



Review

Access to new medications for the treatment of drug-resistant tuberculosis: Patient, provider and community perspectives



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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) is on the rise, and is difficult to treat. The approval of two new drugs, bedaquiline and delamanid, and growing evidence for the use of linezolid, offer renewed hope for addressing MDR-TB. However, access to these medicines remains a significant challenge. These drugs have not been registered for TB in most settings; barriers to preapproval access persist; and high pricing and intellectual property restrictions limit access. Many unanswered research questions about optimal use of these drugs also limit access, particularly for vulnerable populations. This review outlines challenges in accessing drugs encountered from the perspective of clinicians, patients and affected communities, and offers potential solutions.

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1. Introduction

Drug-resistant tuberculosis (TB) is common, and the extent of resistance rising, rendering cure and the interruption of transmission increasingly difficult.¹ Two new drugs, bedaquiline and delamanid, recently received conditional regulatory approval to treat multidrug-resistant (MDR) TB.^{2,3} Mounting evidence also supports the repurposing of antibiotics, such as linezolid—approved for other indications—for MDR-TB.⁴ These drugs offer renewed hope of curing those with MDR-TB and of achieving a world free of TB.⁵ Access to these medications, however, remains a

significant challenge. This article highlights some of these regulatory, financial, and scientific access challenges from the perspectives of patients, providers and programs, with a hope that understanding these barriers will help overcome them.

2. Pre-approval access barriers

Pre-approval access programs, including “compassionate use” (CU) and “expanded access” programs, allow patients with limited therapeutic options to access potentially lifesaving investigational drugs prior to formal regulatory approval.⁶

Janssen, the manufacturer of bedaquiline, initiated a pre-approval access program for bedaquiline in 2011, while the drug was in phase IIb trials. To date, Janssen has successfully provided nearly 500 patients with access to bedaquiline.

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Despite this relative success, early attempts to access bedaquiline in the United States were complicated by a lack of clearly defined mechanisms both for dealing with requests and providing the drug. A physician caring for a patient with extensively drug-resistant (XDR) TB applied for CU access to bedaquiline. Various delays, including the drug being held at U.S. customs, caused two months to pass before bedaquiline reached the patient. The delay was a significant barrier in drug access, and similar delays have been reported elsewhere. Later requests were fulfilled more rapidly.

Moldova, a country with a significant MDR-TB problem, lacks a legal framework for CU, which prevents access. Now, nearly two years after patients, activists and a World Health Organization (WHO) TB program review raised this issue,⁷ it is understood that bedaquiline's European Medicines Agency (EMA) approval allows its import as "humanitarian aid". However, confusion over the legality of importing bedaquiline under CU means that Moldovan patients still have no access to bedaquiline, despite the efforts of civil society and the Moldovan National TB Program, and Janssen's willingness to provide the drug.

Pre-approval access to bedaquiline initially proved challenging for other country-specific reasons in South Africa, which has a large MDR-TB burden, with 15,419 cases reported in 2012 alone.⁸

As one clinician diagnosed with MDR-TB in 2010 in South Africa noted: "I was immediately concerned about survival, as I knew the dismal cure rates globally—48% in 2012.⁹ I heard of a new drug, bedaquiline, undergoing studies in South Africa and tried to gain access through a recently opened CU program. I was told I was not ill enough, as I did not have XDR-TB, despite the fact that the drug had only been studied in patients like me with MDR-TB.

After two months, I started losing my hearing from amikacin therapy. I was forced to choose between my hearing (and effectively, my career) and cure. I was extremely fortunate to gain access to bedaquiline after re-applying, so I could stop the amikacin therapy. I fully comprehended the risk of cardiac arrest associated with this, but facing MDR-TB, I was willing to take it. I was one of only four patients that gained access to the drug before the South African Medicines Control Council closed the CU program."

The South African Medicines Control Council closed this program, citing premature data and an initial preference for a clinical trial instead. Following the US Food and Drug Administration (FDA) approval of the use of bedaquiline to treat MDR-TB in December 2012, and lengthy discussions with the South African National Department of Health, the South African Medicines Control Council finally approved in 2012 a national "Clinical Access to Bedaquiline Programme", which has offered eligible patients in approved sites access to bedaquiline under safe conditions.¹⁰

Pre-approval access to delamanid has been much more limited. Otsuka initiated its CU program only in 2014—after EMA approval was assured and their phase III trial had completed enrollment, and has no expanded access. There are no clear procedures or eligibility criteria identified to guide application for delamanid under CU. To date, fewer than five patients have been enrolled, all of whom live in Europe, where the drug has been approved.

