The Tuberculosis Treatment Pipeline: Moving Beyond "Making the Most of What We've Got"

by Erica Lessem

For decades, those living with tuberculosis (TB) and their providers have operated in conditions of scarcity and neglect: inadequate funding for programs and research, aging infrastructure and outdated technologies, limited scientific understanding, knowledge gaps on existing treatments, low public attention, and absent political will.

The limited response to TB born of these conditions remains entrenched, even with two new drugs conditionally approved by stringent regulatory authorities,[1,2] a new global strategy to end TB from the World Health Organization (WHO) that envisions a world free of TB (with a 95% reduction in TB deaths and 90% reduction in TB incidence by 2035 compared with 2015 levels),[3] and a relative increase in resources for TB drug development since 2006.[4] (Though funding for TB research and development [R&D] is still grossly insufficient, investments in TB drug research, which amounted to US$255 million in 2013, have reached just one-third of the annual target set by the *Global Plan to Stop TB, 2011–2015*.[5])

To their credit, TB treatment researchers are making the most of what they have, cobbling together combinations and treatment strategies to better use existing medicines and the few new and experimental drugs available, as well as exploring adjunct, host-directed therapies to improve treatment. For the first time since 2009, a new drug candidate recently entered phase I (see table 1).[6] Studies are at last under way or coming together to test new drugs in smarter combinations to determine the safety of coadministration and optimal regimens for multidrug-resistant TB (MDR-TB). Innovative trial designs are attempting to shorten treatment for drug-sensitive TB (DS-TB), and improved preventive therapy for TB, including for MDR-TB, is progressing.

But for the most part, these research efforts won't bear fruit for years. Drug sponsors are slow or unwilling to collaborate, pharmaceutical investment is minimal, and TB treatment trials remain lengthy. This work should have advanced long ago – but better late than never.

Table 1. Drugs in Development for Tuberculosis

Drug	Class	Sponsor(s)	Phase
delamanid	nitroimidazole	Otsuka, NIAID, UNITAID	III
pretomanid	nitroimidazole	TB Alliance	III
bedaquiline	diarylquinoline	Janssen, TB Alliance, NIAID, SAMRC, the Union, UNITAID, USAID	IIb/III
AZD5847	oxazolidinone	AstraZeneca, NIAID	IIa
sutezolid	oxazolidinone	Sequella	IIa
TBA-354	nitroimidazole	TB Alliance	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

In the meantime, TB programs, donors, multilateral agencies and nongovernmental organizations providing technical assistance, and pharmaceutical companies have been halting and unambitious in rolling out available strategies and new technologies. Nearly half a million people develop MDR-TB a year, yet less than

one in three is diagnosed, and only one in five starts treatment.[7] According to estimates based on WHO guidelines, bedaquiline or delamanid is clinically appropriate for a third of those who develop MDR-TB (160,000 people per year).[8] Yet despite bedaquiline's being approved for two-and-a-half years, fewer than 1,000 people worldwide have received it outside of a clinical trial.[9] A bedaquiline donation program that opened in April 2015 could improve access if implemented properly, though drug donations are by definition a limited and unsustainable approach.[10] Access to delamanid has been far worse, with fewer than 200 patients receiving it outside of studies, even though it was approved over a year ago.[11] TB drug research and programming alike need an infusion of urgency, coordination, and funding.

Regulatory Spotlight

Regulatory hurdles are one of the major barriers to obtaining medicines for people with TB and the providers who treat them; they can also delay research. In the United States, where the FDA is relatively well equipped to review trial proposals and new drug applications in a timely and rigorous fashion, a lack of flexibility and high fees have discouraged registrations of generic drugs, contributing to drug shortages by leaving the market dependent on a limited number of suppliers. Globally, regulatory inefficiencies plague most regions, countries, and disease areas. China offers an extreme example, with over 18,500 drugs in line for approval at the end of 2014 and wait times of six to eight years.[29] Reviewing research proposals can take years, delaying trial starts and at times derailing studies completely. These general delays, due largely to weak regulatory infrastructure, tend to be exacerbated in TB, where decades without new drugs for approval have left regulators with no experience in evaluating new TB drugs. Submitting applications to multiple national regulatory authorities, with long wait times and varying requirements for data presentation and language of submission, is onerous and resource-intensive. Efforts toward regional harmonization, such as in the East African Community, are welcome.[30]

In spite of these concerns, drug sponsors can and must do more to ensure access to TB drugs. If companies do not file for drug approval in a country, there is no consistent, universal mechanism for access. Work-arounds such as pre-approval access or import waivers are limited in scope, cumbersome, inefficient, and unsustainable. Otsuka has filed for registration of delamanid only in Europe, Japan, and South Korea, where very few patients with MDR-TB live. It still has not registered the drug in any of the high–MDR-TB burden countries that housed its clinical trials (Moldova, Peru, the Philippines, and South Africa), despite sustained international advocacy campaigns to do so. Otsuka notes that additional applications are pending in China, the Philippines, Indonesia, and the United States.[31] Janssen, in contrast, along with Pharmstandard (the Russian company to which Janssen licensed bedaquiline for marketing in the former Soviet republics known as the Commonwealth of Independent States) has made progress in registering bedaquiline in far more countries with high burdens of MDR-TB (see table 3). Manufacturers of older and off-label drugs used to treat TB such as rifapentine, linezolid, and clofazimine must do more to widely register their drugs and seek an indication for TB.[32]

