

Drug-resistant Tuberculosis treatment & access to delamanid in South Africa

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About drug-resistant tuberculosis (DR-TB)

Tuberculosis (TB) is a bacterial infection transmitted through the air by people with active respiratory disease. In 2015, there were an estimated 10.4 million new TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children.ⁱ

The World Health Organisation's (WHO) latest Global TB Report, published on 13 October, reveals that TB deaths jumped to 1.8 million in 2015 from 1.5 million in 2014, with 41% of people estimated to have fallen sick with the disease being left undiagnosed and untreated.

Although the number of TB deaths globally fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015, surpassing HIV in terms of deaths caused (i). Drug-sensitive TB (DS-TB) is treatable with a six-month course of antibiotics: four drugs in the first phase and two drugs in the second.

Drug-resistant TB (DR-TB), however, does not respond to one or more standard TB drugs: multidrug-resistant TB (MDR-TB) is resistant to at least two drugs comprising the backbone of standard TB treatment: isoniazid and rifampicin; extensively drug-resistant TB (XDR-TB) does not respond to fluoroquinolones and one of three injectable drugs used for treating MDR-TB.ⁱⁱ Therefore, treatment regimens for DR-TB must contain at least four working drugs, with higher resistance profiles requiring more drugs.

According to the WHO, an estimated 480,000 people developed some form of MDR-TB in 2015, with just 125,000 (20%) enrolled into treatment. Only half of all MDR-TB patients and about 26% of patients with XDR-TB who initiated DR-TB treatment worldwide in 2013 were successfully cured (i).



Simbongile Xesha (24) undergoes a routine exam to check how she's responding to her DR-TB treatment. © Sydelle Willow Smith



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DR-TB in South Africa

South Africa has one of the highest burdens of TB and DR-TB in the world. In 2015, almost 300,000 people were diagnosed with TB in South Africa, including 20,000 with some form of DR-TB.

Individuals with weak immune systems are more vulnerable to contracting TB, and over 70% of DR-TB patients in Khayelitsha,ⁱⁱⁱ and nearly 60% of people diagnosed with TB in South Africa are co-infected with HIV (i).

Findings from Khayelitsha (above), a sprawling peri-urban township in the Western Cape Province, suggest that nearly half of diagnosed DR-TB cases (45.8%) are the result of direct person-to-person transmission of drug-resistant strains of TB (iii).

Current DR-TB treatment

Drug-resistant forms of TB are much harder to cure than drug-sensitive forms, and the limited treatment options available involve long, complex, toxic and expensive treatment regimens. At present, DR-TB patients have to take more than 10,000 pills that can have detrimental side effects, and suffer through painful daily injections for the first six to eight months.^{iv} New and repurposed DR-TB drugs used in combination have strong potential for improving treatment outcomes.

WHO guidance on DR-TB treatment changed in 2016, recommending a shorter MDR-TB regimen lasting 9-12 months instead of two years.^v Recommended treatment duration for XDR-TB remains unchanged at 18 – 24 months.

The shorter MDR-TB regimen does not include new drugs such as bedaquiline and delamanid, but instead recommends them as 'add-on agents' in specific cases, such as with XDR or pre-XDR-TB or when a patient exhibits intolerance to existing drugs in the regimen.

Critically, a few years after two new drugs — bedaquiline and delamanid— were conditionally approved to treat DR-TB, barely two percent of those who could benefit from these treatments have access to them.^{vi}

According to Otsuka, the Japanese pharmaceutical manufacturer of delamanid, as of June 2016 only 363 patients worldwide had started treatment including delamanid.^{vii} More than 50% of these patients receive the drug through MSF programmes.

Role of delamanid in DR-TB treatment

Delamanid is one of the first new medicines developed for DR-TB treatment in 50 years.

It is only taken for the first six months of DR-TB treatment. The WHO issued interim guidelines on delamanid use to treat MDR-TB in November 2014.^{viii} Delamanid is also included in the 19th WHO Model List of Essential Medicines.^{ix}



Standard treatment for DR-TB entails 9-12 months of taking thousands of pills, some of which cause nausea, drowsiness, psychosis and even permanent deafness. *Photographer: Sydelle Willow Smith*

How available is delamanid in high-burden DR-TB countries, specifically South Africa?

Use of delamanid

In South Africa, Doctors Without Borders (MSF) has obtained special permission to import delamanid, and as of end-October 2016 has 52 DR-TB patients that have initiated treatment on the drug.

