AN ACTIVIST'S GUIDE TO TREATMENT FOR DRUG-RESISTANT TUBERCULOSIS

TAG
Treatment Action Group

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I. INTRODUCTION AND BACKGROUND

In 2020, the World Health Organization (WHO) issued updated guidelines, establishing a new global standard of care for the treatment of **drug-resistant tuberculosis** (DR-TB).[1] The updated guidelines reinforce the use of standardized shorter regimens and move further away from the use of **injectable agents** (see box below) previously considered a cornerstone of treatment for drug-resistant TB.

The WHO first introduced guidelines supporting the use of a standardized shorter regimen for drug-resistant TB in 2016.[2] Over the course of several years, and in response to emerging evidence, the WHO modified the composition of the standardized shorter regimen it recommends under **program conditions**, replacing the injectable agent with bedaquiline.[i] In the latest iteration of its guidelines, the WHO also supports the use of other bedaquiline-based shorter regimens under **conditions of operational research** (i.e., the novel **Nix-TB regimen** and modifications to the standardized shorter regimen).[3]

The new global standard of care offers shorter, more effective, and less toxic treatment regimens. It also brings into clear focus what's at stake when people and communities affected by drug-resistant TB are unable to access the best available treatments—extended morbidity and time away from work resulting in lost income and financial instability, further development and transmission of drug-resistance, and increased risk of permanent disability and death.

We wrote this guide to help activists: unpack the latest WHO guidelines; understand the evidence behind each of the WHO-recommended regimens; identify barriers to availability, accessibility, and affordability; and hold governments and other actors accountable for ensuring all people and communities affected by drug-resistant TB can share in the benefits of scientific progress. This guide suggests actions activists can take to promote equitable access to the new global standard of care for drug-resistant TB.

KEY TERMS

DRUG-RESISTANT TUBERCULOSIS encompasses forms of TB resistant to key medicines (see section II).

PROGRAM CONDITIONS are the routine conditions under which National TB Programs operate and treat TB.

CONDITIONS OF OPERATIONAL RESEARCH require that National TB Programs monitor TB treatment more carefully than under program conditions and collect additional data on the safety and efficacy of medicines and/or treatment regimens not yet proven or endorsed for broader programmatic use, and for which additional research is needed.

the **NIX-TB REGIMEN** (also referred to as BPaL) is a six- to nine-month regimen composed of bedaquiline, pretomanid, and linezolid, and recommended by the WHO under very specific conditions (see section III).

Injectable agents, amikacin, kanamycin, capreomycin, and streptomycin, most of which are also referred to as aminoglycosides, were previously considered a key component of treatment for drug-resistant TB. These medicines, administered daily by injection, have toxic side effects that can cause permanent disability, including hearing loss, and kanamycin and capreomycin have been linked to increased risk of treatment failure and death. Another family of medications used to treat drug-resistant TB known as the carbapenems are also given via injection but are not routinely used and thus are considered as a separate category.

i. Nine- to 12-months of clofazimine, levofloxacin (or moxifloxacin), ethambutol, and pyrazinamide; supplemented by bedaquiline for the first six months and high dose isoniazid, ethionamide (or prothionamide) for the first four- to six-months.

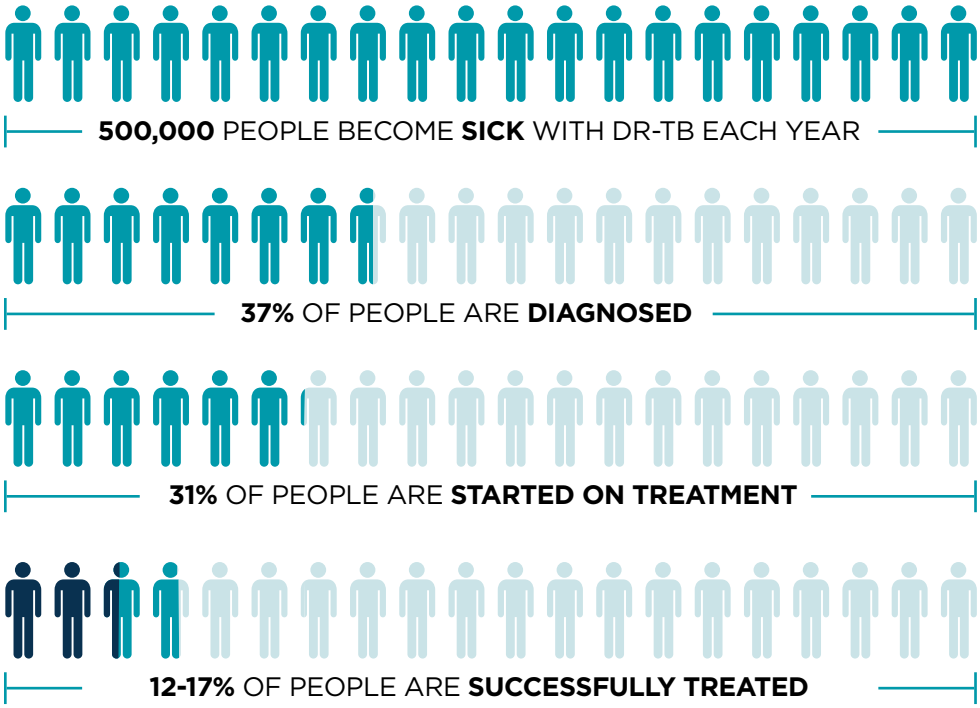
II. DEFINING DRUG-RESISTANT TUBERCULOSIS

Each of the medicines used to treat TB has a specific **mechanism of action** for disabling or killing TB bacteria. Certain bacterial mutations can inactivate or prevent a medicine from entering the TB bacterial cell or from carrying out its mechanism of action. Mutations that confer resistance can be naturally occurring or develop over time following inadequate or irregular drug exposures. Drug-resistant TB can be transmitted from person to person, referred to as primary or transmitted resistance, or developed due to interrupted or incomplete TB treatment, referred to as acquired resistance.[4]

MECHANISM OF ACTION is the method by which a TB medicine inactivates or kills TB bacteria (e.g., by inhibiting energy production [bedaquiline] or growth via cell wall synthesis [delamanid]).

An estimated 500,000 people become sick with drug-resistant TB each year, yet just 37 percent of these people are diagnosed (186,772), and only 31 percent are started on treatment (156,071). Global rates of treatment success among those diagnosed and treated range from 39 to 56 percent, depending on the extent of resistance.[4]

Figure 1. Global gaps in the diagnosis and treatment of drug-resistant TB



Drug-resistant TB comes in many forms. The subcategories that fall under the umbrella of drug-resistant TB are defined by the medicine(s) to which TB bacteria are resistant (see Figure 2).

Prior to 2016, the WHO recommended an 18– to 24–month individualized regimen built on a backbone consisting of a **fluoroquinolone** and an **aminoglycoside** (injectable agent). The legacy of this policy and practice is apparent in the terminology used to indicate the extent of resistance and to determine eligibility for treatment with a standardized shorter regimen (see section III). In 2018, the WHO deprioritized amikacin and recommended against the use of kanamycin and capreomycin for the treatment of drug-resistant TB, but the definitions of pre-extensively

FLUOROQUINOLONES are a class of antibiotic drugs that work by inhibiting bacterial DNA synthesis (e.g., levofloxacin and moxifloxacin).

AMINOGLYCOSIDES, which are administered by injection, are a class of antibiotic drugs that work by inhibiting bacterial protein synthesis (e.g., amikacin, kanamycin, capreomycin, and streptomycin).

drug-resistant TB (pre-XDR-TB) and extensively drug-resistant TB (XDR-TB), and lab capacity to test for resistance to increasingly important newer and repurposed TB medicines have yet to catch up (see Spotlight 1).