At the same time, the WHO, UNITAID, the Global Fund, the Stop TB Partnership's Global Drug Facility (GDF), and others can support these efforts by providing technical support to regulatory authorities, ministries of health, and TB programs. The WHO can also include clofazimine on the Model List of Essential Medicines, as it recently did for bedaquiline, delamanid, and linezolid after advocates, drug sponsors, Médecins Sans Frontières/Doctors Without Borders, and the Global TB Program of the WHO itself called for their inclusion.[33,34]

TB Infection

Table 2. Tuberculosis Infection Clinical Trials

Study/Regimen	Status	Population	Sponsor(s)
A5279 Self-administered daily rifapentine + isoniazid for 1 month (vs. isoniazid daily for 9 months) NCT01404312*	Fully enrolled	People with HIV with positive skin test/IGRA or living in high-TB-prevalence regions	ACTG
A5300/Phoenix 6 months daily levofloxacin (vs. isoniazid)	Protocol development	Household contacts (adults, adolescents, and children ≥2 years) of individuals with MDR-TB	ACTG, IMPAACT
iAdhere (S33) Self-administered once-weekly rifapentine + isoniazid for 12 weeks (with and without electronic reminders) NCT01582711*	Completed	Adults with TB infection	TBTC
4R vs. 9H 4 months daily rifampin (self-administered) NCT00931736*	Fully enrolled	Adults with positive skin test or QuantiFERON-TB blood test, including people with HIV not on ARVs whose efficacy is reduced by rifampin	McGill University, CIHR
V QUIN 6 months daily levofloxacin (vs. placebo)	Protocol development	Household contacts (adults, adolescents, and children down to 3 kg) of individuals with MDR-TB	NHMRC, Vietnam National Treatment Program
I2001 12 weeks of supervised weekly rifapentine + isoniazid	Beginning enrollment Q3 2015	Pregnant women at high risk of TB	IMPAACT

*Clinicaltrials.gov identifier; for more details, see http://www.clinicaltrials.gov.
ACTG: AIDS Clinical Trials Group, U.S. National Institute of Allergy and Infectious Diseases
ARVs: antiretrovirals
CIHR: Canadian Institutes of Health Research
IGRA: interferon gamma release assay – QuantiFERON-TB Gold In-Tube (QFT) or T-SPOT TB test
NHMRC: National Health and Medical Research Council (Australia)
IMPAACT: International Maternal Pediatric Adolescent AIDS Clinical Trials Group
TBTC: Tuberculosis Trials Consortium, U.S. Centers for Disease Control and Prevention

Preventing TB requires infection control to avert transmission and preventive therapy for subclinical TB infection (often referred to as latent TB infection, or LTBI, as it is asymptomatic and is not transmissible), as an improved vaccine is years away (see "Tuberculosis Vaccines Pipeline," p. 163). Modeling demonstrates that rapidly reducing TB incidence and death on the path to elimination depends on treating both active TB disease and TB infection.[12] With an estimated one-third of the world's population infected with TB, we need a much better understanding of who is most at risk of progression from TB infection to active TB disease to target prevention efforts.

Meanwhile, efforts advance to refine prevention strategies. In 2014, the WHO issued refreshingly clear and concise guidelines on testing for and treating TB infection.[13] The guidelines recommend as equivalent six months of daily isoniazid, nine months of daily isoniazid, and three months of weekly rifapentine plus isoniazid. Two additional regimens received a majority vote for WHO recommendation but did not receive consensus from the panel: three to four months of isoniazid plus rifampin daily and three to fourth months of

rifampin alone daily. This last regimen is already recommended by the U.S. Centers for Disease Control and Prevention (CDC) in patients who cannot tolerate isoniazid or have been exposed to isoniazid-resistant TB.[14] A phase III clinical trial comparing four months of daily self-administered rifampin with nine months of daily self-administered isoniazid in adults has completed enrollment; results are expected in 2016.[15]

In the United States, the regimen of 12 once-weekly doses of rifapentine plus isoniazid, also known as 3HP, is being rolled out after having been demonstrated to be noninferior to the standard nine months of isoniazid alone when given as directly observed therapy.[16,17] In 2014, the U.S. Food and Drug Administration (FDA) approved rifapentine's indication for treatment for TB infection when given with isoniazid to people ages two years and over.[18] Research is examining the role of a historic price reduction in increasing access to this regimen in the United States.[19]

