The Tuberculosis Treatment Pipeline: Activity, but No Answers

By Erica Lessem

In the past year, the development of new tuberculosis (TB) drug candidates experienced some setbacks as well as some wise pruning, with the unexpected suspension of enrollment in STAND (a phase III combination trial that includes the new drug pretomanid), the discontinuation of candidate TBA-354 (due to signs of toxicity), and the official end of development of AZD5847 (due to lack of anti-TB activity). In a bright spot, Qurient's Q203 entered phase I, representing a new drug class and a new sponsor in TB clinical trials. But overall, the new TB drug development landscape remains parched, with just five candidates from four classes in development—including bedaquiline and delamanid, which already have conditional marketing approval in some countries. Most of these drugs have been stalled for years. Delays across the board, from sponsors, from regulators, and from funders, are preventing nascent progress from flourishing. The phase III trial for bedaquiline has finally started enrolling—some five years after the phase IIb trial concluded. Sutezolid is still awaiting entry into phase IIb, nearly five years after showing promise in phase IIa. Delamanid's phase III trial is chugging along dutifully, but, due to the lengthy standard-of-care background treatment and follow-up time required in TB clinical studies, won't give results till 2018.

More activity is ongoing among trials testing combinations of drugs already on the market, often called repurposed drugs. But again, most will not bear fruit for several years. These various trials to optimize therapies point to creativity among researchers but also to the poor existing evidence base for use that has left the TB field reliant upon lengthy, poorly tolerated—and, for drug-resistant TB, marginally effective—regimens. Some exciting advances are being made in preventive therapy for TB—these are now reported in the TB prevention chapter (see page 143)—but this chapter will focus exclusively on the development of treatments for active TB disease.

New guidelines from the World Health Organization (WHO) may help improve the treatment of multidrug-resistant TB (MDR-TB) by updating options for stronger treatments in combination regimens, though the newly recommended putative treatment-shortening approach has yet to be validated in randomized controlled trials. However, the updated WHO guidelines will help increase the use and availability of drugs of greater potency such as delamanid, bedaquiline, clofazimine, and linezolid.[1] MDR-TB treatment is still inadequate, with fewer than 10% of those with the disease successfully treated worldwide, and less than 2% of those who may benefit from new drugs receiving them.[2,3] Investment in new alternatives is also scandalously low; in 2014, just US$243 million out of the needed US$740 million were available for TB drug research and development (R&D).[4] Recent global and national strategic plans to address antimicrobial resistance and TB, such as those from the Netherlands, the United States, and the United Kingdom, must go beyond lip service and be met with financial commitments to increase support for TB R&D.[5,6,7,8] Countries with high TB burdens and large economies, such as Brazil, China, India, Indonesia, Russia, and South Africa, must contribute far more to R&D as well as to service scale-up.

UPDATES ON NEW COMPOUNDS IN DEVELOPMENT

Table 1. Drugs in Development for Tuberculosis

Drug	Class	Sponsor(s)	Phase
bedaquiline	diarylquinoline	Janssen (Johnson & Johnson), TB Alliance, NIAID, SAMRC, the Union, UNITAID, USAID	III
delamanid	nitroimidazole	Otsuka, NIAID, UNITAID	III
pretomanid	nitroimidazole	TB Alliance	III
sutezolid	oxazolidinone	Sequella, NIAID	IIa
Q203	imidazopyridine	Qurient, Infectex	I

NIAID: National Institute of Allergy and Infectious Diseases (United States)
SAMRC: South African Medical Research Council
The Union: International Union Against Tuberculosis and Lung Disease
USAID: The U.S. Agency for International Development

Q203

A new compound, Q203, developed by Qurient, entered clinical testing in late 2015.[9] Q203's phase I, single-dose, dose-escalating study has completed enrollment. Results will be shared in 2017, and phase II trials will likely start then.[10] A member of the imidazopyridine class, Q203 targets the respiratory cytochrome bc1 complex, inhibiting the synthesis and homeostasis of adenosine triphosphate (ATP), thereby crippling the energy conversion system in both replicating and nonreplicating TB bacteria.[11] Q203 brings much-needed diversity to the pipeline and is an important addition to early-stage development as TBA-354 drops out of the running. Qurient is developing Q203 with support from the Korea Drug Development Fund and is partnering with Infectex to develop the drug for Russia and the other Commonwealth of Independent States (CIS) markets.

TBA-354

TBA-354, in the same class of drugs as delamanid and pretomanid (the nitroimidazole class), was the first candidate to enter phase I TB trials in six years, but regrettably, this rising star burned out quickly. After a phase I dose-escalating trial showed an association with mild signs of neurotoxicity (repetitive uncontrolled eye movements and overactive reflexes, from which all affected study participants recovered), the TB Alliance voluntarily placed TBA-354 on hold in January 2016 and announced the discontinuation of its development in March 2016.[12,13] This unfortunate event nonetheless represents responsible stewardship and communication of results, and it reinforces the need for more investment in TB R&D since—as in all disease areas—the majority of early-stage drug candidates will fail, necessitating a variety of compounds in development at a given time.