Figure 2. Forms of drug-resistant tuberculosis

DS-TB	rifampicin isoniazid	drug-sensitive or drug-susceptible TB
RR-TB	ⓧ rifampicin isoniazid	rifampicin-resistant TB
HR-TB	rifampicin ⓧ isoniazid	isoniazid-resistant TB
MDR-TB	ⓧ rifampicin ⓧ isoniazid	multidrug-resistant TB
TI/NR-MDR-TB	ⓧ rifampicin ⓧ isoniazid	treatment intolerant or non-responsive MDR-TB
FQ-R-MDR-TB	ⓧ rifampicin ⓧ isoniazid ⓧ fluoroquinolone	fluoroquinolone-resistant MDR-TB
Pre-XDR-TB	ⓧ rifampicin ⓧ isoniazid ⓧ fluoroquinolone aminogycloside	pre-extensively drug-resistant TB
XDR-TB	ⓧ rifampicin ⓧ isoniazid ⓧ fluoroquinolone ⓧ aminogycloside	extensively drug-resistant TB

III. UNPACKING THE WORLD HEALTH ORGANIZATION GUIDELINES

The 2020 update to the *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug Resistant Tuberculosis Treatment*, shifted the global standard of care for drug-resistant TB in a number of important ways. By recommending the use of bedaquiline in place of the injectable agent in the nine- to 12-month standardized regimen and supporting the use of other bedaquiline-based shorter regimens under conditions of operational research, bedaquiline has become a core component of all regimens for the treatment of drug-resistant TB.[5]

DS-TB: drug-sensitive or drug-susceptible TB; TB that is not resistant to any TB medicines.

RR-TB: rifampicin-resistant TB; TB that is resistant to rifampicin.

HR-TB: isoniazid-resistant TB; TB that is resistant to isoniazid.

MDR-TB: multidrug-resistant TB; TB that is resistant to isoniazid and rifampicin

TI/NR-MDR-TB: treatment intolerant or non-responsive MDR-TB; TB that is resistant to isoniazid and rifampicin and does not respond to the standard of care treatment regimen and/or has intolerable treatment-induced side-effects.

FQ-R-MDR-TB: fluoroquinolone-resistant MDR-TB; TB that is resistant to isoniazid, rifampicin, and fluoroquinolones (e.g., levofloxacin or moxifloxacin).

PRE-XDR-TB: pre-extensively drug-resistant TB; TB that is resistant to isoniazid, rifampicin, and fluoroquinolones (e.g., levofloxacin or moxifloxacin) or second-line injectable agents, also referred to as aminogyclosides (e.g., amikacin).

XDR-TB: extensively drug-resistant TB; TB that is resistant to isoniazid, rifampicin and fluoroquinolones (e.g., levofloxacin or moxifloxacin) and second-line injectable agents, also referred to as aminogyclosides (e.g., amikacin).

Regimens for the treatment of drug-resistant TB include:

1. under routine program conditions, and only for RR-/MDR-TB, the nine- to 12-month standardized shorter regimen with bedaquiline given in place of the injectable agent;[ii]
2. under routine program conditions, an 18- to 20-month individualized all-oral regimen composed of four to five medicines selected according to the priority grouping of medicines recommended by the WHO in 2018/2019 (see Table 1);
3. under operational research conditions, modifications to the nine- to 12-month standardized shorter regimen with bedaquiline given in place of the injectable agent. Modifications may include, for example, linezolid given in place of ethionamide/prothionamide; and
4. under operational research conditions, and only for MDR-TB with additional fluoroquinolone resistance (FQ-R-MDR-TB), the six- to nine-month BPaL or Nix-TB regimen, composed of bedaquiline, pretomanid, and linezolid.

Table 1. Groupings of medicines recommended for use in individualized regimens

Group [steps for composing an individualized regimen]	Medicine(s)	Abbreviation(s)
Group A [include all three medicines]	levofloxacin or moxifloxacin	L, Lfx M, Mfx
	bedaquiline	J, Bdq
	linezolid	Lzd
Group B [add one or both medicines]	clofazimine	Cfz
	cycloserine or terizidone	Cs Trd
Group C [add to complete the regimen of four to five effective drugs when medicines from groups A and B cannot be used]	ethambutol	E
	delamanid	D, Dlm
	pyrazinamide	Z, PZA
	imipenem-cilastatin or meropenem	Imp-Cln Mpm
	amikacin (or streptomycin)	Am (S)
	prothionamide or ethionamide	Pto Eto
	p-aminosalicylic acid	PAS

In addition to specifying whether regimens are recommended under routine program or operational research conditions—determined primarily by the quantity and quality of available safety and efficacy data—the 2020 update to the *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug Resistant Tuberculosis Treatment* articulates other important criteria for determining which regimen(s) an individual should be offered. Factors to be considered in selecting a regimen include the individual's **drug susceptibility** profile, previous exposure to second-line TB medicines, type and severity of TB disease, age, and the presence of other coinfections, comorbidities, or conditions.

DRUG SUSCEPTIBILITY PROFILE: the medicines to which an individual has documented susceptibility (or lack of resistance).

ii. Nine- to 12-months of clofazimine, levofloxacin (or moxifloxacin), ethambutol, and pyrazinamide; supplemented by bedaquiline for the first six months and high dose isoniazid, ethionamide (or prothionamide) for the first four- to six-months.

What about people with resistance beyond RR-/MDR-TB?

If someone's strain of TB is resistant to medications contained in the nine- to 12-month standardized shorter regimen, under routine program conditions, they would likely receive an 18- to 20-month individualized regimen constructed according to Table 1. This also applies to people unable to tolerate medications contained in the nine- to 12-month standardized shorter regimen. Alternatively, and depending on a number of factors, most important of which is the extent of drug-resistance, such individuals may receive treatment with a modified version of the nine- to 12-month standardized shorter regimen or the six- to nine-month Nix-TB regimen—but only under conditions of operational research due to uncertainties regarding the safety and efficacy of these regimens (see section IV).

What about people with isoniazid-resistant TB (HR-TB)?

In people with TB that is resistant to isoniazid alone, the WHO recommends a six month regimen composed of rifampicin, ethambutol, pyrazinamide, and levofloxacin.[7] People unable to tolerate treatment with levofloxacin can be treated with six months of rifampicin, ethambutol, and pyrazinamide. Higher doses of isoniazid may be able to overcome resistance conferred by certain mutations (**inhA**), but evidence in humans is limited. Whether or not to include isoniazid, and at an increased or standard dose, is left to provider discretion as there is no clear evidence that the addition of isoniazid to these regimens offers benefit or causes harm to people with HR-TB. The use of fixed-dose combinations (rather than provider discretion) may dictate the inclusion of isoniazid alongside the other medicines recommended for the treatment of HR-TB.

SPOTLIGHT 1: THE IMPORTANCE OF DRUG SUSCEPTIBILITY TESTING

Drug susceptibility testing (DST) is used to determine the extent of drug-resistance and inform regimen selection. Depending on the drug of interest, DST can be performed using **genotypic tests** or **culture**. Rapid genotypic tests (also referred to as molecular tests) are available for detecting rifampicin-resistance and typically inform initial regimen selection. Additional DST, typically performed via **line probe assay (LPA), high throughput testing platforms**, or culture, then determines further drug-resistance and whether any corresponding regimen adjustments are necessary.

Existing molecular tests focus on resistance to rifampicin, isoniazid, the fluoroquinolones, and the injectable agents. Similar to the terminology used to indicate extent of resistance, technologies and lab capacity for DST were built around the 18- to 24-month individualized regimen the WHO recommended prior to 2016, the core components of which were a fluoroquinolone and an injectable agent. As available data, priority medicines, and WHO guidance evolve, so do priorities for DST.

Being able to test for susceptibility to the medicines included in the nine- to 12-month standardized shorter regimen, as well as other medicines in groups A and B, is crucial to informing regimen selection, improving treatment outcomes, preventing further drug-resistance, and guarding against unnecessary potential risks of treatment-related toxicities. For additional information on the methods and technologies used to perform DST and corresponding needs and advocacy messages, please refer to *An Activist's Guide to Tuberculosis Diagnostic Tools*, https://www.treatmentactiongroup.org/publication/an-activists-guide-to-tuberculosis-diagnostic-tools/.[6]

INHA: a mutation that confers low-level resistance to isoniazid, which may be overcome with higher doses.

DRUG SUSCEPTIBILITY TESTING (DST): tests used to determine resistance to medicines.

GENOTYPIC TESTS: tests that detect TB and drug-resistance by amplifying bacterial DNA and detecting genetic mutations that confer resistance to specific medicines (e.g., GeneXpert, Truenat).

