

# Access to TB Testing and Treatments: GeneXpert and Delamanid



Dr Abdu Samya Bashagha examines a patient in Abu Sitta Hospital in Tripoli, Libya, where MSF provides TB care to people from both Libyan and migrant communities. 2022. Photo: Omar Rashid/MSF

# **INTRODUCTION**

Despite being curable, tuberculosis (TB) is one of the world's deadliest infectious diseases. In 2022, an estimated 1.3 million people died—more than two people every minute—and 10.6 million people fell ill with TB. This includes 410,000 people who fell ill with drug-resistant TB (DR-TB).<sup>1</sup>

Timely and effective diagnosis is paramount to successful TB and DR-TB treatment. But globally, a third of people with TB and two-thirds of people with DR-TB are not diagnosed. These gaps cascade into delayed access to treatment, resulting in sickness and death.

Much-needed technological breakthroughs in TB testing and treatment over the last decade promise to significantly change the course of the global TB epidemic. Rapid molecular tests such as Cepheid's GeneXpert can deliver highly accurate diagnosis of TB and DR-TB in two hours and are recommended by WHO as initial tests. Without rapid diagnostic tests that can be used in decentralised settings, early diagnosis and initiation of the most appropriate treatment regimens becomes extremely challenging, if not impossible, and contributes to ongoing transmission of TB and DR-TB at the community level.

In DR-TB treatment, the introduction of newer medicines such as bedaquiline, delamanid and pretomanid has paved the way for all-oral, shorter, more effective, safer regimens. In December 2022, WHO recommended use of two six-month regimens consisting of bedaquiline and pretomanid (BPaLM and

BPaL) in place of existing longer regimens to treat DR-TB.<sup>2</sup> However, the implementation of these new regimens has been lagging, and older, longer regimens with intolerable side effects and sub-optimal outcomes continue to be used in some countries.

The promise of these lifesaving new TB tests and medicines has been kept in check by price and patent barriers. In 2022, only 47% of the 7.5 million people newly diagnosed with TB were diagnosed with the WHO-recommended rapid molecular diagnostics.<sup>1</sup>

At the United Nations High-Level Meeting on TB on 22 September 2023, governments pledged to reach 90% of people estimated to have TB with testing and treatment by 2027.<sup>3</sup> This translates to providing lifesaving treatment for up to 45 million people between 2023 and 2027, including up to 1.5 million people with DR-TB.

In order to translate governments' commitments to reality, the corporations making these lifesaving TB tools need to dismantle the many access barriers currently in place. This report offers case studies of two critical tools, GeneXpert and delamanid, and outlines actions that the corporations making them, Cepheid/Danaher and Otsuka, respectively, need to take to unlock access to these revolutionary, lifesaving medical tools. Broader access to these two tools, together with other new prevention, testing and treatment options, will enable governments and TB treatment providers like Médecins Sans Frontières/Doctors Without Borders (MSF) to prevent many more TB deaths and tackle TB epidemics worldwide.

## **GENEXPERT DIAGNOSTIC TESTS**

GeneXpert is a rapid molecular diagnostic technology developed by the US-based corporation Cepheid, a subsidiary of the financial investment corporation Danaher, that has revolutionised rapid, accurate, near-point-of-care diagnosis of TB and DR-TB, among other diseases. Cepheid produces two tests for TB: the Xpert MTB/RIF Ultra test that can detect drug-susceptible TB (DS-TB) and rifampicin-resistant TB (RR-TB), and the Xpert MTB/XDR test that can detect resistance to fluoroquinolones, a class of drugs that is key in DR-TB treatment, as well as resistance to other key drugs in TB treatment.

Compared to older methods, such as smear microscopy, that miss the presence of TB in at least half of people with TB, and do not provide information on resistance; or culture-based methods, which take weeks to months to give results, GeneXpert's TB tests can detect TB and DR-TB in two hours, and are much more sensitive than smear microscopy. WHO has recommended these Xpert TB tests for several years now. However, due to the high price of the GeneXpert test cartridges, many low- and middle-income countries (LMICs) cannot scale up this TB testing for all people who need it.