Pretomanid

The development of another nitroimidazole, pretomanid, has also been hampered—this time by unexpected fatalities that led to a partial clinical hold on pretomanid and a complete hold for the STAND study.[14] This phase III trial was testing the combination of pretomanid (at different doses) along with moxifloxacin and pyrazinamide (PaMZ) in people with drug-sensitive TB (DS-TB) and some forms of MDR-TB; TAG has previously critiqued the design of this trial, particularly its uncontrolled MDR-TB arm and the regimen's expected vulnerability to resistance.[15] Unfortunately, the experimental regimen was associated with high levels of liver

toxicity, which caused the death of three participants, all in the drug-sensitive PaMZ arms of the study. The study's Data Safety Monitoring Committee (DSMC) promptly recommended a suspension in enrollment in September 2015 and, after further analysis, in November 2015 recommended restart of enrollment with the addition of safety procedures and, at least initially, the exclusion of people with HIV.[16] In May 2016, the DSMC completed its review and concluded that full enrollment could resume regardless of HIV status; in May 2016, the Alliance noted it was preparing all necessary regulatory submissions to prepare for resuming enrollment into the STAND trial.[17]

The NiX-TB trial, which is testing pretomanid, bedaquiline, and linezolid in participants with extensively drug-resistant TB (XDR-TB), is faring better—though there is no randomization or control arm in this open-label study. As of March 2016, 37 patients were enrolled, and 14 patients completed treatment. The TB Alliance reports—though data have not yet been peer reviewed or formally presented at a scientific meeting—that four patients have died early on in treatment due to underlying disease, and that all other patients are doing well and showing good clinical response, with the majority having converted their sputum cultures to negative in the first two months of treatment. Linezolid toxicity has been manageable, though some dose interruptions and dose reductions occurred, mainly after week 9. The first formal interim analysis will occur in the third quarter of 2016.[18]

NC-005, a phase IIb trial that is testing the efficacy and safety of two months of bedaquiline (in a simpler dosing scheme than the currently recommended one), pretomanid, and pyrazinamide in about 240 patients with either DS- or MDR-TB, completed enrollment at the end of 2015 and will have results at the end of 2016.[19] The PRACTECAL study, a multiarm, open-label, randomized controlled pragmatic trial from Médecins Sans Frontières (MSF) that will examine various combinations of pretomanid, bedaquiline, moxifloxacin, linezolid, and clofazimine given for six months to people with MDR-TB in comparison to the WHO standard of care, has received ethics and regulatory approval; MSF anticipates opening enrollment in the third quarter of 2016.[20]

Sutezolid

Readers will be dismayed to learn that sutezolid, an oxazolidinone hoped to be a safer alternative to linezolid, is still stuck in phase IIa some three years after Pfizer ended its anti-infectives program and licensed the promising candidate to the small pharmaceutical company Sequella. Sequella has recently called sutezolid a "companion drug" for its probably ineffective compound, SQ109.[21] Sutezolid is, in fact, a candidate in high demand on its own (unlike SQ109, see more in box "Foul Play in the Federation," page 169). Fortunately, the U.S. National Institutes of Health (NIH) will sponsor the manufacture of 15,000 doses of a 600 mg tablet, which should be ready within six months after a protocol for an AIDS Clinical Trials Group (ACTG) study is given the green light. ACTG study A5289 is under development and currently features sutezolid replacing ethambutol in the experimental arm of a two-stage, adaptive study design to evaluate the pharmacokinetics, safety, and initial efficacy of sutezolid over two and eight weeks in people with DS-TB. It would determine an ideal dose for sutezolid, as well as evaluate interactions between rifamycins and sutezolid and its main metabolite.

If the study is approved for implementation, A5289 will trigger sutezolid's long-awaited entry into phase IIb.[22] Sequella and Johns Hopkins (which owns the intellectual property rights for the development of sutezolid in combinations) should turn over intellectual property rights, and Sequella should also release the toxicity and clinical data on sutezolid to date to the Medicines Patent Pool (MPP). Fortunately, it appears Johns Hopkins has entered into negotiations to do so.[23] If Sequella refuses to turn over early data to facilitate collaboration, it will take other interested parties three to five years and several million dollars to reproduce data to move forward with development—wasted time and money that are simply not available given the scarce resources for TB R&D and the urgent need for new compounds.

Bedaquiline

Bedaquiline's use in programmatic settings is on the rise (see table 2), and data described below support the continued expansion of its use. Indeed, the new WHO MDR-TB guidelines better categorize bedaquiline (and delamanid) as agents that can be added on to an MDR-TB regimen to ensure incorporation of five effective drugs.[24]

Data from South Africa's incorporation of bedaquiline first into a clinical access program and then into routine programmatic use indicate the drug's safety, effectiveness, and importance in treating MDR-TB. The bedaquiline clinical access program, which started with just five sites while the Medicines Control Council (MCC) was reviewing bedaquiline's dossier for marketing approval, enrolled 221 patients for whom other treatment options had been exhausted. Data from the full cohort of 221 patients with follow-up will be available in 2017, but an interim analysis of the 91 patients with MDR- or XDR-TB enrolled by July 2014 (60 of whom had completed treatment) showed that 70 percent had culture converted or remained culture negative—an impressive result for these patients with intractable forms of TB, many of whom had HIV infection and low CD4 counts (as opposed to carefully screened clinical trial participants, who are generally healthier and have fewer complications). The South African experience showed that participants with HIV on appropriate antiretroviral therapy (ART) did quite well on bedaquiline, and participants could easily be switched to nevirapine- or lopinavir/ritonavir-based regimens for the duration of their treatment with bedaquiline and then be placed back on the preferred efavirenz-based fixed-dose ART (whose use is contraindicated with bedaquiline due to drug-drug interactions).[25] Notably, lopinavir/ritonavir does increase bedaquiline exposure compared with no ART (median area under the curve 67,002 vs. 34,730 ng·h/mL, P = .003; median time of highest concentration [Tmax] of 6 vs. 4 hours, P = .003; and terminal half-life of 55 vs. 31 hours P = .004), though clinical implications are unknown.[26]

