



TB briefing paper

An overview of MSF's programmatic use and clinical research with new TB treatment regimens

October 2016



introduction

Each day, 4,900 people die from tuberculosis (TB) – which is more than three people every minute^{1*} – while an estimated 41% of people who fall sick with the disease are left undiagnosed and untreated. It is one of the top ten causes of death worldwide and was more deadly than HIV in 2015.*

At the current rate of progress, the world is 150 years behind schedule to meet the World Health Organisation's (WHO) 2030 targets to reduce TB incidence and death.² According to the WHO, 2016 investments in TB care and prevention in low- and middle-income countries will fall almost US\$2 billion short of the US\$ 8.3 billion needed.³ Furthermore, in 2015, funding for TB research and development, including new tools, such as drugs, diagnostics and vaccines, fell to its lowest level since 2008.⁴

The TB public health crisis is further aggravated as drug-resistant forms (DR-TB) continue to take hold. Effectively tackling the TB epidemic requires advancement in

a number of key areas, including: diagnostics; testing for drug-resistance; developing individual drugs and combining them in regimens for both drug-sensitive and drug-resistant TB; putting in place optimised models of care and regulatory frameworks.

This briefing paper focuses on the critical area of treatment for DR-TB. It provides an overview of the work of Médecins Sans Frontières/Doctors Without Borders (MSF) and its partners, including national ministries of health, in accelerating urgently-needed patient-centered research to improve the quality and availability of treatment regimens for DR-TB.

MSF is one of the biggest non-governmental providers of TB treatment care - including for DR-TB - in the world. MSF has TB treatment projects in 24 countries around the world, and in 2015 supported more than 20,000 TB patients on treatment, including 2,000 patients with DR-TB.



Bedaquiline, one of the new antibiotic drugs used to treat DR-TB at the National Centre for Tuberculosis and Lung Disease in Tbilisi, Georgia.

1 Global Tuberculosis Report 2016, World Health Organization (WHO), October 2016. Available from: http://www.who.int/tb/publications/global_report/en/

NB: The * symbol used for further figures refers back to this reference.
2 Out of Step 2015: TB Policies in 24 Countries, MSF and Stop TB Partnership (STBP), December 2015. Available from: <http://www.msf.org/>

3 All currency in this briefing paper is US\$.

4 2016 Report on Tuberculosis Research Funding Trends, 2005-2015: No Time to Lose. Treatment Action Group (TAG), October 2016. Available from: <http://www.treatmentactiongroup.org/tbrd2016>

drug-resistant TB

acute need for more and better treatment

Drug-resistant forms of TB are much harder to cure than drug-sensitive TB, as the standard TB drugs don't work, and the limited treatment available involves long, complex, toxic and expensive treatment. In 2015, just 20 percent of the 580,000 people newly eligible for multi-drug resistant TB treatment are estimated to have received it.*

In most cases, patients face a minimum of nine months of treatment, usually closer to two years, during which they must swallow more than 10,000 pills in addition to six to eight months of painful daily injections. Debilitating side effects range from nausea, joint pains and gastro-intestinal problems to psychosis and permanent deafness. Many patients have to spend two years in hospital, unable to earn a living, and cut off from friends and family and all semblance of a normal life.

There is also enormous stigma associated with TB, and many TB patients and survivors find themselves ostracised by their communities. On top of all this, the drugs are so ineffective that only just over half of those who embark on treatment will be successfully treated; for the most severe forms, such as extensively drug-resistant TB, the success rate drops to just 28%.*

>>> DEFINING TB

DRUG SENSITIVE TB (DS-TB) describes TB that can be treated with the standard drugs. Eighty-three percent of patients are successfully treated.

DRUG-RESISTANT TB (DR-TB) is used to describe all those forms of TB that show resistance to one or more of the common first-line drugs, including all of the possibilities listed below:

MULTIDRUG-RESISTANT TB (MDR-TB) is defined as TB that is resistant to isoniazid and rifampicin, the two most powerful TB drugs. Just 52 percent of MDR-TB patients are successfully treated.

RIFAMPICIN-RESISTANT TB (RR-TB) is defined as TB that is resistant to rifampicin but not isoniazid.

PRE-EXTENSIVELY DRUG-RESISTANT TB (PRE XDR-TB) is defined as TB that is resistant to the first-line drugs isoniazid and rifampin and either a fluoroquinolone or a second-line injectable drug (but not both).