CULTURE: tests that detect TB and drug-resistance by attempting to grow TB bacteria, including in the presence of TB medicines (a phenotypic test).

LINE PROBE ASSAY (LPA): tests that detect drug resistance by introducing probes that bind to and change color in the presence of bacterial DNA with mutations that confer resistance to specific medicines (a genotypic test).

HIGH THROUGHPUT TESTING PLATFORMS: platforms positioned in centralized laboratories capable of running molecular tests on multiple samples simultaneously (a genotypic test).

What about people living with HIV?

The regimens used to treat drug-resistant TB among people living with HIV are the same as those used to treat people without HIV, though some TB and HIV drug interactions and overlapping toxicities require careful attention and management. For example, people living with HIV on protease inhibitors or efavirenz will have to be monitored closely or switch HIV medications to initiate treatment for drug-resistant TB given interactions with bedaquiline (see Table 2). People living with HIV may also require adjustments to their HIV and/or drug-resistant TB treatment regimens as a result of overlapping toxicities (see Table 3).

Table 2. HIV and DR-TB drug interactions

Antiretroviral medicine	Interaction with DR-TB medicine
ritonavir-boosted protease inhibitors (e.g., lopinavir/ritonavir)	increases bedaquiline levels; should not be used together
efavirenz	decreases bedaquiline levels; should not be used together decreases pretomanid levels; should not be used together

Table 3. Overlapping toxicities between HIV and DR-TB medicines[8,9,10,11,12,13]

Bone marrow suppression/ blood disorders
zidovudine; linezolid

Central nervous system toxicity/ psychiatric effects
efavirenz, didanosine, stavudine, rilpivirine; cycloserine

Hepatotoxicity
abacavir, atazanavir, darunavir, dolutegravir, efavirenz, emtricitabine, lamivudine, lopinavir/ritonavir nevirapine, raltegravir, rilpivirine, tenofovir alafenamide, tenofovir disoproxil fumarate; bedaquiline, ethambutol, isoniazid, PAS, pretomanid, pyrazinamide

Lactic acidosis
stavudine; linezolid

Pancreatitis
didanosine, lopinavir/ritonavir, stavudine; linezolid

Peripheral neuropathy
didanosine, stavudine, zidovudine; cycloserine, isoniazid, linezolid

QT prolongation
atazanavir, efavirenz, rilpivirine; bedaquiline, delamanid, clofazimine, levofloxacin, moxifloxacin

Nephrotoxicity/ renal effects
lopinavir/ritonavir, tenofovir alafenamide, tenofovir disoproxil fumarate; amikacin, streptomycin

Toxicities, antiretroviral medicines, and TB medicines are listed in alphabetical order, not by risk level or importance

BONE MARROW SUPPRESSION/ BLOOD DISORDERS: a reduction in the production of blood cells from the bone marrow. This can manifest as anemia (red blood cells; causing fatigue), neutropenia (white blood cells; increasing risk of severe infection), or thrombocytopenia (platelets; leading to easy bruising or bleeding).

CENTRAL NERVOUS SYSTEM TOXICITY/ PSYCHIATRIC EFFECTS: general terms used to denote a group of neurological and psychiatric adverse effects, including weakness, numbness, dizziness, impaired concentration, confusion, insomnia, depression, agitation, hallucinations, psychosis, and suicidal thoughts.

HEPATOTOXICITY: drug-induced damage or injury to the liver.

LACTIC ACIDOSIS: when lactic acid accumulates in the bloodstream, causing weakness, muscle pain, and nausea.

PANCREATITIS: inflammation of the pancreas.

PERIPHERAL NEUROPATHY: nerve damage in the extremities, which can cause numbness and pain starting in the fingers and toes, spreading upwards.

QT PROLONGATION: a disturbance in the heart's electrical activity that can lead to serious (and sometimes fatal) rhythmic disturbances.

NEPHROTOXICITY/ RENAL EFFECTS: drug-induced damage or injury to the kidneys.

What about children and young people?

Studies are ongoing to inform the appropriate dose and safety of bedaquiline, delamanid, and pretomanid for the treatment of drug-resistant TB among children. Bedaquiline and delamanid have been studied in children down to six and three years old, respectively, and evaluations in younger children are ongoing. A study of pretomanid in adolescents and children is being planned, but will not begin until further investigations of reproductive toxicities observed in animal studies are completed. Currently, adolescents and older children are likely to receive treatment with the nine- to 12-month standardized shorter regimen, while younger children are likely to receive treatment with an individualized regimen with or without delamanid, depending on age (e.g., with delamanid in place of bedaquiline for children between three and five years old; without bedaquiline or delamanid for children younger than three years old). The duration of individualized regimens for children are typically determined by the site and severity of TB disease. Module 4 of the WHO Operational Handbook on Tuberculosis includes age- and weight-based dosing recommendations for drug-resistant TB medicines in children, several of which are now available in child-friendly formulations (see Spotlight 3).[14]

What about pregnant individuals?

Pregnant individuals are typically excluded from clinical trials, limiting data available to inform the treatment of drug-resistant TB during pregnancy. Several medicines used for the treatment of drug-resistant TB are contraindicated during pregnancy. These include the injectable agents (amikacin, streptomycin) and ethionamide/prothionamide, the latter of which may preclude pregnant individuals from receiving treatment with the nine- to 12-month standardized shorter regimen. In settings where ethionamide is replaced with another drug such as linezolid (e.g., in South Africa), pregnant women may receive treatment with a modified nine- to 12-month shorter regimen. Alternatively, pregnant individuals may receive treatment with an individualized regimen, the composition of which is informed by a mix of animal data, expert opinion/experience, and risk-benefit analysis. Data from a cohort of 108 pregnant individuals from South Africa, among which 58 were treated with a bedaquiline-containing regimen, suggest that bedaquiline can be safely used during pregnancy.[15]

What about people with extrapulmonary TB?

Extrapulmonary TB can be more severe and difficult to treat than **pulmonary TB** given variability in the abilities of TB medicines to reach and penetrate sites of TB disease outside of the lungs. Non-severe forms of extrapulmonary TB are generally assumed to be treatable with the same combination of medicines and duration of use as pulmonary TB. However, the studies and program datasets supporting the shorter regimens for drug-resistant TB did not include people with extrapulmonary TB. Given these data gaps and the importance of ensuring adequate drug exposures at the site of TB disease, people with **severe extrapulmonary TB** or **extensive TB disease** are likely to receive treatment with an 18- to 20-month individualized regimen composed of medicines able to penetrate the affected tissues/organs.

What about people being treated for hepatitis C virus (HCV)?

Direct-acting antiviral drugs (DAAs), used to treat HCV, are metabolized in the liver by enzymes that can be inhibited or induced by other drugs. Inhibition of these enzymes can lead to slower drug metabolism resulting in higher drug exposures, and induction can lead to faster drug metabolism resulting in lower drug exposures. The rifamycins (rifampicin, rifapentine), used to treat drug-sensitive TB, are known to induce these enzymes, decreasing the concentration of DAAs to subtherapeutic levels. Limited data are available regarding the effects of medicines used to treat drug-resistant TB on enzymes involved in the metabolism of DAAs. Given the limited knowledge of potential interactions between DAAs and the medicines used to treat drug-resistant TB, people with HCV

EXTRAPULMONARY TB: TB disease in other parts of the body outside of the lungs.

PULMONARY TB: TB disease in the lungs.

SEVERE EXTRAPULMONARY TB: TB disseminated throughout the body (military TB) or TB meningitis (TB in the brain and/or spinal cord).

EXTENSIVE TB DISEASE: cavitary disease affecting both lungs.

DIRECT-ACTING ANTIVIRAL DRUGS (DAAS): a class of drugs used to treat HCV.

undergoing treatment for DR-TB should consult with their health care provider about how to optimally time and safely initiate treatment for HCV.

What about people who use drugs (PWUD)?

