MSF Access Campaign
Technical Brief
SEPTEMBER 2019

MAKING THE SWITCH

Saving More Lives with Optimal Treatment for Drug-Resistant TB

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to isoniazid and rifampicin, with or without resistance to other first-line drugs.[1] Pre-extensively drug-resistant TB (pre-XDR-TB) is defined as resistance to at least isoniazid and rifampicin as well as either second-line injectables or fluoroquinolones (levofloxacin or moxifloxacin) but not both. Extensively drug-resistant TB (XDR-TB) is defined as resistance to at least isoniazid and rifampicin, any fluoroquinolone and any of the three second-line injectable agents (amikacin, capreomycin or kanamycin).[2] XDR-TB is more difficult to treat, and cure, than MDR-TB.

Drug-resistant tuberculosis (DR-TB) requires use of second-line treatment regimens, which may include repurposed or newer TB drugs. The previously recommended DR-TB treatment regimens used by most countries had a high pill burden, long treatment duration (of up to two years), painful daily injections (for up to eight months), severe side effects (due to toxic drugs) and poor treatment outcomes. These suboptimal regimens achieved treatment success rates of only 55% for people with multidrug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) and 34% for people with XDR-TB.[3]

The World Health Organization (WHO) issued new MDR/RR-TB treatment guidelines[4] in March 2019. This technical brief provides a summary of the treatment regimens now recommended by WHO, which represent hope for people with DR-TB and their caregivers because they offer better cure rates and fewer side effects using safer all-oral treatment. Médecins Sans Frontières (MSF) urges countries to make a timely switch to these regimens given the clear benefits of providing bedaquiline for all people with MDR-TB and the urgent need to discontinue use of harmful injectable agents.

In July 2019, WHO Director-General Dr Tedros Adhanom Ghebreyesus called for countries to transition to the all-oral regimens to treat DR-TB by World TB Day, 24 March 2020. By this time 100% of people newly enrolled on treatment should be offered the optimal regimen.[5]

BACKGROUND: NEW WHO TREATMENT GUIDELINES

In August 2018, WHO released the Rapid Communication "Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis," which for the first time recommended all-oral regimens as the standard to treat MDR-TB.[6] Following this communication, WHO released a pre-final text of the "WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis" in December 2018, and released the "Consolidated guidelines on drug-resistant tuberculosis treatment" in early 2019.[4,7] These guidelines replace all other previous WHO recommendations on DR-TB treatment.


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Nataliia began treatment at MSF's DR-TB treatment project in Zhytomyr Oblast, Ukraine in October 2018.

The new WHO recommendations are based on reviews of evidence available from:

- A multi-country meta-analysis of individual patient data
- Phase III trials on delamanid and shorter MDR-TB regimens
- Bedaquiline and delamanid trials in patients under 18 years of age
- Programmatic data using bedaquiline, delamanid and other novel regimens

The multi-country meta-analysis assessed:

- Newer all-oral long regimen: number of drugs that should be used and duration of treatment in order to achieve better treatment outcomes
- Short-course regimen: efficacy and safety compared with the older long regimen (using injectable agents)
- Monitoring: benefit of monthly culture over smear microscopy monitoring

STATE OF DRUG-RESISTANT TB IN 2017:

- **An estimated 558,000 people fell ill with MDR-TB**
- **Only 29% of people with DR-TB were diagnosed**
- **Only 25% of people with DR-TB were started on treatment**
- **Only 55% and 34% of people were successfully treated for MDR/RR-TB and XDR-TB, respectively**
- **Three countries accounted for approximately half of the world's cases of MDR/RR-TB: India (24%), China (13%) and the Russian Federation (10%).**

Source: WHO Global TB Report 2018.[3]

MDR-TB TREATMENT RECOMMENDATIONS

New recommendations for all-oral long regimens

All-oral regimens are the preferred option for treatment of MDR-TB and XDR-TB, as two of the injectable agents – kanamycin and capreomycin – are associated with increased deaths, treatment failures, relapses and very severe side effects, including permanent hearing loss. In the newer long regimens, kanamycin and capreomycin are no longer recommended as treatment options, and amikacin and streptomycin are only recommended when susceptibility has been confirmed and adequate monitoring of hearing loss can be ensured. The groups of drugs in the new long regimens are shown in Table 1.