EXTENSIVELY DRUG-RESISTANT TB (XDR-TB) is defined as TB that is resistant to isoniazid and rifampicin, and also to second-line drugs, including at least one drug from the class of antibiotics known as fluoroquinolones, and at least one of three injectable second-line drugs (capreomycin, kanamycin and amikacin). Only 28 percent of XDR-TB patients are successfully treated.

where we are today reason for hope, but a long way to go

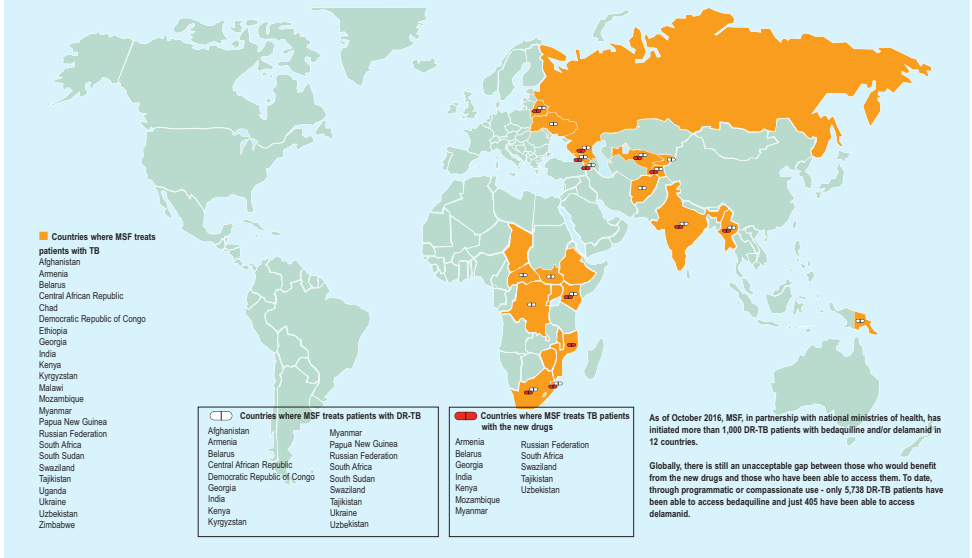
Today there is reason for hope, but significant work needs to be done to make it a reality. The first two new TB drugs developed in nearly 50 years – bedaquiline (Janssen – approved in 2012⁵) and delamanid (Otsuka – approved in 2014⁶) – have shown strong potential to vastly improve treatment outcomes.

While there is a need for greater research into better overall regimens, in the short term older regimens can be made more effective by including one or more of the new drugs with key ‘repurposed’ drugs (drugs that were initially approved to treat different conditions, but have also been

found to be effective for TB). Both of the new TB drugs are already recommended by the WHO⁷ for certain groups of patients, including those with XDR-TB, or for other DR-TB patients for whom other factors (such as co-infection with HIV) increase their risk of poor outcome with current treatment regimens.

Bedaquiline and delamanid are both indicated for use in DR-TB patients when an effective regimen cannot be designed either because of resistance (such as with XDR or pre-XDR-TB) or intolerance to another drug in the regimen. >>>

MSF TB TREATMENT PROGRAMMES



⁵ Bedaquiline was first granted conditional approval to treat DR-TB by the US Food and Drug Administration (FDA) in 2012. For more information see www.tbfacts.org
⁶ Delamanid received conditional approval to treat DR-TB from the European Medicines Agency (EMA) in 2014, and was approved by the Japanese regulatory authority in the same year. For more information see www.tbfacts.org
⁷ The use of bedaquiline in the treatment of MDR-TB - Interim policy guidance, WHO 2013 <http://www.who.int/tb/publications/mdrtb-treatment-guideline/en/>
The use of delamanid in the treatment of MDR-TB - Interim policy guidance, WHO 2014 <http://www.who.int/tb/publications/delamanid-in-mdr-tb-treatment/en/>



Simphiwe, an XDR-TB patient, collects his medication at his local clinic in Khayelitsha, South Africa.

<<< Delamanid is also indicated for use in patients with other risk factors for poor outcomes. An MSF study which reviewed five locations in the former Soviet Union and Africa, found that nearly 35 percent of patients had XDR or pre-XDR-TB, and approximately 70 percent had risk factors for poor outcomes.⁸ The results indicate that demand for both new TB drugs may be much higher than previously expected.⁹

As of October 2016, MSF has initiated more than 1,000 patients on bedaquiline and/or delamanid in 12 countries. Programmatic data has shown promising early results on the effectiveness of these regimens, while patients report that the toxic side effects of treatment are reduced. Delamanid is looking particularly hopeful for certain patients, including people living with HIV and paediatric patients, with WHO recommendations on its use in children above six expected to be released soon.

It is also hoped that using the two new drugs in combination will be particularly effective in treating patients with the most severe forms of drug-resistant TB. In MSF projects in Armenia, Belarus, India, Mozambique, South Africa, and Swaziland, medical teams are already piloting the combination of the two new drugs as part of the regimen for patients with very limited treatment options.

However, a major gap exists between those in need of treatment and those to whom the new drugs are actually available. As of October 2016, only 5,738 patients have been able to access bedaquiline globally through programmatic use (ie outside clinical trials) or compassionate use,¹⁰ the majority of them in South Africa. And just 405 patients have had access to delamanid through programmatic or compassionate use.¹¹ >>>

⁸ Bonnet M, Bastard M, du Cros P, et al. Identification of patients who could benefit from bedaquiline or delamanid: a multisite MDR-TB cohort study, February 2016. *Int J Tuberc Lung Dis* 2016; 20: 177–186.