Tuberculosis Trials Consortium (TBTC) Study 33, the iAdhere trial, sponsored by the CDC, found that adherence to self-administered 3HP, with or without text-messaging reminders, was not equivalent to supervised treatment (noninferiority was not demonstrated). But among the large subset of participants enrolled in the United States, self-administered treatment was noninferior.[20] Treatment completion among U.S. participants was 85.4% (95% CI: 80.4%–89.4%) under directly observed therapy and 77.9% (95% CI: 77.2%–82.6%) under self-administered therapy, which was deemed noninferior. In the United States, treatment completion was only 76.7% (95% CI: 70.9%–81.7%) under self-administered therapy with electronic reminders, which did not achieve noninferiority. Overall treatment completion (including sites in China, South Africa, and Spain[21]) was 87.2% (95% CI: 83.1%–90.5%) under directly observed therapy, 74.0% (95% CI: 68.9%–78.6%) by self-administered therapy, and 76.4% (95% CI: 71.3%–80.8%) by self-administered therapy with electronic reminders, failing to meet noninferiority margins.

This divide in results between the United States (a low-incidence, high-income country) and high-incidence countries such as China and South Africa mirrors a broader split in the approach to preventive therapy for TB. While shortened regimens such as 3HP may confer advantages in some settings, it is unclear if shorter treatment is an advantage in settings with high rates of transmission such as mines in South Africa, as the protective effects of preventive therapy last only for the duration of treatment.[22] Rifamycin-based shorter or intermittent treatment may also not be particularly desirable in people already on daily antiretroviral therapy (ART), especially when direct observation for the TB treatment is required and rifampin and rifapentine interact with some ART components, such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[23]

The WHO guidelines further this divide in strategies for treating TB infection. These guidelines differ in recommendations for high- and upper-middle income countries with lower TB incidence (<100/100,000) and for resource-limited or other middle-income countries. According to the guidelines, the former should systematically test for and treat TB infection in people living with HIV, adult and child contacts of individuals with pulmonary TB, and patients on tumor necrosis factor alpha (TNFα) treatment, on dialysis preparing for organ transplantation, or with silicosis. Resource-limited countries should systematically test for and treat TB infection in people living with HIV and in children under five years old, in whom active TB has been ruled out, who are close contacts of people with TB.

The recently completed Temprano study, conducted in Côte d'Ivoire, had two exciting findings regarding TB prevention in people with HIV. First, among those whose CD4 counts were higher than the original WHO cut-off point of 500 cells/mm^3,[24] starting ART immediately reduced the risk of death and serious HIV-related illness, including TB, by 44% (2.8 vs. 4.9 severe events per 100 person-years; P = .0002). Second, six months of isoniazid preventive therapy independently reduced the risk of severe HIV morbidity by 35% (3.0 vs. 4.7 severe events per 100 person years; P = .005) with no overall increased risk of other adverse events.[25] These results warrant an update to the WHO guidelines: they should emphasize the importance of earlier ART initiation and treatment of TB infection in those with HIV as long as active TB disease is ruled out (even in the absence of testing for TB infection).

Evidence-based strategies for preventing infection with MDR-TB from progressing to active disease are urgently needed. The long-awaited A5300 or Phoenix study is moving slowly through midstage protocol development and approval within the AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT). The study will evaluate the efficacy of levofloxacin compared with isoniazid in preventing TB disease in adults, adolescents, and children in households with a case of active MDR-TB. A related protocol, TB CHAMP (see "Momentum in the Pediatric Tuberculosis Treatment Pipeline," page 137), will compare levofloxacin versus placebo in children five years and younger.[26] A third study, V QUIN, will look at six months of levofloxacin versus placebo in Vietnamese adult, adolescent, and child household contacts of individuals with MDR-TB; enrollment is expected to start in the second half of 2015.[27,28] These will be the first three large-scale clinical trials to build a much-needed evidence-based approach for managing TB infection in those with close contact with someone with MDR-TB. If currently ongoing adult and pediatric trials continue to support delamanid's safety, the ACTG and IMPAACT should work with Otsuka to conduct a similar study using delamanid-based preventive regimens.

Table 3. Research and Access for Late-Stage New Compounds

	Bedaquiline	Delamanid	Pretomanid
RESEARCH			
Pediatrics (see "Momentum in the Pediatric Tuberculosis Treatment Pipeline," p. 137)	Trial not yet started	Trial started June 2013; results expected 2017	Trial not yet started (further preclinical toxicology work pending)
Phase III trial	Trial not yet started (two arms to be added to STREAM trial July 2015)	Enrollment completed November 2013; results expected 2017	STAND trial initiated February 2015; results expected 2018
ACCESS			
Compassionate use program	Started Q1 2011 660 patients enrolled (as of June 5, 2015)	Started Q1 2014 >23 patients enrolled (as of June 4, 2015)	None
Expanded access trials	Started 2011 in Lithuania, Russia (application in China denied)	None	None
Approvals	United States (2012), Russia (2013), European Union (2014), South Africa (2014), South Korea (2014), the Philippines (2014), Peru (2014), India (2015)	Europe (2014), Korea (2014), Japan (2014)	None (not pursuing accelerated approval; waiting for phase III trial completion)
Additional registrations (decision pending)	Armenia, Azerbaijan, Bangladesh, China, Colombia, Georgia, Indonesia, Kazakhstan, Kyrgyzstan, Taiwan, Thailand, Turkmenistan, Uzbekistan, Vietnam	None	None
World Health Organization Essential Medicines List inclusion	Included (April 2015)	Included (April 2015)	N/A
Pricing	Tiered pricing by country income level (per-pill price: high US$159.57; middle US$15.96; low US$4.79); 30,000 treatment courses donated for free	Tiered pricing by country income level (per-pill price US$78 in the United Kingdom and US$111 in Japan; low- and middle-income country details unannounced)	N/A (note: nonprofit TB Alliance has affordability commitment)

