs require similar improvements. Countries must dedicate more funding both for programs to scale up diagnosis of MDR-TB and linkage to care. National treatment programs need to prepare for the rapid adoption and rational use of approved new drugs to ensure access, and reduce the emergence of drug resistance, to both existing and new drugs. This includes both swift adaptation of guidelines and implementation on the ground. A commitment to proper TB treatment requires better forecasting of demand and supply-chain management from treatment programs.

Sponsors must do their share to rapidly register new drugs in countries where they are needed and to deliver drugs quickly once approval is obtained. For example, Janssen made bedaquiline available immediately upon approval in the United States under its compassionate use program, and four months later, the product became commercially available. Yet the burden of the disease remains outside of the U.S. Sponsors are responsible for pricing the drug affordably and for fulfilling any requirements of approval (e.g., further studies or postmarketing surveillance) rapidly and thoroughly.

### Delamanid (OPC-67683)

Otsuka's compound delamanid, a nitroimidazole, shows great promise in treating MDR-TB. While it trails behind bedaquiline in terms of regulatory approvals—decisions from the European and Japanese regulatory agencies are pending, and Otsuka plans to file with the FDA in the near future—it has advanced further than bedaquiline in clinical trials. Enrollment for a phase III trial of an optimized background regimen plus six months of delamanid or placebo has been under way since mid-2012.<sup>54</sup> Indeed, Otsuka is the leading private investor in TB research, dedicating \$65 million in 2011 alone.

Delamanid's apparent safety and efficacy in a two-month phase IIb trial were recently followed-up in a six-month open-label trial.<sup>55</sup> Patients who successfully completed the two-month trial were eligible to enter a longer observational study where they were given delamanid for an additional six months. All patients, including those who did not enter the six-month study, were observed for 24 months to evaluate long-term treatment outcomes. Of those who received delamanid for six months or more, favorable outcomes (defined as five consecutive negative cultures in the preceding 12 months, or treatment completed, but with fewer than five negative—and no positive—cultures) were observed in 74.5% versus 55% of those who received delamanid for two months or less. Only 1% of those receiving long-term delamanid treatment died, versus 8% of those who received short-term or no delamanid.<sup>56</sup>

Delamanid appears generally safe, although it does cause mild-to-moderate QT prolongation.<sup>57</sup> Delamanid is being tested for administration twice daily at 100 mg for the first two months of treatment, and once daily at 200 mg for the following four months.<sup>58</sup> Delamanid's pediatric formulation of small, dissolvable tablets is complete, and a pediatric study has begun in the Philippines.<sup>59</sup> Drug-drug

interaction studies have shown that delamanid plus efavirenz, tenofovir, or lopinavir/ritonavir does not cause any clinically relevant effects, though lopinavir/ritonavir does increase exposure to delamanid by 20 percent.<sup>60,61</sup> Delamanid has been safely administered with other second-line drugs, although QT prolongation is a concern with fluoroquinolones and clofazimine, and drug-drug interaction studies may be necessary to determine if they are safe to use together. Giving delamanid along with the first-line anti-TB drug rifampicin reduced exposure to delamanid by 40–50 percent.<sup>62</sup>

Delamanid is a promising drug. Data support pre-approval access to it for those in urgent need. Otsuka has been collaborating with Médecins Sans Frontières to develop a compassionate use program; however, this has been slow to start. It is imperative that Otsuka initiate compassionate use programs so those in urgent need can benefit from pre-approval access to delamanid, as it may be over a year before delamanid is actually rolled out. Janssen, with more experience in infectious disease drug development, opened a compassionate use program for bedaquiline before filing for approval or initiating phase III studies, while Otsuka has done the opposite with delamanid.

## PA-824

PA-824, like delamanid, is a nitroimidazole—a new drug class for fighting TB. The TB Alliance is developing PA-824 for both drug-sensitive and drug-resistant TB in its novel combination studies, including NC-002 and NC-003. PA-824 is included in the previously described proposed NiX-TB and MARVEL study plans.