A recent case has elucidated that patients treated with bedaquiline are specifically excluded from consideration for delamanid due to Otsuka's concerns that both drugs may cause modest prolongation of the QT interval; the drugs have not yet been studied in combination.¹¹ CU access to delamanid was denied to a patient with the most drug-resistant TB isolate ever identified in the United States, confirmed susceptible only to linezolid and cycloserine, and presumed susceptible to bedaquiline. This patient had a very limited chance of survival without adding an additional

effective drug to the regimen, and was being treated in a facility with intensive cardiac monitoring to reduce potential risk. Due to Otsuka's refusal to provide delamanid, this patient is suffering from permanent disabling side effects of a suboptimal regimen, including hearing loss and peripheral neuropathy. Patients like this have the most to gain from use of novel combinations of drugs, but are specifically excluded by the company's current policy. Notably, in the absence of data on simultaneous use, the WHO's recent guidance on delamanid does not issue a negative recommendation against its use together with bedaquiline.¹² By precluding seriously ill patients from accepting any potential risk of receiving novel drug combinations, Otsuka's restrictive pre-approval access policy leaves patients with a definite risk of dying from drug-resistant TB. This runs in stark contrast to the purpose and practice of compassionate use, designed to offer an otherwise unavailable treatment for the most desperate clinical cases.

A recent prospective study from South Africa showed the poor five-year prognosis for those receiving treatment for XDR-TB: only 11% of patients with XDR-TB had a favorable treatment outcome, and overall mortality was 73%.¹³ These statistics highlight the dire and urgent need for new treatment regimens, but it will be years before these regimens are identified and available, as definitive research studies and new drug registration timelines are lengthy. It is therefore crucial to make pre-approval access available to patients now to give them a chance for survival. These access programs also provide countries with the framework to implement broader policy planning and roll-out of more effective MDR- and XDR-TB regimens at a national level.

3. Registrations, normative guidance and technical assistance barriers

Pre-approval access is critical for select urgent TB cases, but widespread registration of new drugs is required for broad uptake. Unfortunately, slow registration due to limited industry investment and regulatory challenges (such as a lack of harmonization across authorities requiring multiple onerous submission processes, and a lack of capacity among regulators to rapidly review drug applications) has stymied access. So far, bedaquiline is only approved by six regulatory authorities, with several more registrations in high MDR-TB burden countries pending. Otsuka has only filed for approval for delamanid in Europe, Korea, and Japan, home to very few people with MDR-TB; Otsuka has not registered the drug in most of the countries where it held clinical trials.¹⁴ More registrations for both drugs, but especially delamanid, are urgently needed.

The regulatory approval of new drugs for the treatment of TB is just one step that must occur for medications to reach those who need them. In most high-burden TB countries—especially those that rely on external funding—the medication must also be recommended by the WHO; purchased through approved mechanisms and imported; and incorporated into a national plan consistent with the overall strategy of the TB program and that follows WHO recommendations.^{15,16} In addition, countries need to develop updated clinical guidance for the use of new medications, train implementers, and set up systems needed for the monitoring and active pharmacovigilance that are essential parts of new drug introduction.^{17–19}

These steps are crucial, but can be time-consuming and prolong the process of getting the medication to those most in need. The WHO has developed a more streamlined process for introducing new medications for TB under program conditions,¹⁷ but significant hurdles remain. At this writing, although several countries have ordered bedaquiline for the treatment of MDR-TB, not a single patient in a high-burden setting has received bedaquiline or delamanid under program conditions. Most countries are also

planning to introduce these medications in a pilot fashion, which means equity in access may take years to achieve.

A new initiative, supported by UNITAID and implemented by Partners In Health, Médecins Sans Frontières and Interactive Research and Development, is designed to jumpstart uptake of the new drugs by overcoming some of these registration, normative guidance and technical assistance barriers. Known as endTB, it will spur early adoption of these drugs.²⁰ Procuring bedaquiline and delamanid for 3,200 patients across 20 countries over four years, endTB will accompany programs and clinicians in the use of new drugs. Both through an early adoption component of endTB—delivering treatment according to current guidance—and through a rigorous clinical trial, endTB will establish best practices in their use. Moreover, endTB will work with local and global policymakers to ensure that experience and evidence developed through endTB will translate into revised policy and practice. This will end the “chicken-and-egg” phenomenon plaguing introduction of these new drugs: countries are reluctant to administer them because they are not widely used, and they are not widely used because of insufficient safety data from routine use in programs.