People who used drugs (PWUD) are often excluded from participating in clinical trials, limiting data available to inform the treatment of drug-resistant TB among people on **opioid substitution therapies (OST)/ treatment for opioid use disorders (OUD)**. Potential drug-drug interactions and overlapping toxicities between OST and the medicines used to treat drug-resistant TB should inform regimen selection. People on OST and treatment for drug-resistant TB should be closely monitored for signs of opiate withdrawal and other adverse events (e.g., liver toxicity, QT prolongation) requiring dose adjustments or treatment interruptions. Active drug use should not be used as a reason to withhold treatment for drug-resistant TB.[16]

SPOTLIGHT 2: TOOLS FOR TOXICITY AND TREATMENT MONITORING

Active drug safety monitoring and management (aDSM) is a critical component of implementing standardized shorter and individualized longer regimens, and the new and repurposed TB medicines contained therein.[17] In addition to regular **bacteriological investigations** necessary for treatment monitoring, and based on the medications in use, several monitoring tests are necessary at baseline and over the course of treatment. These include **electrocardiography (ECG)**, clinical assessments for peripheral neuropathy and psychiatric disturbances, laboratory assessment of liver and kidney function, and **blood profiles**.[18] Baseline and routine testing for hearing loss is also necessary in what should be relatively rare scenarios in which an injectable agent is indicated as part of the regimen.

IV. KNOWING YOUR EVIDENCE-BASE

The **individual patient dataset (IPD)** used to inform the 2020 update to the *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug Resistant Tuberculosis Treatment* contained over 13,000 patient records from 55 different studies in 38 countries, including recent additions from the following programs, observational studies, and clinical trials:[19]

- the Department of Health of South Africa provided a dataset comprised of approximately 4,000 individuals treated with the nine- to 12-month standardized shorter regimen (with bedaquiline given in place of the injectable agent) and in whom final treatment outcomes and follow up data were available;[20]
- Médecins Sans Frontières (MSF) provided datasets comprised of approximately 200 individuals from India and Uzbekistan, and the National TB Program in Belarus provided a dataset comprised of approximately 100 individuals,[21] treated with regimens of interest expressed in a public call for data issued by the WHO in August 2019;[22]

OPIOID SUBSTITUTION THERAPIES (OST)/ TREATMENT FOR OPIOID USE DISORDERS (OUD): a type of harm reduction intervention that treats opioid dependence by replacing opioids (like heroin) with prescribed drugs that can manage or reduce opioid cravings and prevent sudden withdrawal.

ACTIVE DRUG SAFETY MONITORING AND MANAGEMENT (ADSM): a package of requirements and tests that, when implemented alongside new medicines and regimens, can help to detect, manage, and report suspected or confirmed drug toxicities.

BACTERIOLOGICAL INVESTIGATIONS: microscopy or culture-based tests for live, replicating TB bacteria used to monitor whether treatment is working.

ELECTRO-CARDIOGRAPHY (ECG): a test that measures the electrical activity in your heart to check for irregular rhythms.

BLOOD PROFILES: laboratory assessment of liver and kidney function, a complete blood count, and other tests for organ function that can be monitored in the blood.

INDIVIDUAL PATIENT DATASET (IPD): raw individual patient data from multiple studies and settings combined into a single dataset that can then be used to answer questions about and identify trends regarding the safety and efficacy of medicines or regimens.

- Partners in Health (PIH), MSF, and Interactive Research and Development (IRD) provided a dataset from the endTB project observational study comprised of 1,000 individuals treated with bedaquiline- and/or delamanid-containing regimens of variable composition and duration;[23,24]
- the South African Medical Research Council provided preliminary results from a cohort of 108 individuals with drug-resistant TB, of whom 58 were treated with a bedaquiline-containing regimen during pregnancy between 2013 and 2017 in KwaZulu-Natal;[25] and
- the TB Alliance provided a dataset from the Nix-TB trial comprised of approximately 100 individuals treated with the six- to nine-month BPaL (bedaquiline, pretomanid and linezolid) regimen.[26]

The conditions under which the nine- to 12-month standardized and modified shorter regimens, the 18- to 20-month individualized regimen, and the six- to nine-month Nix-TB regimen are recommended reflect differences in the quantity and quality of the data available to support each regimen (see Table 4), and the patient populations included in these studies and cohorts. Future data collected from programs implementing these regimens, as well as ongoing clinical trials (see Table 5) and operational research initiatives, will contribute additional safety and efficacy data, fill important knowledge gaps, and inform future updates to WHO guidelines.[27]

Table 4. Regimen, indication, criteria for use, supporting evidence

Regimen	Indication	Criteria for use	Supporting evidence
1 **Nine- to 12-month standardized shorter regimen** Nine- to 12- months of clofazimine, levofloxacin (or moxifloxacin), ethambutol, and pyrazinamide; supplemented by bedaquiline for the first six months and high dose isoniazid, ethionamide (or prothionamide) for the first four- to six-months	RR-, MDR-TB	Program conditions	Program data[28] [South Africa] N=4,000; 71% HIV-positive Regimen associated with improved treatment outcomes and a reduction in loss to follow up compared to the injectable containing nine- to 12-month standardized shorter regimen Further research: STREAM II (see Table 5)
2 **18- to 20-month individualized all-oral regimens** Four to five medicines selected according to the priority grouping of medicines recommended by the WHO in 2018/2019	RR-, MDR-, TI/NR MDR-, FQ-R-MDR-, pre-X-, XDR-TB	Program conditions	IPD meta-analysis[29] [38 countries] N=13,000 Group A and B drugs associated with improved treatment outcomes and reduced mortality Group C drugs associated with limited or no benefit; amikacin associated with modest benefits (kanamycin and capreomycin associated with worse treatment outcomes); ordered preferentially considering potential benefits vs. harms Treatment outcomes improved with the use of drugs to which an individual's strain of TB is known to be susceptible

Regimen	Indication	Criteria for use	Supporting evidence
3 Nine- to 12-month modified shorter regimens Modifications to the composition of the nine- to 12-month standardized shorter regimen	RR-, MDR-, TI/NR MDR-, FQ-R-MDR-, pre-X-, XDR-TB	Operational research conditions	Interim data from endTB Project observational study[30] [Armenia, Bangladesh, Belarus, South Korea, Ethiopia, Georgia, Haiti, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Myanmar, Pakistan, Peru, South Africa, Vietnam] N=1,244 [Bdq: 848; Dlm: 354; Bdq + Dlm: 42]; 11.7% HIV-positive Demonstrated safety of bedaquiline and delamanid (most toxicities associated with injectable agents and linezolid) Culture conversion within six months among 78% of participants on delamanid-containing regimens and 85% of participants on bedaquiline-containing regimens Successful treatment outcomes among 77.6% of participants receiving newer drugs and 84.8% in the subset of participants who received all-oral regimens (N=259)[31] Further research: endTB; endTB-Q; MDR-END (see Table 5)
4 Nix-TB regimen Six- to nine- months of bedaquiline, pretomanid, and linezolid	TI/NR-MDR-, FQ-R-MDR-, Pre-X-, XDR-TB	Operational research conditions	Interim data from open-label single-arm Nix-TB study[32] [South Africa] N=109; 51% HIV-positive Successful treatment outcomes among 90% of participants; most participants required a reduction in dose or an interruption of linezolid during treatment Further research: Nix-TB; ZeNix; TB PRACTECAL (see Table 5)

