

OUT OF TIME: ACCESS TO TREATMENT FOR DR-TB

An update on the latest developments in DR-TB medicines

In 2014, 1.5 million people died from tuberculosis (TB), displacing HIV as the top infectious disease killer, according to the World Health Organization's (WHO) 2015 Global Tuberculosis Report. The latest figures for multidrug-resistant TB (MDR-TB) were no less disturbing: only 26% of people estimated to have acquired MDR-TB in 2014 were diagnosed, and only 23% were put on treatment.¹ Only about 50% of people who start the gruelling two-year treatment for MDR-TB are successfully treated, while for people with extensively drug resistant TB (XDR-TB), the treatment success rate drops to 26%.²

A significant obstacle to radically improving outcomes for drug-resistant TB (DR-TB) patients in the short term is the inadequacy of current treatment regimens: patients must endure two years of treatment with severe side effects and unacceptably low cure rates. With two new TB drugs now available and increasing evidence of the potential value of some "group 5" drugs (existing drugs that are not approved to treat MDR-TB) in treating MDR-TB emerging, clinicians must have access to the full toolbox of potentially effective drugs, so they can create individualized regimens that offer each DR-TB patient the best possible cure available today. This fact sheet provides an overview of price and availability of the key medicines being used to treat DR-TB today.

To fundamentally improve DR-TB treatment outcomes, however, robust new regimens containing multiple novel and better tolerated drugs are desperately needed to completely replace the old, toxic drugs that remain a part of the current recommended DR-TB regimens.

Slow progress in accessing promising new TB drugs

Clinical evidence of bedaquiline and delamanid

Bedaquiline (Bdq, marketed by Janssen) and delamanid (Dlm, marketed by Otsuka) are the first new drugs to be registered for use against TB in over 40 years. The two new drugs were conditionally approved based on their phase IIb clinical data, although completion and publication of phase III data is still critically important. Delamanid's phase III clinical trial completed enrolment in November 2013, with results expected in 2017. Bedaquiline's phase III clinical trial, which expands on the existing STREAM trial looking at efficacy of shorter treatment regimens, has yet to commence.

The long-awaited drug-drug interaction study (AIDS Clinical Trials Group's A5343 trial) to examine possible effects of the two new drugs on the heart (QT prolongation) has yet to start; until the results of this trial are known, there is a reluctance by either manufacturer to combine and test the drugs as a part of new treatment regimens.

To fill the gaps in manufacturer-initiated, regimen-based clinical research, there are a number of trials being planned or conducted by other entities, including MSF, to test new DR-TB regimens containing bedaquiline or delamanid.³

MSF is currently collaborating with Partners in Health (PIH) and Interactive Research & Development (IRD) on the 16-country 'endTB project', which will provide access to new bedaquiline- and delamanid-containing regimens to a total of 3,200 MDR-TB patients, including 600 people in five countries who will be enrolled in clinical trials to study the efficacy of novel MDR-TB treatment regimens.⁴ In addition,

Médecins Sans Frontières (MSF) has been providing TB care to patients across the world for over three decades, often working alongside national health authorities to treat patients in a wide variety of settings, including conflict zones, urban slums, prisons, refugee camps, and rural areas. MSF's first programmes to treat DR-TB opened in 1999, and the organisation is now one of the largest non-governmental providers of DR-TB care in the world. In 2014, MSF provided TB treatment in over two dozen countries to 21,500 patients, including 1,800 treated for DR-TB.

MSF's TB-PRACTECAL trial will evaluate the safety and efficacy of six-month bedaquiline-containing regimens in Uzbekistan and Swaziland.

