

The Tuberculosis Treatment Pipeline: A Breakthrough Year for the Treatment of XDR-TB

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INTRODUCTION

Arguably, the most critical questions in TB treatment today are “What is the optimal regimen for the treatment of multi-drug resistant TB (MDR-TB)?” and “What is the optimal regimen for the treatment of extensively drug-resistant (XDR) and pre-XDR-TB?” To both of these questions we have at best interim answers. The World Health Organization (WHO)-recommended shortened nine-month “modified Bangladesh” regimen for the treatment of MDR-TB (kanamycin, moxifloxacin, prothionamide, clofazimine, isoniazid, pyrazinamide, and ethambutol) has only observational data to support it and involves a large number of difficult-to-tolerate drugs.¹ In addition, a number of experimental regimens that are currently in randomized controlled trials (RCTs) that utilize new drugs such as bedaquiline and delamanid seem set to surpass it by significantly reducing both the number of drugs and the duration of treatment. At present, there is no standard of care for pre-XDR and XDR-TB, although one experimental regimen is performing remarkably well in an ongoing clinical trial.

The Nix-TB trial is a single-arm trial that is still ongoing (see the bedaquiline section below for more details), but its success in appearing to treat XDR and pre-XDR-TB with far fewer drugs in far less time than ever before nevertheless represents a medical breakthrough with multiple positive implications for the outcomes of all forms of DR-TB, for the real-world use of the first new TB drug from a new class approved in 40 years (bedaquiline), and for raising the hopes of people with TB and their providers—along with a host of regulatory and access issues. Treatment outcomes for people with XDR and pre-XDR-TB are typically extremely poor, with five-year mortality rates as high as 73%.² Thus, even though the evidence for the Nix-TB regimen is still very limited and does not come from an RCT, it has set a high bar for other treatment regimens for advanced, previously poorly treatable disease. Although calling the Nix-TB regimen the “standard of care” for XDR and pre-XDR-TB may be premature, a strong case can be made that any XDR and pre-XDR treatment trials in the foreseeable future should include the Nix-TB regimen as the control arm, especially given the questionable ethics of using the existing so-called standard of care, which, in addition to being difficult to tolerate and having poor outcomes, has no randomized clinical trial data to support it.

Although the Nix-TB regimen has put a flag in the sand as far XDR and pre-XDR-TB is concerned, the situation is much more complicated when it comes to MDR-TB. Multiple combinations of new, old, and repurposed drugs are currently being studied in multiple ongoing trials across the world (see table 2 for a summary of these trials). With some notable exceptions, such as the NEXT-TB trial, most critical trials will only report results in 2021, and even then we will not be guaranteed clear answers. Even so, as is the case with the recent recommendation of the shorter MDR-TB regimen, the WHO may again change their guidance prior to the scientific question being settled. Incidentally, results from STREAM stage I, the RCT that is comparing the now WHO-recommended shorter MDR regimen to the previous WHO standard of care, is only expected in 2018.

In an important initiative aimed at focusing and directing TB drug development, the WHO has developed a set of target regimen profiles (TRPs) that lay out profiles for rifampin-susceptible TB, rifampin-resistant TB, and for a pan-TB treatment regimen. Although a highly effective, very short course pan-TB regimen would be a major step forward in the fight against TB, there is no universal agreement as to what extent a pan-TB regimen should be prioritized in drug development, nor is there agreement as to what exactly it means (the WHO TRP definition describes it as being applicable where drug-susceptibility testing [DST]

is not available, whereas most advocates would want a pan-TB regimen to be of use in all forms of TB, as they would want DST to be universally available and accessible). It is notable, however, that a pan-TB TRP has been included in these TRPs and that the 3P Project—an innovative drug development initiative and funding framework—explicitly aims to support the development of a pan-TB regimen.³

Even with the WHO's TRPs in place and with much debate over TB drug development in recent years, there are still many unanswered questions as to the optimal pathways for the development of various specific drugs and regimens. Some researchers are attempting to use experimental data, experiments in mice, and various mathematical techniques to predict which combinations of drugs at which dosages are likely to be most effective. One study in a mouse model, for example, identified a regimen of clofazimine, bedaquiline, ethambutol, and pyrazinamide as having significant potential.⁴ Given that there are thousands of possible drug and dose combinations, such studies may be important for ensuring that research dollars are optimally spent, although it should be acknowledged that these models are often based on very limited data that may or may not be relevant to the treatment of humans.