### What we know

### GeneXpert TB test prices

GeneXpert tests entered the LMIC market at a negotiated concessional price from 2012 onwards. The price of the TB/RR-TB test cartridge (Xpert MTB/RIF Ultra) was set at US\$9.98, and the XDR-TB test cartridge (Xpert MTB/XDR) at \$19.80 (reduced to \$14.90 in January 2023), for public purchasers and

non-governmental organisations (NGOs) in 145 LMICs. The price of \$9.98 for the TB/RR-TB test was a result of a 10-year "buy down" of the test by WHO and Unitaid in 2012.<sup>i</sup>

While Cepheid's sales of this test increased exponentially in the following years, its price did not change until September 2023.

## Cost of production

Because of lack of transparency from Cepheid on how much it costs to produce the GeneXpert tests, MSF commissioned an independent engineering consultancy company to estimate these costs in 2018 and published the results in 2019.<sup>4</sup> The analysis showed that at 10 million annual sales volumes, the cost to produce one GeneXpert test is between \$3.00 and \$4.60. The analysis also showed that there is no major difference in the cost of producing GeneXpert tests for different diseases such as TB, HIV, hepatitis and more. Therefore, the difference in the prices of the cartridges for TB (\$9.98 for the TB/RR-TB test vs \$19.80 for the XDR test) Cepheid charged for years is not grounded in cost data. Cepheid has thus for years charged countries 2-4 times what it is estimated to cost to produce these TB tests. Further, Cepheid received **over \$250 million in public funding**, primarily from the US government, for the research and development (R&D) of GeneXpert, which makes these high prices even more unjustified.

### 2023 price reduction

On 19 September 2023, under unprecedented pressure from the "Time For \$5" campaign and TB activists, Danaher and Cepheid announced that they will sell the TB/RR-TB test cartridge (Xpert MTB/RIF Ultra) "at cost" to countries with a high burden of TB. The corporations reduced the price of the Xpert MTB/RIF Ultra test by 20%, from \$9.98 to \$7.97 per test. They also committed to "validating the cost of the test annually with an internationally accredited third-party assessment" and to adjusting pricing accordingly. While Cepheid had reduced the price of the XDR-TB test cartridge to \$14.80 from \$19.80 earlier in 2023, the corporations did not include this cartridge or cartridges for any other diseases in their September 2023 price reduction despite analysis showing no significant difference in the cost to produce different cartridges.

### What we need

While the 20% reduction in the price of the TB/RR-TB test is a significant step in the right direction, the test for XDR-TB, the most severe form of TB, continues to be prohibitively priced at \$14.90 per test cartridge for governments.

In 2022, over 30% of all people with multidrug-resistant (MDR)/RR-TB who were tested globally for fluoroquinolone resistance had lab-confirmed resistance. Fluoroquinolone resistance testing allows clinicians to make an informed choice on the most appropriate treatment with the best chance of success. The GeneXpert XDR-TB test (Xpert MTB/XDR) is the only rapid way to test fluoroquinolone resistance in decentralised settings. Without access to this test, facilities must rely on culture-based drug susceptibility testing or line probe assays for fluoroquinolone resistance testing, which can only be performed in centralised lab facilities and take weeks to provide results.

<sup>&</sup>lt;sup>i</sup> In 2012, Unitaid, the United States Agency for International Development (USAID), the Bill and Melinda Gates Foundation (BMGF) and the United States President's Emergency Plan for AIDS Relief's (PEPFAR) Office of the U.S. Global AIDS Coordinator and Health Diplomacy negotiated a "buy-down" with Cepheid, based on estimated sales volumes of > 4.7 million assays a year. Cepheid was given an upfront payment of US\$11.1 million to establish a ceiling price of US\$9.98 per Xpert MTB/RIF assay for a 10-year period. Furthermore, according to the agreement with Cepheid, any improved assay would be priced at that same amount, or lowered in price, if any component was removed, or if any royalties expired during the time period (original or improved assays).