⁹ Milmick C, Van den Hof S. Using existing data to illustrate—and close—the gap in access to new anti-tuberculosis drugs. *Editorial February 2016: J Tuberc Lung Dis* 2016

¹⁰ Compassionate use allows for the use of medicines in patients with life-threatening

diseases and without other treatment options, before clinical and regulatory approvals have been finalised.

¹¹ All figures from DR-TB Scale-Up Treatment Action Team (DR-TB STAT): www.dr-tb-stat.org/about/, October 2016.

The figures also show that there are currently 5022 bedaquiline orders and 1036 delamanid orders through the Global Drug Facility: www.stoptb.org/gdf/

<<< Both drugs have been conditionally approved based on their phase IIb clinical data, and the WHO has issued interim guidelines (for bedaquiline in 2013, and for delamanid in 2014) which recommend the use of either drug for six months in selected patients.

However, the completion of phase III trials and publication of related data on these drugs is critically important and would help resolve outstanding questions about their safety for specific groups. For example, almost no evidence exists to date on use with wider cohorts of patients, including in treating extra-pulmonary TB, TB in pregnant women or children. There is even less evidence available for their combined use, with any patient types.

So far clinical trials have also only studied a six-month regimen. In some cases, longer treatment may be necessary, so data on safety and efficacy of extended treatment are needed.



XDR-TB patient Hanif, in the waiting area of MSF's clinic in Mumbai.

THE NEW DRUGS: LIMITED ACCESS

There are a number of reasons for the massive gap between the number of patients who could benefit from the new drugs today and the number actually receiving them. The pharmaceutical companies which developed the drugs have been slow in applying for registration, including in countries with a high TB burden.¹²

In addition, the TB guidelines in many countries, including many high burden countries, urgently need to be updated to reflect WHO guidelines. Further, some countries will not approve registration of the drugs before clinical development is finalised, and some will not allow importation waivers, which could provide access before full registration. Often, the companion drugs, such as clofazimine, imipenem and linezolid, are unavailable.

Even when the new drugs are available, their high price is often a barrier to their use. Janssen does have a donation programme for bedaquiline in countries that are eligible for funding from the Global Fund to Fight AIDS, TB, and Malaria. However, many middle income countries, including high-burden countries are excluded from this programme instead having to pay \$3,000 for a six-month course, while high-income countries have to pay ten times that. In any case, donation programmes are unsustainable, often reach limited numbers of patients, and do not address the underlying issues needed to assure global access to everyone who needs it.

Meanwhile, Otsuka charges countries that are eligible for Global Fund support \$1,700 for a six-month treatment course of delamanid. It is not clear what the costs are to all countries (the UK price is \$28,000 and Japan is \$33,600). These prices are on top of the costs of the companion drugs, which can run as high as \$5,000.¹³

¹² In 2015, WHO redefined the lists of high-burden countries (HBC). Countries are categorised under HBC/TB, HBC/HIV-TB and HBC/MDR-TB. Each list accounts for 85-89% of the global burden. Full lists and their overlap are listed in the Global Tuberculosis Report 2016, available from: https://www.who.int/tb/publications/global_report/en/
¹³ July 2016 Update to DR-TB Drugs Under the Microscope: Sources and prices for drug-resistant tuberculosis medicines, 4th Edition. MSF Access and endTB.org, March 2016. Available from: http://www.msfastaccess.org/sites/default/files/MSF_assets/TB/Docs/UPDATE_MSF_REPORT_DR-TB_DRUGS_UTM_JUL_2016.pdf

towards better TB treatment regimens

an overview of MSF's involvement

To address the TB public health crisis, a global response across regulatory, scientific, commercial, financial and political sectors is needed. However, the slow rate of progress means that patients remain years away from getting the cures that they need, people will continue to die, and TB and its drug-resistant forms will continue to spread.

While advocating for the mobilisation of the necessary resources and political will, MSF has, along with its partners, decided to invest significantly in accelerating patient-centred research. At present these efforts to increase use of, and access to, more effective TB treatment regimens containing the new drugs include:

>>> In partnership with national ministries of health, MSF projects in 12 countries are treating people with DR-TB with regimens that include the new drugs, in line with WHO recommendations. Some of these projects are part of the endTB¹⁴ initiative between MSF, Partners In Health and Interactive Research & Development, financed by UNITAID.

>>> Running two TB clinical trials - TB PRACTECAL in conjunction with partners including the London

School of Hygiene and Tropical Medicine, and other global leaders in medical research,¹⁵ and a trial as part of the endTB project - in partnership with Harvard Medical School and others¹⁶ - to find new, shorter combination treatments for DR-TB that include the new drugs. Patients' needs are at the heart of both trials, which aim to find treatments that are effective, short, contain no injectables, and have manageable side effects.