The TB Alliance and NIAID cosponsored a phase I thorough QT safety study to evaluate any effects PA-824 will have on the rate at which the heart conducts electrical impulses. The clinical trial studied whether PA-824 and moxifloxacin had additive or synergistic effects on the QT interval. Results should be available soon.<sup>63</sup>

The ACTG has completed enrollment of study A5306, a phase I safety, tolerability, and pharmacokinetic interaction study of PA-824 with two common antiretrovirals, lopinavir/ritonavir and efavirenz, as well as with rifampicin.<sup>64</sup> Results from the efavirenz/PA-824 arm showed that the two drugs were well tolerated when given together, and PA-824 did not affect efavirenz concentrations. Efavirenz reduced exposure to PA-824 modestly; the clinical implications of this reduction, though, are unknown and warrant further study.<sup>65</sup> Results from the lopinavir/ritonavir and rifampicin arms should be available soon.



## Russian Regulatory Reforms Required

Two compounds, perchlozone and SQ109, are racing through Russian research and regulatory processes. Yet the paucity of promising peer-reviewed data on either drug raises concerns about the compounds themselves, the transparency of their developers, and Russian regulatory capacity.

### Perchlozone

Perchlozone from JSC Pharmasyn-tez is a new drug from the thiosemicarba-zone drug class. Perchlozone was approved in Russia for treating MDR-TB in November 2012, but has not yet been appropriately scrutinized via traditional clinical and peer-review processes. In fact, no peer-reviewed data in English are available.

Despite having only been studied for three months in humans, the drug was approved for use for six months on top of a background regimen. The drug's recommended dosage is 9.5–12.5 mg/kg, although it was studied at 20–30 mg/kg. Perchlozone costs EUR2,000–4,000 per six-month course depending on the patient's weight.

Pharmasyn-tez has initiated what they call a phase IV trial in Russia—although it will only involve 340 patients—to administer perchlozone for six months along with a 12–18 month course of fluoroquinolones and other drugs to people with DS- and DR-TB, and including HIV coinfecting individuals. The company is considering registration in African countries and the Commonwealth of Independent States (CIS).<sup>66</sup> The company's failure to publish peer-reviewed data on the drug and its substandard clinical trial designs are unacceptable. It is essential that Pharmasyn-tez make all existing data available for external, unbiased peer review before additional clinical studies are initiated.

### SQ109

SQ109 is an ethylenediamine antibiotic, in the same drug class as ethambutol, though with a novel mechanism of action—both affect cell-wall assembly, but SQ109 appears to do so by inhibiting the MmpL3 protein (see table 2), whereas ethambutol likely inhibits arabinosyl transferase.<sup>67,68</sup> Early in vitro and mouse studies showed SQ109 does not exhibit cross-resistance with ethambutol, and is effective at killing *Mycobacterium tuberculosis*.<sup>69</sup> The drug appeared synergistic in vitro with isoniazid, rifampicin, and bedaquiline, and additive with sutezolid; mouse studies indicated that SQ109 was more effective than ethambutol when given with isoniazid and rifampicin in reducing the number

of colony forming units.<sup>70,71,72,73</sup> The company claims that unpublished data show in vitro synergy with amikacin, capreomycin, clofazimine, and moxifloxacin, and additivity with cycloserine, ethionamide, kanamycin, and para-aminosalicylic acid.<sup>74</sup>

No evidence from humans yet supports the continued development of SQ109. The drug appears safe and well tolerated, but results from a phase IIa trial cosponsored by the European and Developing Countries Clinical Trials Partnership (EDCTP) showed that the drug has no early bactericidal activity (EBA).<sup>75,76</sup>

Sequella is optimistic that it will be effective in treating TB when given for longer periods, despite the lack of any clinical evidence to support that view. Sequella announced in November that the first person had been enrolled in a pivotal trial in Russia and Kazakhstan, which is being run by a little-known Russian company called Infectex.<sup>77</sup> In this trial, SQ109 is being given for six months on top of an 18-month background regimen, compared with the background regimen alone. This study will have two-year follow-up and both clinical and mycobacterial endpoints, although it will involve only 84 participants—unacceptably small for a registrational trial. Sequella assures that the trial is only for registration in Russia and the Commonwealth of Independent States (though the data may be included in other applications), is led by an esteemed principal investigator, and is being conducted according to International Conference on Harmonisation guidelines. However, as with perchlozone above, there are no data yet to support a registration trial, and approval standards are significantly lower in Russia or in the CIS than elsewhere in the world. We recommend that Russia and the CIS improve their regulatory capacity to oversee development of urgently needed TB drugs.