MSF has already had positive results using a bedaquiline-containing regimen in Armenia and Chechnya, Russian Federation, where we are supporting some of the largest cohorts of XDR-TB patients receiving bedaquiline in the world. Of the 26 XDR-TB patients receiving bedaquiline from MSF in Armenia, 22 (84%) displayed sputum culture conversion at 6 months; In Chechnya, 27 out of 36 (75%) MSF patients who have completed 6-months of treatment are culture negative. Similarly successful culture conversion rates were reported for non-MSF compassionate use cohorts in France and South Africa (97% and 77%, respectively).⁵ Additionally, there were no significant adverse events associated with the use of bedaquiline among MSF's Armenian cohort. A study in South Africa demonstrated similar safety and efficacy even when bedaquiline was given in combination with antiretroviral therapy (ART) to TB/HIV co-infected persons (59.3% of the cohort were TB/HIV co-infected), another sign that bedaquiline has the potential to be transformative in how MDR-TB is treated in the coming years.⁶

Access to bedaquiline and delamanid

Access to bedaquiline and delamanid is severely limited. Outside of clinical trials, approximately 700 patients have accessed bedaquiline through compassionate use and about 2,000 are receiving or will receive bedaquiline as part of routine use as of November 2015, and only about 100 have received delamanid through compassionate use. This is despite the fact there are an estimated 48,000 patients with XDR-TB globally and at least twice as many with pre-XDR-TB and MDR-TB who would meet WHO criteria for the new drugs.⁷

Compassionate use is an early access mechanism which allows patients suffering from life-threatening diseases without any other treatment options to access a medicine before its clinical and regulatory approvals are finalized. Compassionate use programmes are only available to people living in countries with the necessary legal framework in place. Ultimately, however, compassionate use programmes are controlled at the discretion of pharmaceutical firms. Janssen has run a compassionate use programme for bedaquiline since 2011, but it is currently being phased out; Otsuka has run a compassionate use programme for delamanid since 2014.⁸

It is critical that new drugs be incorporated into routine, programmatic DR-TB treatment protocols, although there are major barriers to overcome before this will be possible for bedaquiline and delamanid.⁹ Significant barriers include limited registration of the new drugs, as well as the high price of existing DR-TB medicines, which the new drugs must be combined with in treatment regimens (*see page 7 "MDR-TB Drugs: Target Prices vs. Current Prices"*). South Africa has committed to treating 3,000 DR-TB patients with regimens including bedaquiline;¹⁰ so far, however, just 1,009 patients have started treatment with bedaquiline as of November 2015 (*see page 4 "Spotlight on access to linezolid in South Africa"*).

Bedaquiline has been granted conditional or full marketing authorization by the National Medicine Regulatory Agency (NMRA) in seven of the 27 high MDR-TB burden countries, and submission is pending in nine others. Delamanid has conditional or full marketing authorization in just four countries: Japan, the United Kingdom, Germany, and South Korea, none of which are among the world's 27 high MDR-TB burden countries.

Drug donation programmes for bedaquiline and delamanid

Janssen and Otsuka have announced drug donation programmes for bedaquiline and delamanid, respectively. In December 2014, USAID and Janssen Therapeutics (a Johnson & Johnson affiliate) announced a donation programme for bedaquiline, with the official agreement signed in March 2015; the terms of this agreement specify that 30,000 treatment courses would be donated over a four-year period to more than 100 Global Fund to Fight AIDS, TB, and Malaria (GFATM)-eligible low- and middle-income countries through Stop TB Partnership's Global Drug Facility (GDF).¹¹ In October 2015, USAID announced Georgia as the first recipient of donated bedaquiline.¹²

Not all countries are all eligible for these donations, however; South Africa, for instance, is ineligible and there appears to be a quota on the number of Commonwealth of Independent States (CIS) countries that will be allowed to participate in this drug donation programme.

Beyond the programme's delayed start, there are major downsides like the administrative charge levied by the GDF and fears that other pharmaceutical companies will follow suit, opting for donation programmes offered to select countries rather than offering an affordable price for all low- and middle-income countries.