Questions continue to be raised as to whether enough data are gathered before proceeding to phase III trials in TB, which, if true, would reduce the odds of success in phase III. A proposed solution is to expand the scope of phase II trials by carrying out more phase IIc trials, in which experimental regimens are studied for longer periods than in current phase IIa and IIb trials.⁵ Consistent with this thinking, a recent meta-analysis concluded that, "The existing evidence base supporting Phase II methodology in tuberculosis is highly incomplete. In future, a broader range of drugs and combinations should be more consistently studied across a greater range of Phase II endpoints."⁶

In addition to these various strategies aimed at optimizing the progress of new candidates in the TB drug development pipeline, economic factors have a significant role in how and in which combinations drugs are developed. Although we can now report some progress (see below), the development of sutezolid has been delayed by many years for reasons relating to its ownership. Otsuka recently announced its intention to develop its new drug candidate, OPC-167832, in combination with delamanid (Otsuka's other TB drug). The entry of a new compound into the pipeline is welcome, but it is unclear whether, and at what stage, this new compound will be made available for testing with compounds not owned by Otsuka.

As has been the case in recent years, drug regulators will play a critical role in shaping the research that does or does not get done. Important decisions will again have to be made regarding the amount of evidence required for drug registration (see clofazimine below) and the potentially valuable role that phase IIc trials may have in optimizing TB drug development. In relation to TB, regulators also have the particularly difficult task of ensuring that enough data are gathered both on the safety and efficacy of individual drugs and on the safety and efficacy of combinations of drugs. With the likely lowering of regulatory standards through the 21st Century Cures Act in the U.S. and so-called Adaptive Pathways in Europe, there is a risk that critical data on new and repurposed drugs may not be gathered and that the evidence base for these drugs may remain insufficient, perpetuating the unacceptable situation that has been the case with virtually all MDR-TB drugs for decades.

Finally, the developments reported in this chapter must be considered against a background of a TB R&D landscape that remains largely defined by the fact that it is woefully underfunded. According to the latest TAG *Report on Tuberculosis Research Funding Trends*, investment in TB research dropped by \$US53.4 million, from \$674 million in 2014 to \$620.6 million in 2015.⁷ This is less than one-third of what the *Global Plan to Stop TB* estimates is required. Although there is now some momentum behind a planned UN High-Level Meeting on TB in 2018 (it will be preceded by a Ministerial Meeting in November 2017), the true test of governments' commitment in the fight against TB will ultimately not be the declarations that will come from these meetings, but the concrete financial investments that governments make in the fight against TB, particularly in TB R&D.

UPDATES ON NEW COMPOUNDS IN DEVELOPMENT

Table 1. Drugs in development for tuberculosis

Drug	Class	Sponsor(s)	Phase
bedaquiline	diarylquinoline	Janssen, TB Alliance, NIAID, SAMRC, the Union, Unitaid, USAID	III
delamanid	nitroimidazole	Otsuka, NIAID, Unitaid	III
pretomanid	nitroimidazole	TB Alliance	III
sutezolid	oxazolidinone	Sequella, NIAID, TB Alliance	IIa (developers will have to repeat early stage studies, see text)
Q203	imidazopyridine	Qurient, Infectex, PanACEA	II
SQ109	1,2-ethylene diamine	Infectex, Sequella, PanACEA	II (phase III controversially claimed in Russia, see text)
PBTZ169	DprE1 inhibitor	Nearmedic, iM4TB, BMGF	II
OPC-167832	carbostyryl	Otsuka, BMGF	I
LCB01-0371	oxazolidinone	LegoChem Biosciences	II

BMGF: Bill and Melinda Gates Foundation; NIAID: National Institute of Allergy and Infectious Diseases (U.S.); PanACEA: Pan African Consortium for the Evaluation of Antituberculosis Antibiotics; SAMRC: South African Medical Research Council; The Union: International Union Against Tuberculosis and Lung Disease; USAID: The U.S. Agency for International Development