Sequella will conduct a conventional phase IIb MDR-TB study of SQ109 plus an optimized background regimen, compared with an optimized background regimen alone, if it is able to obtain sufficient resources.<sup>78</sup> In 2012, Sequella invested US\$4.5 million in developing SQ109 and other TB products, which is not enough to adequately evaluate a new drug in humans.<sup>79</sup>

In the meantime, the recently initiated phase IIb Multi-Arm Multi-Stage (MAMS) study conducted with the assistance of the EDCTP includes SQ109 in two out of five study arms, in combination with moxifloxacin and high-dose rifampicin.<sup>80</sup> NIAID planned a thorough QT safety study in healthy volunteers that will occur in 2013. However, with TB research budgets under extreme pressure, and based on currently available evidence, expending resources on SQ109 does not appear to be an appropriate use of limited public research funding.

## Sutezolid (PNU-100480)

Sutezolid, also known as PNU-100480, is an oxazolidinone, like linezolid and AZD5847. In vitro and mouse models suggest that sutezolid may be more active than linezolid against TB. As linezolid has serious side effects, including optic and peripheral neuropathy and anemia, safer oxazolidinones are needed.<sup>81</sup> Like linezolid, sutezolid does not induce or inhibit the enzyme CYP3A4, important to the metabolism of many other TB and HIV drugs, meaning its potential for drug-drug interactions may be lower.<sup>82</sup> Appropriate drug-drug interaction studies should be conducted to confirm this. Sutezolid is of great interest to the TB research community, yet since TAG first reported on the drug in the *2009 Pipeline Report*, Pfizer has only completed two phase I and one phase IIa clinical trials, in addition to preclinical work.<sup>83,84,85,86</sup>

In 2012, Pfizer reported results of its first study of sutezolid in TB patients, which showed the drug to be safe and active against TB. Fifty-nine South African participants with DS-TB with and without HIV, but not on antiretrovirals, were assigned to one of three arms: 600 mg of sutezolid twice daily, 1,200 mg daily, or the standard four-drug therapy for DS-TB for the first two weeks of treatment. The study found no treatment-related serious adverse events and no effect on QT interval, although temporary, asymptomatic liver-enzyme elevations were observed.<sup>87</sup> Other TB drugs such as pyrazinamide also raise liver enzymes. A recent mouse study revealed that combinations including sutezolid were more effective than the standard first-line regimen, and could improve HIV-associated TB treatment by avoiding the use of rifamycins, which often interact with antiretroviral therapy.<sup>88</sup>

Sutezolid warrants further research right now.<sup>89</sup> Several proposed new studies—including the previously described NiX-TB study evaluating a regimen of entirely new drugs in people with pre-XDR- and XDR-TB, and the MARVEL study of multiple proposed MDR-TB treatment arms—include sutezolid. However, Pfizer has been unwilling to make sutezolid available to clinical research consortia such as the TBTC, TB Alliance, or ACTG to advance it and test its potential with existing or other experimental TB drugs. Pfizer must commit to both more rapidly advancing the development of sutezolid on its own, and to making the compound available for collaborative study in combination with other new and existing drugs.

**Table 4. Enrolling Clinical Studies for Active Tuberculosis**

Study/Regimen	Stage	Indication	Sponsor
<b>C213</b> delamanid for 6 months plus 18–24 months individualized background regimen, and 6–12 months follow-up	Phase III	DR-TB	Otsuka
<b>STREAM</b> 9 months clofazimine, ethambutol, moxifloxacin, and pyrazinamide, with prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of 4 months	Phase III	DR-TB	The Union, MRC-UK
<b>MAMS-TB-01</b> 3 months of different combinations of ethambutol, isoniazid, moxifloxacin, pyrazinamide, rifampicin (10, 20, or 35 mg/kg) and <b>SQ109</b>	Phase IIb	DS-TB	PanACEA, EDCTP
<b>AZD5847</b> 500 mg once or twice daily, 1,200 mg once daily, or 800 mg twice daily	Phase II (2-week EBA study)	DS/DR-TB	AstraZeneca

Note: Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds.