In April 2015, Otsuka announced its "FightTBack Initiative," a plan to provide donations of delamanid to 20% of diagnosed MDR-TB patients by 2020.¹³ Despite requests for additional details about the programme, little publically-available information is available. While MSF welcomes efforts to expand access to DR-TB drugs, we remain critical of donation programmes as they do not ensure sustainable access to essential medicines like delamanid.¹⁴

Drawbacks of drug donation programmes

Although drug donation programmes are sometimes touted as generous initiatives on the part of drug companies to solve access problems, there are a number of reasons why donations fail to ensure long-term, sustainable access to essential medicines. While MSF does accept donated medicines in some exceptional cases, it is generally critical of donation programmes. Below are some of the main points of contention regarding drug donations:

- **Unsustainability:** Continued donations are entirely dependent on the choices of the donor, so recipient sovereignty is threatened.
- **Insufficient scale:** In general, donations can only meet a fraction of a country's disease burden.
- **Challenging indication restrictions:** Drug indications may be overly narrow, preventing countries from using drugs in ways that meet public health objectives.
- **Inadequate consultation with recipient countries:** Donations may not meet the actual public health needs of recipients.
- **Country eligibility concerns:** Potential recipients may be excluded from programmes for reasons that are irrelevant to public health needs.
- **Burdensome requirements for recipients:** Programmes may impose added logistical and operational burdens to strained health systems with onerous requirements concerning pharmacovigilance, monitoring, evaluation, etc.
- **Time delays:** Lengthy donation negotiations may prolong the period in which patients cannot access the medicine.
- **Costs incurred by recipient countries:** Recipients often must bear the costs of sorting, storing, distributing, and potentially destroying expired donated medicines, ironically making ostensibly free drugs quite costly.
- **Anti-competitive impacts on drug markets:** Generic manufacturers may be dissuaded from entering a recipient country, preventing competitive generic markets from emerging.
- **Temporary "solution":** May reduce public pressure around the access problem, making it harder to expand access to the drug in the future. Additionally, donations are usually time-limited, so they are inherently not durable solutions.
- **Potential distortion of rational use:** Less-effective medicines which are donated may be used instead of more-effective medicines.
- **Market priming:** Recipients may be pressured to purchase a drug from the donor once the donation programme has ended.
- **Disincentivising future biomedical R&D:** Other firms may be disincentivised from engaging in future R&D to create improved medicines for lack of a viable commercial market.

Barriers to accessing repurposed DR-TB drugs

TB indications

Repurposed “group 5” DR-TB drugs have shown potential to be transformative in DR-TB treatment regimens; however, since all group 5 drugs (e.g. clofazimine, linezolid, imipenem/cilastatin) lack a DR-TB indication, there are problems procuring, importing, and dispensing these drugs for off label use.¹⁵ For example, linezolid is generally indicated for other antibiotic-resistant Gram-positive bacterial infections, but not for tuberculosis. Currently, clofazimine’s indication is limited to leprosy.¹⁶ Lack of a TB indication may also lead to reluctance to incorporate group 5 drugs into national TB management guidelines.

Drugs on the WHO Essential Medicines Lists (EML)

In April 2015, the WHO released the updated 19th edition of its EML. For the first time, this EML includes MDR-TB indications for bedaquiline, delamanid, and linezolid, which should spur governments to update their national EMLs.¹⁷ A thorough literature review allowed experts to justify the addition of linezolid to the WHO EML with a TB indication, despite the lack of registration for this particular disease. Although clofazimine is still not listed on the WHO EML as a TB medicine, it is included in the WHO Prequalification Programme’s invitation to manufacturers of API and Finished Pharmaceutical Products in reference to second line anti-tuberculosis medicines.¹⁸ This should be understood by generic manufacturers as an

Spotlight on access to linezolid in South Africa

Although not originally developed or indicated for TB, multiple studies have shown that inclusion of linezolid in the treatment of DR-TB, including for those co-infected with HIV, improves culture conversion rates and treatment outcomes.¹ In South Africa, unfortunately, high prices charged by a single supplier and a subsequent duopoly has limited access, and linezolid remains out of reach of many DR-TB patients.