Therefore, the price reduction seen for the TB/RR-TB test should be extended to the XDR-TB test, as well as all other GeneXpert tests in Cepheid's Global Access Program.

Cepheid and Danaher's "at cost" price of \$7.97 varies considerably from the \$5 cost published in 2019 by MSF. We welcome the corporations' offer for an independent third-party evaluation of the cost of its tests, and call on them to ensure the methodology used and the results of the annual analysis are shared publicly in a timely and transparent manner. We also call on the corporations to ensure that the annual cost analysis includes all GeneXpert tests provided to LMICs though Cepheid's Global Access Program.



TB activists demanding a reduction in the price of the GeneXpert TB tests in September 2023 in New York City, USA. Photo: Sheila Shettle

## **DR-TB DRUG DELAMANID**

Together with bedaquiline, delamanid was the first new medicine developed and marketed in half a century for the treatment of DR-TB. It received conditional approval from the European Medicines Agency (EMA) in 2014 for its use in adults (50mg tablet) and in 2021 for its use in children (25mg dispersible tablet)

### What we know

### <u>Price</u>

In September 2023, Otsuka reduced the price of delamanid from \$1,700 to \$1,190 for a six-month treatment course for countries purchasing through the Stop TB Partnership's Global Drug Facility (GDF).<sup>5</sup> This 27% price reduction is a significant step, but the price is still much too high for countries and treatment providers that need it to scale up DR-TB treatment. According to researchers, delamanid could be produced and sold profitably for a price between \$30 to \$96 for a six-month treatment course, less than 10 times the current price.<sup>6</sup>

## <u>Patents</u>

Otsuka's primary patent on the basic compound of delamanid expired in October 2023.<sup>7</sup> The corporation also has secondary patents and patent applications on delamanid, but generic manufacturers based in India have said these will not block the entry of generic versions of the medicine. Indian corporation Lupin appears to be most advanced in the process of developing a generic version of delamanid, and should be ready to supply it from 2024 onwards.

### <u>Licenses</u>

In 2017, Otsuka licensed delamanid to the pharmaceutical corporations R-Pharm and Viatris for supply and registration of delamanid in countries where it has no commercial presence. Viatris supplies delamanid to India and most other LMICs, while R-Pharm supplies to Russia. This licensing arrangement did not lead to any reduction in price of delamanid since 2017 as the corporations operated in different markets. Even though Otsuka's primary patent on delamanid has expired, it is unclear whether Otsuka's license terms still restrict Viatris from supplying to countries excluded from the scope of their license.

#### What we need

Otsuka should commit to non-enforcement and withdrawal of all remaining patents on delamanid for DR-TB, including process patents, in all LMICs, to speed up the availability of more affordable generic versions of the medicine. Following a massive campaign led by activists, and joined by countries and Unitaid, such a step was recently taken by another pharmaceutical corporation, Johnson & Johnson (J&J), regarding the other new lifesaving DR-TB drug, bedaquiline. Otsuka and its partners, Viatris and R-Pharm, should implement the necessary steps so as to bring the price of delamanid closer to the estimated cost-based generic price of \$30 -- \$96 per treatment course of six months.

In order to enhance competition on price, Otsuka should allow Viatris to supply delamanid directly and through GDF in countries excluded from their license agreement, where Otsuka keeps direct supply.

Furthermore, the recommended daily intake of four 50mg tablets presents an adherence challenge for patients. Otsuka and other manufacturers should explore options to decrease the current pill burden in order to enhance acceptability and affordability of treatment regimens comprising delamanid.