Table 1: Groups of drugs in the new long regimens

Groups & Steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin or moxifloxacin	Lfx or Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine or terizidone	Cs or Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem/cilastatin or meropenem	Ipm/Cln or Mpm
	Amikacin or streptomycin	Am or S
	Ethionamide or prothionamide	Eto or Pto
	p-aminosalicylic acid	PAS

Summary: New WHO recommendations for MDR-TB/RR-TB treatment

What regimens to use?

All-oral long regimens are the preferred standard, though the short-course regimen may be offered to selected patients when there is no previous resistance to any of the drugs (except for isoniazid).

What medicines to use?

- Drugs in Groups A and B include mainly repurposed drugs (drugs initially approved to treat other diseases), such as moxifloxacin, levofloxacin, linezolid and clofazimine.
- The core drugs to treat MDR-TB are levofloxacin/moxifloxacin, linezolid and bedaquiline in Group A and clofazimine and cycloserine in Group B. Among the newer drugs, bedaquiline should be given to all patients, as it is one of the core drugs (Group A). As shown in Figure 2, bedaquiline is the drug with the least risk of side effects among all second-line drugs.
- The injectables kanamycin and capreomycin should not be used, while amikacin and streptomycin are recommended only if there is confirmed susceptibility and if monitoring of hearing loss can be ensured.
- Delamanid remains as a Group C drug and is among the preferred add-on drugs in Group C to complete regimens when medicines from Groups A and B cannot be used.
- In children, bedaquiline is approved for patients between 6 and 17 years of age; delamanid is approved for children 3 years of age and older.

How many drugs?

- Treatment should start with 4 effective drugs for the initial 6 months and should include 3 effective drugs thereafter.
- Five drugs should be given if (i) more than one drug is expected to cease after 6 months, (ii) drug susceptibility testing (DST) is unavailable and local prevalence of resistance to one of the drugs is known to be high, or (iii) agents included in the regimen are unlikely to cure the patient (i.e. if there are not enough drugs from Groups A or B).

For how long?

For the long regimen, a total treatment duration of 18 to 20 months is recommended, including 15 to 17 months of treatment after culture conversion.

How to monitor treatment?

Monthly monitoring with culture over smear is recommended for patients on DR-TB treatment.

"The evidence of improved cure rates and lives saved for people with drug-resistant TB using bedaquiline is crystal clear. Bedaquiline is crucial to offering patients a fighting chance without the toxic side effects of drugs that need to be injected."

- Dr Anja Reuter, MSF TB doctor, South Africa

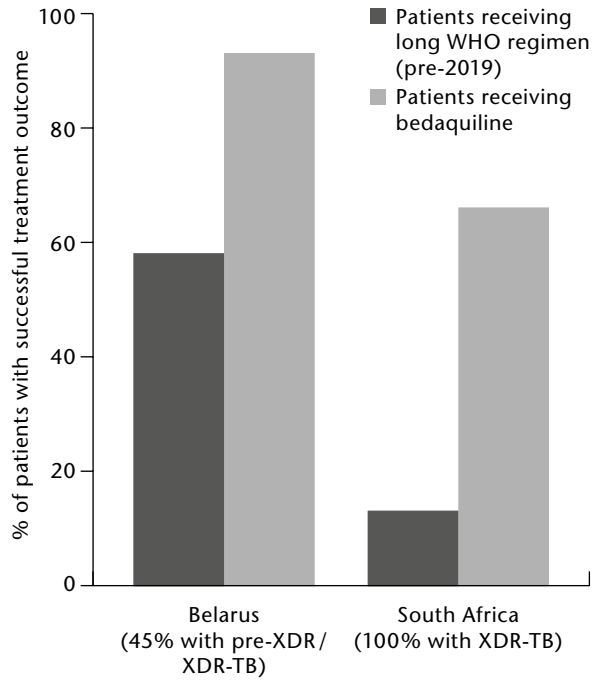
Evidence in support

In addition to the meta-analysis showing poorer treatment outcomes for patients receiving kanamycin and capreomycin, increasing evidence supports the benefits of the new all-oral regimens:

- A study from South Africa showed mortality among 1,016 patients with MDR- or XDR-TB who received bedaquiline was a third of that among patients who did not receive the drug.[8]
- Another study from South Africa showed that patients who were switched from second-line injectables to bedaquiline had a one-third decrease in unfavourable treatment outcomes. Additionally, early initiation of bedaquiline was associated with an increase in sustained culture conversion.[9]
- Initial experience in Belarus is also encouraging. Among 192 patients with MDR-TB who received bedaquiline-containing regimens, 178 (93%) were treated successfully, compared to just 58% of patients who did not receive bedaquiline.[10]
- A meta-analysis comprising 12,030 patients from 25 countries showed that bedaquiline was associated with increased treatment success.[11]

As shown in Figure 1, among two cohorts of people treated for DR-TB in Belarus[10] and South Africa[12], markedly higher treatment success rates were achieved among patients who received bedaquiline compared to those who did not.

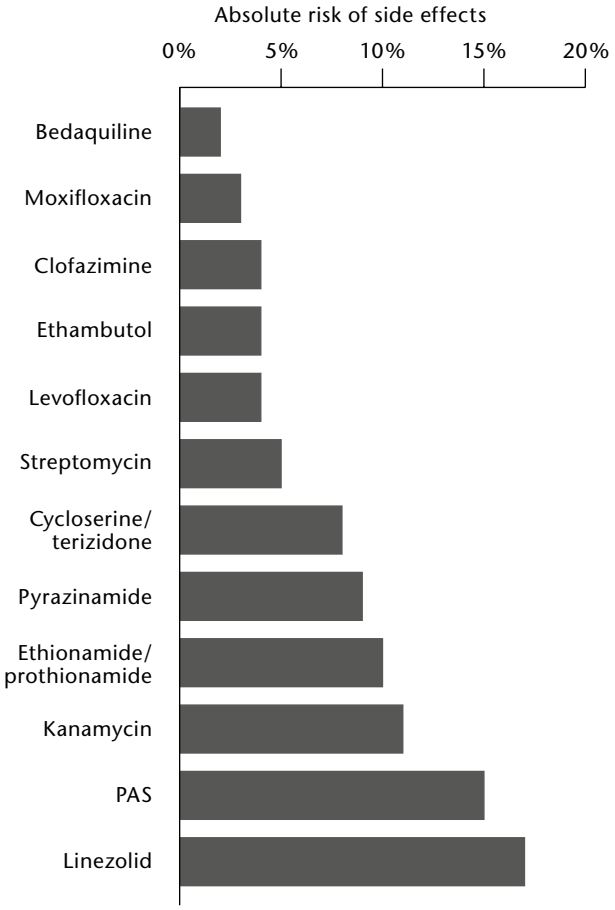
FIGURE 1:
TREATMENT SUCCESS RATES AMONG PEOPLE WITH MDR-TB, PRE-XDR-TB AND XDR-TB WHO RECEIVED BEDAQUILINE



Source: Adapted from New drugs save lives of patients with multidrug-resistant TB in Belarus (WHO)[10] and Olayanju et al.[12]

In addition to enabling substantially improved rates of treatment success, there is also evidence of bedaquiline's superior safety compared to other second-line drugs. As shown in Figure 2, the multi-country meta-analysis demonstrates that bedaquiline has the lowest absolute risk of serious adverse events (2%); linezolid has the highest risk (17%).[6] An interim analysis from the endTB trial also showed that linezolid has the highest risk of side effects, with 11% of patients receiving linezolid experiencing at least one toxicity commonly attributed to linezolid (peripheral neuropathy, optic neuritis or myelosuppression).[13]

FIGURE 2:
SERIOUS ADVERSE EVENTS IN PEOPLE ON LONGER MDR-TB TREATMENT REGIMENS



Source: Adapted from the WHO Consolidated guidelines on drug-resistant tuberculosis treatment, 2019[7]

"I lost my hearing when I was 24 because of the brutal side effect of an injected DR-TB drug. I was devastated by this loss, which took a heavy financial, emotional and mental toll on me. How many more people will have to die or go deaf, waiting to access safer and more effective drugs that can save their lives without such devastating side effects?"
- Nandita Venkatesan, DR-TB survivor, India

The benefits of dropping injectable agents

Injectable agents used in DR-TB regimens frequently cause severe hearing loss. The endTB interim analysis demonstrated that approximately 20% of patients who received an injectable agent experienced hearing loss and 36% of patients who received an injectable agent experienced at least one injectable-related toxicity (hearing loss, acute renal failure or hypokalaemia/hypomagnesemia).[13] In the STREAM trial, the proportion of patients who experienced hearing loss on the shorter regimen was demonstrated to be similar to the proportion who experienced hearing loss on the longer regimen* (despite the shorter duration of treatment with injectable agents).[14]

In many studies, severe adverse events have been shown to be associated with poor treatment outcomes. People with MDR-TB identify side effects as barriers to treatment adherence;[15] therefore, using recommended regimens that do not include injectable agents would likely lead to better adherence and improved outcomes.