N/A: not applicable

Active TB Disease

For the first time in six years, a new drug candidate for TB has entered phase I clinical trials.[35] TBA-354, the newest nitroimidazole under study, is in the same class of drugs as delamanid and pretomanid (formerly PA-824).

Little progress has been made on other early-stage candidates. For example, there is still no evidence to suggest that SQ109 has clinical activity in persons with TB disease. In preliminary results presented at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI), the PanACEA MAMS-TB-01 trial indicated no benefit in time to stable culture conversion over 12 weeks of including SQ109 rather than ethambutol in standard therapy for drug-sensitive TB (median 63 vs. 62 days; adjusted hazard ratio 0.82; 95% CI: 0.55–1.24; P = .35). Even when SQ109 was given with double the standard dose of rifampin, there was no apparent advantage in time to culture conversion over standard therapy (median 66 vs. 62 days; adjusted hazard ratio 0.73; 95% CI: 0.48–1.13; P = .16). Final clinical outcomes from this study are still pending.[36]

The resulting small number of plausible new compounds (six) and narrow diversity of new drug classes (two, as linezolid from the oxazolidinones is already on the market) for TB treatment remain a serious concern (see table 1).

For most of these products, progress remains glacially slow. Since Pfizer's abandonment of TB R&D and its decision to license sutezolid (an oxazolidinone potentially less toxic and more potent than linezolid) to the small, underfunded company Sequella, the drug's development has completely stalled.[37] The Johns Hopkins University, which owns some of the intellectual property rights to sutezolid, is in a unique position to ensure that the drug is developed and marketed responsibly. Johns Hopkins should make the transfer of intellectual property rights conditional on Sequella's meeting firm deadlines for conducting studies and ensuring specific and strong provisions for collaborative research, fair pricing, and availability pre- and postapproval for people with TB and TB programs.[38]

AZD5847, another oxazolidinone, has languished. AstraZeneca, its sponsor, has exited the TB field, and results from a phase IIa U.S. National Institutes of Health–sponsored trial completed in 2013 remain unpresented.[39] We urgently need new candidates to come through preclinical development, yet companies like Vertex have been sitting on promising compounds such as VXc-486 without advancing them or allowing others to do so.[40]

With so few options, researchers are focusing on repurposing what's available, for both drug-sensitive and drug-resistant TB (DR-TB). Efforts are also picking up to evaluate the utility and safety of host-directed therapy.[41]

DS-TB

The quest for shorter treatments for DS-TB continues, with a commitment to optimizing the use of older treatments and some creative thinking on how to use new ones.

Better use of rifamycins, whose potent anti-TB activity and likely current underdosing offer promise, could potentially be one avenue for shortening DS-TB treatment. TBTC Study 31/ACTG A5349, a phase III trial that will test whether a higher dose of 1,200 mg daily rifapentine with or without moxifloxacin can shorten DS-TB treatment to four months in people with and without HIV, will begin enrollment in mid-2015. HIRIF, a two-month phase IIb trial comparing rifampin at 10 (standard), 15, and 20 mg/kg daily on top of the standard regimen, has completed enrollment in Lima, Peru; top-line results are expected by the end of 2015.[42] A two-week study found that more than tripling the standard dose of rifampin to 35 mg/kg was safe and well tolerated, at least over this short period, and was associated with higher rates of early bacterial killing.[43]

A higher dose of rifampin (40 mg/kg) from this study is currently under analysis, and, if it is shown safe, even higher doses may be examined.[44]

The potential efficacy benefits and safety of higher doses of rifampin appear promising so far in a longer study. The above-mentioned PanACEA MAMS-TB-01 trial found that three months of dosing with 35 mg/kg of rifampin, in addition to standard isoniazid, ethambutol, and pyrazinamide, improved time to stable culture conversion over 12 weeks on liquid (though not on solid) media over the standard DS-TB treatment (median 48 vs. 62 days; adjusted hazard ratio 1.75; 95% CI: 1.21–2.55; P = .003). The experimental culture conversion rate was the highest ever reported in a TB trial. Another experimental arm containing 20 mg/kg of rifampin, along with moxifloxacin, showed statistically nonsignificant improvements in time to stable culture on liquid (again, not on solid) media over 12 weeks (hazard ratio 1.42; 95% CI: 0.98–2.05). All arms appeared safe and well tolerated, though a slightly higher percentage of patients (14% vs. 10%) experienced grade 3 adverse events in the higher-dose rifampin-containing arms than in the control arm, with potentially higher rates of hepatic adverse events that resulted in a change of treatment in the 35 mg/kg rifampin arm.[45] Final analysis of the study is under way.