Bedaquiline

Bedaquiline is the most widely used of the new drugs for the treatment of TB. By April 2017, an estimated 8,828 patients had received the drug—5,387 of whom were in South Africa.⁸ Concerns about the safety of bedaquiline were based on the ten deaths in the interventional arm of the registrational phase IIb C208 study, and the risk of QT prolongation (a potentially dangerous disturbance in the heart's electrical activity). The accumulating evidence for the drug from the thousands of patients who have gotten it under routine programmatic use, however, suggests that the drug is in fact quite safe and that the risk of QT prolongation is manageable in the vast majority of cases. A guidelines development group convened in June and September 2016 to review the WHO's 2013 interim guidance on bedaquiline and made some important updates to the language—including on the use of the drug in people with HIV and in adolescents—and recommended the use of bedaquiline in anyone with MDR-TB who were not eligible for the shortened regimen, but did not change the overall conditional recommendation on the use of the drug, and, disappointingly, WHO only issued a meeting report rather than updated guidelines.⁹

In arguably the most important TB-related study findings reported in the last year, the bedaquiline-containing Nix-TB regimen has proven to be highly effective in the treatment of XDR-TB, pre-XDR-TB, and treatment-intolerant or treatment-non-responsive MDR-TB. The Nix-TB trial is a single-arm, open-label trial of bedaquiline, pretomanid (formerly Pa-824), and linezolid given for six months, with an extra three months added if participants are sputum culture positive at four months.¹⁰ Interim findings were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in February 2017. Of the 72 patients enrolled in the study, 40 had finished treatment and 31 had finished six months of follow-up. Four patients died—all in the first eight weeks. Of the 31 who finished six months of follow-up, only two had relapsed or been re-infected. It should be stressed that further follow-up is ongoing and more relapses may yet occur (in phase III trials, patients are normally followed up for at least one year to ensure relapse-free cure). Remarkably, all of the surviving patients were culture negative at four months—74% were

already negative at eight weeks. The expected linezolid toxicities of peripheral neuropathy (painful nerve damage) and myelosuppression (a decrease in bone marrow activity leading to fewer red and white blood cells and platelets) were said to be “common but manageable.” Seventy-one percent of patients had at least one linezolid dose interruption. It is expected that more up-to-date findings will be presented at other meetings, including the 2017 Union World Conference on Lung Health.

The TB Alliance, which sponsors the Nix-TB trial, is planning a further trial of 180 people using the Nix-TB regimen, but with the key difference that the four study arms will be randomized to different linezolid doses and durations (details in the linezolid section below), in the hope of reducing this toxicity without sacrificing efficacy. Given that this trial (known both as NC-007 and ZeNix) is designated as a phase III trial, it is intended to allow for the registration of this regimen for the treatment of XDR-TB, pre-XDR-TB, and treatment-intolerant and treatment-non-responsive MDR-TB.¹¹ It is not known whether the TB Alliance will seek conditional registration prior to the completion of this study, nor is it known what steps will be taken to ensure wider pre-approval access to the regimen. Enrollment in ZeNix is anticipated to start in October 2017—results are not anticipated until January 2022.

A retrospective, observational study of 428 DR-TB patients given bedaquiline-containing regimens in 15 countries recently showed encouraging safety and efficacy. Sputum smear and culture conversion rates in MDR-TB cases were 88.7% and 91.2%, respectively, at the end of treatment. Bedaquiline was interrupted as a result of adverse events in 5.8% of cases. A single patient died after having had electrocardiographic abnormalities that, according to the study authors, were “probably non-bedaquiline related.”¹²

Meanwhile, bedaquiline continues to be used in a number of other ongoing randomized controlled trials that will, in coming years, provide important additional information on its safety and its use in combination with various other drugs. The bedaquiline phase III study, STREAM stage II, is ongoing and results are expected in December 2021.¹³ Other important trials including bedaquiline are NEXT-TB (now due to be completed late in 2019 as a result of contractual delays),¹⁴ study TB-PRACTECAL AKA 1541 (estimated study completion in March 2021),¹⁵ and endTB (estimated study completion in April 2021) (see table 2 for more details on these studies).