### ACCESS MILESTONES FOR DR-TB DRUG BEDAQUILINE

Bedaquiline, an oral TB drug developed by the US-based corporation J&J, and brought to market in 2012, is now the backbone of DR-TB treatment regimens recommended by WHO. It has facilitated improved, shorter, better-tolerated and more-effective treatment regimens for people with DR-TB.

J&J first priced bedaquiline in LMICs at \$900 (2014) and then at around \$400 (2018) for a six-month treatment course, keeping it out of reach of people with DR-TB.

Research commissioned in 2016 by the MSF Access Campaign showed that bedaquiline could be sold profitably at a price of \$48 -- \$102 for a six-month treatment course. After years of bilateral talks and advocacy to get the corporation to drop the price of this lifesaving drug did not prove fruitful, MSF launched a public campaign in 2019 with the message: "J&J - A Dollar A Day." Public pressure resulted

in a major initial win in 2020 of a roughly 30% price drop for this drug from \$2/day to around \$1.50/day by J&J, or around \$275 for six months, down from \$400.<sup>8</sup>



TB activists and survivors demanding a reduction in price of bedaquiline at the 2019 Union World Conference on Lung Health in Hyderabad, India. Photo: Siddharth Singh/MSF

The high prices J&J has charged over the years are the result of the 20-year patent monopoly enjoyed by the corporation in line with international trade rules. While the corporation's primary patent on bedaquiline expired in July 2023, it has, or has applied for, secondary patents in many countries to extend its monopoly.

In 2019, Nandita Venkatesan and Phumeza Tisile, TB activists and DR-TB survivors from India and South Africa respectively, challenged J&J's secondary patent application on bedaquiline in India beyond its July 2023 expiry. In March 2023, the Indian Patent Office rejected J&Js patent extension, allowing generic manufacturers to launch affordable versions from July 2023 onwards.

In the wake of renewed public pressure since the beginning of 2023 by MSF, CSO allies, and the global TB community, including a new group of online "TB fighters", a <u>series of incremental developments</u> culminated in a drop in the price of bedaquiline by J&J to \$130 for six months treatment, bringing it much closer to the generic price target.<sup>9</sup>

In September 2023, following continued pressure from MSF, the TB Fighters, Unitaid and governments to drop its secondary patents, J&J announced its intent not to enforce any of its patents for bedaquiline.

This major victory marks the successful end of a more than a decade-long push for access to affordable bedaquiline. While a massive win for the TB community, the effects of J&J's decisions, at long last, to offer an affordable price and to not enforce secondary patents, go beyond TB. They set a precedent for other corporations and producers of all current and future medicines of public health importance to place people's lives before profits.

# endTB TRIAL: EFFICACY AND SAFETY RESULTS, AND REGIMEN PRICES

In 2023, two randomised controlled trials (RCTs), endTB and endTB-Q, co-led by MSF, Partners in Health (PIH) and Interactive Research and Development (IRD), reached major milestones.<sup>10</sup> The endTB trial tested five new nine-month treatment regimens for fluoroquinolone-susceptible RR-TB including delamanid and/or bedaquiline combined with other oral TB drugs and compared them to the standard of care control arm. The trial enrolled 754 patients across eight countries and the final results provide breakthrough evidence for new all-oral, shortened regimens to treat MDR-TB. Results were presented at the 53rd Union World Conference on Lung Health in Paris in November 2023.

The endTB trial results are complementary to those previously provided by another MSF-led clinical trial, TB-PRACTECAL, which showed the effectiveness of a novel all-oral six-month regimen, BPaLM, recommended since 2022 by WHO as the preferred regimen for treatment of MDR/RR-TB.<sup>2</sup>

The five experimental regimens evaluated in the endTB trial are shown in Table 1.