These approaches to optimize rifamycins, with or without the addition of moxifloxacin, are among the most straightforward options for potentially shortening DS-TB treatment using existing drugs.

A study in India showed that four-month therapy adding moxifloxacin to first-line treatment (either with daily or intermittent therapy in the continuation phase) was equally effective to the local standard of care (which consists of the standard first-line drugs given for six months of treatment, but only thrice weekly).[46] The moxifloxacin-containing arms all performed better than the control in terms of favorable outcomes at the end of treatment (92% vs. 81%; P < .03). Twelve months following treatment, the three four-month regimens tested had TB recurrence rates (5.2%, 6.6%, and 4.6%, respectively) similar to the control (4.6%) (P-values were all much greater than .05). Moderate and severe adverse events were slightly higher in the experimental arms (6–9% versus 4%). Whether these regimens would perform equally well when compared with a control of daily dosing is unclear, however.

REMoxTB failed to show that a four-month regimen substituting moxifloxacin for either ethambutol or isoniazid is noninferior to the current standard of care, with 7.8% (95% CI: 2.7–13.0) and 9.0% (95% CI: 3.8–14.2) fewer participants with favorable outcomes, respectively.[47] Similarly, as previously reported, the OFLOTUB study failed to show any benefit for using gatifloxacin in a treatment-shortening regimen.[48] Though disappointing, these definitive results add to an evidence base clearly indicating that exchanging one standard first-line TB drug for a fluoroquinolone is not enough to meaningfully reduce treatment duration without a much greater risk of relapse than the six-month standard of care. However, these results provide support for another approach to thinking through shortening treatment for TB.

For DS-TB, a curative regimen with a shorter duration would increase success rates in practice and reduce the emergence of new resistant organisms. While REMox and OFLOTUB four-month regimens did not demonstrate noninferiority against the six-month standard of care, they worked in a large majority of patients (in REMox, 77% and 76% vs. 85%). It is arguable that we are overtreating a majority of those with DS-TB to avoid relapses in a minority. However, we do not know how to identify which individuals will be cured in a shorter-than-standard time, despite the results noted.

A clinical trial is now in design to test treatment-shortening options that seek to produce relapse-free cure in most patients, accepting that in a clinical trial there may be more relapses than with the current standard of care. TRUNCATE-TB will use an adaptive design to test several two-month DS-TB regimens including new and repurposed drugs (including high-dose rifampin, linezolid, clofazimine, delamanid, and bedaquiline); it will also attempt to identify who may be at increased risk of relapse.[49] The study plans to start enrolling at the end of 2015. To be successful, this approach requires reliable prediction of those who will benefit from

the shortened regimens and the appropriate selection of patients, care, and follow-up, which programs are already responsible for but are often failing to deliver. Research to understand preferences about the risks and benefits of shortened treatment is also necessary prior to uptake; some patients may prefer a longer treatment if it makes a second round of treatment less likely. Although TRUNCATE-TB's approach will be risky until we can reliably identify who can benefit from it, it reflects the sort of exciting and highly innovative thinking that is urgently needed to break TB treatment and research out of its calcification. Sponsors should make drugs available to TRUNCATE-TB for this effort.

The APT study, sponsored by Johns Hopkins and funded by the FDA's Orphan Products Grants Program, will also examine the role of a new drug, in this case pretomanid, in DS-TB treatment. This phase II trial will add pretomanid to isoniazid, rifampin, and pyrazinamide for eight weeks to assess time to sputum culture conversion and safety.[50]

The ACTG is developing a protocol to study clofazimine in DS-TB, based on preclinical work from the Johns Hopkins University. The current proposal is to test the addition of clofazimine at 100 or 50 mg daily for 12 weeks to the standard of care versus the standard as a control.[51]

Studies for DS-TB and Some Forms of DR-TB

Two new trials from the TB Alliance are also looking at using new drugs to treat DS-TB, in addition to some forms of DR-TB, by treating patients based on the drugs to which their TB is susceptible rather than resistant. The phase III STAND-TB trial, designed to evaluate four- and six-month regimens of pretomanid, moxifloxacin, and pyrazinamide, has started, following promising results of the regimen in a two-month phase II study.[52]

NC-005, a two-month phase II study looking at pretomanid, bedaquiline, and pyrazinamide, has also begun (this trial will also include moxifloxacin in an arm for people with MDR-TB).[53] Both trials are admirable in their attempts to develop a new compound (pretomanid) in new, optimized combinations (rather than as add-ons to the existing standard of care like bedaquiline and delamanid). Both also offer hope for the tremendous advantage of all-oral regimens with greatly reduced pill burdens, fewer drugs (and potentially fewer side effects), and shorter treatment for DS-TB and some MDR-TB. However, with only three drugs with limited capacity to protect against the development of resistance, the STAND regimen may be risky (especially among persons with MDR-TB) and may require broad access to rapid drug susceptibility testing that doesn't yet exist to detect resistance to the drugs in the regimen. Both trials include people with MDR-TB in an open-label, nonrandomized arm without a control, raising questions about how to interpret these data if follow-up, randomized controlled trials are not planned, especially if STAND's results are equivocal.