Khayelitsha is the only primary healthcare site using delamanid for outpatients in the country. Other health facilities in South Africa have initiated a small number of patients on delamanid through a compassionate use agreement with Otsuka.

South Africa has one of the largest patient cohorts on delamanid in the world, though many more patients could

benefit across the country if delamanid were more widely available.

Potential Demand

An estimated 7,000 DR-TB patients per year in South Africa could benefit from the inclusion of DLM in their treatment regimen, if WHO guidance is applied in full (viii). Delamanid is particularly relevant for addressing the DR-TB epidemic in South Africa with its high rates of HIV co-infection. Delamanid can be used in DR-TB regimens of people who are also taking the standard fixed-dose combination treatment for HIV, which contains efavirenz (viii).

The South African government has shown a strong commitment to scaling up access to treatment for new and re-purposed DR-TB drugs like bedaquiline and linezolid, and expresses similar ambitions for delamanid.

The high potential demand for delamanid and the government's interest in making it available suggests South Africa is a reliable future market for delamanid.

Barriers to accessing delamanid in South Africa

Clinical Access Programme

The South African NDOH has entered into discussions with Otsuka regarding the establishment of a clinical access programme (CAP) to provide early access to delamanid for select patients at approved clinical sites.^x This type of programme would be similar to the bedaquiline CAP which ran from 2013-2015, and would allow early access to delamanid for some patients before the product is registered.

While this is a welcome development, to date there has been no public commitment from Otsuka or the South African NDOH as to how many courses will be made available through the CAP, and over what period of time— and whether this will be sufficient to meet demand prior to registration.

Registration

Otsuka first received regulatory approval for DLM in 2014 from the European Medicines Agency (EMA)^{xi} and Japan's Pharmaceuticals Medical Devices Agency (PMDA). As of March 2016, however, the drug is only registered in the European Union, Japan, South Korea and Hong Kong.

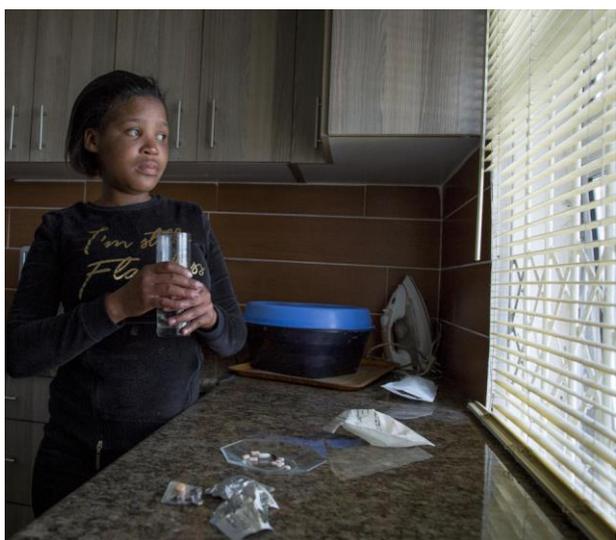
Delamanid is not yet registered in most high burden DR-TB countries, or any country where clinical trials have taken place, including South Africa.

Registering delamanid with South Africa's Medicines Control Council (MCC) would allow the NDOH to incorporate the use of delamanid into national clinical guidelines, and place it on the national Essential Medicines List. These measures would improve access to delamanid for the national TB programme.

At present, clinicians wishing to prescribe delamanid must access the drug on a case-by-case basis from Otsuka, a time-consuming process which also requires obtaining a special import waiver from the MCC.

Other countries in the region with a high burden of DR-TB — such as Swaziland and Lesotho — also rely on MCC approvals, suggesting that registration in South Africa would also improve access to delamanid for patients in these countries.

The process of registration is likely to take at least one year in South Africa, even if the application is fast-tracked for approval.



Sixteen-year-old Sinthemba of Khayelitsha is among the very few DR-TB patients in the world who have access to delamanid, a new drug produced by Japanese pharmaceutical company, Otsuka. © Sydelle Willow Smith

Price

In February 2016, Otsuka announced a price of US\$1,700 for Global Fund-eligible countries to purchase a six-month course of delamanid through the Global Drug Facility (GDF). This price is equivalent to US\$283 per person per month (pppm). While South Africa is a Global Fund-eligible country, it procures medicines independently of the Global Fund and GDF. Otsuka has not disclosed what its pricing strategy for South Africa will be upon registration.