Based on this positive experience, and with the MCC's approval of bedaquiline, the South African Department of Health launched a framework for routine programmatic use of bedaquiline in June 2015.[27] Under this framework, bedaquiline can be used in the public sector without review by the national or provincial program in anyone 18 years or older with pre-XDR-TB (TB that is resistant to either a fluoroquinolone or an injectable, as well as isoniazid and rifampin) or XDR-TB, whose TB shows *InhA* and *KatG* mutations (indicating resistance to isoniazid), who has intolerance to second-line drugs (such as drug-induced hearing loss or psychosis), or who has a history of surgery, as long as he or she has no personal or family history of QT prolongation (a potentially dangerous disturbance in the heart's electrical activity, for which bedaquiline increases the risk). The South African treatment program does allow for people who are under 18, who are pregnant, or who have MDR-TB treatment failure without proven second-line drug resistance to receive bedaquiline per individual case review and approval.

Over 1,000 patients from all but one (Mpumalanga) of South Africa's provinces have now received bedaquiline. The vast majority have XDR-TB (39%) or pre-XDR-TB (40%); 12% received bedaquiline due to intolerance of other drugs, 8% due to *InhA* and *KatG* mutations, and 1% because they were surgical candidates. For the first time, a new TB drug has been added to routine management for MDR-TB, and it is going very well.[28,29] In a separate analysis of the 598 patients who started bedaquiline between March and end of September 2015, the most common reason for denying bedaquiline initiation was having too few potentially effective drugs in the proposed background regimen, pointing to the urgent need for companion drugs such as linezolid and delamanid. Indeed, provinces that quickly scaled up bedaquiline use were those that had linezolid access, as well as those that had tools to detect need for bedaquiline (genotypic second-line drug resistance testing and capacity to detect high-frequency hearing loss).[30]

More data to inform the optimal use of bedaquiline come from a French cohort of patients started on bedaquiline between 2011 and 2013. In this cohort of 45 patients, 33 patients received bedaquiline for longer than six months (the duration that was studied in phase IIb clinical trials and hence the recommended

duration of treatment under conditional approvals and in WHO guidance);[31] some patients received bedaquiline for up to 768 days, with a median of 360 days. Patients receiving courses of bedaquiline for more than six months were more likely to have hepatitis C (58% vs. 17%, $P = .020$), to have been previously treated for TB (94% vs. 25%, $P < .001$), and to have sputum culture-positive TB (97% vs. 75%, $P = .048$). In those who received a standard six-month course of bedaquiline, 75% achieved cure, versus 82% of those receiving a longer course. There were no significant differences in adverse events in the two groups. These findings indicate that prolonged bedaquiline use is well tolerated, at least in this small cohort, and that good outcomes may be partially explained by the decision to extend bedaquiline treatment in select challenging cases. The clinicians from the French program therefore recommend extension of bedaquiline in cases that would have fewer than four effective drugs if bedaquiline were stopped, that have delayed microbiological response (i.e., culture positivity after four months of treatment), and risk factors for poor outcomes (e.g., extensive lung disease, low body mass index, high acid-fast bacilli [AFB] positivity, or HIV), as long as prerequisites such as pharmacovigilance, close monitoring, patient consent, treatment tolerability, and expert opinion are in place.

All countries with MDR-TB burdens should follow France's and South Africa's examples and safely incorporate bedaquiline into their treatment programs. Ministries of health in countries such as India and the Philippines have been negligent in making this drug available to their citizens who so desperately need it: despite registration and availability of the drug and guidelines for its use in country, as of May 31, 2016, neither has started a single patient on treatment under routine programmatic conditions.

Indeed, further research supports the increased use of bedaquiline. A new analysis of the phase II, randomized, double-blind C208 stage 2 study of bedaquiline showed that only two out of ten participants receiving bedaquiline who had either converted or relapsed acquired resistance to companion drugs, versus 16 out of 30 in the background regimen plus placebo arm. No participant developed pre-XDR-TB or XDR-TB in the bedaquiline arm, versus six and two participants, respectively, in the placebo arm. Though the number of participants in this analysis is very small, these data point to bedaquiline's potential ability to protect against the amplification of resistance to other drugs. Notably, one out of ten participants in the bedaquiline arm showed a greater than fourfold increase in the minimum inhibitory concentration of bedaquiline, indicating potential acquired resistance to the new drug, though this does not necessarily correlate with clinically observed lack of drug efficacy.[32] Some clinical cases of resistance to bedaquiline have been reported.[33]