#### Table 1: endTB regimens and their composition

Bdq: bedaquiline; Dlm: delamanid; Cfz: clofazimine; Lzd: linezolid; Mfx: moxifloxacin; Lfx: levofloxacin; Z: pyrazinamide

endTB regimens 1, 2, 3, achieved favorable outcomes in 89%, 90.4%, and 85% of participants, respectively, and demonstrated, in all analysis, non-inferiority to the standard of care control arm (which achieved 80.7% of favourable outcomes). In addition to non-inferiority, endTB regimen 2 was shown to be superior to the control arm.

Regimen 5 also showed a very good treatment response at 85.6% and was non-inferior to the control arm in one of the primary analysis populations, representing an additional strong alternative for treatment of patients affected by MDR/RR-TB in situations when the other regimens cannot be used.

An important element of this trial is the epidemiological diversity of the study population, which included people affected by comorbidities that occur commonly with MDR-TB like HIV, hepatitis C, diabetes and substance-use disorders, across eight countries.

Furthermore, all drugs used to build the endTB regimens are recommended for use in children and exist as paediatric formulations, highlighting their potential for regimens that can be used to treat children with MDR-TB.

These excellent results establish the success of these multiple all-oral shorter regimens in treating MDR/RR-TB across patient groups, giving countries and clinicians additional tools to address the challenges of DR-TB treatment with a patient-centred approach, tailoring treatment to the specific characteristics and comorbidities of patients.

The second RCT, endTB-Q, aims to find a simpler, less toxic, shorter regimen for fluoroquinoloneresistant MDR-TB. The experimental regimen contains bedaquiline, delamanid, clofazimine, and linezolid, is delivered for six or nine months, and compared to the latest recommended standard of care for treatment of fluoroquinolone-resistant MDR-TB. In March 2023, enrolment was completed with a total of 324 patients across six countries (India, Kazakhstan, Lesotho, Pakistan, Peru and Vietnam). Final results, expected in 2025, could bring additional groundbreaking evidence for new patient-centred approaches in treatment of these extremely complex forms of DR-TB.

Table 2 provides the price countries would pay for treating one patient with endTB regimens, and compares them against the prices that these regimens could be available for if the newer drugs bedaquiline, pretomanid and delamanid were priced at their estimated cost-based generic price.

Regimen (no. of months)	Current regimen price (in US\$)*	Potential regimen price with optimal generic competition (in US\$)**
<u>endTB 1 (9)</u>	\$290	\$189 \$262
Bdq-Lzd-Mfx-Z		
<u>endTB 2 (9)</u>	\$341	\$264 \$337
Bdq-Cfz-Lfx-Lzd-Z		
<u>endTB 3 (9)</u>	\$2,023	\$183 \$352
Bdq-Dlm-Lfx-Lzd-Z		
<u>endTB 4</u> (9)	\$1,956	\$242 \$337
Dlm-Cfz-Lfx-Lzd-Z		
<u>endTB 5 (9)</u>	\$1,977	\$262 \$358
Dlm-Cfz-Mfx-Z		
BPaLM (6)	\$416	\$189 \$386

#### Table 2: The price of end-TB regimens

\*based on lowest prices from GDF (October 2023) for people weighing 35-50kg \*\*based on lowest prices from GDF, except cost-based generic prices for Bdq, Dlm, Pa

Due to the unjustified high price of delamanid, endTB 3, 4 and 5 are all priced in the range of \$2,000 per patient. A reduction in the price of delamanid that brings it closer to its estimated cost-based generic price will bring the price of these regimens down to the current price of the BPaLM regimen and allow countries to roll them out at the scale needed. After expiry of Otsuka's primary patent in October 2023, generic competition is expected by Q2 2024.

# CONCLUSION

Results from the endTB trial provide groundbreaking additional evidence for all-oral shorter regimens for MDR/RR-TB, giving countries and clinicians new tools to address the challenges of DR-TB treatment with a patient-centred approach.

The expiry of the primary patents on bedaquiline and delamanid in 2023 offers the possibility of scaling up access to shorter, safer and more effective regimens to treat DR-TB in countries with a high burden of TB.