DR-TB: Drug-resistant TB DS-TB: Drug-sensitive TB EBA: Early bactericidal activity

INTERTB: International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis

MRC-UK: British Medical Research Council

The Union: International Union Against Tuberculosis and Lung Disease

## EXISTING COMPOUNDS

### Clofazimine

Clofazimine—already FDA-approved for treating Hansen’s disease (leprosy) since 1986—has piqued the interest of TB researchers by appearing successful when administered off-label for DR-TB in several studies, and it was included in the nine-month standardized treatment regimen for MDR-TB known as the “Bangladesh regimen,”<sup>90,91,92</sup> though the work in question was not conducted according to good clinical practice (GCP) and thus would not be acceptable to a stringent regulatory authority. This enthusiasm is hampered by clofazimine’s side effects: skin discoloration is common and QT prolongation is a concern; clofazimine is more rarely associated with depression, with two suicides reported.<sup>93</sup> The Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) study, the phase III bedaquiline trial, study NC-003, and the proposed MARVEL

study all include clofazimine, and will provide more information on clofazimine's safety and efficacy for treating DR-TB. Novartis, clofazimine's sponsor, has refused to provide study drug for these efforts, and access has challenged both research and programmatic efforts. A wealthy drug company with little to lose by expanding access to the niche drug for an underserved population, Novartis must facilitate the development of improved treatment for patients with DR-TB.

## Fluoroquinolones

Gatifloxacin and moxifloxacin are both fluoroquinolones with broad-spectrum antibiotic activity and TB treatment-shortening potential, but unfortunately face prevalent preexisting resistance in many parts of the world.

Preliminary results from the RIFAQUIN study from the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB) were recently reported, revealing that using moxifloxacin and rifapentine together for six months for active, drug-sensitive TB can simplify treatment to once-weekly dosing in the continuation phase—including in people with HIV with CD4 counts of 150 cells/mm<sup>3</sup> or higher and not on ART.<sup>94</sup> Prior studies of intermittent regimens, however, led to increased treatment failure, relapse or resistance among patients with TB and HIV, so this approach merits further study in coinfecting populations.<sup>95</sup> The RIFAQUIN regimen, while promising for intermittent therapy, could not shorten effective treatment to four months.<sup>96</sup> Data from the phase III REMox TB study, comparing moxifloxacin substituted for either ethambutol or isoniazid to shorten treatment to four months, should be available by early 2014.<sup>97</sup>

The TBTC's RioMAR study examined the role of replacing ethambutol with moxifloxacin, as well as rifampicin with rifapentine, during the intensive phase of treatment; enrollment closed, and data analysis will begin shortly.<sup>98</sup> As described above, the TB Alliance and NIAID cosponsored a phase I thorough QT study of PA-824 and moxifloxacin; results are pending.<sup>99</sup>

Moxifloxacin is included in the New Combination 2 (NC-002) study and is featured in the STREAM study.

While gatifloxacin has taken a backstage to moxifloxacin due to moxifloxacin's rapid killing activity and to gatifloxacin's removal from the market in many countries due to side effects, information on gatifloxacin might help broaden the understanding of whether fluoroquinolone use has a role in first-line TB treatment shortening.<sup>100</sup> Two years ago, the European Commission's OFLOTUB consortium completed a trial replacing ethambutol with gatifloxacin to evaluate gatifloxacin's potential to shorten first-line treatment to four months. Results were delayed due to issues with funding and data management, but are expected by the end of 2013.

Gatifloxacin was used in the “Bangladesh regimen,” an all-oral drug regimen that may have the potential to simplify MDR-TB treatment and shorten it to nine months. Follow-up studies based on this regimen such as the STREAM study, however, are using other fluoroquinolones such as levofloxacin or moxifloxacin.