A recent analysis of C209, the phase II single-arm open-label trial of bedaquiline plus background regimen in 233 adults with MDR-TB (including XDR-TB and pre-XDR-TB), showed high rates of culture conversion and good outcomes with bedaquiline, regardless of type of MDR-TB. Of 205 participants included in the modified intention to treat analysis, 40% had pre-XDR-TB or XDR-TB, and 66% had extensive cavitation. Yet outcomes were still good: using a conservative measure of cure (the old WHO definition of five consecutive negative cultures), 61% of participants were cured, and only 16% failed, 7 percent died, and 15% transferred out or were lost to follow-up at 120 weeks after treatment initiation. Of 37 patients with XDR-TB, 23 (62%) culture converted, and all remained culture negative during the trial—though follow-up data were only available for 16 of 23 participants for a median of 5.4 months. In multivariate analysis, cure was associated with newly diagnosed MDR-TB (82% versus 71% cured in previously treated participants, $P < .05$), and with lower AFB score (90% of sputum smear-negative cases had negative cultures by week 120 versus only 52% for participants who had an AFB score of 3, $P < .05$).[34]

The STREAM-II study, which will test bedaquiline in a nine-month injectable-free regimen, as well as a six-month combination, finally started enrolling in March 2016[35]—more than three years since the drug's approval from the U.S. Food and Drug Administration (FDA), which was conditional upon the timely conduct of a phase III trial. Mongolia is the first country to start enrollment; significant MDR-TB clinical trial capacity development for STREAM-II should benefit the field of TB R&D overall. The Union, the study's sponsor,

attributes the delay in the study's start to the greater burden required for a registrational trial (versus the pragmatic design of STREAM-I, described in the next section), including the requirement for export permits and couriering study samples when trial host countries do not have registered laboratories.

Despite these challenges, Janssen—bedaquiline's sponsor—could certainly have committed more resources to speed bedaquiline's entry into phase III, as required by the FDA. The gap between bedaquiline finishing phase IIb and entering phase III spans nearly five years; meanwhile, the paucity of data has contributed to the limited use of bedaquiline. Janssen's legal department has been delaying support for another important and long-awaited study, ACTG study A5343, which will test delamanid and bedaquiline in combination to determine if together they cause unsafe levels of QT prolongation, for which each drug individually increases the risk. Some patients have already been treated with a combination of bedaquiline and delamanid without adverse events; one patient from the Democratic Republic of the Congo experienced no QT prolongation, but a Tibetan patient from living in India did experience asymptomatic increases in QTc from <450 to 486 ms after eight doses of the new drugs. This observed increase was manageable, and no harm to the patient occurred, but it does reinforce the need for more information on the impact of the two drugs together.[36,37] Janssen's lack of urgency on A5343, coupled with its deplorable delays on initiating pediatric research even after receiving public contributions to expedite it (see "Pediatric Tuberculosis Treatment Pipeline," page 181), clearly point to Janssen's plummeting contributions to TB R&D since bedaquiline's approval—for which Janssen received a handsome reward of a priority review voucher as well as substantial tax credits. Janssen is looking into determining a breakpoint for resistance to guide drug susceptibility testing in line with the terms of its conditional FDA approval, though this appears to be scientifically challenging to determine.[38]

Public resources are furthering bedaquiline's research. The NExT study in South Africa, which is testing the drug in a six-month injectable-free regimen, has started enrolling in Cape Town, but bureaucratic delays from the South African Medical Research Council have meant that only one study site is open.[39] Bedaquiline and delamanid will also be tested together and separately as part of nine-month injectable-free regimens in the UNITAID-funded endTB trial, which sponsors MSF and Partners In Health anticipate to begin enrollment in late June or early July 2016.[40]

Delamanid

Delamanid's phase III trial, which started in a much timelier fashion than bedaquiline's (although it was arguably also more urgent, given the poor design of delamanid's phase IIb trial), is in follow-up, with results expected in 2018. These results, though eagerly anticipated for the information they will give about delamanid's safety and efficacy, will not inform the drug's optimal use in combinations, as the study design just adds it to the old WHO-recommended background regimen. The above-noted publicly funded endTB and A5343 trials should provide important information about delamanid's use, as will studies MDR-end (sponsored by the Korean Center for Disease Control to test an injectable-free regimen of delamanid, linezolid, levofloxacin, and pyrazinamide against the current standard of care in people with fluoroquinolone-susceptible MDR-TB, which is currently enrolling[41]), A5356 (the ACTG's study of linezolid and delamanid for MDR-TB), and VTEU (sponsored by the NIH Division of Microbiology and Infectious Diseases to test a delamanid-containing, injectable-free MDR-TB regimen against the standard of care).[42] Otsuka, delamanid's sponsor, which has been the lead private-sector investor in TB R&D for years, is much more advanced than Janssen in terms of its pediatric (see "Pediatric Tuberculosis Treatment Pipeline," page 181) and prevention (see "Tuberculosis Prevention Pipeline," page 143) research.