The opportunity to improve adherence and models of care

WHO-recommended injectable-free regimens represent a better chance for a cure. Injectable-free regimens also present an opportunity to improve treatment adherence and enable effective, patient-centred models of care.

Advantages of the injectable-free regimens include:

- Less pain and discomfort for people with DR-TB
- Decentralised services and ambulatory care with community, home-based directly observed therapy (DOT) – proven to yield better treatment outcomes for patients and to be more cost-effective than traditional DOT[16]
- Potential for multi-month prescription of medicines for stable people with DR-TB, which makes administering and receiving treatment more convenient
- Reduced costs, associated with reduction in consumables needed to provide injections (e.g. needles and syringes) and reduction in need for audiometry and renal function monitoring (i.e. testing for creatinine and electrolytes)
- Increased opportunity for skilled healthcare workers to focus on responsibilities other than DOT from the first month of treatment, as there is no need for audiometry testing and injections, which also facilitates self-administered treatment

While these new all-oral DR-TB regimens provide an opportunity to improve current models of care, there is still a need to monitor side effects, especially given the high rates of side effects observed with some of the recommended drugs. People receiving linezolid (Group A) require routine monitoring of platelets and haemoglobin, as well as clinical monitoring of neuropathy and optic neuritis – both of which can result in permanent disabilities if they are not identified on time. The use of bedaquiline will still require electrocardiogram monitoring to assess QT prolongation.

Additionally, WHO now recommends monthly monitoring of sputum using culture for all people treated for DR-TB. Sufficient resources must be made available to ensure an adequate specimen referral system, particularly if people are not being followed up at facilities where culture is conducted.

Treating with bedaquiline

In Belarus, increased use of bedaquiline showed benefits, even among people more likely to have poorer treatment outcomes, including people living with HIV, and people with pre-XDR-TB and XDR-TB. Among 244 people who were treated with bedaquiline – 96% of whom had either pre-XDR-TB or XDR-TB – the treatment success rate increased to 87%, similar to treatment outcomes for people who were treated for DS-TB.[17] Furthermore, studies showed replacing injectable agents (kanamycin and capreomycin) with bedaquiline was more cost-effective in South Africa, India and Russia,[18,19] and yielded improved rates of treatment success in South Africa.

In the new WHO guidelines, the use of bedaquiline for more than six months remains as "off-label". However, growing evidence supports the extended off-label use of bedaquiline. In a multi-country analysis of five cohorts of patients with MDR- or XDR-TB that included patients in MSF TB treatment programmes, of 537 participants, 36 people (7%) received bedaquiline for more than six months. The effectiveness and safety of bedaquiline was demonstrated, with 78% of people reaching culture conversion at six months of treatment. The treatment success rate was 66% and only 11% had any severe side effects.[20]

Furthermore, in an MSF-led retrospective analysis, among a cohort with difficult-to-treat DR-TB in Armenia and Georgia, 19% of people with culture conversion reverted to culture positive after stopping bedaquiline at six months. This proves the need to ensure that DR-TB regimens contain enough effective drugs throughout the entire duration of treatment, which necessitates extended use of bedaquiline beyond 6 months in many instances.[21]

Depending on the tolerability of the treatment regimen, MSF believes many people with MDR/RR-TB will need bedaquiline for the full duration of the 18-month long-course treatment regimen. MSF urges countries to explore the option of operational research and systematic data collection on the use of bedaquiline and delamanid beyond six months to facilitate a prompt update of DR-TB treatment guidelines.

Treating with bedaquiline and delamanid together

The combined use of bedaquiline and delamanid also remains as off-label in the new guidelines, though the combination provides an opportunity for successful treatment for many people with limited treatment options due to resistance to, or side effects from, other core drugs.