## Linezolid

Pfizer’s linezolid was approved in 2000 to treat drug-resistant, gram-positive bacteria.<sup>101</sup> While TB is not gram-positive, linezolid has occasionally been in use to treat DR-TB, although information on the drug’s safety for long-term use was minimal. Linezolid’s efficacy against MDR- and XDR-TB appeared strong in vitro, but more modest in mice.<sup>102,103,104,105,106,107</sup>

NIAID and the South Korean Ministry of Health and Welfare sponsored a phase IIa study of linezolid in South Korea. Pfizer donated study drug. Forty-one patients without HIV whose current pulmonary XDR-TB treatment had been failing for at least six months were enrolled; participants had, on average, been treated five previous times for TB. Participants were randomized to add 600 mg of linezolid on top of background drugs daily, either immediately or after two months. After four months or after culture conversion, whichever came first, patients were randomized again to continue linezolid at a dose of either 600 mg or 300 mg daily for at least another 18 months.<sup>108</sup>

Starting linezolid immediately increased the percentage of patients whose TB converted after four months (79% vs. 35%;  $P = 0.001$ ); 87 percent of patients had negative sputum culture within six months of first taking linezolid. Thirteen of 38 patients who received linezolid completed therapy without relapse, 17 patients were still receiving treatment per protocol, and eight patients withdrew early.<sup>109</sup> Follow-up of all patients will be completed at the end of 2013; investigators claim that, to date, no additional failures or relapses have been recorded.<sup>110</sup> With the early conversion rates, and supposed potential for high treatment success rates, these results could exceed previously documented XDR-TB treatment success rates. For example, in a Latvian study of 48 XDR-TB patients treated with individually tailored regimens, 38% were cured, 8% died, 6% did not complete treatment, and 48% had an unfavorable outcome.<sup>111</sup>

Linezolid’s activity, however, came at a cost: 82 percent of patients had clinically significant adverse events possibly or probably related to linezolid, and three patients out of 38 discontinued therapy. Adverse effects included anemia, neutropenia (abnormally low amounts of certain white blood cells, which can affect immunity), optic neuropathy, peripheral neuropathy (causing pain or numbness in the limbs), and rhabdomyolysis (the breakdown of skeletal tissue, which can lead

to kidney failure). Patients switched to 300 mg of linezolid daily after the second randomization had fewer adverse events than those who continued taking 600 mg. Nearly all events resolved after drug discontinuation or dose reduction. Despite the addition of a single drug to a failing regimen, only four cases of linezolid resistance were observed. Drug resistance was determined by a lack of clinical response or relapse, an increase in minimum inhibitory concentrations as compared to baseline levels, and DNA sequencing revealing mutations previously shown to be associated with linezolid resistance.<sup>112</sup>

While linezolid may be effective at treating extreme cases of drug-resistant pulmonary TB, adverse events are frequent and require close monitoring. A safer drug in the same class would be better.<sup>113</sup> Until then, Pfizer, linezolid's sponsor, must make the drug more affordable—its current high cost is a major barrier to access.

## Rifamycins

Several studies are ongoing to determine the effect and safety of using rifampicin for DS-TB therapy in higher doses than the currently used dose of 10 mg/kg, which was selected not based on a maximum-tolerated dose, but rather because the drug was originally expensive, so a low dose was selected. The EDCTP-funded HIGHRIF group within the Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics (PanACEA) has found with its HR1 two-week safety and early bactericidal study that administering up to 35 mg/kg of rifampicin is safe and well tolerated, and that early bactericidal activity increases with the dose.<sup>114</sup> The group is planning to extend this study further with even higher doses.