However, given Otsuka's limited-access strategy (if one can even call it a strategy), only a few hundred people have received delamanid outside of clinical trials, despite the fact that up to two-thirds of people with MDR-TB may benefit from it, according to WHO guidance.[43] Otsuka has finally made some much-needed and long-called-for changes, including allowing for the co-administration of bedaquiline and delamanid

under compassionate use, ending a formal blanket exclusion of pregnant women in the compassionate use program, and including delamanid in the Global Drug Facility catalogue. But this is just the tip of the iceberg, with approvals for delamanid still only in low-TB-burden regions of the European Union, Japan, and South Korea. Submissions are in progress for delamanid in China, Hong Kong, Indonesia, the Philippines, and Turkey.[44] Otsuka has still not filed in the vast majority of high burden countries, including in trial-site countries of Moldova, Peru, and South Africa, and in other countries with large epidemics, such as India. Table 2 provides a direct comparison of how each of the new drugs in phase III is faring on important research and access milestones. Access to bedaquiline and delamanid is particularly important as research continues to highlight the importance of early treatment in interrupting MDR-TB and XDR-TB, given extensive ongoing transmission in households, communities, and hospitals.[45]

Foul Play in the Federation: Unvalidated TB Drugs in Russia

Perchlozone and SQ109—not included in table 1, as there are no peer-reviewed clinical trial data in English to support their efficacy—are bulldozing their way forward into the Russian market. Perchlozone, developed by JSC Pharmasyntez, was approved for the treatment of MDR-TB in Russia in 2012, at a different dose and duration than those studied in the two small trials off which approval was based (see the *2013 Pipeline Report* for more details). It has since been added to the List of Vital and Essential Medicines in Russia, and the Russian Association of Pulmonologists recommends it for empiric TB treatment.[46]

In addition to the uncertain safety and efficacy of perchlozone, its clinical value for the treatment of MDR-TB might be limited because of its mode of action. A recent study demonstrated that perchlozone is a prodrug activated by monooxygenase EthA. This same enzyme activates the second-line drugs ethionamide and prothionamide[47] and is frequently mutated in the dominant MDR clones in Russia, which therefore raises the possibility that significant rates of preexisting resistance to perchlozone might exist due to prior use of ethionamide or prothionamide.[48] Moreover, the recommendation by JSC Pharmasyntez to prescribe perchlozone in combination with prothionamide is questionable.[49] This underlines the importance of a recent call to require the elucidation of resistance mechanisms as part of the approval of new TB drugs, as is already the case for antivirals.[50]

SQ109 appears to be following an equally troubling path. Developed by Sequella, the same company that has been unable to move promising candidate sutezolid forward for the past three years, SQ109 was found to have no discernable antimicrobial or clinical activity when used in combination therapy for drug-susceptible TB.[51] Sequella licensed SQ109 to Russian company Infectex, which conducted a measly but putatively registrational trial of 80 patients.[52] Despite the lack of a proper and robust trial, and no generation of peer-reviewed data or plans to do so, Sequella announced that SQ109 will be registered in Russia this year.[53]

The use of unvalidated drugs carries great costs to the patient, society, and the economy. Perchlozone's safety is unclear, its efficacy is unvalidated and may be impeded by known preexisting drug resistance, and its price tag of US$1,458 for three months is hefty.[54] SQ109, though probably safe, has no evidence of efficacy, is likely to also add substantial costs to treatment, and could endanger lives if it is used instead of a more effective drug. The use of these drugs is not only unwarranted but dangerous. Pharmasyntez, Infectex, and Sequella are each acting unethically in pursuing marketing approval before clinical evidence supports doing so. Roszdravnadzor, the Russian regulatory authority, is failing to protect public health and urgently needs to change its policies to end, rather than encourage, poor science and indiscriminate marketing. On a troubling note, Qurient, sponsor of the above-mentioned Q203, has also arranged to partner with Infectex for Russia and the other CIS countries and should be extremely careful to ensure an ethical and scientifically rigorous approach to the development of this important new compound.

Table 2. Research and Access for Late-Stage New Compounds

	Bedaquiline	Delamanid	Pretomanid
RESEARCH			
Pediatrics (see Pediatric TB Treatment, page 181)	Enrollment started May 2016	Trial started June 2013; delamanid appears safe in children age 6 and up, with further results from younger age groups expected 2017	Trial not yet started (further toxicology work pending)
Phase III trial	Enrollment started March 2016	Enrollment completed November 2013; results expected 2018	Enrollment in STAND trial started February 2015; on hold since September 2015
Latent TB infection trial (see TB Prevention, page 143)	None	Feasibility study successful; PHOENIx trial expected to start later in 2016	n/a
ACCESS			
Number of patients receiving drug under programmatic conditions	6,000 treatments shipped (as of April 2016)	1,100 treatments shipped (as of May 2016)	None
Pre-approval access programs	Started Q1 2011, ended Q3 2015; >800 patients from 47 countries enrolled	Started Q1 2014; ongoing	None
Expanded access trials	Started 2011 in Lithuania, Russia (application in China denied)	None	None
Approvals	2012: United States 2013: Russia 2014: EU, Peru, Philippines, South Africa, South Korea 2015: Armenia, India, Turkmenistan, Uzbekistan, Macau (import license)	2014: EU, Japan, South Korea 2016: Hong Kong	None (not pursuing accelerated approval; waiting for phase III combination trial completion)
Additional registrations pending	Azerbaijan, Bangladesh, Belarus, Brazil, Burundi, Cameroon, China, Colombia, Ethiopia, Ghana, Hong Kong, Indonesia, Kazakhstan, Kenya, Mexico, Moldova, New Zealand, Rwanda, Switzerland, Taiwan, Tanzania, Thailand, Uganda, Vietnam Note: Kyrgyzstan rejected due to lack of phase III data	Turkey (submissions in progress for China, Philippines, Vietnam)	None
WHO Essential Medicines List inclusion	Included (April 2015)	Included (April 2015)	n/a
Pricing	Tiered pricing by country income level plus donation program (treatment course price: high US$26,000; middle US$3,000; low US$900); 30,000 treatment courses donated to Global Fund–eligible countries	US$28,000–$33,000 in Europe; US$1,700 in Global Fund–eligible countries	n/a (note: nonprofit TB Alliance has affordability commitment)