Growing evidence demonstrates the safety and efficacy of the combination. In Mumbai, 37 people – 19 with pre-XDR-TB and 18 with XDR-TB – were treated with delamanid and bedaquiline. The combination proved to be safe and achieved high rates of culture conversion.[22] In a recent randomised study with 84 participants in South Africa and Peru, the combined use of bedaquiline and delamanid was shown to be safe, with no participant experiencing grade 3 or 4 QTcF prolongation.[23]

* Routine audiometry was only available in South Africa

Short-course regimen vs. previous long regimen: Key guidance from new WHO guidelines

- Under programmatic conditions, the short-course regimen achieves relapse-free cure rates of 85% in patients with no previous use of, or resistance to, second-line drugs. WHO now recommends that kanamycin must be replaced with amikacin.
- The short-course regimen has been shown to be non-inferior to the previously recommended long regimen (with injectable agents) and therefore remains as an alternative option under certain conditions, such as: (i) when resistance to fluoroquinolones and second-line injectables are excluded *before* starting treatment and (ii) when active TB drug safety monitoring and management (aDSM) is in place, including audiometry testing to assess hearing loss while on injectable agents.
- The implementation of modified regimens – especially replacing injectable agents with bedaquiline (oral short-course regimen) – can be implemented under operational research conditions.
- A patient centred-approach is advised, including providing patients (i) with enough information to take an informed decision concerning the short regimen and (ii) with adequate support to participate in DOT to achieve good outcomes.
- Patient exclusion criteria for the short-course regimen include (i) baseline resistance or intolerance to any drug within the short-course regimen (except isoniazid), (ii) exposure to any of the drugs for more than one month, (iii) pregnancy, (iv) disseminated, meningeal or central nervous system TB, and (v) extrapulmonary TB in patients with HIV.

CHILDREN WITH DR-TB

Tuberculosis is among the top ten causes of paediatric deaths worldwide, with more than 60% of cases of TB in children remaining undetected or unreported.[24] In 2014, an estimated 25,000 children developed MDR-TB.[25]

Despite increased access to GeneXpert MTB/RIF rapid molecular testing, diagnosis remains limited due to the scarcity of TB bacilli in children to confirm infection, as well as children's difficulty coughing up enough sputum for diagnosis. With current diagnostic tools, clinical diagnosis remains key to reducing the diagnostic gap and ensuring children receive adequate MDR-TB treatment.

While good outcomes have been reported in children receiving MDR-TB treatment,[26] hearing loss remains a significant challenge – even following completion of treatment[27] – and can lead to life-long disabilities. The new shorter, all-oral DR-TB regimens present an important opportunity to improve treatment outcomes with safer regimens.

Delamanid is now recommended for children 3 years of age and older; bedaquiline is recommended for children 6 years of age and older. The recently developed child-friendly second-line formulations for MDR-TB[28] (pyrazinamide, ethambutol, levofloxacin, moxifloxacin, ethionamide, isoniazid and cycloserine) will improve adherence and tolerability of MDR-TB treatment among children.

Paediatric formulations of the newer TB drugs bedaquiline and delamanid are still missing for younger age groups. While delamanid is currently recommended for children aged 3 and older, the current 50 mg formulation marketed for adults can only be used for children aged 6 and older. Until paediatric trials are completed, delamanid 25 mg and 50 mg dispersible tablets are available only through compassionate use from Otsuka for children aged 3 and older. Bedaquiline cannot be used for children less than 6 years old, leaving this age group with limited treatment options.

MSF supports and encourages the use of the newer TB drugs and new paediatric formulations in all-oral regimens for children diagnosed with MDR-TB to ensure better outcomes and reduce the risks of side effects and life-long disability.

PREGNANT WOMEN WITH DR-TB

Although TB is a recognised risk factor for increased morbidity and mortality among pregnant women,[29] safety data on the use of second-line TB drugs to treat MDR-TB during pregnancy remains scarce. Among Group A drugs, bedaquiline is the only drug classified as "Category B*" by the US Food and Drug Administration (based on animal studies). Given the limited treatment options available, MSF supports the use of bedaquiline in pregnant women in order to build an effective regimen to ensure the best possible outcomes.

PRE-XDR-TB AND XDR-TB TREATMENT RECOMMENDATIONS

Globally, it is estimated that almost 96% of notified cases of MDR-TB result from resistance transmission (i.e. from one person to another) rather than from people developing resistance while on treatment (acquired, or secondary, resistance).[30] Countries must understand baseline resistance patterns in order to design more effective treatment regimens.