Initial findings from the ongoing NC-005 phase II trial presented at the 2017 CROI suggest that a combination of bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPamZ) has both good bactericidal activity and safety.^{16,17} The TB Alliance is planning to test this regimen in a larger phase III trial, NC-008.

Another important phase II trial to watch is trial A5343, which in its three arms adds bedaquiline, delamanid, and a combination of the two to the WHO-recommended shortened MDR-TB regimen (with clofazimine removed in each case as a result of the increased risk of QT prolongation when used with bedaquiline). The study should provide critical information about the safety and pharmacokinetics of using these two new drugs together. HIV-positive study participants will be given the integrase inhibitor dolutegravir, which will provide useful information on the use of dolutegravir with the new TB drugs. Recruitment has been slower than anticipated, however, and ClinicalTrials.gov lists January 2019 as the anticipated primary completion date and January 2021 as the final study completion date.¹⁸

Delamanid

The delamanid phase III trial is listed as “completed” on ClinicalTrials.gov and top-line findings are expected to be presented at the Union World Conference on Lung Health in October 2017.¹⁹ Although the trial will provide critically important data on delamanid specifically—and a sub-trial will provide data on the use of delamanid with antiretrovirals (ARVs)—it is unlikely to herald the introduction of a new

MDR-TB treatment regimen, as the intervention arm in the study simply adds delamanid to an existing background regimen, the old, pre-“Bangladesh,” 24-month regimen.

Delamanid is also being tested in a number of interesting new regimens, most notably in the endTB trial (see table 2). The MDR-END trial, which is evaluating a regimen containing delamanid, linezolid, levofloxacin, and pyrazinamide for 9 or 12 months, is also potentially important (completion expected at the end of 2019).²⁰ The same regimen as the MDR-END trial, with arms for various shorter durations, will be studied in the H-35265 trial (recruitment to start August 2017 and study completion expected in August 2021).²¹ As noted earlier, the A5343 trial should provide useful data on the use of delamanid in combination with bedaquiline.

On World TB Day 2017, South Africa’s Minister of Health announced that the country would launch an expanded access program to provide delamanid to 400 patients in that country. The drugs are being donated by Otsuka. As with the bedaquiline expanded access program in South Africa, the delamanid program should provide useful real-world data on the safety of the drug.

Despite the progress in South Africa, the delamanid compassionate use program has been extremely slow to get off the ground. Only 563 patients worldwide have received delamanid as of April 2017—most of whom are in MSF projects.²² As of April 2017, delamanid has only been registered with four regulatory authorities (with dossiers submitted in four additional countries).

The struggle in recent years to get compassionate access to the new TB drugs has highlighted the complexities created by differing legal mechanisms for early access in different countries and different levels of willingness from drug developers to engage in such programs. In response to this, Treatment Action Group and the Global TB Community Advisory Board have proposed a unified compassionate access entity that would help facilitate compassionate access to new drugs.

Pretomanid

It has been a mixed year for the development of pretomanid. On the positive side, it is one of the three drugs in the remarkably effective Nix-TB regimen (see the bedaquiline section above). It will also be included for further study in people with XDR and pre-XDR-TB and people with non-responsive or treatment-intolerant MDR-TB in the ZeNix trial, and as part of the bedaquiline-pretomanid-moxifloxacin-pyrazinamide regimen in the NC-008 trial.

Less encouragingly, in December 2016, the TB Alliance took the decision not to re-open enrollment in the controversial phase III STAND trial. Enrollment in the trial was placed on hold following three deaths in the intervention arm; at the time there were fears that the deaths may have been pretomanid related. The trial, which tests the combination of pretomanid, moxifloxacin, and pyrazinamide for the treatment of both DS and DR-TB, was cleared to resume enrollment, but will continue only with participants that were already enrolled, leaving the trial underpowered. The decision not to resume enrollment, presumably out of increased interest in other regimens, raises ethical questions regarding the expectations study participants have that the studies they take part in will produce meaningful (and sufficiently powered) findings. Even prior to the hold, the STAND trial was controversial given differing views as to whether sufficient phase II data existed to warrant proceeding to phase III, and whether the study design would allow for meaningful interpretation of a range of possible results.