EU: European Union; WHO: World Health Organization
n/a: not applicable as has not yet received marketing approval

OPTIMIZING THE USE OF APPROVED AND REPURPOSED DRUGS

Rifamycins

The quest for optimizing the use of rifampin, one of the most potent TB drugs and a backbone of DS-TB treatment, continues with several studies planned and underway to test much higher doses than the current standard 10 mg/kg. A two-month study to increase the dose to 15 or 20 mg/kg showed no significant increase in adverse events (no grade 4 liver enzyme increases; rates of grade 3 increases in liver enzymes were 1% in 10 mg/kg arm vs. 2% in the 15 mg/kg arm vs. 4% in the 20 mg/kg arm, P = .15).[55] Increasing the dose of rifampin to correct what is likely current underdosing may help reduce the pervasive resistance to this important drug. A recent interesting, if unvalidated, artificial model has shown rifampin is excellent at penetrating TB lesions, a breeding ground for bugs in people with cavitary TB disease.[56] If the model and the hypothesis that drug penetration improves outcomes are accurate, this may also help explain the widespread emergence of rifampin resistance, as the lack of penetration of other drugs means rifampin is effectively given as monotherapy.

Rifapentine, also in the rifamycin class, is the linchpin of shortened treatment for latent TB infection (see "TB Prevention Pipeline," page 143), and is now being studied by the Tuberculosis Trials Consortium (TBTC) and ACTG in Study 31/A5349 for its potential—with or without moxifloxacin—to shorten DS-TB treatment to four months.[57] Study 31 has started enrollment in Fort Worth, Hanoi, Hong Kong, Kampala, Port-au-Prince, and Soweto, but is behind schedule due to bureaucratic and regulatory delays. Additional funding for the TBTC, whose budget has either been cut or flatlined for the past several years, is critical to allow for timely enrollment and important additional activities such as biobanking at TBTC sites to gather as much useful data as possible from the study. In the meantime, additional funding for Study 31/A5349 from the NIH via the ACTG will support enrollment and allow for biobanking at ACTG sites.

One notable study, TRUNCATE-TB, aims to reduce treatment for most people with DS-TB to two months, using combinations of new and repurposed drugs, including the rifamycins. The approach taken in this trial is to allow larger proportions of patients to fail initial therapy than would otherwise be tolerated in conventional trials but treat again those who are not cured. The primary endpoint is the proportion cured at two years, whether or not they required additional treatment following relapse. By definition, this will result in a greater degree of illness in a number of participants but will benefit those who are cured quickly with shorter treatment durations. This is a philosophical shift from historical TB trials, which have aimed to cure as many patients as possible and do not tolerate relapses, which usually require longer treatment durations. The randomized controlled TRUNCATE-TB trial will examine four two-month regimens, compared with the standard DS-TB treatment. Experimental regimens involve an arm with high-dose rifampin (35 mg/kg), linezolid, isoniazid, pyrazinamide, and ethambutol; a second arm that is the same but substituting clofazimine for linezolid; a third arm that uses rifapentine, levofloxacin, linezolid, and pyrazinamide; and a fourth arm that has bedaquiline, linezolid, isoniazid, pyrazinamide, and ethambutol. TRUNCATE-TB has complete protocol and ethics committee approvals in the United Kingdom and Singapore and should begin enrollment by the end of 2016. Planned trial site countries include Indonesia, the Philippines, Thailand, Vietnam, and China (if regulators allow it).[58]

Fluoroquinolones

Fluoroquinolones are arguably the most important element in MDR-TB treatment; resistance to fluoroquinolones greatly increases the likelihood of a poor outcome.[59] As such, several studies for MDR-TB continue to use fluoroquinolones. A recent randomized controlled trial in Korea compared treatment outcomes from levofloxacin or moxifloxacin and found they had similar treatment success rates (84.4% vs.

79.7%, P = .53 [a nonsignificant difference]), though rates of musculoskeletal adverse events were higher in those receiving levofloxacin (37.7% vs. 14.9%, P = .001).[60] Because moxifloxacin causes higher QT prolongation than levofloxacin, knowing levofloxacin has comparable efficacy is very useful in designing regimens with other QT-prolonging drugs, such as bedaquiline and delamanid. The Opti-Q study, sponsored by Boston University and the U.S. National Institute of Allergy and Infectious Diseases, is exploring the best dose for levofloxacin and should have results in 2018.[61,62]

Moxifloxacin is being used in the STREAM-I trial, a nine-month regimen for MDR-TB based on the modified Bangladesh regimen of multiple existing drugs (described in previous *Pipeline Reports*), including an injectable and clofazimine. Follow-up is ongoing; in the meantime, this regimen has received WHO endorsement for use in previously untreated patients with rifampicin-resistant TB or MDR-TB.[63] The recommendation is based on observational cohort data, with very low certainty in the evidence, calling into question the rationale for and the objectivity of recommending this regimen. Randomized controlled clinical trial data are essential for understanding how well this regimen truly works in the indicated population, and scale-up of drug susceptibility testing (see "TB diagnostics pipeline," page 129) must accompany shortened regimen rollout. However, given that the brutal 18–24-month standard of care for MDR-TB has also not been validated in randomized controlled clinical trials and is very difficult for patients, many may be eager for access to a shortened regimen.