DR-TB

While Otsuka completes its phase III trial that adds delamanid to the current standard of care for MDR-TB, investigators are struggling to advance trials to understand how to better use delamanid and bedaquiline as part of optimized regimens for MDR-TB.

Bedaquiline is entering STREAM II – laudably redesigned after TB communities called for the inclusion of a control arm[54] – which will assess its potential to contribute to a six-month regimen, or a nine-month injection-free regimen, in combination with several older drugs.

The NExT study will evaluate bedaquiline in people with MDR-TB in a much sleeker, injection-free, six-month regimen along with linezolid, levofloxacin, pyrazinamide, and either high-dose isoniazid or ethionamide – depending on the MTB genotype. With funding from the South African Medical Research Council, this trial has the potential to change the standard of care in South Africa, which has already been a leader in providing

bedaquiline to people with MDR-TB with limited treatment options.[55] However, Janssen appears unwilling to donate drug for this study. The NExT investigators had originally planned to include delamanid, but even though they proposed a rigorous safety substudy, Otsuka would not permit delamanid and bedaquiline to be studied together until the ACTG's A5343 trial to examine the effects of the two drugs on QT prolongation, a disturbance in the heart's electrical activity, was completed. Unfortunately, due to slow movement from Janssen and bureaucratic delays from the U.S. National Institutes of Health (NIH), A5343 has yet to start.

Two more programmatic-style clinical trials will look at different combinations including bedaquiline or delamanid. The UNITAID-funded endTB trial will evaluate at least five new all-oral regimens containing one new anti-TB drug (either bedaquiline or delamanid), no more than five drugs per arm, and no more than two QT-prolonging drugs per arm (companion drugs are moxifloxacin or levofloxacin and pyrazinamide plus linezolid, clofazimine, or both). The design is still being finalized, but current plans are to compare the five experimental arms with a control arm that includes either bedaquiline or delamanid according to current WHO guidance for their use. The trial is designed to be able to detect up to three effective regimens. The endTB study will be conducted in Georgia, Kazakhstan, Kyrgyzstan, Lesotho, and Peru. Enrollment may begin as early as December 2015. The TB-PRACTECAL trial is a randomized, controlled, open-label, phase II/III trial. It will evaluate the safety and efficacy of six-month regimens containing bedaquiline, pretomanid, and linezolid alone, with moxifloxacin, or with clofazimine for the treatment of adults with MDR-TB or extensively drug-resistant TB (XDR-TB). These experimental regimens will be compared against a control of the WHO standard of care. Médecins Sans Frontières is sponsoring the trial, and the TB Alliance is donating pretomanid. Patient recruitment will start in the third quarter of 2015.

The commendable NiX-TB trial from the TB Alliance is examining the combination of three compounds that are new or to which there is little preexisting resistance due to limited use – bedaquiline, linezolid, and pretomanid – in XDR-TB.[56] Testing this innovative regimen is appropriate in these individuals given their limited other treatment options, and it provides one way, albeit limited, for South Africans in urgent need to gain access to multiple new drugs. If Sequella were to make sutezolid available, the drug would be an excellent candidate for inclusion in this study.

A few other trials seek to improve MDR-TB treatment without new drugs. STREAM I, a randomized controlled trial comparing a nine-month regimen – clofazimine, ethambutol, moxifloxacin, and pyrazinamide plus isoniazid, kanamycin, and prothionamide in the first four months only – with the current WHO standard of care met its enrollment target in March 2015;[57] results are expected at the end of 2017 or early 2018.[58] This experimental modified–Bangladesh regimen (so called as it was first introduced in a flawed observational cohort study in Bangladesh, with cohort sizes undefined prior to starting the study, high risk of selection bias, and sequential enrollment of cohorts allowing confounding due to socioeconomic improvements)[59] is far from ideal given the large number of drugs, associated side effects, and inclusion of an injectable. But it does have potential to provide a shorter, standardized treatment for MDR-TB using older, accessible drugs. The rigorous STREAM II trial is needed to provide definitive answers about the suitability of the regimen for routine use.[60]

Opti-Q, a phase II study led by Boston University and sponsored by the U.S. National Institute of Allergy and Infectious Diseases and the TBTC, is enrolling adults with MDR-TB in South Africa and Peru. As a parallel to the rifampin work for DS-TB, Opti-Q is attempting to determine the optimal dosing for levofloxacin.[61]

Novartis has expressed interest in developing clofazimine for MDR-TB; the drug (approved for leprosy) has already been used as an off-label treatment for decades. The company is designing a more conventional trial to add the drug to a standard background regimen to assess the anti-TB activity of clofazimine, which in a two-week study showed no early bactericidal activity but is thought to work against TB over longer periods of time, especially given its long half-life.[62,63]

A TB Alliance early bactericidal activity trial will look at different dosing strategies for linezolid in the hope of later identifying strategies to minimizing its toxicities while preserving efficacy.[64] The ACTG may develop a two-month study of clofazimine to more clearly define a tolerable dose for use in DR-TB treatment.