HIGHRIF was part of the larger HR2 two-month study that looked at rifampicin dosages up to 20 mg/kg. Final analysis will be conducted this summer, but preliminary results show that toxicity was limited.<sup>115</sup>

The group recently started the above-described MAMS study, which tests one group with 35 mg/kg of rifampicin, a second with 20 mg/kg of rifampicin combined with moxifloxacin, and a third with 20 mg/kg of rifampicin combined with SQ109.<sup>116</sup> The INTERTB group will soon publish the results of the RIFATOX trial, which tested the toxicity of rifampicin at 900 mg and 1,200 mg daily for the first four months of the standard six-month regimen (which typically includes up to 600 mg daily of rifampicin).<sup>117</sup> Based on these results, a phase III study called RIFASHORT is planned to look at the treatment-shortening potential of high-dose rifampicin.<sup>118</sup> The NIAID HIRIF study, due to start in Peru this year, features high-dose rifampicin.<sup>119,120</sup> Médecins Sans Frontières (MSF)/Epicentre is planning RIFAVIRENZ, a drug-drug interaction study of high-dose rifampicin and efavirenz expected to start in September 2013.<sup>121</sup>

Current enthusiasm around optimizing rifamycins to improve DS-TB treatment includes rifapentine, the approved drug from Sanofi recently shown to enable shortened courses of LTBI treatment. Rifapentine has a longer half-life than rifampicin, and may be suitable for regimens that shorten treatment or allow for less frequent dosing for active TB as well. Indeed, the above-described RIFAQUIN study showed that replacing rifampicin with rifapentine (and isoniazid with moxifloxacin) in the continuation phase of treatment allowed for once-weekly dosing.<sup>122</sup>

The TBTC conducted Study 29, which showed that substituting 10 mg/kg of rifapentine for rifampicin, and dosing only five days weekly in the intensive phase, was safe. However, it was not significantly more active than the standard rifampicin regimen, so studies of higher doses of rifapentine were proposed.<sup>123</sup> Therefore, the TBTC conducted Study 29X, to determine the safety and estimate the efficacy of using 10, 15, and 20 mg/kg of rifapentine daily with isoniazid, pyrazinamide, and ethambutol for the eight-week intensive treatment phase. All doses appeared safe and well tolerated.<sup>124</sup> Based on these results, the TBTC is planning a phase III, treatment-shortening trial of rifapentine.

ACTG 5311, a phase I safety and pharmacokinetic study at four U.S. sites, was designed to evaluate different strategies to optimize exposures to rifapentine: twice-daily dosing and use of different food types, including foods likely to be available in most international settings. The study was closed to new enrollment, and dosing was stopped in all patients at the end of May 2013.<sup>125</sup> Pending data from the RioMAR study, which replaces rifampicin with rifapentine and ethambutol with moxifloxacin during the intensive phase of treatment will further characterize the role of rifapentine in TB therapy.<sup>126</sup>

Even if these research endeavors prove successful, however, using rifapentine to improve treatment for people with TB may still be a long way off. Currently, rifapentine is just too expensive. Sanofi must match its commitment to TB research with a commitment to access by lowering the drug price.

Of all the rifamycins, rifabutin may be the most suitable for treating people on certain anti-HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, as it interacts less with them than rifampicin and rifapentine do. While rifabutin's importance in treating coinfecting individuals is well established, there are some unanswered questions about optimal dosing, which some drug-drug interaction studies are seeking to answer. The British Medical Research Council's EARNEST rifabutin pharmacokinetics study is looking at whether rifabutin should be taken daily or three times weekly with the protease inhibitor lopinavir/ritonavir to find the right balance between drug levels and side effects in people with HIV and TB.<sup>127</sup> The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) will soon publish results from a study in people with HIV and pulmonary



TB in Vietnam on the most appropriate dose of rifabutin when given with protease inhibitors and other anti-HIV treatment. These results will inform the dosing for any future phase III trials comparing the safety, tolerability, and efficacy of rifabutin and rifampicin with protease inhibitor–based ART.<sup>128</sup>

**Table 5. Planned Late-Stage Clinical Studies for Active Tuberculosis**

Study/Regimen	Status	Indication	Sponsor
<b>C210</b> 9 months <b>bedaquiline</b> , clofazimine, ethambutol, isoniazid, kanamycin, levofloxacin, prothionamide, pyrazinamide	Phase III Protocol development	DR-TB	Janssen
<b>Nix-TB</b> <b>bedaquiline</b> , <b>PA-824</b> , <b>sutezolid</b> —proposed	Phase III (noncontrolled 6-month salvage study) Protocol development	Pre-XDR/ XDR-TB	TB Alliance
<b>MARVEL (A5319)</b> <b>bedaquiline</b> , clofazimine, levofloxacin, <b>PA-824</b> , pyrazinamide, <b>sutezolid</b> given for 8 weeks in various combinations	Phase II/III (2-month, with safety measures at 24 weeks) Protocol development	DR-TB	ACTG
<b>HIRIF</b> rifampicin 10, 15, 20 mg/kg daily, isoniazid, ethambutol, pyrazinamide in the intensive phase	Phase IIb (2-month) Not yet recruiting	DS-TB	Harvard University, NIAID