At the urging of patients, clinicians, and civil society organizations, South Africa’s regulatory body, the Medicines Control Council (MCC), registered Hetero’s generic linezolid in late 2014, marketed in South Africa by Sanofi. However, limited competition has not resulted in significant price reductions. Currently, Pfizer sells linezolid for R875 (~US\$64) per pill in the private market, while Hetero’s product costs R655 (~US\$48) per pill, pointing to the need to introduce further competition.¹ Public sector prices are discounted but remain high.

In 2015, South Africa’s National Department of Health (NDOH) tried to secure affordable linezolid through its anti-infectives tender, requesting bids for 114,500 units of 10x600mg tablet packs to be supplied between 1 October 2015 and 30 September 2017.^{1,1}

While this is one of the largest known global demands for linezolid, no manufacturers offered reasonable prices, leaving individual South African provinces to purchase linezolid directly from registered manufacturers, if they could afford it. While MSF pays just over US\$5,750 (~R80,000) for a two-year course of Hetero linezolid (~R109 or US\$7.90 per pill), the same supplier’s product is being offered for nearly 50% more to South African provinces, with Pfizer’s price more than double that amount. This is unacceptable given that, as a recipient of GFATM support, and as a country with one of the largest TB burdens in the world, South Africa should be offered prices comparable to the GDF, where linezolid now costs between US\$5.35-\$5.48 per pill.¹

It is imperative that Pfizer and Sanofi immediately offer more affordable linezolid prices in South Africa. At the same time, generic suppliers with stringent regulatory authority approval in other countries should apply for registration in South Africa. The MCC should prioritize rapid approvals of other quality-assured generic linezolid suppliers to promote a more competitive marketplace, and so that more people with DR-TB in South Africa will have access to this essential life-saving medicine.

incentive to develop clofazimine products, and to pursue WHO pre-qualification or registration by a stringent regulatory authority (SRA), as required by the GFATM.

Registration status and import waivers

Another major access problem is the severely limited national registration of repurposed DR-TB drugs. Clofazimine may be registered with a TB indication in the US by 2020, following the US Food and Drug Administration's review of an orphan drug filing and specific clinical trials by Novartis. While linezolid is registered in some countries, it is not registered with a TB indication in any country. These medicines should be registered with TB indications as soon as possible, with a particular emphasis on registration in high MDR-TB burden countries. In the interim, countries should consider granting import waivers to these medicines that are still unregistered locally whenever manufacturers obtain either WHO Prequalification Programme approval or registration by a SRA.

MDR-TB Drugs: Target Prices vs. Current Prices

Price drops

While regimen prices remain high, recent reductions in the prices of some drugs used to treat DR-TB have brought regimen prices down to a range of US\$1,800-\$5,000 per treatment course (without any 'group 5' or new drugs included). Except for clofazimine/amikacin/ethionamide, whose prices have remained steady, and kanamycin/PAS sodium, whose prices have increased since 2013, all DR-TB medicines have seen their price decrease over the past three years for a number of reasons.¹⁹ Higher order volumes and the expiration of patents have played a role in reducing the lowest global price of some DR-TB drugs (e.g. linezolid).

Competition from generic manufacturers of quality-assured finished products has also brought DR-TB drug prices down (e.g. linezolid, capreomycin, prothionamide, levofloxacin). In other cases, there are now more manufacturers of the active pharmaceutical ingredients (API), while the number of manufacturers of the finished product remains the same (e.g. cycloserine).

A key factor behind these price drops has been the joint GFATM-GDF Expert Review Panel mechanism, which since 2009 has been successfully attracting new manufacturers of quality-assured DR-TB medicines. However, even with reductions in price at a global level, individual countries—especially middle-income countries that purchase outside of GFATM-GDF—may still lack competitive markets to access similarly low prices.