Table 5. Ongoing and planned clinical trials

Study Name	Experimental Arms [Control/ Comparator Arm]	Indication	Estimated to Complete
NEXT NCT02454205	6–9JLzLxZ(Eto or H_{Hd} or Tzd) [12–24mo IA-containing regimen]	MDR-TB	Dec 2020
TB PRACTECAL NCT02589782	6JPaMLz 6JPaLzC 6JPaLz [9–20mo local SOC]	MDR-TB Pre-XDR-TB XDR-TB	Mar 2021
MDR-END NCT02619994	9–12DLzLxZ [20mo IA-containing regimen]	MDR-TB	Jun 2021
Nix-TB NCT02333799	JPaL [none]	TI/NR MDR-TB Pre-XDR-TB XDR-TB	Oct 2021
ZeNix NCT03086486	$6JPaLz_{1200}$ $2JPaLz_{1200}$/4JPa $6JPaLz_{600}$ $2JPaLz_{600}$/4JPa [none]	TI/NR MDR-TB Pre-XDR-TB XDR-TB	Dec 2021
SimpliciTB NCT03338621	4JPaMZ [2HRZE/4HR]	DS-TB MDR-TB	Jan 2022
endTB NCT02754765	9JLzMZ 9JLzLxCZ 9JLzLxDZ 9DLzLxCZ 9DMCZ [9–20mo SOC]	MDR-TB	May 2022
STREAM II NCT02409290	$4JCLxEZH_{Hd}$Pto/5JCLxEZ $2JCLxZH_{Hd}$K/4JCLxZ [$4CLxEZH_{Hd}$KPto/5CLxZE]	MDR-TB	July 2022
endTB-Q NCT03896685	6JDLzC 9JDLzC [9–20mo SOC]	FQ-R-MDR-TB	Dec 2022
BEAT TB CTRI/2019/01/017310	6-9JDLzC [none]	Pre-XDR-TB XDR-TB	Jan 2023
BEAT-Tuberculosis NCT04062201	6JDLz (Lx, C or both) [9-12mo SOC]	RR-TB MDR-TB FQ-R-MDR-TB	Mar 2023
MYL-XXX- 1234 [Mylan phase III]	6JPaMZ $6JPaLz_{600}$ [9-12mo SOC]	RR-TB MDR-TB	Protocol in development
ACTG 5373/FIRST	$6H_{Hd}$RZE [2RZELx/4RLx]	HR-TB	Protocol in development

*Unless otherwise indicated (i.e., experimental dosing indicated by numbers in subscript), numbers represent the duration of treatment in months (mo). Letters represent the individual drugs comprising each regimen (see Table 6). Slashes are used to separate intensive and continuation phases of treatment

Table 6. TB medicines abbreviations cheat sheet

amikacin	Am	**levofloxacin**	L, Lfx, Lx
bedaquiline	J, Bdq	**linezolid**	Lzd, Lz
clofazimine	C, Cfz	**meropenem**	Mpm
cycloserine	Cs	**moxifloxacin**	M, Mfx, Mx
delamanid	D, Dlm	**p-aminosalicylic acid**	PAS
ethambutol	E	**pretomanid**	Pa
ethionamide	Eto	**prothionamide**	Pto
high dose	Hd	**pyrazinamide**	Z, PZA
imipenem-cilastatin	Imp-Cln	**rifampicin**	R, RIF
injectable agent	IA	**standard of care**	SOC
isoniazid	H, INH	**streptomycin**	S
kanamycin	K, Kan	**terizidone**	Trd, Tzd

V. DETERMINING THE ACCESS BARRIERS

Historically, knowledge gaps have played an outsized role in restricting access to newer medicines and regimens for drug-resistant TB and slowed the speed at which they have been taken up by National TB Programs. Though important limitations remain, **registration**, **intellectual property**, and pricing barriers are now more obviously impeding access to the medicines needed to compose the standardized, modified, and individualized regimens that the WHO recommends (access to diagnostic tests is another critical factor discussed in depth in *An Activist's Guide to Tuberculosis Diagnostic Tools*).

Repurposed medicines, including moxifloxacin, levofloxacin, linezolid, and clofazimine, are registered for other indications and used **off-label** for the treatment of drug-resistant TB. In contrast, new drugs, including bedaquiline, delamanid and pretomanid, that were developed specifically for TB are considered **new chemical entities**. There are several **pre-approval** regulatory pathways through which new drugs can be accessed ahead of registration.[33] However, broad, equitable, and sustainable access to new drugs requires global and national regulatory approvals.

Table 7 provides an overview of where new drug applications for bedaquiline, delamanid, and pretomanid have been approved, filed, or are being planned. The sponsors of all three of these medicines first filed regulatory applications with stringent regulatory authorities (SRAs) in high-income countries (i.e., the U.S. Food and Drug Administration [FDA] and/or the European Medicines Agency [EMA]) and are at various stages of filing with regulatory authorities in low- and middle-income countries, and with the **WHO Prequalification Program**.

REGISTRATION: the process through which drug sponsors seek regulatory approval.

INTELLECTUAL PROPERTY: a category of property, including knowledge and products, over which companies can claim ownership.

REPURPOSED MEDICINES: medicines initially developed and indicated for other diseases that have been repurposed to treat TB (e.g., clofazimine was originally developed to treat leprosy).

OFF-LABEL: product labels specify the disease(s) or condition(s) for which regulatory authorities have approved the use of a medicine. Off-label use is when a medication is used to treat a disease or condition for which it has not been approved.

NEW CHEMICAL ENTITIES: entirely new drugs, defined by their unique chemical structure.

PRE-APPROVAL: before global and/or national registration/regulatory approval by regulatory authorities.

WHO PREQUALIFICATION PROGRAM: a global regulatory mechanism for assuring the quality of medicines and other health technologies.

Table 7. Approved, filed, and planned country registrations (as of 22 July 2020)

Medicine	Approved	Filed	Planned
bedaquiline - adults	Armenia, Belarus, Brazil, Burundi, Cameroon, China, Democratic Republic of Congo, Ethiopia, European Union, Hong Kong, Iceland, India, Indonesia, Israel, Japan, Liechtenstein, Macau, Mexico, Moldova, Mongolia, New Zealand, Norway, Peru, Philippines, Russian Federation, Rwanda, South Africa, South Korea, Taiwan, Tanzania, Thailand, Turkey, Turkmenistan, Uganda, Ukraine, United Kingdom, United States, Uzbekistan	Ghana, Kenya, Malaysia, Myanmar, Namibia, Nigeria, Tajikistan, Vietnam, Zambia, Zimbabwe	Bahrain
bedaquiline – children	12 < 18 years: Brazil, European Union, Taiwan, United States 5 < 12 years: United States	12 < 18 years: European Union, Hong Kong, India, Peru, Russian Federation, South Korea, Thailand 5 < 12 years: European Union	12 < 18 years: Burundi, Cameroon, Democratic Republic of Congo, Ethiopia, Ghana, Indonesia, Kenya, Malaysia, Myanmar, Namibia, Nigeria, Philippines, Rwanda, South Africa, Tanzania, Turkey, Ukraine, Vietnam, Zambia, Zimbabwe 5 < 12 years: Brazil, Burundi, Cameroon, Democratic Republic of Congo, Ethiopia, Ghana, Hong Kong, India, Indonesia, Kenya, Malaysia, Myanmar, Namibia, Nigeria, Peru, Philippines, Russia, Rwanda, South Africa, South Korea, Taiwan, Tanzania, Thailand, Turkey, Ukraine, Vietnam, Zambia, Zimbabwe
delamanid	China, European Union, Hong Kong, India, Indonesia, Japan, Kazakhstan, Mongolia, Peru, Philippines, Russian Federation, South Korea, South Africa, Turkey, Turkmenistan, Ukraine, United Kingdom	Azerbaijan, Brazil, Mexico, Morocco, Uzbekistan	Armenia, Belarus, Cameroon, Democratic Republic of Congo, Ethiopia, Georgia, Ghana, Kenya, Kyrgyzstan, Malawi, Moldova, Mozambique, Nigeria, Pakistan, Tanzania, Uganda
pretomanid	India, United States	Democratic Republic of Congo, Ethiopia, European Union, Mozambique, Philippines, South Africa, Thailand, Vietnam, Zimbabwe	Australia, Azerbaijan, Bangladesh, Belarus, Brazil, Cambodia, Cameroon, Georgia, Indonesia, Kazakhstan, Kenya, Kyrgyzstan, Laos, Moldova, Myanmar, Nigeria, Pakistan, Peru, South Korea, Tajikistan, Turkmenistan, Ukraine, Uzbekistan

Repurposed medicines used off-label for TB are off-patent in most countries, some more recently than others. The introduction of multiple quality-assured generic suppliers of these medicines in recent years has led to dramatic price reductions globally. Sponsors of new TB drugs, bedaquiline, delamanid, and pretomanid, however, still benefit from patent protections, and control the prices of these medicines directly and through voluntary licenses granted to generics companies. Table 8 provides an overview of the companies that have patent monopolies (patent holders) and the companies that have been permitted by patent holders (licensees) to commercialize bedaquiline, delamanid, a pretomanid in certain territories, as well as the prices they charge for these essential medicines.