>>> MSF and partners¹⁷ are working together to launch a better, faster way to develop new TB treatments, known as the 3P project. This initiative will use innovative, collaborative approaches to finance and coordinate R&D in order to expedite TB drug research with the ultimate aim of delivering a one-month-or-less cure for all forms of TB that works for everyone, everywhere.

While these gather pace, MSF is also piloting the use of shorter regimens of the old drugs, with patients receiving treatment for nine months rather than two years, as per the WHO's 2016 guidelines. While this is a positive step toward offering patients shorter treatment, the regimen still contains an injectable drug, and does not incorporate new or re-purposed treatments.

>>> HIV

Globally at least one-third of people living with HIV/AIDS are co-infected with TB, and in 2015, 1.2 million new TB cases were recorded in people living with HIV.* TB is also a leading killer of people living with HIV, accounting for 35 percent of HIV deaths in 2015.* Because of certain drug interactions, bedaquiline is more complicated to use in HIV patients. This is less of a problem with delamanid, which can be given to HIV patients taking the common fixed-dose combination of ARVs, which come as one-pill-a-day.¹⁸ This reduces the number of pills these very vulnerable patients have to take, which can also help improve adherence.

>>> CHILDREN

In 2015, an estimated 1 million children became ill with TB and 170 000 children died of TB (excluding children with HIV).* TB in children is difficult to diagnose, and while the basic principles of treatment are the same as for adults, many of the drugs are still not available in formulas suitable for paediatric patients. The compassionate use programme for delamanid has provided it to a small group of children from six years old and a clinical trial is forthcoming, but bedaquiline has not been studied at all among under-18 year olds. MSF has treated children with regimens containing delamanid in different locations. Preliminary data from 17 children looks promising. There have been no deaths and 10 have finished 24 weeks of treatment with a favourable status (ie. they are still on treatment but so far have been responding well).

¹⁴ More information on the endTB initiative is available at: www.endtb.org
¹⁵ A full list of PRACTECAL partner organisations, plus more information about the trial is available at: www.msfor.org.uk/tb-practecal

¹⁶ endTB clinical trial partners are MSF, Partners in Health, Epicentre, Harvard Medical School and the Institute of Tropical Medicine Antwerp, funded by UNITAID

¹⁷ Partners include: The Union, South African Medical Research Council, Medicines Patent Pool, Stop TB Partnership, C-Path, TB Alliance, the WHO's Global TB Programme as well as civil society representatives from affected countries.

More information is available at: <http://www.msffacess.org/spotlight-on/3p-project-new-approach-developing-better-treatments-tb>

¹⁸ The one-pill-a-day antiretroviral (ARV) contains TDF-3TC-EFV. Delamanid co-administered with antiretroviral drugs or anti-TB drugs shows no clinically relevant drug-drug interactions in healthy subjects. Mallikarjun S, Wells C, Petersen C et al. July 2016. Available at: <http://acc.asm.org/content/early/2016/07/19/AAC.00509-16.full.pdf>

Spotlight on Armenia and the Russian Federation (Chechnya)

MSF has had positive results using regimens containing bedaquiline in Armenia and Chechnya, in the Russian Federation, where it is supporting some of the world's largest cohorts of XDR-TB patients receiving bedaquiline outside South Africa.

In Armenia, as of October 2016, 99 patients have been started on bedaquiline by MSF, 35 patients with delamanid - of these, 7 are on a combination of the new drugs.

In 2015, an initial analysis of the first 62 patients in Armenia that had been started on bedaquiline showed 80 percent had undetectable TB bacillus at six months. All of the patients had difficult-to-treat strains of DR-TB - and had been able to access the drug through compassionate use. Their risk of poor outcome was high, and therefore results were exceptional.

As of October 2016, MSF has started 115 XDR-TB patients on treatment regimens containing bedaquiline, and 15 with delamanid in Chechnya in the Russian Federation. MSF analysis shows that of 60 patients initiated on bedaquiline, sputum culture conversion (meaning the TB bacillus was not detectable) was achieved in nearly two-thirds after six months -with the median average being just over two months.¹⁹ By contrast, in 28 patients treated with regimens only containing the older drugs, just under 40 percent achieved sputum culture conversion after six months. The median average for the conversion was nearly four months.²⁰

Ruslan's story

In June 2014, 32-year old Ruslan Ozdoyev became MSF's first XDR-TB patient in Chechnya to start a new treatment regimen containing bedaquiline. Within two months of treatment he became smear-negative for TB. On 15 July 2016, Ruslan was declared cured.

"I was admitted to the hospital with the most complicated diagnosis of tuberculosis. I weighed 75 kg before the disease. After I fell ill, my weight dropped to 40 kg. I was taking drugs, but there was no improvement. In July 2014 they started me on a new treatment. In the beginning it was very tough. I was nauseous, vomited, but began to get better after some time. All was going well. From 40 kg I gained weight to 70 kg. I want to thank everyone who took care of me. Now this is the treatment that really works."