Note: Novel drug candidates in **boldface** to distinguish from existing/repurposed compounds.

DR-TB: Drug-resistant TB DS-TB: Drug-sensitive TB XDR-TB: Extensively drug-resistant TB

ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases

EDCTP: European and Developing Countries Clinical Trials Partnership

NIAID: U.S. National Institute of Allergy and Infectious Diseases

PanACEA: Pan-African Consortium for Evaluation of Anti-tuberculosis Antibiotics

## Research and Policy Recommendations

### 1. Governments and donors need to increase funding for TB research at least threefold.

At US\$250 million per year in 2011 out of a target of US\$740 million, funding for TB research and programs is only a fraction of what it needs to be, and these budgets are shrinking.<sup>129</sup> In the United States, sequestration (the automatic, across-the-board spending cuts triggered by congressional inaction earlier this year), as well as subsequent cuts to the NIH (the leading funder of TB research and development) and the CDC's extremely productive Tuberculosis Trials Consortium are undermining already underfunded research programs. A recent review points to the need for countries with high TB burdens to take a greater share in funding research and development for TB according to their gross domestic product, their disease burden, and the size of their treatment program.<sup>130</sup> Without increased research budgets, the new drugs and regimens urgently needed to improve TB care will not be developed.

### 2. Sponsors must commit to developing their drugs and making them accessible to other research groups.

For both new and existing drugs, a commitment from sponsors to ensuring rapid drug development is essential. This means investing in the development of compounds with human and financial resources. It entails working with research consortia and other TB drug developers early on to study drugs in combination, both to optimize their use and to make clinical research more efficient. Once new drugs or regimens are approved, sponsors must swiftly fulfill conditions of approval, including further studies and postmarketing surveillance. In particular:

- AstraZeneca should continue to invest in AZD5847 and begin to engage with community groups;
- Janssen must fulfill its postmarketing requirements quickly for bedaquiline, and work to close other research gaps including potential drug-drug interactions with delamanid and other drugs, and dosing and safety concerns in special populations including children;
- Novartis needs to make clofazimine available for TB research studies;
- Otsuka should facilitate the NIH's interaction work with bedaquiline to ensure it advances as quickly as possible;

- Pharmasintez needs to make its full data available for peer review and create a sound, responsible development plan for perchlozone before pursuing further research studies or registration;
- Pfizer must commit to developing sutezolid and making it available to research consortia for developing optimized combinations;
- Sanofi should maintain its support for the TBTC to enable research on rifapentine to continue amid public financial austerity; and
- Sequella should be more transparent and amenable to sharing SQ109 data so its suitability for further development can be appropriately assessed.

### **3. More research is needed in important vulnerable populations.**

TB is a disease of the vulnerable and marginalized, and yet research into important TB-affected communities is scarce or comes too late. TB drug sponsors and researchers must commit to studying TB drugs as thoroughly as possible, and as quickly as safety allows, in children, women (including pregnant women), people with HIV, people with hepatitis B and C, people who use alcohol, and people who inject drugs or are on opioid substitution therapy. Comprehensive drug-drug interaction studies or modeling need to be done with antiretrovirals, with methadone and buprenorphine, with hormonal contraception, and with other TB drugs, as many interact or have overlapping toxicities (such as heart and liver toxicity). Regulatory authorities can play an important role by appropriately encouraging and providing incentives for research in these populations.