Table 8. Intellectual property

Medicine	International (PCT) patent applications* (expiry)	Company	Price per month	Geographic scope**
bedaquiline	base compound: WO2004011436 (Jul 2023) fumarate salt: WO2008068231 (Dec 2027)	Johnson & Johnson (J&J)/ Janssen (patent holder)	**Adult form:** LMIC: US$45-57† HIC: US$5,000 **Pediatric form:** LMIC: US$33 HIC: US$2,500	Global (minus Georgia and CIS countries)
		Pharmstandard (licensee)	CIS: US$246	Russian Federation, Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Kazakhstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan
delamanid	base compound: WO2004033463 (Oct 2023)	Otsuka (patent holder)	LMIC: US$283 HIC: US$5,000	Australia, Canada, China, Egypt, European Union, Iceland, Liechtenstein, Norway, Switzerland, Hong Kong, Indonesia, Japan, Myanmar, Philippines, South Korea, Singapore, Taiwan, Thailand, Turkey, United States, Vietnam
		R-Pharm Russia/ R-Pharm Germany (licensee)	Unknown	Russian Federation, Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Kazakhstan, Moldova, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
		Mylan (licensee)	LMIC: US$283 South Africa: US$157	Global (minus Otsuka + R-Pharm)
pretomanid	combination regimen (BPaL): WO2017066053A1 (Oct 2036)	TB Alliance (patent holder)	NA	No plans for direct commercialization
		Mylan (licensee)	LMIC: US$61 HIC: US$600	214 countries (70 exclusive) – see medspal.org
		Macleods (licensee)	Unknown	143 countries – see medspal.org
		Hongqi Pharma (licensee)	Unknown	China, Taiwan, Hong Kong, Macau

*Please note that not all relevant international (PCT) applications are listed here. For a more detailed overview of relevant patents and their current status by country (granted, pending, filed) visit medspal.org, conduct a national patent search, or contact your national patent office

**Geographic scope refers to territories where patent holders retained or licensed rights to commercialize products, not territories where patents are granted, pending, or filed

†LMIC price range listed for bedaquiline reflects a baseline price of US$57 per month plus up to 20% free goods at annual volumes above 125,000 treatment courses. Up to 30% free goods is possible at annual volumes above 200,000 under the agreement negotiated between J&J and the Stop TB Partnership Global Drug Facility (GDF).[34]

LMIC means low- and middle-income countries; HIC means high-income countries; and CIS refers to member states of the Commonwealth of Independent States

The introduction of generic suppliers should lead to reductions in the prices of new TB medicines, but limited volumes and exclusivities prevent true generic competition. Researchers from the University of Liverpool estimate that generic versions of repurposed and new TB medicines can be sold at profit for between US$4–17 per medicine per month (see Table 9b).[35] The nuance is that these estimates assume annual volumes of 108,000 treatment courses, well above the annual bedaquiline and delamanid volumes reached in 2019.[36] Table 9a provides estimated price ranges for standardized, modified, and individualized regimens for the treatment of drug-resistant TB. Comparing current and target generic prices for the key repurposed and new medicines that make up these regimens lays bare that bedaquiline, delamanid, and pretomanid are driving up the costs of treatment for drug-resistant TB. This is where activists should focus their advocacy and energy.

Table 9a. The cost of treatment regimens for drug-resistant TB[37,38]

Regimen	Estimated Price* (2020, US$)
Nine- to 12-month standardized shorter regimen 6 Bdq 4 Cfz E HdH Lfx Pto Z / 5 Cfz E Lfx Z	US$540
Nine- to 12- month modified shorter regimens 6 Bdq 2 Lzd 4 Cfz E HdH Lfx Z / 5 Cfz E Lfx Z 6 Bdq Lfx Lzd Cfz Dlm 6 Bdq Lzd Cfz Dlm	 US$481 US$2,150 US$2,136
18- to 20-month individualized regimens 6 Bdq Lfx Lzd Cfz Cs / 12 Lfx Lzd Cfz Cs 12 Bdq Lfx Lzd Cfz / 6 Lfx Lzd Cfz 18 Bdq Lfx Lzd Cfx 20 Bdq Lzd Cfz Dlm	 US$1,168 US$1,077 US$1,298 US$7,317
Six- to nine-month Nix-TB regimen 6 Bdq Pa Lzd	 US$905

*Estimated regimen prices assume the monthly price of bedaquiline to be US$45, reflecting 20% free goods available at annual volumes above 125,000 treatment courses.

Table 9b. What is driving the cost of drug-resistant TB treatment regimens

Medicine	Current Price* (per patient per month)	Target Price for Generic Versions (per patient per month)**
moxifloxacin (M; Mx; Mfx)	US$10	US$4–8
levofloxacin (L; Lx; Lfx)	US$2.50	US$7–17
linezolid - 600 mg (Lz; Lzd)	US$13	US$5–13
clofazimine (Cfz)	US$15	US$4–11
bedaquiline (J; Bdq)	US$45-57	US$8–17
delamanid (D; Dlm)	US$283	US$5–16
pretomanid (Pa)	US$61	US$5–16

*Lowest GDF price: http://www.stoptb.org/gdf/drugsupply/drugs_available.asp.

**Target price ranges are based on the estimated costs of active and inactive pharmaceutical ingredients, formulation, packaging, and a cost-plus model, which includes a reasonable profit margin: https://doi.org/10.1093/jac/dkw522.

For a comprehensive overview of TB drug supply, pricing, and patent issues by medicine, refer to MSF's issue brief, DR-TB Drugs Under the Microscope, 7th Edition.[39]

SPOTLIGHT 3: PEDIATRIC FORMULATIONS

Pediatric formulations of levofloxacin, moxifloxacin, cycloserine, clofazimine, ethambutol, isoniazid, ethionamide, pyrazinamide, and PAS are available via the Global Drug Facility (GDF) and have so far been launched in 56 countries.[40] These formulations have been quality-assured by the WHO Prequalification Program but are unlikely to be registered at the national level in most countries, given the lack of incentive for companies to do so (i.e., when the required registration costs and effort exceed market potential). In the absence of national registration, in most places these formulations can be imported using waivers under special access schemes.

A 20 mg pediatric formulation of bedaquiline was recently approved by the U.S. Food and Drug Administration (FDA), and a 25 mg pediatric formulation of delamanid is available via Otsuka's compassionate use program. A pediatric formulation of linezolid is under development. A dispersible formulation of pretomanid has been developed, though pediatric investigations have yet to begin and are pending until additional safety data are available.

VI. TAKING ACTION

There are several actions activists can take to help overcome the barriers discussed in the previous sections and to promote equitable access to treatment for drug-resistant TB.

1 Collect information to support appeals to national and subnational policy makers to adopt the global standard of care articulated in the 2020 update to the WHO consolidated guidelines on drug-resistant tuberculosis treatment and informed by evolving scientific evidence.

- Review your National Strategic Plan (NSP) and TB Treatment Guidelines to look for policies that are misaligned with WHO guidance;
- Request information on the number of drug-resistant TB treatment starts by regimen, and compare these figures with local incidence estimates;
- Examine the national drug-resistant TB donor landscape (i.e., the overall program budget, the percent funded, and the proportion that is domestic vs. donor funding);
- Understand the mechanisms and sources of funding used to procure medicines for drug-resistant TB and how corresponding government tenders work;
- Look into the availability of nutritional, economic, and mental health support or other assistance programs for patients undergoing treatment for drug-resistant TB; and
- Survey healthcare workers and former and current TB patients to understand their experiences and concerns, document policy-practice gaps, and articulate barriers to accessing treatment.

2 Apply pressure to government and other national and local actors to increase the number of people with drug-resistant TB that are diagnosed and treated with the standardized, modified, or individualized regimens recommended by the WHO.

- Generate demand by empowering TB-affected communities to conduct TB diagnosis and treatment literacy trainings and to monitor the availability of TB tests and treatment regimens locally;
- Create links between members of TB-affected communities and community-based and civil society organizations;

- Build rapport with the National TB Program and providers in the private sector to understand their positions and needs, and to identify entry points and opportunities for advocacy;
- Write to members of parliament and officials at government agencies, including those at the district or other sub-national levels, involved in appropriating domestic and donor funding to health programs;
- Engage members of your Country Coordinating Mechanism (CCM) and any other bodies that inform funding requests made to international donors.