Also controversially, gatifloxacin, used in the original Bangladesh regimen and then abandoned due to safety concerns, recently received endorsement in the new WHO MDR-TB treatment guidelines. [64] Like levofloxacin, gatifloxacin has less risk of QT prolongation than moxifloxacin, and observational studies and the OFLOTUB trial did not indicate safety issues (though in the trial the drug was only given for four months).[65] While more drugs in the arsenal to treat TB are helpful, re-adding gatifloxacin is confusing for countries and further fragments the challenging market for MDR-TB drugs, especially because there is no current quality-assured source of gatifloxacin due to its withdrawal from the market over safety concerns and because supporting evidence is of very low quality.

Because of the fluoroquinolones' good activity against TB, they continue to be examined for shortening treatment for DS-TB, for example in the above-mentioned TBTC Study 31 and as part of TRUNCATE-TB.

Of note, the FDA has recently recommended against the routine use of fluoroquinolones for more minor infections such as acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections when other treatment options exist, noting that because of serious side effects, the harms outweigh the benefits, so for these conditions, fluoroquinolones should be reserved for those without alternative treatment options.[66] This does not apply to MDR-TB and DS-TB, which are certainly more serious conditions, but does again point to the need for safer, better treatment options more generally for TB.

Clofazimine

Clofazimine, a riminophenazine long used for the treatment of leprosy and off-label for MDR-TB, is finally moving toward formal evaluation for TB in randomized controlled trials. Novartis has planned study CLAM320B2202, a phase IIb/III randomized, open-label trial to evaluate the efficacy and safety of clofazimine (at 200 mg once daily for six months followed by 100 mg once daily for the remaining 12 to 18 months of treatment) plus background regimen compared with background regimen alone in people with MDR-TB. Enrollment was anticipated to start in March 2016 but is now projected to start in April 2017.[67] The ACTG is planning a phase IIc study of clofazimine, added to standard therapy with a treatment duration of four months, for DS-TB. Clofazimine also plays an important role in the above-mentioned ongoing and planned PRACTECAL, STREAM-I, STREAM-II, and endTB studies.

The new WHO MDR-TB treatment guidelines recognize clofazimine's and linezolid's importance, elevating them as "core second-line agents" on par with cycloserine/terizidone and ethionamide/prothionamide and preferable to para-aminosalicylic acid for constructing a regimen.[68]

Linezolid

Linezolid, of increasing importance for MDR- and XDR-TB, has manageable but nonetheless challenging side effects, including painful nerve damage. The TB Alliance examined the early bactericidal activity (EBA) of linezolid over two weeks as part of its efforts to determine an ideal dose and dosing schedule for linezolid to support the above-mentioned NiX-TB trial. The study found that all daily doses, from 300 mg to 1,200 mg, given as either once-daily or twice-daily doses, demonstrated EBA, and there was a statistically significant dose response from 300 mg to 1,200 mg daily, indicating that higher doses provided greater activity, with no difference between once- and twice-daily dosing for the same total daily dose. As a result, the TB Alliance has changed the NiX study dosing of linezolid from 600 mg twice to 1,200 mg once a day.[69] Mouse model data suggest that linezolid may only be needed for one to two months, which might also be worth exploring in clinical trials.

As noted previously, linezolid availability is critical to the successful rollout of bedaquiline. One-year posttreatment outcome data from a small clinical trial of linezolid in South Korea whose four-month sputum-culture conversion data were previously reported further indicate that linezolid is an important drug for treating XDR-TB. Of 38 patients receiving linezolid, 27 had negative results on sputum culture one year after treatment end, 3 were lost to follow-up, and 8 withdrew from the study (including 4 who failed on linezolid treatment, as previously reported). Of the 27 participants completing the study, 4 had a dose reduction from 600 to 300 mg. Among 13 participants assigned to continue receiving 600 mg, 9 had to reduce the dose to 300 mg due to adverse effects. All serious adverse events resolved after the discontinuation of linezolid. Though the study design was questionable, as linezolid was effectively given as monotherapy, only 4 out of 38 participants, or 11% of those receiving linezolid, developed resistance to linezolid. In total, 27 of 38 patients (71%) with chronic XDR-TB were cured at one year after termination of treatment.[70]

To inform the use of linezolid for people with HIV on ART, a retrospective study of linezolid use for the treatment of pre-XDR-TB and XDR-TB in people with HIV in Khayelitsha, South Africa, and Mumbai, India, showed that the rate of culture conversion in patients treated with linezolid is better than previously reported among XDR-TB cohorts and that people with HIV on ART were able to tolerate prolonged linezolid exposure, adding to the body of evidence supporting linezolid's use in challenging cases.[71] Recent efforts to increase generic competition and bring down prices for linezolid in South Africa have been successful thanks to strong advocacy.[72] The Global Drug Facility has announced a 70% decrease in the price of linezolid.[73]