### **4. Trial sponsors and implementers should engage TB-affected communities in the design, implementation, and posttrial communications of TB research.**

Community engagement contributes to research that is ethical, efficient, and in the best interests of people affected by the condition being studied. As laid out in the *Good Participatory Practice Guidelines for TB Drug Trials*,<sup>2</sup> communities need to be engaged in the various stages of the development of new interventions, including design, research implementation, results dissemination, and posttrial access. TB-affected communities, including representatives from the special populations mentioned above, must be better included, particularly in key decisions affecting research. Communities should be engaged in trial design to push for efficacy outcomes that will adequately address community needs.

At each step of research, communities must be included to ensure participant safety and health, both during and after trials. In implementation stages, communities can be engaged to help maximize and streamline enrollment and retention. Posttrial, communities can help effectively disseminate results to participants, other advocates, and policy makers. Some sponsors and research consortia have made notable progress in including TB-affected communities in research in recent years, but more needs to be done to solicit and incorporate the perspective of communities, particularly in the design stages, when soliciting input in a timely fashion can actually make a substantive impact.

**5. TB researchers, drug sponsors, and regulators need to collaborate to develop an efficient path for testing new drugs and determining optimal combinations.**

With limited trial-site capacity and scarce financial resources, those involved in TB research should collaborate to determine an efficient way forward for testing new drugs and combinations. More investment in biomarkers and other basic research is required to identify endpoints that can shorten and simplify clinical trials. Researchers and regulators must be innovative and flexible to allow for clinical trial designs that make TB drug development more efficient. The use of promising novel drugs such as bedaquiline needs to be optimized through thoughtful research into combinations. Candidates without demonstrated efficacy, such as SQ109, are not an appropriate use of limited public research funding.

**6. Regulatory authorities must build capacity and expertise to appropriately regulate clinical trials, early access, accelerated approval, postmarketing studies, and pharmacovigilance for new TB drugs and regimens.**

Research and development of new TB drugs are ultimately meaningless if improved treatment options are not approved and available to those who need them. Regulatory agencies—particularly those in high TB burden countries—must scale up their ability to rapidly and carefully review submissions. This is as important in drug registration as it is in clinical research, where study design and drug importation approvals can be unnecessarily lengthy and cumbersome. Russia and the CIS in particular must improve their review process to ensure that studies—especially registration trials—are appropriately designed and conducted, and that only drugs with robust and peer-reviewed data on safety, efficacy, and dosing receive marketing approval. Regulatory authorities must build their capacity to enforce conditions of approval (i.e., drug registries and other postmarketing surveillance, and completion of required further studies).

## **7. National Treatment Programs need to improve their services, supply-chain management, and ability to rapidly adopt and appropriately implement new tools.**

Countries must scale up TB diagnosis and linkage to care, particularly for drug-resistant TB. This includes remedying inadequate forecasting and drug-supply management to prevent stock-outs and address problems with commodity distribution. Programs need to increase their flexibility and capacity to rapidly adopt new drugs and regimens, through both adaptation of guidelines and actual implementation of those guidelines.

## **8. Drug sponsors and manufacturers must make licensed drugs accessible and affordable.**

Drug sponsors and manufacturers have a responsibility to ensure access. When sufficient safety and efficacy data are available, sponsors of promising drug candidates need to provide their compounds through compassionate use or other responsible pre-approval access programs to people who cannot wait for treatment. Sponsors must move quickly to register new drugs in countries where they are needed. Once approved, companies must price drugs affordably, and manufacturers must work to maintain a steady, safe drug supply.

- Janssen should continue to file for approval in a range of countries, and price bedaquiline accessibly;
- Otsuka's compassionate use program for delamanid is overdue and needs to be initiated immediately, as it will likely be over a year until the drug is commercially available;
- Pfizer needs to lower the price of linezolid; and
- Sanofi should immediately lower the price of rifapentine to enable the taxpayers who funded its development to benefit from its implementation.

## **Conclusions**

With a sparse drug pipeline and TB incidence and deaths declining slowly, we are not close enough to realizing the vision of zero TB deaths, new infections, and suffering. Budget cuts, the increase of DR-TB, and scientific challenges all threaten progress. But if donors, sponsors, researchers, regulators, and manufacturers all commit the necessary resources and will, the potential to improve TB care and ultimately end the disease is huge.

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