3 Hold drug sponsors and generics suppliers of bedaquiline, delamanid, and pretomanid accountable for making these medicines available, accessible, and affordable.

- Demand transparency on volumes, costs of goods, pricing, and the terms and conditions of licensing agreements;
- Push for a single global access price based on costs-of-goods-sold (COGS; the amount it costs a manufacturer to produce a medicine) and annual volumes;
- Work with lawyers, academics, and public interest organizations to explore national pro-access policies, legal safeguards, and other mechanisms available to support market entry of additional generics manufacturers;
- Advocate for new medicines and their generic equivalents to be registered with your national regulatory authority, and for your national regulatory authority to expedite its review of applications for the registration of drug-resistant TB medicines.

4 Advocate for governments, drug sponsors, and other funders of TB research and development (R&D) to continue to invest in initiatives designed to fill critical data gaps and further optimize treatment for drug-resistant TB.

- Read up on and sensitize policymakers to the TB treatment pipeline,[41] including how, if proven, the medicines and regimens contained therein may make treatment for drug-resistant TB shorter, simpler, safer, and more effective;
- Encourage your government to increase its investments in TB R&D,[42] and to contribute to the development of appropriate incentives for, and innovative models of, research that promote transparency, collaboration, and access;
- Set up or apply to participate in community advisory boards (CABs) or other mechanisms through which TB-affected communities can engage with TB drug and study sponsors to ensure that research investments reflect community needs and priorities.

VII. OVERCOMING RESISTANCE TO IMPLEMENTING NEW REGIMENS

Activists will hear many excuses for not implementing the standardized, modified, and individualized treatment regimens recommended by the WHO. Some common excuses are outlined below, along with the evidence and arguments that activists can use to overcome them.

EXCUSE: The newer drugs and regimens are too expensive.

RESPONSE: Yes, the newer drugs and regimens are expensive, but the costs of treating drug-resistant TB with sub-optimal regimens are far greater. These include extended morbidity and time away from work resulting in lost income and financial instability, further development and transmission of drug-resistance, and increased risk of permanent disability and death. Increased demand and volumes are necessary to generate interest among generic suppliers and manufacturing efficiencies that can lead to price reductions. Governments can negotiate with drug companies directly or in coalition with other governments and international agencies to pool procurement power and leverage higher, consolidated volumes to bring down costs. If negotiations fail, governments have other tools at their disposal that they can use to provide access to essential medicines priced out of reach or otherwise inaccessible (e.g., compulsory licensing).

EXCUSE: Bedaquiline and delamanid cannot be used together.

RESPONSE: This is not true. Though both drugs can have QT prolonging effects, a study designed specifically to evaluate whether bedaquiline and delamanid could be safely used together (ACTG A5343; NCT02583048) found that the combined effect on the QT interval of co-administering bedaquiline and delamanid is "clinically modest and no more than additive" and demonstrated the cardiac safety of the combined use of these drugs for drug-resistant TB.[43] In the 2020 update to *WHO Consolidated Guidelines on Tuberculosis, Module 4: Treatment – Drug Resistant Tuberculosis Treatment*, the WHO reviewed these and other data, and supports that bedaquiline and delamanid can be safely combined for the treatment of drug-resistant TB.

EXCUSE: Neither bedaquiline nor delamanid can be given for more than six months.

RESPONSE: This is not true. There is no evidence that suggests extending the duration of bedaquiline or delamanid treatment beyond six months poses any harm. The studies upon which bedaquiline and delamanid were initially approved only evaluated the use of these medicines over the first six months of treatment; however, observational data, including from the endTB Project, have demonstrated the safety and potential importance of extending treatment with these medicines beyond six months in certain situations (e.g., delayed culture conversion, intolerance to other key medicines in the regimen requiring interruption or discontinuation). Automatically discontinuing the use of bedaquiline or delamanid after six months may unnecessarily weaken the regimen for the remainder of treatment, putting individuals at increased risk of unfavorable treatment outcomes.

EXCUSE: The injectable agents are more affordable and have been used for decades.

RESPONSE: The injectable agents may be less expensive, but they are also more difficult to administer and less safe and effective than the new and repurposed TB medicines recommended in their place. In fact, the individual patient data meta-analysis the WHO commissioned to inform the 2020 update to its treatment guidelines found an association between the use of kanamycin and capreomycin and worse treatment outcomes. In the same meta-analysis, amikacin demonstrated modest benefits, but its use has also been associated with frequent, serious adverse events, including permanent hearing loss.[44] When you factor in the costs of monitoring for and managing adverse events like hearing loss, the use of injectable agents can actually be very expensive.

EXCUSE: Programs need to finish using up existing stock of injectable agents.

RESPONSE: The WHO recommends against the use of kanamycin and capreomycin and that amikacin only be used in salvage situations (i.e., when an effective regimen cannot otherwise be composed). Given this guidance, and the real and serious risk of unnecessary harm the continued use of these medicines presents, it is unethical to administer these agents for the purpose of using up existing stocks. In fact, the Global Fund and other donors explicitly support and are willing to fund the destruction of agents that are no longer recommended by the WHO.[45] Amikacin can be used to treat other serious bacterial infections and so excess stocks could also be given to other disease programs in country, if needed.[46]

EXCUSE: Evidence specific to the country is required to expand access to new regimens.

RESPONSE: Clinical trials and observational research studies often enroll participants from multiple sites in multiple countries to ensure that a diverse and representative population is included in the study, and that the results can be applied across different populations, geographies, and settings. Country programs may want to conduct operational research to better understand and optimize the implementation of new regimens in their settings, but the conduct of local clinical trials is not necessary for the purpose of establishing the safety and efficacy of recommended regimens and can delay access to improved treatment regimens.

EXCUSE: New TB drugs must be "protected".

RESPONSE: Clinicians and programs should be more concerned with protecting the patients they serve. The impulse to "protect new drugs" can have the opposite effect and denies people their rights to health and to benefit from scientific progress. The best way to protect new drugs is by optimizing the regimens within which they are given and ensuring that patients are adequately supported to complete treatment. It is a violation of human rights to reserve drugs for use by future TB patients when they could be used to optimize treatment outcomes for people with drug-resistant TB today.

EXCUSE: Programs are too overwhelmed by COVID-19 to implement new treatment regimens.

RESPONSE: Implementing all-oral shorter regimens for drug-resistant TB can actually ease the burden on health programs involved in both the response to TB and COVID-19 and protect TB patients from unnecessary risks of COVID-19 exposure. The use of injectable TB medicines requires face-to-face interactions and daily visits to a healthcare provider, putting TB patients at risk of exposure to COVID-19 and stressing health facilities and staff. Implementing new, all-oral treatment regimens for drug-resistant TB will help minimize TB patient visits to health facilities.[47]