Target prices

A recent study compiled target price ranges for MDR-TB drugs based on estimated costs of active pharmaceutical ingredients, excipients, formulation, packaging, and a reasonable profit margin.²⁰ Treatment courses like that used in the nine-month STREAM regimen ('Bangladesh regimen') are currently priced from a little over US\$800 to more than US\$1,800, but could be priced as low as US\$100-\$400 per patient-course. For the individual drugs clofazimine (Cfz), linezolid (Lzd), bedaquiline (Bdq), delamanid (Dlm), and moxifloxacin (Mfx), the estimated "target" prices per patient per month (PPPM) with robust generic competition are listed below, along with the current price available from GDF:

	Cfz	Lzd	Bdq	Dlm	Mfx
Target price range (PPPM US\$)	6.20-16.40	4.90-12.80	8.80-16.40	3.50-8.60	3.50-9.40
Current GDF price (PPPM US\$)	76	164	150	5,60 (not available through GDF)	13.11

Annex 1: Key DR-TB drugs: access status and recommendations for action

	Access	Recommendations
Bedaquiline (Bdq)	<ul style="list-style-type: none"> • Conditional approval (US December 2012, EU March 2014) • Currently restricted use for pre-XDR/XDR²¹ • Around 2,000 receiving as part of routine use as of November 2015 • Approximately 700 patients in 42 countries via compassionate use programme; in September 2015 the programme started to be phased out, although an extension for some countries may be possible • NDRA registration: registered in 7 of the 27 high MDR-TB burden countries and submissions in 9 of the others (rejected in Kyrgyzstan) (as of 30 September 2015) • 6 months supply: \$900 lower-income countries, \$3000 middle-income countries, \$30,000 upper-income countries • Donation programme launched in April 2015 through USAID/GDF for 30,000 treatment courses over 4 years. All GFATM-eligible countries. Quota for CIS countries. • Access in Russia and select CIS countries via Pharmstandard (price \$3,345/treatment course in May 2015) • IP barriers (compound & multiple secondary patents) until 2029 that limit generic competition or development of FDCs • Not clear if Janssen will engage in bilateral or Medicines Patent Pool-led voluntary license negotiations • No evidence on safety of combining with Dlm (awaiting NIH DDI study, starting Q1 2016) 	<ul style="list-style-type: none"> • Proactive plan to move from donation to sustainable and affordable price as soon as possible • A better price than \$3,000/course offered to middle-income countries; lower- and middle-income countries should be offered the same low price • Reduction of intellectual property barriers through use of TRIPS flexibilities or voluntary licensing • High-burden TB countries' NMRA must prioritise registration • Janssen to prioritize high-burden countries for registration • Rapidly commence trials looking at combining Bdq with other new drugs and in shorter regimens • Rapidly start phase III and paediatric trials
Delamanid (Dlm)	<ul style="list-style-type: none"> • Conditional approval (EMA April 2014) • Registration: Japan, the UK, Germany, and South Korea • 6-month supply: \$28,000 in the UK, \$33,600 in Japan • International donation programme (FighTBack) announced in April 2015 to give access to 20% of all diagnosed and treated MDR-TB patients by 2020; concerns about the eligibility criteria; to be confirmed whether through GDF • Around 100 patients have accessed via compassionate use programme, including 37 patients being treated by MSF in 	<ul style="list-style-type: none"> • Proactive plan to move from donation to sustainable and affordable price as soon as possible, especially for middle-income countries • Otsuka develops and publishes its access policy • Any licenses signed are non-exclusive, with a strong preference to work through the Medicines Patent Pool • Reduction of intellectual property barriers through use of TRIPS flexibilities or through voluntary licensing • Otsuka rapidly pursues registration in high-burden TB countries

