Ready, Set, Slow Down: New And Promising DR-TB Drugs Are Grabbing Headlines But Not Reaching Patients

MSF on the policies underpinning the deadly DR-TB treatment gap

The Global DR-TB Crisis

Drug-resistant tuberculosis (DR-TB) is a major global health emergency: An estimated 480,000 people have multi-drug resistant TB (MDR-TB), yet only 30% are diagnosed and treated. Resistant forms of TB, including extremely-drug resistant TB (XDR-TB), are increasingly spreading directly from person to person. In Belarus, Kyrgystan and Kazakhstan, the World Health Organization's (WHO) new sobering *Global TB Report 2014* includes MDR-TB rates of 25-35% among newly diagnosed TB cases.[a] For people lucky enough to receive medical care they face two years of toxic treatment, including painful injections, thousands of pills, in a regimen that is expensive (USD 1500-5000 per treatment course) with abysmal cure rates. Undiagnosed and untreated the disease continues to spread and kill. The lack of good and affordable drugs, increasing levels of resistance, and the sheer number and breadth of DR-TB cases present a grave global challenge.

THE FACTS 2014

- 9 million people affected by TB, and 1.5 million deaths
- 480,000 people with MDR-TB, yet only one in five treated
- 136,000 MDR-TB cases diagnosed
- In parts of Eastern Europe and Central Asia MDR-TB rates in re-treatment cases are reaching 75%
- Cure rates for MDR-TB at best are 48%, dropping to 22% for XDR-TB, 2013

Finally, an opportunity exists to turn this crisis around. Bedaquiline, the first new class of TB drug in 50 years, received accelerated approval for treating MDR-TB in 2012. A second new drug, delamanid, received approval in 2014. The TB drug pipeline has five new drugs in clinical testing. The WHO Prequalification Programme has approved nearly a dozen new sources of DR-TB medicine and re-purposed group five medicines, like clofazimine and linezolid, are showing effectiveness against TB. However, phase one of the TB pipeline is empty, the new drugs are only currently available through a small number of compassionate use programmes and there are no trials currently underway incorporating them into new regimens. Clofazimine and linezolid are not yet registered for TB, which causes a significant barrier to their use. **New treatments provide new hope, yet no one drug can solve the crisis; what is urgently needed is an arsenal of regimens that are patient focused, quality assured, safe, and efficacious, along with further developments in timely and accurate diagnosis.**

New Drugs Provide New Hope But Remain Largely Out Of Reach

Bedaquiline (Janssen) received fast-track approval by the US Food And Drug Administration (FDA) in December 2012, but the company has only submitted dossiers for registration in 15 countries, and its pricing structure remains a barrier, especially when added to the existing costly regimen. Cost is particularly an issue for Middle Income Countries (MIC). A coalition of civil society and global health actors has asked the company to revise its prices for low and middle-income countries, which is USD 900 and USD 3,000 respectively for a six-month course. Government funding contributed to research and development (R&D) for bedaquiline, and Janssen received a US FDA priority review voucher worth potentially 50% of its clinical trials costs. How these contributions are reflected in the end price however is not transparent. Some countries are also facing difficulties in meeting requirements for the pharmacogivilance, which forms another costly barrier, together with the lack of country-level approval of the drug.

Delamanid (Otsuka) received approval by the European Medicines Agency and Japan Pharmaceuticals Medical Devices Agency in 2014 but the company only submitted dossiers for registration in Europe and Japan and its pricing structure outside of these places is unknown. So far, delamanid is only marketed in the UK and in Germany. It is not clear whether the company intends on submitting dossiers for registration in endemic countries.

Compassionate use (CU) programme: MSF offers the new drugs to patients via compassionate use programmes, in countries that have the necessary regulations in place. Early results from the use of a bedaquiline-containing treatment in MSF's Armenia project show culture conversion at two months was achieved by 55% (11/20) of patients, and at six months by 88% (15/17) of patients. MSF has not yet prescribed delamanid to patients but hopes to do so in the future.

Repurposed Drugs Promising But Barriers Prevent Wider Use

Linezolid (Pfizer) is an antibiotic that does not have a registered indication for TB. Further, the Pfizer price is prohibitive. A cheaper generic version from Hetero is registered in the United Kingdom, and four manufacturers (Teva, Mylan, Glenmark and Gate Pharma) have tentative approval from the US FDA and should be able to market their product when the basic patent on linezolid expires in the US in November 2014. Many countries were previously unable to access low-cost versions due to Pfizer's patents, and secondary patents from Pfizer could present legal obstacles in some countries in the future. In South Africa, MSF is using linezolid as part of a regimen for patients diagnosed with pre-XDR and XDR-TB, but was paying approximately USD 65 per pill for the Pfizer product. After a long legal effort MSF, thanks to an import waiver, has been granted permission to use Hetero linezolid, which is 88% less expensive than the original, though still costly at USD 8 per pill. Continued registration delays mean that other treatment providers in South Africa still do not have access to lower priced generics.

