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 in October 2016, 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 remains 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] Treatment regimens for DR-TB must contain at least four working drugs, with higher resistance profiles requiring more drugs (including new drugs) in order to have an effective regimen.

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).

Sinethemba Kuse (19) from Khayelitsha received delamanid as part of a regimen for XDR-TB. She was declared cured on 22 September 2017 © *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, with an estimated annual incidence of 454,000 people. In 2015, almost 300,000 people were diagnosed with TB in South Africa, including over 20,000 with some form of DR-TB. More than 13,000 DR-TB patients were started on treatment (i).

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 (BDQ) and delamanid (DLM), 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 BDQ and DLM— were conditionally approved to treat DR-TB, barely five percent of those who could benefit from these treatments have access to them.[vi] According to Otsuka, the Japanese pharmaceutical manufac-

turer of DLM, as of March 2017 only 496 patients worldwide had received DLM under programme conditions.[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. The standard treatment duration is for the first six months of DR-TB treatment. The WHO issued interim guidelines on DLM use to treat MDR-TB in November 2014,[viii] and on its use in treating children and adolescents in 2016.[ix] Delamanid is also included in the 19th WHO Model List of Essential Medicines.[x]

Sinethemba, former XDR-TB patient in Khayelitsha with her two counsellors. *Photographer: Sydelle Willow Smith*

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

Use of delamanid

On World TB Day (March 24) 2017, Otsuka and the South African National Department of Health launched the Delamanid Clinicial Access Programme (DCAP). The DCAP provides early access to DLM for patients meeting program eligibility criteria at approved clinical sites.

The DCAP is intended to be similar to the bedaquiline CAP which ran from 2013-2015 in South Africa, and provided early access to bedaquiline for over 200 patients prior to the drug's registration. Otuska has initially pledged 400 courses of DLM to the DCAP, but indicated that further treatment courses could be provided if necessary. To date, only 10 patients have been enrolled through the DCAP.

At present, if DR-TB patients are not eligible for DCAP, or cannot access a DCAP site, clinicians wishing to prescribe DLM must access the drug for free on a case-by-case basis from Otsuka—a time-consuming process which also requires obtaining a special import waiver from the Medicines Control Council (MCC). Health facilities in South Africa have initiated at least 50 patients on DLM through this compassionate use agreement.

Doctors Without Borders/Médecins Sans Frontières (MSF) in South Africa has obtained special permission to import DLM for its DR-TB programs in Khayelitsha (Western Cape) and Eshowe (KZN), the former of which has the only primary healthcare sites offering DLM for outpatients in the country. Currently, this mechanism is used when patients are not eligible under the DCAP. Over 100 DR-TB patients have initiated treatment on the drug through this routine programmatic use since December 2015. MSF pays $1,700 per six-month treatment course.

Potential Demand

South Africa currently has one of the largest patient cohorts in the world on DLM, though access remains severely limited.

The WHO recommends DLM be added to treatment regimens of all person at high risk of treatment failure, which includes people living with HIV. This suggests that as many as 70% of all DR-TB patients in South Africa could benefit from the inclusion of DLM in their treatment regimen (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 repurposed DR-TB drugs like bedaquiline and linezolid, and expresses similar ambitions for DLM. Launching the DCAP is a first progressive step towards this. The high potential demand for DLM and the government's interest in making it available suggests South Africa is a reliable future market for DLM.

Barriers to accessing delamanid in South Africa

Clinical Access Programme

Since the DCAP launch in March 2017, only 10 patients have been enrolled and received DLM , of which five were enrolled at the MSF-supported site in Khayelitsha. This underutilization of the DCAP can be attributed to a number of factors, including clinicians having easier access to bedaquiline as a treatment option, and therefore wanting more safety and efficacy evidence on DLM prior to using it more broadly. There are also a limited number of registered DCAP sites, and currently limited DCAP eligibility criteria. An amended protocol is being reviewed by the MCC which, once approved, would allow for use of DLM in adolescents and children over age 6, in cases of XDR-TB, and in combination with bedaquiline in specific instances.

While expanded eligibility may increase interest in DCAP, at the same time, there is a need to ensure all currently eligible patients are being offered the choice of DLM to strengthen their regimen and improve their likelihood of treatment success.

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 October 2017, the drug is still only registered in the European Union, Turkey, Japan, Hong Kong and South Korea – countries with very low DR-TB burdens—and conditionally approved for registration in India.

Delamanid is not yet registered in most high burden DR-TB countries, or any country where clinical trials have taken place, including South Africa. After months of delays, Otsuka's local partner, Mylan, filed for registration of DLM in South Africa in July 2017. The process of registration is likely to take at least one year in South Africa, even if the application is fast-tracked for approval.

Registering DLM with South Africa's MCC would allow the NDOH to incorporate the use of DLM into national clinical guidelines, and place it on the national Essential Medicines List. These measures would improve access to DLM for the national TB programme, by allowing any site (not only DCAP sites) initiating DR-TB treatment to offer DLM, and eliminating the need to apply for compassionate use of DLM.

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 DLM for patients in these countries.

Price

In February 2016, Otsuka announced a price of US$1,700 for Global Fund-eligible countries to purchase a six-month course of DLM 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.

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 DLM at US$3.50-US$8.60 pppm.[xii] This is 98% less than the current lowest global price offered by Otsuka.

Patents

Otsuka holds multiple patents on DLM, including patents which could prevent the development of combination therapies for new and improved DR-TB regimens. In South Africa, secondary patents on DLM 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?

- **The MCC can approve amendments to the DCAP protocol,** to allow additional patient groups in South Africa to benefit from access to DLM**.**
- **Clinicians at DCAP sites** should submit applications for all eligible patients, to support improved patient outcomes and contribute to the evidence base around DLM use. Special attention should be given to children—where DLM can be used to alleviate the painful and dangerous daily injections in this population—and persons at high risk of treatment failure, such as people with HIV, people with diabetes, and people with extensive diseases, in addition to people who have second-line drug resistance or intolerance.
- **Fast-track registration of DLM by the MCC** is critical for incorporating DLM use into national treatment guidelines, and expanding access to all DR-TB treatment sites across the country.
- **South Africa should always have access to the lowest global price Otsuka or Mylan offers for DLM.** 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 DLM** signed between Otsuka and the MPP. Further, Otsuka can choose not to enforce its patents on DLM in South Africa to enable future generic competition.
- Otsuka can **publish a DLM access plan** for countries with a high burden of DR-TB, outlining intentions for registration, clinical access programmes, procure-ment, pricing, patents, and other relevant issues.

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[i] World Health Organisation*, Global Tuberculosis Report 2016*

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[vi] MSF. *Four Years and Counting: Slow scale-up of newer MDR-TB drugs covers less than 5% in need.* [Online] MSF: Geneva 2017.

[vii] Stop TB Partnership and Medecins Sans Frontieres, Out of Step Report. July 2017.[Online]

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