Instead of STAND, the TB Alliance is now focusing on NC-008, a phase III trial that tests the STAND regimen plus bedaquiline. The use of this BPamZ regimen is supported by promising results from the NC-005 trial (see above).

Pretomanid is also being studied in multiple arms of the phase II/III TB-PRACTECAL study (see table 2).

Sutezolid

Although development of the oxazolidinone sutezolid began alongside that of linezolid in the mid-1990s, it has taken much longer to yield results. Linezolid was approved by the U.S. Food and Drug Administration (FDA) in 2000, whereas sutezolid is paralyzed in phase IIa, with no clinical progress since 2012.²³ Even with significant toxicities, linezolid is proving to be an important drug for the treatment of highly resistant forms of TB (see discussion of the Nix-TB trial in the bedaquiline section). If, as some hope, sutezolid turns out to be as effective as linezolid, but safer, then it could turn out to be a critically important drug for the future of TB treatment, potentially replacing linezolid in emerging XDR-TB regimens such as that in the Nix trial.

After being in limbo for some years at Pfizer, the pharmaceutical company Sequella acquired the license to sutezolid in 2011.²⁴ Over the following six years, Sequella did virtually nothing to further develop the drug. Some of the drug's intellectual property is, however, held by Johns Hopkins University. In January 2017, after extensive negotiations, Johns Hopkins licensed sutezolid to the Unitaid-funded Medicines Patent Pool (MPP). This move essentially opens up the further development of sutezolid to any interested party willing to agree to the license terms offered by the MPP.

One obstacle to the development of sutezolid is that, even though patent barriers were removed by the MPP license, pre-clinical and early clinical data already conducted by Pfizer and Sequella have not been shared either publicly or directly with other developers. This means that interested developers, such as the TB Alliance, will have to repeat some of this early research, which will further delay the development of sutezolid. Had Sequella shown more competence and urgency regarding the development of sutezolid, its reluctance to share this data would have made sense as part of a strategy to be first to market. As it stands, there is little evidence that the company has the means to further develop this potentially important drug.

A proposed development pathway has been presented at meetings by the Aurum Institute in which sutezolid would be tested as part of a regimen together with bedaquiline and delamanid in a single-arm trial in patients with XDR-TB.²⁵ Should that trial succeed (although definitions of success are unclear, as there is no proposed control arm for comparison), the trial would be expanded to patients with MDR-TB with the eventual goal of verifying a pan-TB regimen that could be used in cases in which DST is not available, but there is evidence indicating that patients' isolates may not be fully susceptible. Whether regulators and ethics boards will accept the lack of a control arm in these trials is unclear. Some advocates argue that the rationale for an uncontrolled study is no longer acceptable, as the Nix-TB trial has provided a feasible potential comparator regimen, and that any trial of a new regimen for the treatment of XDR-TB should include the regimen used in the Nix-TB trial as a control.

SQ109

Preliminary results of a putative phase IIb/III trial of the drug SQ109 were presented at a meeting in Moscow in November 2016. This trial, however, had only 140 participants—a low number for a phase III MDR-TB trial—and it appears that no post-treatment follow-up was reported. According to the website of Infectex, the company with the rights from Sequella to develop SQ109 in Russia, the results “demonstrate satisfactory profile of safety and tolerability of SQ109 as well as the increase in effectiveness of the standard regimen of chemotherapy in combination with SQ109 in patients with multidrug-resistant tuberculosis.”²⁶ We have not been able to find these results reported in a peer-reviewed medical journal.

Meanwhile, the two SQ109-containing arms in a PanACEA trial testing high-dose rifampin were stopped early because pre-specified efficacy thresholds were not met.²⁷ SQ109 may nevertheless still have a future in combination with other drugs provided that any anti-TB activity of the agent in humans can be convincingly demonstrated.