To ensure good treatment outcomes, countries with high baseline rates of resistance to drugs from Groups A and B need to ensure patients will receive effective regimens throughout the entire duration of treatment. The new WHO guidelines also apply to people with resistance to either a fluoroquinolone or a second-line injectable agent (pre-XDR-TB) or both (XDR-TB).

* Category B drugs: Drugs for which animal reproduction studies have failed to demonstrate a risk to the foetus and there are no adequate and well-controlled studies in pregnant women

Since the new long treatment regimens do not include recommended injectable agents in Groups A or B, people with pre-XDR-TB who are resistant to injectables require no further treatment adjustment and should be treated with drugs from Groups A and B. People with pre-XDR-TB should not be given amikacin and streptomycin (from Group C), when constructing the drug regimen.

No person who is resistant to fluoroquinolones (whether with pre-XDR-TB or XDR-TB) should be given fluoroquinolones from Group A. Group A fluoroquinolones can be replaced with a drug from Groups B or C in order to construct an effective treatment regimen. MSF proposes that all people who are resistant to Group A fluoroquinolones be treated with delamanid and bedaquiline in combination for longer than six months due to the high probability of culture reversion when bedaquiline is limited to six months.[18]

COSTS OF REGIMENS

The estimated costs of long and short regimens constructed according to the new WHO DR-TB treatment recommendations are presented below. All regimen prices are calculated based on Stop TB Partnership Global Drug Facility (GDF) pooled procurement prices according to the lowest price available for each quality-assured medicine in the GDF catalogue dated 5 August 2019.[31]

Table 2: Cost of Regimens Based on New WHO Recommendations

Regimen (number of months)	**Regimen price** (based on lowest GDF price, as of August 2019[28])
Fluoroquinolone-sensitive	
I. Longer regimens	
Lfx-Bdq-Lzd-Cfz-Cs (6) / Lfx-Lzd-Cfz-Cs (12) 5 drugs in intensive phase	US$ 1,278
Lfx-Bdq-Lzd-Cfz (6) / Lfx-Lzd-Cfz (12) 4 drugs in intensive phase	US$ 915
Lfx-Bdq-Lzd-Cs (6) / Lfx-Lzd-Cs (12) 4 drugs in intensive phase	US$ 1,026
Lfx-Bdq-Lzd-Cfz (12) / Lfx-Lzd-Cfz (6)	US$ 1,315
Lfx-Bdq-Lzd-Cs (12) / Lfx-Lzd-Cs (6)	US$ 1,426
Lfx-Bdq-Lzd-Cfz (18)	US$ 1,669
Lfx-Bdq-Lzd-Cs (18)	US$ 1,786
II. Shorter regimens	
Km-Mfx-Pto-Cfz-Z-H^{h}-E (4) / Mfx-Cfz-Z-E (5)*	US$ 407
Am-Mfx-Pto-Cfz-Z-H^{h}-E (4) / Mfx-Cfz-Z-E (5)	US$ 411
Fluoroquinolone-resistant	
Bdq-Lzd-Dlm-Cfz (20)	US$ 7,670
Bdq-Lzd-Dlm-Cfz-Cs (20)	US$ 8,093
Bdq-Lzd-Dlm-Cfz-Cs-Imp/Cln (20)	US$ 11,680
Mfx-Bdq-Lzd-Dlm-Cfz (20)†	US$ 7,869
Mfx-Bdq-Lzd-Dlm-Cs (20)†	US$ 7,998
Other shorter regimens	
Bdq (6)-Lzd (2)-Lfx-Cfz-Z-H^{h}-E (4) or Lfx-Cfz-Z-E (5)‡	US$ 607
Bdq-Lfx-Pto-Cfz-Z-H^{h}-E (4) or Bdq-Lfx-Cfz-Z-E (6)§	US$ 763

* Regimen no longer recommended by WHO but still used by some countries

† Mfx-based regimens should be adapted based on presence of Lfx resistance

‡ Modified short regimen implemented in South Africa

§ Under operational research conditions

Am=amikacin, Bdq=bedaquiline, Cfz=clofazimine, Cs=cycloserine, Dlm=delamanid, E=ethambutol, H^{h}=high-dose isoniazid, Ipm/Cln=imipenem/cilastatin, Lfx=levofloxacin, Km=kanamycin, Lzd= linezolid, Mfx=moxifloxacin, Pto=prothionamide, Z=pyrazinamide