Clofazimine (Novartis) is a drug that is used in the treatment of leprosy. It does not have an indication for TB and Novartis, the originator company, severely restricts its use for TB. However, the use of clofazimine is increasing with its inclusion in the shortened nine-month MDR-TB regimen with both the STREAM trial and countries using it in operational research with this shortened regimen. It is vital that it is registered for use in TB and that alternative quality assured suppliers are found.

Imipenem/cilastatin is another antibiotic that is used in the treatment of XDR-TB. It is an intravenous preparation, which presents significant programmatic barriers to its widespread use. MSF has been able to use it as part of our compassionate use programmes by inserting portacaths (long term intravenous access lines). However, to scale-up its use for TB a more user-friendly preparation needs to be developed.

Patients Priced Out Of The Equation By Unaffordable DR-TB Drugs

The cost of each TB drug must be considered in the context of its contribution to the total cost of a regimen. TB programs are already struggling to scale-up access to today's USD 1500-5,000 MDR-TB regimens. As evidence of new and repurposed drugs efficacy in combinations grows, countries may face tough financial choices in trying to provide these more effective treatment regimens to patients in need. Middle-income countries in particular are disproportionally affected by high drug prices, as they shoulder the bulk of the global TB burden, but often have severely underfunded TB budgets. MSF suggests USD 500 per treatment course for low and middle-income countries is a reasonable price in the absence of competition and would result in more countries scaling-up life saving treatment. **See 'Group 5 Drugs Chart' for pricing information.**

Additional MSF Resources DR-TB

- Out of Step: Deadly implementation gaps in the TB response, msfaccess.org/outofstep
- Under the Microscope: Sources and prices for drug-resistant tuberculosis medicines, msfaccess.org/utm2013
- Beyond the Microscope: Addressing the critical need for better TB diagnostics, msfaccess.org/content/beyond-microscope

Médecins Sans Frontières (MSF) *is an international medical humanitarian organization that has been involved in TB care for 30 years and began its first programmes to treat MDR-TB in 1999. The organisation is now one of the largest NGO treatment providers for DR-TB.*

GROUP 5 DRUGS		
	MANUFACTURERS & PRICE	GLOBAL DRUG FACILITY (GDF) POOLED PROCUREMENT
BEDAQUILINE (Bdq)		
Approval status	Janssen: Stringent regulatory authority (SRA) approved	GDF Quality Assurance Policy
100mg tablet	Janssen: High-income: USD 159.57; upper middle-income: USD 15.96; least-developed/resource-limited countries: USD 4.79	Available for purchase, but price is not public
CLOFAZIMINE (Cfz)		
Approval status	Novartis: SRA approved	GDF Quality Assurance Policy
50mg soft-gel capsule	Novartis: Price not available	USD 0.62 (Novartis via Pharmaworld)
100mg soft-gel capsule	Novartis: Price not available	USD 1.61 (Novartis via Pharmaworld)
DELAMANID		
Approval status	Otsuka: SRA approved	
50mg tablet	UK: USD 78; Japan: USD 111	
IMIPENEM/CILASTATIN		
Quality status	SRA approved	GDF Quality Assurance Policy
500/500mg vial, powder for injection	Demo, Labatec, Panpharma, MSD, Fresenius Kabi France	USD 7.32-10.64
LINEZOLID (Lzd)		
Approval status	Hetero & Pfizer: SRA approved	GDF Quality Assurance Policy
600mg tablet	Pfizer: Price not available	USD 6.9 (Hetero)
100mg/ml suspension powder	Pfizer: Price not available	

MSF Urges Immediate Action To Increase Access To Lifesaving DR-TB Drugs

TB-Endemic Countries: Ensure national TB treatment guidelines, Standard Treatment Guidelines and Essential Medicines Lists (EML) are regularly updated in line with WHO guidance, including for Group 5 medicines; enact procedures that allow importation and dispensation of quality-assured Group 5 medicines not yet registered; implement the necessary legislation for CU; proactively reach out to quality-assured manufacturers, enabling fast track registration for priority TB medicines; recognize market authorisations granted by stringent National Medicine Regulation Authorities (NMRA), and make use of international regulatory flexibilities such as the collaborative registration process at the WHO prequalification programme.

World Health Organization: Ensure all DR-TB medicines, including new compounds, are added onto the WHO EML and the Expression of Interest of WHO Prequalification Programme; issue timely interim guidance for new compounds and regimens and update final treatment guidelines; give guidance to countries on initiating CU programmes, facilitating fast track registration of the new compounds and new regimens; support countries in their use of the collaborative registration process at WHO prequalification programme and make attempts to expand this process to stringent NMRAs.