Q203

Q203 is an experimental TB drug that is being developed by the pharmaceutical company Qurient. Similar to bedaquiline, it functions by inhibiting energy metabolism, although it is thought that the two drugs could work synergistically. A phase I dose-escalation study is under way and an EBA study is expected to start before the end of 2017.²⁸

PBTZ169 and BTZ043

PBTZ169 is an experimental DprE1 inhibitor that is active on the mycobacterial cell wall and is being developed by iM4TB (a non-profit supported by the Bill and Melinda Gates Foundation). According to ClinicalTrials.gov, a phase I safety and dose-finding study has been completed, but the results have not yet been published.²⁹

In the same class as PBTZ169 is BTZ043, which is being developed by the PANACEA consortium. The compound has shown promising safety and efficacy in a mouse model; phase I trials in humans are expected to start soon.

OPC-167832

At the 2016 Union World Conference on Lung Health, the pharmaceutical company Otsuka announced its development of a new drug in the carbostyryl class called OPC-167832, indicating that it will be co-developed with delamanid (Otsuka's other TB drug). Human trials are reportedly underway (although we failed to find any trials listed on ClinicalTrials.gov, the EU Clinical Trials Register, or the WHO International Clinical Trials Registry Platform) and the FDA has granted fast-track status.³⁰ It is as yet unclear whether Otsuka will allow OPC-167832 to be tested as part of other novel regimens with drugs owned by other companies.

LCB01-0371

LCB01-0371 is an experimental oxazolidinone that is being developed by LegoChem BioSciences. A phase II safety and early bactericidal activity study of the drug is expected to be completed in late 2017.³¹

OPTIMIZING THE USE OF APPROVED AND REPURPOSED DRUGS

One of the persistent problems in TB is the relative weakness of the evidence base. It is unclear whether certain long-used drugs are used at optimal dosages and in optimal combinations. In recent years, however, there has been a resurgence in studies reappraising and repurposing drugs that have been on the market for some time, for decades in some cases.

Isoniazid

Isoniazid is a long-standing component of the standard DS-TB treatment regimen and is also used in high doses in the shortened MDR-TB regimen. The ongoing ACTG5312 trial is testing whether increasing the

dosage of isoniazid can help to overcome existing low-level resistance to the drug. The study is expected to report in 2018.³² High-dose isoniazid is also being used in the NEXT-TB trial.

The need to determine optimal treatment in the face of isoniazid resistance is underlined by a recent meta-analysis that showed substantially worse outcomes in patients with isoniazid mono-resistance receiving standard DS-TB treatment compared with patients who have fully drug-susceptible TB.³³ It is anticipated that these findings may lead to updated guidelines for the treatment of TB in people with isoniazid mono-resistance, but the implementation of such guidelines would be complicated by the fact there are currently no quick and affordable tests for isoniazid resistance (see TB diagnostics chapter, page 91).

Rifamycins

A recently published study concluded that increasing the dosage of rifampin to 35 mg/kg (the current standard is 10 mg/kg) was safe, reduced the time to culture conversion in liquid media, and could be a promising component of future, shorter regimens for DS-TB. The study tested four experimental arms with rifampin dosages of 35 mg/kg, 20 mg/kg, and 10 mg/kg in various regimens against the standard of care for DS-TB. The only arm to show significantly faster culture conversion in liquid media was the DS-TB standard of care with the rifampin dose increased to 35 mg/kg. Arms containing SQ109 and moxifloxacin failed to show superiority to the standard of care.³⁴

Rifampin's sister drug, rifapentine, is being tested in study TBTC 31/ACTG A5349 as part of two four-month regimens for the treatment of DS-TB. The first experimental regimen in this trial simply replaces rifampin with rifapentine and reduces the continuation phase to two months. The second experimental regimen is the same as the first, but replaces ethambutol with moxifloxacin and continues moxifloxacin for the continuation phase. This study is ongoing and is only expected to be completed in late 2019.³⁵

The much-anticipated TRUNCATE-TB trial will test whether DS-TB treatment can be shortened to two months for some patients using combinations of new and repurposed drugs, including the rifamycins. After being a possibility for years, this trial is now expected to start recruitment in August 2017.