4. Pricing and procurement barriers

Pricing and procurement can also pose important barriers for access to drugs for those who need them. National TB programs are generally under-resourced, and the additive costs of new drugs can be prohibitive. Some countries rely heavily on donor support, such as from the Global Fund to Fight AIDS, Tuberculosis and Malaria, to procure medicines for MDR-TB (though several high MDR-TB burden countries are being phased out of Global Fund eligibility).²¹ The Global Fund has worked with some countries to reallocate existing budgets toward the procurement of bedaquiline, for example; however, the Global Fund will only fund procurement of new drugs for programs meeting WHO-specified conditions.^{22,16} Moreover, high drug prices mean that fewer patients can be reached with the same amount of money, and that limited funding must be diverted away from other important areas such as investments in health systems or procurement of essential companion drugs. Domestic and donor funding can go much farther when drugs are affordable.

In some cases, TB programs may simply not procure a drug due to pricing challenges. One South African patient's struggle to overcome XDR-TB by taking linezolid illustrates that high drug prices can have a devastating impact:

“I was diagnosed with TB in late 2010. After about three weeks, the doctor diagnosed me with MDR-TB. I took the MDR-TB drugs for some time, then one morning I woke up and everything was so quiet; I tried to turn on the television but still there was no sound. So the next morning I told the hospital nurse that I can't hear, she sent me to the audio department where the audiologist wrote down that I was deaf. Then I was told that I now had pre-XDR-TB.

I had to take even more toxic drugs, and undergo surgery that left me with a collapsed lung and a broken rib. Now I was at home taking the pre-XDR-TB drugs at the clinic, only to be told they had stopped working. Luckily enough I met a new doctor who explained that I now had XDR-TB. She said that there was a drug that might cure me but there was no guarantee. She also said the drug is very expensive and it is not easily available. The drug I was told about is linezolid.

I took linezolid with the other old drugs, and after two years it worked and finally I was cured of XDR-TB. It was sure not an

easy journey at all, but I was lucky enough to get the drug through Médecins sans Frontières (MSF).²³

In South Africa, the high price (nearly USD70 per 600 mg tablet) of brand-name linezolid limits the number of patients treated. Now MSF has special permission to procure affordable generic linezolid; however, widespread access is urgently needed. Had the patient above been able to access linezolid earlier, she may not have lost her hearing or required surgery.

Difficulties accessing linezolid also challenge the uptake of new drugs, as TB drugs must be given as part of effective regimens. For example, Romania accounts for one-third of all TB cases in the European Union (EU) and has far more cases of MDR-TB than any other EU member state.²⁴ Yet linezolid, which is left off the list of approved TB drugs and available only in brand-name form at a very high price, is inaccessible to most. This in turn makes bedaquiline also inaccessible: due to an inability to provide an adequate background regimen, the vast majority of patients at the Global Fund-supported MDR-TB treatment center in Bucharest who could have benefitted from bedaquiline under CU were never able to access it.

Romanian doctors have expressed frustration at their inability to treat patients with XDR-TB. According to one: “*We do not treat XDR-TB in Romania. XDR-TB patients receive the same treatment as MDR-TB.*” Some Romanian patients with XDR-TB have managed to purchase linezolid, at great cost, from online pharmacies in order to qualify for bedaquiline. However, most XDR-TB patients are unable to do this, especially those from vulnerable groups. The Romanian TB program's inability to provide the necessary drugs to form appropriate regimens represents a missed opportunity.

5. Research and development barriers

Access to new and repurposed medications is also hindered by insufficient clinical evidence guiding their optimal use, especially in effective combinations. Delamanid and bedaquiline have each been approved as single agents on top of a lengthy, difficult to tolerate background regimen. An understanding of how these drugs can contribute to shorter, less toxic and more tolerable regimens is urgently needed. Additionally, the development of and access to rapid, reliable drug susceptibility tests to guide appropriate treatment and monitor the development of resistance is important to accompany new therapies.