Manufacturers [**See 'Challenges in Accessing New and Repurposed TB Drugs' chart**]**:** Provide access to innovative medicines through CU; proactively register new medicines in countries where clinical trials take place and other high-burden TB countries; register quality-assured Group 5 medicines and new compounds, even in small markets; ensure an affordable, transparent price for all DR-TB medicines for all low- and middle-income countries; accelerate combined drug research to create appropriate regimens; ensure that intellectual property barriers (patents and test data) do not preclude generic competition or development of appropriate fixed-dose combinations or other formulations.

Donors: All donor and middle-income countries should step up political and financial commitment and support scale-up of new treatments, by promoting the exclusive use of quality-assured TB medicines; and consider long-term innovation and access strategies, through support for the creation of the 3Ps Project (see msfaccess.org/push-pull-pool).

CHALLENGES IN ACCESSING NEW AND REPURPOSED TB DRUGS

Development stage	Access barriers	What needs to happen
Bedaquiline (Bdq), *Janssen*		
- Accelerated approval from US FDA, conditional approval from EMA, full approval in the Russian Federation, all based on phase IIb data. Approved by the Ministry of Food and Drug Safety (MFDS) in South Korea 3/2014 - Phase III in planning - Recommended by WHO for use in DR-TB patients with no other treatment options	- Price: USD 900 for low-income countries (LICs), USD 3,000 for middle-income countries (MICs) for a six-month course as well as costly pharmacovigilance requirements - Intellectual property barriers (compound and multiple secondary patents) until 2029 that limit generic competition or development of fixed dose combinations - Delays in registration with multiple NMRAs - Little data on use with other new TB drugs (e.g. delamanid) - Not yet included in the WHO EML	- Access to a more affordable price, especially for MICs - Reduction of intellectual property barriers through use of TRIPS flexibilities or voluntary licensing - High burden TB countries' NMRAs must prioritise registration -Inclusion on the WHO EML - Rapidly commence trials looking at combining Bdq with other new drugs and in shorter regimens
Clofazimine, *Novartis*		
- Registered for use in treating leprosy. Recommended by WHO as a Group 5 drug for TB treatment	- Does not have an indication for TB - Only one quality-assured manufacturer makes this drug and quantities may not be sufficient for scale up of clofazimine-containing regimens, including new shortened regimens - Not yet included in the WHO EML for TB	- Novartis should pursue obtaining a TB indication for clofazimine - 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 ingredient and finished product of clofazimine should pursue WHO prequalification - Inclusion on the WHO EML for TB
Delamanid (Del), *Otsuka*		
- Full approval by EMA, and PMDA in Japan, based on phase IIb data. Phase III finished enrolling. WHO recommendations under development	- Global price strategy is not yet known. The price for a 6-month course is USD 28,000 in the UK and USD 40,000 in Japan - Only currently registered in the European Union and Japan - Intellectual property barriers (compound and secondary patents) until 2031 that limit generic competition or development of fixed dose combinations - No proactive plans to register in high-burden TB countries or trial countries - Little data in use with other new TB drugs (e.g. bdq) - Not yet included in the WHO EML	- Pricing for L&MICs must be affordable and enable access - Reduction of intellectual property barriers through use of TRIPS flexibilities or through voluntary licensing - Otsuka must urgently register this medicine in high-burden TB countries and trial countries; in the meantime, del should be accessible through CU programmes - Increased transparency from manufacturer on price and registration questions -Inclusion on the WHO EML once WHO recommendations made - Rapidly commence trials for combining del with other new drugs and in shorter regimens
Linezolid (Lzd), *Pfizer*		
- Registered for use in treating resistant infections caused by typical bacteria. Recommended by WHO as a Group 5 drug for TB treatment	- Does not have an indication for TB - Intellectual property barriers (secondary patents) that could preclude importation of low-cost generics until 2021 in some countries - Despite the entry of one generic manufacturer (Hetero), price remains an issue - Not yet included in the WHO EML for TB	- Pfizer or Hetero should register lzd in all high burden TB countries as a priority - Pfizer and Hetero should pursue a TB indication for this drug - Price reductions to improve affordability - Use of TRIPS flexibilities, if needed, to remove remaining secondary patents in countries where treatment scale up is needed - Inclusion on the WHO EML for TB
PA824, *TB Alliance*		
- In Phase II development. Phase III trial planned (STAND-TB)	- As it will not be registered as a single drug, important it is made available for development of drug combinations beyond those currently being trialled - No plans for CU	- Review possibility of allowing access to PA824 for CU as soon as Phase II trials are successfully completed - Allow access to PA824 for use in trials combining it with other new drugs and additional shorter regimen trials