DRUG SUSCEPTIBILITY TESTING (DST) FOR EVIDENCE-BASED TREATMENT DECISIONS

The continued spread of DR-TB is a major global threat to effectively fighting TB. Timely diagnosis through DST and rapid treatment initiation are crucial to preventing the transmission of DR-TB. Access to universal DST is a key component of the WHO End TB Strategy and vital for placing people on effective treatment.[32]

Scale-up of DST in many TB high-burden countries has been very limited; in 2017, only 24% of newly confirmed people with TB and 70% of people previously treated for TB were tested for rifampicin resistance.[3] Furthermore, only 67% (32/48) of TB, TB/HIV, and DR-TB high-burden countries[33,*] have national TB diagnostic algorithms that include WHO-recommended rapid diagnostic testing (usually Xpert MTB/RIF)[†] as the initial test for all people with presumptive TB.[3]

In 2017, 27% (13/48) of high-burden countries had not implemented the Hain second-line line probe assay at the country level.[34] Of the notified people with MDR/RR-TB, only half were tested for resistance to both fluoroquinolones and second-line injectable agents.[3] The new WHO treatment guidelines recommend rapid testing for fluoroquinolone resistance through line probe assays for all people starting any of the recommended treatment regimens, whether long or short course.[7]

DST should guide the design of regimens for people with DR-TB. Unfortunately, most countries using newer drugs (bedaquiline and delamanid) and repurposed drugs (linezolid and clofazimine) do not have DST available at the country level. It is imperative that countries treating with any of the Group A and Group B drugs expedite implementation of DST or link with regional supranational laboratories (SRLs) that can provide testing to ensure proper patient management and assess acquired resistance to these drugs while under treatment. At this time, in settings where DST is limited for currently recommended second-line drugs (especially drugs from Groups A and B), treatment decisions should be based on individual treatment history and, when available, country surveillance data.

Rapid, target-based sequencing for DR-TB shows increasing promise and may play a significant role in clinical management in the future.[35] In order to address the limited scale-up of DST, donors should fund capacity-building for regional SRLs to conduct DST for new and repurposed drugs so that countries that lack capacity are able to access DST through these SRLs.

RECOMMENDATIONS

Political will and sufficient financial investment are needed to stop senseless deaths from TB by diagnosing and treating DR-TB in a timely and effective manner and rapidly adopting WHO RR/MDR-TB guidelines on all-oral regimens. All-oral regimens will translate to fewer side effects for people with DR-TB such as hearing loss, renal failure and pain, which are all caused by injectable agents.

Governments, the WHO and donors should collaborate to overcome barriers to effective TB treatment by implementing the following recommendations.

Governments

- Update national guidelines and place new drug orders by September 2019
- Ensure 100% of people are monitored and managed using aDSM by November 2019
- Ensure 100% of people diagnosed with DR-TB have access to all-oral, bedaquiline-containing regimens by World TB Day, 24 March 2020
- Ensure that recommendations are translated to children and pregnant women, who historically have faced delays in access to the best available treatment
- Promote patient health knowledge and autonomy in making tough choices about treatment approaches
- Include civil society and embed qualitative research within monitoring and evaluation processes for national programmes
- Utilise TRIPS flexibilities and other safeguards to ensure sustainable supply of TB drugs and diagnostic tools by encouraging alternative suppliers, which increases competition and lowers prices
- Prioritise testing for diagnosis and ensure access to quality phenotypic drug-resistance testing for all relevant drugs, including newer drugs, as recommended by WHO
- Ensure that GeneXpert MTB/RIF rapid molecular testing is the first-line TB diagnostic test for all
- Implement specimen transport referral systems to ensure access to rapid diagnosis, DST and monitoring of people's response to treatment
- Scale up DST for people with RR-TB to ensure every person is placed on the best treatment regimen possible, and scale up DST for fluoroquinolones (including high dose moxifloxacin) to guide treatment choices for the new long regimen
- Ensure monthly treatment monitoring for all drugs using culture for all people treated for DR-TB

* The 48 countries on at least one of three lists of high-burden countries: (i) TB high-burden countries, (ii) TB/HIV high-burden countries, (iii) MDR-TB high-burden countries.