Delamanid (Dlm) [cont'd]	<p>Armenia, Belarus, Georgia, India, Russian Federation, and South Africa as of November 2015.</p> <ul style="list-style-type: none"> • Patent barriers (compound and secondary patents) in place until 2031 that limit generic competition or development of FDCs • Slow discussions with generic companies for potential voluntary license • No evidence on safety of combining with Bdq (awaiting NIH DDI study, starting Q1 2016) 	<p>and clinical trial countries; in the meantime, Dlm should be widely accessible through compassionate use or other early access programmes</p> <ul style="list-style-type: none"> • Rapidly commence trials looking at combining Dlm with other new drugs and in shorter regimens
Clofazimine (Cfz)	<ul style="list-style-type: none"> • Indication limited to leprosy • Recommended by WHO as a Group 5 drug for TB treatment • Not yet included in the WHO EML for TB • Single quality-assured producer • Part of stage 1 and 2 of STREAM trial • In April 2014, US FDA agreed to review a filing under orphan drug designation by Novartis for phase II clinical trial of Cfz; this could possibly lead to registration with TB indication by 2020 • GDF Price: \$1.2672 per 100mg tablet, \$770 for 20-month treatment course 	<ul style="list-style-type: none"> • Novartis should rapidly pursue obtaining a TB indication for Cfz • A better price is offered to lower- and middle-income countries • Tech transfer for API production to allow sustained availability; prioritize reformulation to a presentation more suited to hot and humid environments, and allowing dosing adaptation • Current and future generic manufacturers of active pharmaceutical ingredients and finished product of Cfz should pursue WHO prequalification • Inclusion on the WHO EML for TB
Linezolid (Lzd)	<ul style="list-style-type: none"> • No TB indication registration dossier (anywhere) although dispensed for TB since before 2008 • Recommended by WHO as a Group 5 drug for TB treatment • On WHO EML with TB indication (2015) • Secondary patents could preclude importation of low-cost generics until 2021 in some countries, although likely that generic producers will challenge or ignore the secondary patents • Price down by 22% since 2013 thanks to 3 manufacturers in 2015 (including 2 quality-assured generic ones: Hetero, Macleods) compared to 2 manufacturers in 2013 (including one sole generic company), but price remains an issue • GDF price: \$5.35-5.48 per 600mg tablet, \$3,253- \$3,332 for 20-month course 	<ul style="list-style-type: none"> • Pfizer, Macleods, Hetero should register Lzd in all high-burden TB countries as a priority • Countries should update their national EML with Lzd for TB based on the April 2015 WHO EML update • Pfizer, Macleods, Hetero should pursue a TB indication for this drug using the literature review gathered by the WHO EML expert committee • New generics companies (US FDA tentatively approved) should register Lzd in high burden TB countries • Price reductions and additional competitors to improve affordability and price transparency • Use of TRIPS flexibilities, if needed, to remove remaining secondary patents in countries where treatment scale up is needed and where secondary patents may be written in such a manner to interfere with entry of generics

Annex 2: 2015 Prices for Selected DR-TB Drugs

	Intake per day	Months	Lowest unit price for a quality-assured source (US\$)	Lowest cost for regimen (US\$)	Highest unit price for a quality assured source (US\$)	Highest cost for regimen (US\$)
Capreomycin 1gr vial	1	8	3.80	912.00	8.00	1920.00
Cycloserine 250 mg caps	3	24	0.19	403.92	0.60	1296.00
Ethionamide 250 mg tab	3	24	0.06	133.92	0.10	211.68
Moxifloxacin 400 mg tab	1	24	0.44	314.64	0.66	475.20
Pyrazinamide 400 mg tab*	4	24	0.02	55.58	0.02	67.68
			Total cost	1820.06		3970.56

	Intake per day	Months	Lowest unit price for a quality assured source (US\$)	Lowest cost for regimen (US\$)	Highest unit price for a quality assured source (US\$)	Highest cost for regimen (US\$)
Capreomycin 1gr vial	1	8	3.80	912.00	8.00	1920.00
PAS/ PAS Sodium	2	24	1.31	1919.52	1.69	1919.52
Ethionamide 250 mg tab	3	24	0.06	133.92	0.10	211.68
Moxifloxacin 400 mg tab	1	24	0.44	314.64	0.66	475.20
Pyrazinamide 400 mg tab*	4	24	0.02	55.58	0.02	67.68
			Total cost	3335.66		4595.08

* price obtained from the GDF catalogue.

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- ³ RESIST-TB. DR-TB Clinical Trials Progress Report. [Online] Updated 2015 October 19 [Cited 2015 November 9]. Available from: http://www.resisttb.org/?page_id=1602
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