Nischaya's story



©Atul Loke/Panos Pictures

Nischaya is 18 years old, lives in a tiny brick house in a Mumbai slum, together with her brother, parents and grandparents. She was diagnosed with TB four years ago, and was put on treatment in a public hospital. Her health didn't improve after six months of treatment, and she was then diagnosed with MDR-TB. At that point, the family decided to turn to a private doctor.

"We knew that it was going to be an expensive affair. We sold our gold jewellery and a small piece of land to save her life," says her father Vishwas. Unfortunately, even after 20 months of treatment, Nischaya's health did not improve. "We spent a huge amount of money, around 450,000 rupees (\$6,700), but the treatment didn't work. It was a complete waste of time and money," he says.

"One night she had terribly high fever for two, three days. We tried some home remedies, but it didn't work. I decided to take her to the doctor, but before we could reach there, she fell off my shoulders and collapsed, right there on the road. I didn't know what to do. I sat there for three or four minutes in shock, thinking that she was dead. After being taken to the doctor, she recovered."

From a family friend, Vishwas found out about MSF, and Nischaya was offered treatment at MSF's private clinic, where she was diagnosed with XDR-TB. After eight months of treatment for XDR-TB, Nischaya's sputum samples were still positive. In September 2015, she became one of a handful of patients eligible to receive the new TB drug delamanid. A year later her health has improved and she is gaining weight. Nischaya is now studying hard to pass her high school examinations later this year.

¹⁹ Median time to culture conversion was 63.5 days (range 5-155 days)

²⁰ Median time to culture conversion was 117 days (range 38 - 178 days)

in focus: south africa

South Africa has one of the highest burdens of TB and DR-TB in the world, with more than 20,000 people diagnosed with DR-TB in 2015.*



Nanyanyiso Baloi takes her treatment regimen for pre-XDR-TB, which includes delamanid and bedaquiline, at home in South Africa.

The South African National Department of Health (NDoH) has proactively sought access to new DR-TB treatments, including bedaquiline, delamanid and linezolid, and incorporated them into use in the National TB Programme once products are registered locally. From December 2012 to early 2015, a clinical access programme offered early access to bedaquiline in select sites, including an MSF-supported site in Khayelitsha, Western Cape.

Following registration in October 2014, the NDoH has developed guidance on how to use bedaquiline within the National TB Programme. Today, around 3,400 DR-TB patients have started treatment with regimens including bedaquiline in South Africa, around 60 percent of all bedaquiline use in the world. 168 of these patients were initiated on bedaquiline in Khayelitsha.

Steps to establish a clinical access programme for delamanid are also underway, with the NDoH in discussions with Otsuka, and clinical sites preparing to initiate patients.²¹

While this is a welcome development, it is unclear if the programme will provide a sufficient number of treatment courses to meet demand for delamanid prior to local registration of the drug which is needed for the NDoH to incorporate the drug into clinical guidelines, and negotiate a purchasing price.

Unfortunately, Otsuka has yet to file for registration of delamanid in South Africa, a process which can take years, even when applications are expedited.

An estimated 7,000 DR-TB patients per year in South Africa could benefit from the inclusion of delamanid in their treatment regimens, if WHO guidelines were applied in full.

Delamanid is of particular interest for use in South Africa, given that it is possible to take delamanid together with the standard fixed-dose combination treatment for HIV. In South Africa, 57 percent of people diagnosed with TB are also HIV-positive.*

Otsuka must urgently apply for registration of delamanid in South Africa. It must also ensure sufficient treatment courses are available to meet demand, before registration is complete.

MSF will support Khayelitsha as a site for delamanid clinical access, once the national programme is underway. However, since December 2015, MSF has had special permission to import delamanid for programmatic use in Khayelitsha – initially through a donation programme and now purchased through the Global Drug Facility, at a cost of \$1,700 per six-month treatment course.

As of October 2016, MSF has initiated 50 DR-TB patients in Khayelitsha on regimens containing delamanid - the largest cohort in South Africa. Twenty of these patients are on regimens combining both bedaquiline and delamanid - six of whom have completed six-month courses of the two drugs, and have been approved to take it as part of their treatment regimens beyond eight months.

²¹ Delamanid clinical access programme expected, Health-E news, The South African Health News Service, 29 March 2016. Available at: <https://www.health-e.org.za/2016/03/29/south-africa-to-roll-out-delamanid/>

Treating patients with the new drugs now

As of October 2016, MSF, in partnership with national ministries of health, is treating patients in 12 countries with the new drugs, in combination with older or repurposed drugs, including clofazimine, imipenem linezolid, moxifloxacin, levofloxacin and pyrazinamide.

MSF has supported the treatment of 781 patients with bedaquiline, including 6 children, in 11 countries (Armenia, Belarus, Georgia, India, Kenya, Mozambique, Russian Federation, South Africa, Swaziland, Tajikistan and Uzbekistan; with the largest cohorts of patients in Georgia and South Africa).