Fluoroquinolones

As with a number of TB drugs, the optimal dose for the fluoroquinolone levofloxacin is not known. The phase II Opti-Q study, which is designed to answer this question in patients with MDR-TB, has finished recruiting and is expected to be completed in late 2017. The study will evaluate levofloxacin doses of 11 mg/kg, 14 mg/kg, 17 mg/kg, and 20 mg/kg, all taken with an optimized background regimen.³⁶

Levofloxacin is also being used in the H-35265 trial, the NEXT trial, the STREAM trial, and in a Chinese study in which it is added to the current DS-TB standard of care regimen given for four and a half months instead of the normal six months.³⁷ Moxifloxacin is similarly being used in a number of ongoing trials (see table 2).

Clofazimine

Clofazimine, a riminophenazine that has long been used for the treatment of leprosy, is recognized as a "core second-line agent" in the latest WHO guidelines even though there is only limited evidence from trials on its use for the treatment of TB. Last year we reported that Novartis's planned phase II C/III clofazimine study CLAM320B2202 was set to start in April 2017. The study would have provided valuable data on the safety and efficacy of clofazimine by comparing a background regimen plus

clofazimine to a background regimen plus placebo. Given the inclusion of clofazimine in the new WHO guidelines, the planned study design was, however, no longer viable, as clofazimine is now part of the standard of care. In response, Novartis opted to cancel the study and the company is now seeking a TB indication without a phase III study. Given the drug's large body of safety data to support its use and indications of its efficacy from routine use, the broader access that a TB indication would provide may be warranted. However, there are many important gaps in our knowledge about the drug, including its individual contribution to the efficacy of a TB treatment regimen, optimal dosing and duration of treatment, and interactions with other drugs. It is not known whether regulators will make registration conditional on conducting additional trials, as was the case with bedaquiline in the U.S. and delamanid in the EU. One concern is that the recently passed 21st Century Cures Act will allow for such early approvals without the necessary checks and balances to ensure that enough is ever learned about the drugs in question. The half-century legacy of poorly studied drugs for MDR-TB should warn us against jumping once again down a slippery regulatory slope towards access without answers.

Some limited data on clofazimine should, however, be forthcoming from the END-TB, TP-Practecal, STREAM stage I and STREAM stage II trials, although these trials are not designed for, or powered to, measure clofazimine-specific effects. Some retrospective, individual patient data on the use of clofazimine currently being compiled by Dick Menzies at McGill University should also shed some light on the drug. In addition, a phase IIc trial called A5362 (also called Clo-Fast) is being planned in which clofazimine will be added to the standard of care for DS TB with the treatment duration being reduced from six months to four months.³⁸

Linezolid

Linezolid is an oxazolidinone with potent activity against TB. There is compelling evidence that it improves culture conversion and cure rates when added to treatment regimens for drug-resistant tuberculosis. However, linezolid has a narrow therapeutic window, and the optimal dosing strategy remains unknown.³⁹

Linezolid is also one of the three drugs that make up the regimen used in the Nix-TB trial (see bedaquiline section above). Although significant linezolid-related toxicity was reported in the Nix-TB trial, it appears to have been manageable in all of the cases reported thus far. Optimizing the dosing and duration of linezolid in this regimen is the key focus of the planned ZeNix follow-up trial. In ZeNix, four arms will receive either linezolid 1200 mg once daily for six months, linezolid 600 mg once daily for six months, linezolid 1200 mg once daily for 2 months, or linezolid 600 mg once daily for 2 months.

Linezolid is also part of experimental regimens being studied in the H-35265, NEXT-TB, END-TB, and MDR-END DR-TB trials.

Although linezolid is mainly being studied and used for drug-resistant forms of TB, it is also being used in at least two trials for drug-susceptible TB. In one ongoing trial, it is hypothesized that replacing ethambutol with linezolid will increase the sputum culture conversion rate by 15% after two months.^{40,41} Another ongoing study will evaluate the two-week mycobactericidal activity, safety, tolerability, and pharmacokinetics of six different dosing schedules of linezolid in people with DS-TB.⁴²

Nitazoxanide

Nitazoxanide is a broad-spectrum antiparasitic and antiviral drug that was first developed in the 1980s and, in recent years, has been explored as a potential treatment for TB. A phase II, 14-day, early bactericidal activity study of nitazoxanide in treatment-naïve patients with drug-susceptible, uncomplicated pulmonary TB is scheduled to complete by the end of 2017.⁴³

Carbapenems

Carbapenems represent a potentially unique anti-tuberculosis option. Emerging evidence demonstrates that they target the *Mycobacterium tuberculosis* cell wall and β -lactamase. A recent review concluded that they appear to kill TB, at least in the active phase, with possible greater potency when given along with a β -lactamase inhibitor.⁴⁴ Imipenem and meropenem are increasingly being used as companion drugs in delamanid- or bedaquiline-containing regimens in the treatment of extensively resistant strains, but must be delivered intravenously multiple times daily. The evidence for carbapenems for the treatment of TB is, however, still highly limited.