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A recent study estimated target prices for DR-TB drugs, which could be achievable through the establishment of robust generic competition. The study set a target price for delamanid at US\$3.50-US\$8.60 ppm. This is 98% less than the current lowest global price offered by Otsuka.

Patents

Otsuka holds multiple patents on delamanid, including patents which could prevent the development of combination therapies for new and improved treatment DR-TB regimens. In South Africa, delamanid secondary patents are valid until at least 2032.^{xiii}

Voluntary licenses of patent rights have played an important role in improving access for developing countries to more affordable generic versions of ARV medicines for HIV, prior to patent expiration. Companies manufacturing DR-TB medicines could place their intellectual property rights in the Geneva-based Medicines Patent Pool (MPP),^{xiv} and offer licensing terms that facilitate access to new DR-TB medicines for all developing countries.

Generic availability of new DR-TB medicines could allow a DR-TB treatment regimen to be priced below US\$500 per patient. This would allow countries to scale up access for all patients in need to strengthened DR-TB regimens (iv).

How can access to delamanid improve?

- Otsuka can **make delamanid available through a clinical access programme** in sufficient quantities to meet South Africa's programmatic demands, prior to registration of the drug.
- There is urgent need for Otsuka to **file for registration** of delamanid in high-burden DR-TB countries like South Africa — which was a site for clinical trials of the drug—as soon as possible, and for the MCC to process this registration as quickly as possible.
- **South Africa should always have access to the lowest global price Otsuka offers for delamanid.** Long-term access to affordable prices is important for the sustainability of the national TB programme.
- **South Africa should be included in the geographic scope of any voluntary license for delamanid** signed between Otsuka and the MPP. Further, Otsuka can choose not to enforce its patents on delamanid in South Africa to enable future generic competition.
- Otsuka can **publish a delamanid access plan** for high-burden countries like South Africa, outlining intentions for registration, clinical access programmes, procurement, pricing, patents, and other relevant issues.

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- ⁱ World Health Organisation, *Global Tuberculosis Report 2016*
- ⁱⁱ WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis.; 2014.
- ⁱⁱⁱ Cox H, Hughes J, Daniels J, et al. Community-based treatment of drug-resistant tuberculosis in Khayelitsha, South Africa. *Int J Tuberc Lung Dis.* 2014;18(4):441-8. doi:10.5588/ijtld.13.0742.
- ^{iv} Médecins Sans Frontières Access Campaign. *DR-TB Drugs Under the Microscope, 4th Edition*; 2016.
- ^v WHO. *WHO Treatment guidelines for drug-resistant tuberculosis.* 2016. Available at: <http://www.who.int/tb/MDRTBguidelines2016.pdf>
- ^{vi} MSF. First new TB drugs in half a century reach just 2% of people who need them. Press Release. 3 December 2015. [Cited 2016 Jan 27]. Available from: <http://www.msfaccess.org/about-us/media-room/press-releases/first-new-tb-drugs-half-century-reach-just-2-people-who-need-them>
- ^{vii} Global Drug Resistant TB Initiative (GDI), *June 2016 Update on Programmatic Introduction of New TB Drugs* [Online]
- ^{viii} World Health Organization. *WHO interim guidance on the use of delamanid in the treatment of MDR-TB.* [Online] WHO; Geneva, 2014.
- ^{ix} World Health Organization. *WHO Model List of Essential Medicines (19th Edition).* [Online] 2015 August.
- ^x Lopez Gonzalez L. *Delamanid Clinical Access Programme Expected.* Health-e. 29 March 2016. Available at: <https://www.health-e.org.za/2016/03/29/south-africa-to-roll-out-delamanid/>
- ^{xi} European Medicines Agency. Delyba - delamanid. [Online] EMA, 2015, August 12
- ^{xii} Gotham D et al. Target generic prices for novel treatments for drug-resistant tuberculosis. 15th European AIDS Conference, Barcelona, abstract PS2/4, October 2015.
- ^{xiii} Fix the Patent Laws. *Patent barriers to medicine access in South Africa: A case for patent law reform.* September 2016. Available at: <http://www.fixthepatentlaws.org/wp-content/uploads/2016/09/MSF-FTPL-report-FINAL-VERSION.pdf>
- ^{xiv} Medicines Patent Pool. *TB Alliance and the Medicines Patent Pool Sign Memorandum of Understanding to Improve Access to TB Medicines in Resource-Limited Nations*; April 2016