MSF has supported the treatment of 236 patients with delamanid, including 21 children, in 10 countries (Armenia, Belarus, Georgia, India, Kenya, Mozambique, Myanmar, Russian Federation, South Africa and Swaziland; with the largest cohorts in India, Georgia and South Africa).

Of those patients being treated with the new drugs, MSF has supported the treatment of 41 with a combination of bedaquiline and delamanid in six countries (Armenia, Belarus, India, Mozambique, South Africa and Swaziland), with the largest cohort in South Africa. The cohort of eight patients in India includes MSF's first paediatric patient on this combination.



©Sydelle Willow Smith

Simbongile Xesha collects her medication from the local primary care clinic in Khayelitsha, South Africa.

“

This treatment is giving better results but I haven't recovered still. The first time I came here I was looking forward to escaping, but now I'm psychologically prepared, I'm calm and ready to follow the treatment.

”

Giorgi Mikava, a patient at the National Centre for Tuberculosis and Lung Disease in Tbilisi, Georgia

Mphenguli's story

Mphenguli Mabundza, aged 50, from Swaziland, was first diagnosed with TB in 1998, contracted while working in mines in South Africa; he was diagnosed with MDR-TB in 2011. Years of erratic treatment followed, with no improvement in his condition. Finally in 2015, he started receiving a regimen containing the new drugs.

“I started the new treatment in July 2015. At first the treatment was unbearable. But after two weeks there was a significant change in my health. Before I started the treatment, I was constantly bloated and my legs were swollen. But soon after starting the new treatment I felt a huge relief. The constipation and the swelling on my legs stopped. I could feel the change. I continued with the treatment. I was

discharged upon successfully completing my injection phase. Now I am continuing with treatment from home. With the previous treatment would take about 20 tablets in the morning, and then I'd take a few in the evening. Now I take four tablets in the morning, plus the medication for the side effects.

I'm grateful to God for giving me a chance at life. Yes, I'm still sick, but I'm feeling a lot better and I'm with my family. I'm thankful that the medication did not mess up my brain. Also I did not at any point have negative thoughts. I'm really grateful for that. Yes, the pain is still somewhat there, but it's not so bad. I am just happy to be alive and I'm still there for my children. I look forward to the day the doctor will tell me that I'm done with my treatment.”

Spotlight on Georgia

MSF started supporting the Georgian Ministry of Health to provide regimens including bedaquiline and delamanid in 2014, initially under a compassionate use scheme.

Since 2015, Georgia has been one of 15 countries participating in the endTB project. As of July 2016, more than 200 patients were receiving either bedaquiline or delamanid as part of an improved regimen – the highest number supported by MSF in any country. In late 2016, endTB will also launch a clinical trial in Georgia to develop shorter, less toxic and more effective treatments based on these two new drugs.

“

I was getting really unbearable pain in my gallbladder and liver. And I asked the doctor how we could stop the pain. For a week we stopped taking [one of the old drugs] and the pain was gone. Then when we started again the pain has started again in my stomach and it spread towards my kidneys. I had problems in my heart, too. Since I started taking this new medicine I have had no problems. Now I feel so good.

Nugzar Papashvili is a patient at the National Centre for Tuberculosis and Lung Disease in the capital, Tbilisi

”



Nugzar Papashvili having a medical check up.

“

A lot of things have changed. I feel better as I am taking this new medicine, the number is reduced and my body can accept them better. I'm taking two tablets of delamanid twice a day. I get injected once and take vitamins. Totally I take seven tablets. Before it was 17 or 18 tablets a day.

Ajiba Teimuraz is a patient at the Regional Centre of Infectious Pathology, AIDS and Tuberculosis in Batumi

”



Giorgi Mikava, patient at the National Centre for Tuberculosis and Lung Disease in Tbilisi.

“

TB is not as dangerous nowadays. It can be cured, if you follow the treatment. When I first started taking the treatment, my body couldn't accept TB medicines. I had stomach aches and was vomiting. But afterwards the doctors changed the medicine and gave me bedaquiline. After taking this I'm feeling OK, I simply have a bit of low calcium.

Yulia Dilebashvili is a patient at the National Centre for Tuberculosis and Lung Disease in the capital, Tbilisi

”

in focus: india

India has the highest TB burden in the world, with an estimated 2.8 million new cases each year, more than one-quarter of the world's total.* Drug-resistance is a particular problem.

©Anil Lake / Panos Pictures



XDR-TB patient Hanif, taking his daily TB medication at home in Mumbai.

India has the highest TB burden in the world, with an estimated 2.8 million new cases each year, more than one-quarter of the world's total.* Drug-resistance is a particular problem with 2.5% of new TB patients and 16 percent of patients requiring re-treatment presenting with forms of DR-TB.*

MSF has been using bedaquiline in India since 2013 and delamanid since 2015 – with some promising signs for their efficacy in patients with no other treatment options. In its project in Mumbai, MSF found that in 16 out of 20 patients being treated with combinations containing either bedaquiline or delamanid had no sign of the TB bacillus after six months of treatment.