Pre-approval Access Spotlight

The TB Alliance, as a nonprofit, has the challenge of identifying funding for its endeavors. To provide compassionate use access for pretomanid – which should be in place already as the drug has entered phase III – the Alliance is looking to establish a precedent of a philanthropically funded pre-approval access program. It is now assessing costs and identifying donor prospects – work that should have begun years ago. The Alliance, along with donors, should include planning for pre-approval access as part of any late-stage clinical development program.

Meanwhile, only a few dozen patients have received delamanid under Otsuka's nominal compassionate use program. Otsuka is withholding compassionate use of delamanid from gravely ill patients receiving bedaquiline. Though there is not enough safety information yet to give the two drugs together routinely for MDR-TB, some people with MDR-TB have no remaining treatment options for combination therapy; alternatives may lower their chances for relapse-free and disability-free cure and increase their chances of developing further drug resistance. For these individuals, the potential benefits far outweigh the potential risks, but Otsuka's inflexibility and short-sightedness leave them at great risk of disability and death.[65,66] Otsuka recently announced an initiative to improve the availability of delamanid with a goal to "reach 20% of all diagnosed and treated patients in quality programmes by 2020," but details are vague, and terms such as "quality" hint at continued highly restricted access to delamanid.[67] Otsuka has still not consulted with community groups on the development of this access strategy.

CONCLUSIONS AND RECOMMENDATIONS

With few new drugs to work with, inadequate investment from drug sponsors, and limited funding, TB treatment researchers are in the difficult position of trying to do more with less. Remarkable advances are being made in TB prevention research, and momentum is gathering for their translation into implementation, though important questions remain about what strategies are best suited for which settings and about which drugs can safely and effectively prevent MDR-TB given the current absence of clinical trial data. For active TB disease, overdue research is finally happening or in development. For all forms of active TB, studies to determine the best dosing, and to test strategies to shorten treatment, are under way. Some truly innovative approaches for DS-TB are also in development, though they carry big questions for eventual implementation if they are successful in trials. And, finally, a number of innovative MDR-TB trials looking at new drugs in better combinations have been designed, testing regimens that may improve efficacy and reduce side effects for DR-TB, though their results are years away. Access to new drugs remains inexcusably slow and difficult for patients, programs, and investigators alike. To resolve this, and to ensure the development and availability of improved treatment strategies for TB:

- **Move promising preclinical drug candidates into clinical development more quickly.** The TB drug pipeline is too sparse and homogenous. Pharmaceutical companies, philanthropic donors, and public institutions must increase funding for TB drug discovery and development to build a robust pool of drug candidates.

  - Top-grossing pharmaceutical companies such as Merck, Roche, and Gilead have been conspicuously absent from TB drug development and should immediately make compound libraries and funding available for TB R&D.
  - Pfizer and AstraZeneca should return to TB R&D and, at a minimum, contribute funding to the institutions that have taken over their TB compounds.
  - GlaxoSmithKline and Sanofi, which are currently investing in TB drug discovery and preclinical work, must sustain their investments and ensure continued collaboration.
  - Otsuka, Johnson & Johnson, and Novartis, which are all currently investing in clinical compounds for TB, should continue investing in early-stage work as well.
  - Vertex should either invest adequate resources immediately to advance VXc-486 or give over the development rights to another organization that will.