† Even though Molbio TrueNat has not been recommended by WHO, India has rolled out the test in some states.

WHO

- Provide guidance and technical support to countries to facilitate swift transition to regimens free of the injectable agents kanamycin and capreomycin
- Provide guidance and technical support to countries to manage (i) financial and logistical constraints on drug supply, (ii) local programmatic challenges, and (iii) competing priorities that emerge with implementation of the new recommendations
- Ensure all supranational reference laboratories have DST capacity for newer drugs and sequencing capacity to support external testing for all countries
- Support countries to conduct operational research on shorter oral regimens (in collaboration with donors)

Donors

- The Global Fund should allow countries to repurpose funding for injectable agents (kanamycin and capreomycin) to other core medicines to facilitate rapid adoption of the new treatment guidelines
- The Global Fund and Unitaid should allocate funds to countries to make the switch to newer regimens and cover the costs of disposing kanamycin and capreomycin stock
- Donors should (i) support and significantly increase funding for TB R&D, including collaborative research platforms such as the Life Prize and other initiatives that aim to develop regimens, (ii) commit to share data and molecules, and (iii) ensure that end products are affordable and accessible

THE DR-TB TREATMENT REGIMENS WE NEED THE TB R&D PIPELINE TO DELIVER

- **All-oral treatment** *(no injectables)*
- **Shorter duration** *(6-9 months)*
- **Effective for all forms of DR-TB** *(including RR-, MDR-, XDR-, pulmonary and extra-pulmonary TB)*
- **Appropriate formulations for children as well as adults,** *including pregnant women*
- **Various effective regimens with novel classes of drugs** *(each from a distinct class of drugs, including at least 2-3 from a new drug class)*
- **Less toxic, with limited side effects** *(requiring minimal routine safety monitoring)*
- **Minimal drug-drug interactions** *(particularly with antiretroviral therapy and family planning)*
- **Easy to transport, store and administer** *(no cold chain, long half-life, simple dosing schedule)*
- **Conducive to good antimicrobial stewardship to prevent drug resistance**
- **Affordable** *(less than $500 per treatment course)*

CONCLUSION

Treatment regimens for MDR-TB and XDR-TB have long consisted of toxic drugs, including injectable agents that often lead to permanent hearing loss. Treatment outcomes for people with MDR-TB and XDR-TB have remained unacceptably low for many years for numerous reasons, including drug toxicity, limited treatment options and treatment monitoring, long treatment durations, and failure to put people at the centre of their care.

Although long treatment durations can be prohibitive to treatment adherence and more R&D is required to achieve shorter and safer DR-TB regimens, the new WHO recommendations on long, all-oral DR-TB regimens are a strong step in the right direction. They should be followed to provide people with safer and more tolerable treatment, improve treatment outcomes and prevent unnecessary deaths. Importantly, the new all-oral regimens can also facilitate an evolution to a model of care that empowers people and supports them to complete treatment with less disruption to their lives. While the benefits of implementing the new all-oral long regimens are clear, making the switch requires political commitment, sufficient financing, adequate healthcare worker training, policy updates and multi-sectoral engagement.

MSF AND DR-TB

MSF is the largest non-governmental provider of DR-TB treatment and supports national TB programmes in 40 countries. MSF provided TB treatment to 19,000 people in 2018, including 2,840 people with DR-TB.

MSF strives to implement optimal TB diagnostic tools, treatments and models of care in order to give people the best chance to survive drug-resistant forms of the disease. MSF is conducting research on new DR-TB treatments through two clinical trials: endTB and PRACTECAL.

endTB is a randomised controlled trial comparing five new, all-oral, nine-month MDR-TB regimens to the WHO-recommended standard of care. Five experimental regimens including bedaquiline and/or delamanid with various combinations of clofazimine, linezolid, moxifloxacin or levofloxacin, and pyrazinamide. Trial outcomes are expected by 2022.[36]

PRACTECAL is a randomised controlled phase II-III trial evaluating six-month MDR-TB treatment regimens containing bedaquiline and pretomanid in combination with existing and repurposed TB medicines. Both MDR-TB and XDR-TB patients are included in the trial. Trial outcomes are expected by 2021.[37,38]

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