Carbapenems

Carbapenems such as meropenem and imipenem are beta-lactams—antibiotics with a good safety profile and low potential for interaction with antiretrovirals. Historically, they have received little attention for TB because of the high intrinsic resistance of mycobacteria to these drugs, although this can be overcome with the addition of amoxicillin/clavulanate.[74] Carbapenems have been used more frequently due to the need for companion drugs for bedaquiline. A recent proof-of-concept randomized controlled study gave two kinds of carbapenems—orally available faropenem (at 600 mg three times a day) or intravenous meropenem (at 2 g three times a day)—or the standard of care for 14 days to people (15 in each arm) with untreated, DS-TB. This study found that faropenem had no detectable EBA: estimated fall in $\log_{10}$ colony-forming units was 0.00 (95% confidence interval [CI]: −0.002 to 0.002, P value vs. control < .001), likely due to the very low exposures to the drug measured in in blood during the trial. In contrast, meropenem had good EBA, with a

fall in $\log_{10}$ colony-forming units of 0.11 (95% CI: 0.009 to 0.13) versus the control's 0.17 (95% CI: 0.15 to 0.19), though the control was still significantly better ($P < .001$).[75] Meropenem use was not associated with any grade 3 or 4 events (compared with four in the control arm and three in the faropenem arm). Diarrhea was observed frequently in both the meropemen and faropenem arms, likely from the amoxicillin/clavulanate. The study's findings indicate the need for further optimization of the use of this class for TB, including determining whether amoxicillin/clavulanate is necessary, reducing dosing to once or twice daily, prioritizing the development of orally bioavailable carbapenems, and testing faropenem medoxomil (an unapproved formulation that may have higher exposures and EBA against TB than faropenem alone) for use against TB.

Ertapenem, another carbapenem, may merit further study. A recent retrospective study in the Netherlands of 12 patients who received ertapenem as part of their treatment between 2010 and 2013 and in whom drug exposure was evaluated showed that ertapenem was well tolerated and had a favorable pharmacokinetics/pharmacodynamics profile in people with MDR-TB. Though not orally available, ertapenem requires only once-daily dosing, in contrast to meropenem's thrice-daily dosing.[76]

RECOMMENDATIONS

1. **Government agencies, pharmaceutical companies, and foundations must dramatically scale up funding for TB R&D.** In line with the third pillar of the WHO's End TB strategy, which calls for R&D, countries must commit more resources to TB drug development.[77] The U.S. government, which is the leading funder of TB R&D, should increase funding levels to $300 million by 2018 to keep its critical investments at pace with inflation. TAG suggests that this should entail an additional $17 million from the NIH, $15 million from USAID, $16 million from the U.S. Centers for Disease Control and Prevention, and $5 million from the FDA for TB R&D.[78] European Union countries, particularly Germany, should double their TB R&D funding, and Brazil, China, India, Russia, and South Africa should each triple their funding for TB R&D.[79] Activists in other countries should call for commensurate increases in their own settings.

   Companies such as Otsuka and Sanofi should maintain strong levels of investment, and Janssen needs to recommit to further developing bedaquiline, as significant work remains despite bedaquiline's conditional approval, and to moving the most promising of its pipeline of bedaquiline analogues further toward clinical study. Other pharmaceutical companies and philanthropic organizations should also begin to invest in TB R&D.

2. **Donor and high-TB-burden governments should create and invest in mechanisms that build access to TB drug development, and drug developers should participate in them.** The inability to access data hampers collaborative TB drug development, which is essential because TB must be treated with a combination of drugs to prevent the development of resistance. The inability to access drugs hampers TB treatment and cure and threatens to render the limited R&D that is occurring less useful. Fortunately, members of the TB community have proposed feasible and appealing solutions that should be actively pursued. These include remedying loopholes in the FDA's priority review voucher system to ensure innovation and drug availability and fair pricing[80] and should also entail product developers licensing their compounds to and sharing data with the MPP, which recently received a mandate to work on TB drug development and could possibly play a key role in brokering combination drug development.[81] MSF's proposed 3P ("Push, Pull, Pool") project may also provide an interesting, innovative, and potentially transformative approach to spur the development of regimens and ensure their availability post-approval, though the devil here will lie in the details of how it is actually executed.[82]

3. **Drug and trial sponsors must expedite the development of preclinical and clinical candidates.** Delays in TB research and development are widespread and atrocious. The TB drug development pipeline remains frighteningly sparse, pointing to the urgent need to advance preclinical work to allow viable candidates into clinical studies. Clinical development for the few products in the pipeline has been unacceptably slow, with drugs taking over five years to advance from one stage to the next. In particular, Janssen's and Sequella's failures to rapidly move bedaquiline and sutezolid, respectively, through important studies are deplorable.

4. **Ministries of health, regulatory authorities, and ministries of finance should prioritize the timely introduction of evidence-based TB treatment, and donors and providers of technical assistance should ensure they are supporting rather than hindering scale-up.** Drug development will not affect the TB epidemic and improve the lives of people affected by TB unless new interventions are available to communities and people who need them. Unfortunately, country-level demand for important new products such as delamanid and bedaquiline has been weak, and implementation slow. USAID, which has partnered with Janssen to make bedaquiline available via a donation program, literally cannot give the drug away for free to enough people. Poor advice from technical assistance providers has worsened the situation and excused complacency. All parties, national and global, must be much more ambitious and supportive of new ways to find and treat TB.

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