J&J and Otsuka should commit to withdrawing all remaining patents for these compounds in countries with a high TB burden, and Otsuka together with its partners, Viatris and R-Pharm, should take the steps necessary to make delamanid more affordable and accessible to all people who need it.

After years of campaigning and advocacy, the 20% price reduction for the GeneXpert TB/RR-TB test (Xpert MTB/RIF Ultra) by Danaher/Cepheid is a welcome development for governments and TB treatment providers in LMICs. This price reduction should be extended to the test for XDR-TB (Xpert MTB/XDR), as well as GeneXpert tests for all other diseases. The corporations should also ensure the results of their promised cost evaluation are shared publicly in a timely and transparent manner.

These steps are necessary for the successful realisation of governments' commitments to scale up TB testing and treatment, and to save many more lives, by 2027.

#### REFERENCES

<sup>4</sup> MSF. Time for \$5: GeneXpert diagnostic tests. [Online]. 2019 Dec 2 [Cited 2023 Nov 13]. Available at: https://msfaccess.org/time-for-5-brief

<sup>&</sup>lt;sup>1</sup> WHO. Global Tuberculosis Report 2023. [Online]. 2023 Nov 7 [Cited 2023 Nov 13]. Available at: <u>https://www.who.int/publications/i/item/9789240083851</u>

<sup>&</sup>lt;sup>2</sup> MSF. MSF responds to groundbreaking updated WHO guidelines for drug-resistant tuberculosis. [Online]. 2022 Dec 15 [Cited 2023 Nov 13]. Available at: <u>https://msfaccess.org/msf-responds-groundbreaking-updated-who-guidelines-drug-resistant-tuberculosis</u>

<sup>&</sup>lt;sup>3</sup> UN General Assembly. Political declaration of the high-level meeting on the fight against tuberculosis. [Online]. 2023 Oct 5 [Cited 2023 Nov 13]. Available at: <u>https://documents-dds-ny.un.org/doc/UNDOC/GEN/N23/306/91/pdf/N2330691.pdf</u>

<sup>&</sup>lt;sup>5</sup> Stop TB Partnership. September 2023 medicines catalog. [Online]. 2023 Sep [Cited 2023 Nov 13]. Available at: https://www.stoptb.org/sites/default/files/gdf\_medicines\_catalog\_0.pdf

<sup>&</sup>lt;sup>6</sup> Gotham D, Fortunak J, Pozniak A, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother 2017;72(4):1243-1252. [Cited 2023 Nov 13]. Available at: https://doi.org/10.1093/jac/dkw522

<sup>&</sup>lt;sup>7</sup> Medicines Patent Pool. MedsPaL Medicines Patents and Licenses Database. Delamanid 50mg. [Online]. [Cited 2023 Nov 13]. Available at: <u>https://www.medspal.org/?product%5B%5D=Delamanid+50+mg&page=1</u>

<sup>&</sup>lt;sup>8</sup> MSF. Johnson & Johnson TB drug price reduction is important step, and governments need to urgently scale up better treatment. [Online]. 2020 Jul 6 [Cited 2023 Nov 13]. Available at: <u>https://msfaccess.org/johnson-johnson-tb-drug-price-reduction-important-step-and-governments-need-urgently-scale-better</u>

<sup>&</sup>lt;sup>9</sup> Perrin C, Gupta S, Joseph R. Johnson & Johnson's patenting & pricing strategy for TB medicine bedaquiline: a cautionary tale for new TB medicines. Geneva Health Files. [Online]. 2023 Oct 6 [Cited 2023 Nov 13]. Available at: <u>https://genevahealthfiles.substack.com/p/johnson-and-johnsons-patent-bedaquiline-tb</u>

<sup>&</sup>lt;sup>10</sup> EndTB. Testing novel, short, all-oral regimens for MDR-TB. [Online] [Cited 2023 Nov 13]. Available at: https://www.endtb.org/clinical-trial