- **Revitalize research on compounds languishing in early-stage clinical development.** Sutezolid and AZD5847 have been stalled in phase IIa for years, primarily due to reprehensible neglect from pharmaceutical companies Pfizer and AstraZeneca.
  - Pfizer and AstraZeneca must ensure sustained funding for the development of early-stage potential TB products.
  - Sequella should develop sutezolid in collaboration with other drug sponsors and research consortia and, in its quest for capital to do so, ensure that access provisions are in place.
  - The NIH must resolve the internal bureaucratic delays that contributed to the slow progression of AZD5847.
- **Increase funding for TB R&D.** TB drug R&D is dramatically underfunded. Brazil, Russia, India, China, and other high–TB burden countries with large economies should be investing more in strategies to end TB. Janssen, Otsuka, and Sanofi, the few pharmaceutical companies with functional clinical TB programs, must sustain their investments in TB drug R&D. Other private-sector drug developers must get into TB, including the developers of tedizolid, an approved oxazolidinone that may have potential for TB and may be less toxic than linezolid. Tedizolid is currently caught in an industry merger; its developer, Cubist, was acquired by Merck in December 2014, and the legal and practical challenges of transferring compounds across companies have led to its development stalling.[68,69] Pfizer and AstraZeneca have abandoned the field completely and should at a minimum provide financing to the organizations (Sequella and TB Alliance) to which they've transferred their TB products to ensure their continued advancement.
- **Invest existing resources wisely.** With limited funding, public research agencies and research consortia should pursue only the strategies and drug candidates with true potential for added benefit. Adaptive designs offer one avenue for efficiency. Indeed, the publicly supported MAMS-TB-01 trial was able to reduce its sample size when an interim analysis showed SQ109-containing arms were not worth further investment.
- **Design studies with high scientific rigor.** A desperate need for new MDR-TB treatment options is not an excuse to cut corners scientifically or ethically. The TB Alliance should think seriously about how a regimen tested in people with MDR-TB in a nonrandomized, uncontrolled manner will be received by global normative bodies, TB programs, and communities. Though challenges exist with the current standard of care, by the time STAND and NC-005 have progressed, results from STREAM will be available that may offer a scientifically validated control arm (and potentially a shorter one if the experimental regimen is successful) for follow-up studies in people with MDR-TB, if warranted.

- **Make new drugs available for pragmatic and investigator-initiated research.** As all TB drugs must be used in combination, and we have so little information on the best use of all the new drugs – and many of the older ones – collaboration is essential for advancing TB treatment. In particular, given how sponsors have limited postmarketing access to the new TB drugs, they have an even greater responsibility to make procuring drugs for research easier (they should also more generally expand access to their drugs, as noted below). The MARVEL study was derailed by a lack of collaboration from Otsuka, Sequella, and the TB Alliance.
    - Janssen should make bedaquiline available rapidly and free of charge for essential studies, including A5343 and NExT, and the TB Alliance (which has the rights to bedaquiline for DS-TB) should provide it to TRUNCATE-TB.
    - Otsuka should make delamanid available for study in more innovative regimens, including for MDR-TB prevention, and should not wait for the A5343 results to discuss future plans to include delamanid and bedaquiline in the same regimen.
- **Plan for access earlier and ensure early/emergency access when needed before approval.** Sponsors and regulators are both responsible for ensuring access pre- and post-approval. Pre-approval access, including compassionate use and expanded access trials in places where no framework for compassionate use exists, should be routine components of any clinical development program.
    - Donors such as USAID, UNITAID, and the Global Fund should consider providing support to the TB Alliance to implement an already overdue compassionate use program for pretomanid, which is particularly urgent if it is safe to coadminister pretomanid with bedaquiline.
    - Otsuka still needs to make delamanid available to more people in need under compassionate use, including in certain urgent cases in conjunction with bedaquiline. Otsuka has failed to register delamanid even in countries where it was tested and to make it available through the GDF. With stringent regulatory authority approval, inclusion in the Model List of Essential Medicines, and relatively broad WHO recommendations in place, there is no excuse for these delays.
    - Janssen must make the bedaquiline donation widely available and successful at building a sustainable market for the drug, rather than using it as a promotional, tax-saving public relations gesture that creates onerous and drug-specific parallel procurement systems and doesn't actually broaden access. Janssen still needs to reduce the price of bedaquiline, particularly for middle-income countries, to enable medium- and long-term access.
    - Sanofi must widely register rifapentine for both TB infection and disease, starting in countries where clinical trials to support its registration were conducted.
    - Trial sponsors, when different from drug sponsors, should ensure availability and affordability commitments up front from drug sponsors before conducting research. Innovations resulting from research funded by public institutions have a special obligation to be affordable.
- **Improve regulatory structures and harmonize them regionally.** Flexible, rigorous regulatory agencies are key to protecting citizens and facilitating access to safe, effective new medical interventions. Review processes should be simpler and faster while maintaining high standards. Regulatory authorities need technical support from their counterparts at stringent regulatory authorities in Canada, the European Union, Japan, and the United States, the WHO, and implementing agencies – and more funding to this end.

- **Support robust postmarketing safety monitoring without making it a barrier to rollout.** WHO recommendations for active pharmacovigilance for bedaquiline and delamanid should not prevent programs from getting these drugs. Technical partners should offer assistance to programs in developing simple, effective, and logical systems for monitoring and reporting drug-related adverse events. The WHO, the GDF, USAID, the Global Fund, and other partners should make clear that onerous cohort event monitoring is not a requirement for initiating procurement of these drugs. These partners should also develop an overarching global body to collect and analyze national data and disseminate findings to inform future use of the drugs.

We have a long way to go. But we are building political will to address the structural, financial, and scientific deficits that sustain and encourage this epidemic. And with two new drugs, shorter treatment for TB infection, and potentially dramatically shorter treatment regimens for MDR-TB infection and active DS-TB and DR-TB disease under study, there is potential to do more than ever to treat, cure, and ultimately end TB. Let us not squander this unprecedented and all-too-rare opportunity.

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