Faropenem is an oral penem of a class closely related to the carbapenems. A study scheduled to complete in March 2018 will evaluate the early bactericidal activity of faropenem with amoxicillin/clavulanic acid in patients with pulmonary TB.⁴⁵

Table 2. Regimens in advanced-stage clinical trials

Study Name	Experimental Arms	For Treatment of	Number of Participants	Phase	Estimated Study Completion Date
NEXT-TB	BDQ, LZD, LEVO, PZA, ETH/INH/TRZ	MDR	300	III	Late 2019
END-TB	BDQ, LZD, MOXI, PZA, BDQ, LZD, LEVO, PZA, CFZ, BDQ, LZD, LEVO, PZA, DLM, DLM, LZD, LEVO, PZA, CFZ, DLM, MOXI, CFZ, PZA	MDR	750	III	April 2021
MDR-END	DLM, LZD, LEVO, PZA	MDR	238	II	Late 2019
TB-PRACTECAL	BDQ, PRE, LZD, MOXI BDQ, PRE, LZD, CFZ BDQ, PRE, LZD	MDR	630	II/III	March 2021
Nix-TB	BDQ, PRE, LZD	XDR, pre-XDR	200	III	October 2021 (results published on ongoing basis)
ZeNix	BDQ, PRE, LZD	XDR, pre-XDR	180	III	January 2022
H-35265	DLM, LVX, LZD, PZA	MDR	300	III	August 2021
STREAM stage II	BDQ, CFZ, LEVO, EMB, PZA, INH, PRO, BDQ, CFZ, LEVO, PZA, INH, KAN	MDR	1155 (with stage I)	III	December 2021
STREAM stage I	MOXI, CFZ, EMB, PZA, INH, PRO, KAN	MDR	1155 (with stage I)	III	2018
Delamanid phase III	DLM + background	MDR	511	III	Completed (top-line findings late 2017)

BDQ: bedaquiline; CFZ: clofazimine; DLM: delamanid; ETH: ethionamide; EMB: ethambutol; INH: isoniazid; LEVO: levofloxacin; KAN: lanamycin; MOXI: moxifloxacin; PRE: pretomanid; PRO: prothionamide; PZA: pyrazinamide

RECOMMENDATIONS

- Governments, and especially the governments of countries with high TB burdens, should dramatically increase their investment in TB R&D. It is imperative that total global investment increases from the current \$600 million/year to the estimated \$2 billion/year that is needed. Whether or not governments manage to meet this need will provide a concrete test of the actual political will behind the various political commitments that will be made at the 2018 UN High Level Meeting on TB.
- The TB Alliance must urgently initiate an expanded access program for pretomanid so that more patients with XDR, pre-XDR-TB, or non-responsive or treatment-intolerant MDR-TB can have the option of trying the NiX regimen. Given that the TB Alliance is a non-profit organization, donors should provide financial support for this expanded access program.
- Medicines regulators should continue to ensure that sufficient data on the safety and efficacy of new drugs are gathered before drugs are approved. Efforts at deregulation through the 21st Century Cures Act in the U.S. and via Adaptive Pathways in the EU should be resisted. At the same time, regulatory delays in high-TB-burden countries must be addressed as a matter of urgency.
- Drug developers should include more phase IIc/III trials in their development plans to reduce the risk of failure in phase III.
- Governments and donors should support the establishment of and fund the operations of an international pre-approval access mechanism as proposed by Treatment Action Group and the Global TB Community Advisory Board.
- Governments must ensure that all people, irrespective of the form of TB that they have, have access to optimal TB treatment regimens as indicated by the available scientific evidence, and to DST to guide the choice of that optimal regimen.

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