Want more information?
Write to communications@treatmentactiongroup.org

REFERENCES

1. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: Treatment; Drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. https://www.who.int/publications/i/item/9789240007048.
2. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis: 2016 update. Geneva: World Health Organization; 2016. https://apps.who.int/iris/rest/bitstreams/1061087/retrieve.
3. World Health Organization. Rapid communication: Key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019. https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/.
4. World Health Organization. Global tuberculosis report 2019. Geneva: World Health Organization; 2019. https://www.who.int/tb/publications/global_report/en/.
5. World Health Organization. Key changes to treatment.
6. Branigan D. An Activist's Guide to Tuberculosis Diagnostic Tools. New York: Treatment Action Group; 2020. https://www.treatmentactiongroup.org/publication/an-activists-guide-to-tuberculosis-diagnostic-tools/.
7. Fregonese F, Ahuja SD, Akkerman OW, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2018 Apr;6(4):265–275. https://doi.org/10.1016/S2213-2600(18)30078-X.
8. U.S. Department of Health and Human Services [Internet]. AIDSinfo: Drugs. (cited 2020 June 3). https://aidsinfo.nih.gov/drugs/.
9. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014. https://www.who.int/tb/publications/pmdt_companionhandbook/en/.
10. World Health Organization. WHO operational handbook on tuberculosis. Module 4: Treatment. Drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. https://www.who.int/publications/i/item/9789240006997.
11. Janssen Therapeutics. Highlights of prescribing information for Sirturo (bedaquiline). 2012 December. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf.
12. TB Alliance. Highlights of prescribing information for Pretomanid. 2019 September. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212862Orig1s000TOC.cfm.
13. Otsuka Novel Products GmbH. Summary of product characteristics: Deltyba (delamanid). 2014 April. https://www.ema.europa.eu/documents/product-information/deltyba-epar-product-information_en.pdf.
14. World Health Organization. WHO operational handbook.
15. Loveday M, Hughes J, Sunkari B, et al. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. Clin Infect Dis. 2020 Mar 6. https://doi.org/10.1093/cid/ciaa189. [Epub ahead of print]
16. World Health Organization. Policy guidelines for collaborative TB and HIV services for injecting and other drug users: An integrated approach. Geneva: World Health Organization; 2008. http://whqlibdoc.who.int/publications/2008/9789241596930_eng.pdf
17. World Health Organization. Active drug-safety monitoring and management: framework for implementation. Geneva: World Health Organization; 2015. https://apps.who.int/iris/bitstream/handle/10665/204465/WHO_HTM_TB_2015.28_eng.pdf?sequence=1.
18. World Health Organization, Stop TB Partnership Global Drug Facility and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Frequently asked questions on the WHO rapid communication 2019: Key changes to the treatment of drug resistant TB, Version 1.1. Geneva: World Health Organization; 2020. (cited 2020 June 10). https://www.who.int/tb/areas-of-work/drug-resistant-tb/faqs-updated-final-version.pdf?ua=1.
19. World Health Organization. Global TB Programme Newsflash: Meeting on update of the WHO drug-resistant TB treatment guidelines, 12-14 November 2019 [Internet]. Geneva: World Health Organization; 2019 November 9. https://mailchi.mp/who/results_call_data?e=2898848a73.
20. Schnippel K, Ndjeka N, Maartens G, et al. Effect of bedaquiline on mortality in South African patients with drug-resistant tuberculosis: A retrospective cohort study. Lancet Respir Med. 2018 Sep; 6(9):699–706. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30235-2/fulltext.

21. Skrahina A, Hurevich H, Setkina S, et al. Bedaquiline containing regimens for the treatment of multi- and extensively drug-resistant tuberculosis at the programmatic level in Belarus. Prospective cohort study. Eur Respir J 2019;54:Suppl.63,OA2136. doi: 10.1183/13993003.congress-2019.OA2136.

22. World Health Organization. Public call for individual patient data on treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2019 August 1. https://www.who.int/tb/features_archive/Public-call-individual-patient-data-treatment-drug-res/en/.

23. Khan U, Huerga H, Khan AJ, et al. The endTB observational study protocol: Treatment of MDR-TB with bedaquiline or delamanid containing regimens. BMC Infect Dis. 2019 Aug;19(1):733. doi: 10.1186/s12879-019-4378-4.

24. endTB. Bedaquiline- and delamanid-containing regimens achieve excellent interim treatment response without safety concerns: endTB interim analysis [Internet]. 2018 July 13. (cited 2020 June 10). http://www.endtb.org/resources/endtb-interim-analysis-july2018.

25. Loveday M, et al. Maternal and infant outcomes..

26. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020 Mar;382:893-902. doi:10.1056/NEJMoa1901814.

27. Cox V, McKenna L, Acquah R, et al. Clinical perspectives on treatment of rifampicin-resistant/multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. Forthcoming 2020.

28. Schnippel K, et al. Effect of bedaquiline on mortality.

29. Ahmad N, Ahuja S, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: An individual patient data meta-analysis. Lancet. 2018 Sep;392(10150):821-834. doi: 10.1016/S0140-6736(18)31644-1.

30. endTB. endTB interim analysis.

31. Franke, M. Final outcomes of patients in the endTB observational cohort. Paper presented at: 50th Union World Conference on Lung Health, Symposium SP-13-C3. 2019 October 31. Hyderabad, India.

32. Conradie F, et al. Treatment of highly drug-resistant tuberculosis.

33. Lessem E. An activist's guide to regulatory issues: Ensuring fair evaluation of and access to tuberculosis treatment. New York: Treatment Action Group; 2015. https://www.treatmentactiongroup.org/publication/an-activists-guide-to-regulatory-issues/.

34. Johnson & Johnson. Stop TB Partnership and Johnson & Johnson, with support from USAID and The Global Fund, Announce Price Reduction for SIRTURO® (bedaquiline) for Treatment of Drug-Resistant Tuberculosis in Low- and Middle-Income Countries [Press release]. Geneva: Johnson & Johnson; 2020 July 6. https://www.jnj.com/stop-tb-partnership-and-johnson-johnson-with-support-from-usaid-and-the-global-fund-announce-price-reduction-for-sirturo-bedaquiline-for-treatment-of-drug-resistant-tuberculosis-in-low-and-middle-income-countries.

35. Gotham D, Fortunak J, Pozniak A, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother. 2017 Jan;72(4):1243–1252. https://doi.org/10.1093/jac/dkw522.

36. DR-TB STAT. Global summary of bedaquiline and delamanid use [Internet]. 2020 March (cited 2020 June 9). http://drtb-stat.org/country-updates/..

37. Médecins Sans Frontières Access Campaign. DR-TB drugs under the microscope, 7th edition. Geneva: Médecins Sans Frontières Access Campaign; Forthcoming 2020. https://msfaccess.org/drtb-drugs-under-microscope.

38. Stop TB Partnership Global Drug Facility. Stop TB Partnership's Global Drug Facility (STBP/GDF) FAQs on bedaquiline price reduction and free goods [Internet]. Geneva: Stop TB Partnership Global Drug Facility; 2020 July 6. http://www.stoptb.org/assets/documents/gdf/drugsupply/2020.07.06%20FAQs%20for%20bedaquiline%20price%20announcement.pdf.

39. Médecins Sans Frontières Access Campaign. DR-TB drugs under the microscope.

40. Stop TB Partnership Global Drug Facility. Accelerating the Roll-Out of TB Innovations through the Stop TB/GDF Launchpad: The Stop TB/GDF Pediatric Drug-Resistant TB Initiative. Progress Report presented to the Stop TB Partnership Coordinating Board. 2019 (cited 2020 June 18). http://www.stoptb.org/assets/documents/about/cb/meetings/32/32-09%20Global%20Drug%20Facility/Pre%20read/32-9-1.1%20STBP%20GDF%20Paediatric%20DRTB%20Initiative%20EB%20Pre-Read.pdf.

41. McKenna L. The Tuberculosis Pipeline Report. New York: Treatment Action Group; 2019. https://www.treatmentactiongroup.org/wp-content/uploads/2019/12/pipeline_tb_treatment_lm_final.pdf.

42. Barr L. Tuberculosis Research Funding Trends, 2005–2018. New York: Treatment Action Group; 2019. https://www.treatmentactiongroup.org/resources/tbrd-report/tbrd-report-2019/.

43. Dooley KE, Rosenkranz SL, Conradie F, et al. QT effects of bedaquiline, delamanid or both in MDR-TB patients: The DELIBERATE trial (Abstract 84). Paper presented at: 26th Conference on Retroviruses and Opportunistic Infections. 2019 March 4–7; Seattle, Washington. http://www.croiconference.org/sessions/qt-effects-bedaquiline-delamanid-or-both-mdr-tb-patients-deliberate-trial.

44. Reuter A, Tisile P, von Delft D, et al. The devil we know: is the use of injectable agents for the treatment of MDR-TB justified? Int J Tuberc Lung Dis. 2017:21(11):1114–1126. http://dx.doi.org/10.5588/ijtld.17.0468.

45. World Health Organization, Stop TB Partnership Global Drug Facility and the Global Fund to Fight AIDS, Tuberculosis and Malaria. Frequently asked questions on WHO rapid communication.

46. Cox V, et al. Clinical perspectives on treatment.

47. Cox V, Wilkinson L, Grimsrud A, et al. Critical changes to services for TB patients during the COVID-19 pandemic. Int J Tuberc Lung Dis. 2020 May 1:24(5);542-544. https://doi.org/10.5588/ijtld.20.0205.

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