There is a desperate need for additional drugs to treat MDR-TB. One promising class is the oxazolidinones: sutezolid and AZD5847 are under development with the hope that they may share linezolid's activity against MDR-TB but have fewer adverse events.²⁵ But Pfizer transferred the rights to sutezolid, leaving its future uncertain, with limited product available for further studies. Similarly, AstraZeneca, maker of AZD5847, announced it would no longer pursue TB drug development. There is clearly a need for partnering with industry to ensure that promising agents are fully developed.

Vulnerable populations—such as children, people with HIV, and people who use drugs and alcohol—are routinely excluded from research, limiting access later on. A lack of data from pharmacokinetic and safety studies in children to inform dosing limits pediatric access to new TB drugs. While Otsuka's development of delamanid for children is advancing, Janssen's initiation of pediatric studies of bedaquiline has been much slower. This discordance may in part be attributable to differing regulatory requirements: the EMA, where Otsuka first registered delamanid, requires a Pediatric Investigational Plan, whereas the U.S. FDA, where Janssen first registered bedaquiline, exempts orphan drugs—such as those for TB—from requirements for pediatric studies.

TB disproportionately affects people with HIV, and co-infection rates of HIV and MDR-TB can reach 70%.⁴ Despite this high burden, HIV-infected MDR-TB patients are often excluded from TB drug trials. For bedaquiline and delamanid, only 14% and 1% of participants in the respective phase 2 clinical trials were HIV-infected.^{26,27} Few study participants were receiving ART and all had relatively high CD4 levels, and were therefore not representative of typical patients. Similarly, data on linezolid in HIV-infected MDR-TB patients are lacking; fewer than 10% of patients in two recent systematic reviews were HIV-infected.^{28,29} This lack of evidence of the efficacy and safety of new drugs in HIV-infected patients is a barrier to access. WHO states that ‘special caution’ is required for the use of bedaquiline in HIV-infected adults.³⁰ In particular, concerns about potential drug-drug interactions and additive side effects with ART have resulted in cautious guidance around use of new drugs in people with HIV,³¹ and registrations (such for bedaquiline in South Africa) only for patients not receiving ART.³² Given the burden of MDR-TB among HIV-infected individuals and the clear benefits of early initiation of ART with TB treatment, access to new TB drugs for HIV-infected individuals is required.³³

Persons who use alcohol and recreational drugs are also at increased risk for TB, as well as HIV and hepatitis C, but these conditions are often an exclusion criterion for participation in clinical trials. There is little research on new medications in this population. These individuals commonly have co-morbidities, making drug-drug interactions a major concern. Substance use (or opioid substitution therapy) and medications used to treat TB, HIV and hepatitis C can also have overlapping risk of cardio- and hepatotoxicity. A better understanding of how MDR-TB can be safely treated in persons using alcohol and other recreational drugs is an urgent need, but the exclusion of such persons from research and program use leaves this population behind.

6. Conclusions

New drugs to treat MDR-TB provide renewed hope for patients and clinicians. However, access to these drugs is very limited, particularly in countries with the highest TB burdens and least resources. This paper presents some significant challenges faced by patients, providers, and programs in accessing new and repurposed drugs to effectively treat MDR-TB. Barriers to pre-approval access can be devastating to individuals suffering from highly resistant disease, while delays in research, registration and the provision of technical assistance hinder access in a more widespread manner. Costs are another significant barrier to access, for both new drugs and repurposed agents, and urgent collective action is needed to bring the price of these products to an affordable level for patients and programs. Optimal benefit from new drugs will require use in combination with existing and repurposed drugs in new regimens; however, research is lacking into such combinations. In addition, research is needed to inform use in key populations such as children and people with HIV.

Overcoming each of these individual barriers will require specific solutions. Companies need to design and implement pre-approval access programs early in the course of drug development, provide clear guidance and transparent eligibility criteria, and work with countries to ensure that expedited requests and rapid shipment can be arranged. Countries need to develop regulatory and legal frameworks that allow for pre-approval drug use for patients with MDR-TB. Work to develop normative guidance and technical assistance around these issues should begin while awaiting formal WHO guidance and arrival of the new and repurposed drugs in country. The TB community must take the lead, rather than allowing profit-driven companies to decide the “fair” market value of these drugs. Researchers, funders, and regulators must support innovative research to assess new, shorter and more

tolerable drug combinations that include new drugs, and includes vulnerable groups. Frank and open communication between all stakeholders with an interest in improving the lives and health of persons affected by MDR-TB is an essential action step to effectively address all of these barriers. We hope that sharing the experiences presented in this paper will continue this dialogue.

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