Prior to being offered treatment by MSF, most of these patients had often been treated with ineffective regimens for several years by public and private practitioners. For others there has been primary transmission of the extensively resistant strain, meaning that they have been directly exposed to the resistant bacteria in the community or during their visits to health facilities. The MSF project experience has shown that it is better to introduce the new drugs to the treatment regimen at an early stage, rather than as a last resort when all other options have failed.

For many patients in India and worldwide, treatment options are extremely limited, and a combination of bedaquiline and delamanid is required to build an effective regimen. In its Mumbai project, MSF

started treating patients with regimens using both new drugs in combination in early 2016. So far, eight patients have been initiated on this combination, including a paediatric patient. The initial experience in Mumbai shows promising results in terms of efficacy and safety.

However, the number of patients benefitting is just a fraction of those in need, and many patients continue to die because access to the new drugs is so restricted.

Bedaquiline received market approval in 2015 in India, but its roll-out has been far too slow. Outside of a government pilot programme in six locations, access to the drug is restricted to a compassionate use mechanism, whereby an application needs to be filed on a patient-name basis to import the drug for each individual patient.

Delamanid is still not registered in India. Only a handful of patients have been able to be treated with it - through the compassionate use / patient name mechanism.

MSF believes that while further clinical research is needed, sufficient evidence exists to show that both bedaquiline and delamanid should be made available to patients for whom it is lifesaving. MSF is advocating for speeding up expanded roll-out of both new drugs, as well as the introduction of the necessary safeguards to ensure professional management of their administration.

Clinical trials

Because MSF has so many TB treatment projects across varied locations, it is well placed to analyse data and contribute to the body of knowledge on how the new drugs work with different patient cohorts. This analysis can support recommendations within the current system, such as adding new drugs to existing treatments. For example, MSF programmatic data from Armenia and Georgia was shared with WHO for analysis of the revision of its guidelines on bedaquiline, expected by the end of 2016.

Although there is significant value in programmatic data, clinicians and regulators need robust data to make sufficiently informed and accurate risk-benefit analysis of the drugs through the completion of phase III clinical trials. Clinical trials are internationally recognised as the most robust kind of data, as they exclude any element of chance and bias when analysing data. This includes ensuring that there is a randomised selection process for patients to help eliminate bias towards a particular cohort, and full documentation of the effects at all stages.

Progress with developer-initiated clinical trials for the new TB drugs has been painfully slow. Bedaquiline was approved in 2012, yet Janssen did not start phase III trials until 2016 (through an agreement for the research to be incorporated into the STREAM II trials). While this is a welcome development, it is still four years later than would be expected. Delamanid, approved in 2014, has entered phase III trials, with results expected in 2018.

To help fill the gaps in regimen-based clinical research, a number of entities have initiated or are planning clinical trials. The list includes the STREAM trials and TB Alliance's NIX-TB and NC-005 trials²¹. For its part, MSF is involved in two separate trials to find new combination treatments using the new drugs, which are effective, short, contain no injectables and have manageable side effects.

TB PRACTECAL is a clinical research project involving MSF, the London School of Hygiene and Tropical Medicine (LSHTM) and other global leaders in medical research, as well as ministries of health in affected countries. It will involve a total of 630 patients from five study sites, starting in Uzbekistan before the end of 2016, and in Belarus and a southern African country in early 2017. It aims to identify effective and

tolerable treatments containing bedaquiline and another new drug, pretomanid, with no injectables and as few pills as possible, taken for just six months.

The trial will study three regimens containing bedaquiline, pretomanid and linezolid, with or without moxifloxacin or clofazimine in two stages. Stage one of the study, which is equivalent to a phase II study, plans to identify regimens containing the new drugs bedaquiline and pretomanid for further evaluation based on safety and efficacy outcomes after eight weeks of treatment. This will lead seamlessly to stage two of the study (equivalent to phase III), which will evaluate the long-term safety and efficacy of the best performing new regimens, compared with the WHO recommended standard of care used locally.

endTB's clinical trial (a partnership between MSF, Partners in Health, Epicentre, Harvard Medical School and the Institute of Tropical Medicine Antwerp, financed by UNITAID), of which MSF is sponsor, will begin in late 2016. In collaboration with ministries of health, the clinical trial will involve 750 patients in six countries (potential sites include Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, South Africa), of which Georgia, Kyrgyzstan and South Africa are MSF projects. It will study the safety and efficacy of several "user-friendly" MDR-TB treatment regimens, each containing either bedaquiline, delamanid or both, in combination with old or repurposed drugs, for nine months, and without injectables.



A DR-TB patient showing her TB medication in Mumbai, India.

²¹ For more information on DR-TB clinical trials, see Progress Report DR-TB clinical trials, Research Excellence to Stop TB Resistance (RESIST TB) provides detail on DR-TB clinical trials. Available at: http://www.resisttb.org/?page_id=1602&e=RESIST_TB (Research Excellence to Stop TB Resistance)

The next generation of TB treatment

In the longer term clinical research and trials are critical. As it is in the nature of TB to develop resistance, there is also a need to ensure a healthy pipeline of new treatments.

MSF is a founding partner of the 3P project, a new initiative working to develop a short-course treatment regimen (less than one month) that will be effective against all forms of TB, including drug-resistant TB, that will work for all patients, including children and people living with HIV. The 3P project aims to deliver new TB regimens within the time it takes to develop a single drug.

Currently, individual drugs are first approved by drug regulatory authorities,

and only then do clinical trials into how they can be used together with other drugs start, as is required for TB. This has been one of the reasons for the slow pace of clinical research into bedaquiline and delamanid.

The 3P project uses innovative funding strategies to incentivise collaborative research, for example by awarding prize money for promising new TB drugs at an early stage, facilitating the early sharing of clinical data and intellectual property so that promising candidates can easily be combined, and offering grant-based funding to pay for clinical trials that combine new drugs into affordable, effective and patient-friendly treatments for TB.

Sinethemba's story



Sinethemba Kuse, aged 16, lives with her grandmother and four other family members in Khayelitsha, South Africa. Here she describes the day she learnt she had drug-resistant TB, and her initiation on the new drug delamanid.²²

“That day was 24 December – just imagine being told that you have MDR-TB just before Christmas. The same day the doctor gave me tablets which I collected from the TB room and I also got an injection. The nurse told us the injectable medicine can damage my ears and kidneys. The injections were painful. I was scared of the needle because I had to be injected every day. Sometimes I would bleed and I even got lumps. I drank a lot of tablets, so I would vomit or be dizzy. Sometimes I would ask my grandma if I could skip the injections.

When we came back from the Eastern Cape, we went to the clinic again for more tests and I

gave more sputum. The results came back and Doctor Kunene told us that I had XDR-TB, not just MDR-TB. This was way more serious. I just said to myself that this is it, I'm going to die, because many who suffer from XDR-TB die. I just slept and worried. I could see my grandma was also hurting and all the family members too.

Dr Kunene introduced us to Thandi, a counsellor working with DR-TB patients, and explained that I didn't have to die. I just had to take my tablets every day. Doctor Kunene told us about a new medication that is available in Khayelitsha and not a lot of people have the luck to get it, and you have to sign papers for it. He also told us about the side effects, that it could damage the heart. And Dr Jenny of MSF explained to us more about this new drug called delamanid. In February 2015 I started taking it. All I can say is that there is hope and I trusted it with my life and it worked. My gran and everybody started noticing the difference; even my gran's church friends saw the change.

I have gained weight and I love singing, reading books. I don't sleep a lot anymore. It really helped me and I would say that TB does not kill. It can be cured with proper treatment. Also thank you to the people who invented delamanid because it can change a lot of lives.”

²² Sinethemba's blog is available on MSF's TB and Me patient blogging site: <http://blogs.msf.org/en/patients/blogs/tb-me>

going forward

With 1.8 million recorded deaths from TB in 2015*, this growing public health emergency is increasingly aggravated as drug-resistant forms take a grip. New developments, including the first new TB drugs in 50 years, offer some reason for hope for people in need of DR-TB treatment.

However, the treatment gap between those in need of the new drugs and those who can access them is unacceptably high. In some regions up to 70 percent of DR-TB patients are eligible for treatment with the new drugs, far more than was initially expected.

Moreover, using them in combination with the older drugs still known to have unbearably toxic side effects can only be a short-term solution. Clinical research into more effective TB regimens, including of the new drugs, is critically needed. Because progress in developer-initiated clinical research has been far too slow, numerous entities – including MSF and partners – have decided to run their own clinical trials in conjunction with national ministries of health.

Meanwhile, because patients with life threatening TB do not have the time to wait, MSF is already working to provide them with the shortest, least toxic and most effective treatments it can, using the best of the available knowledge and the best drugs available.

These efforts are just the beginning. Patients remain years from getting the cures they desperately need. Far greater efforts must be made to diagnose and treat DR-TB patients, to save lives and slow the spread of TB.

The world needs to see an urgent intensification of efforts across regulatory, scientific, commercial, financial and political sectors to invest in research and accelerate access for patients. Much more needs to be done to create the incentives and conditions that ensure that TB research efforts are fully funded and are patient-driven to address public health priorities for TB.

TB is a global crisis, one which requires a global response. Only then can we stop unnecessary deaths and the spread of this virulent disease and its drug-resistant forms.



XDR-TB patient Hanif, at home in Mumbai, with his children.

©Atul Loke/Panos Pictures



Design by: Alice Bridgwood/alice.bridgwood@gmail.com