



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

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# SHORTER TREATMENT

## FOR DRUG-RESISTANT TUBERCULOSIS

### November 2023

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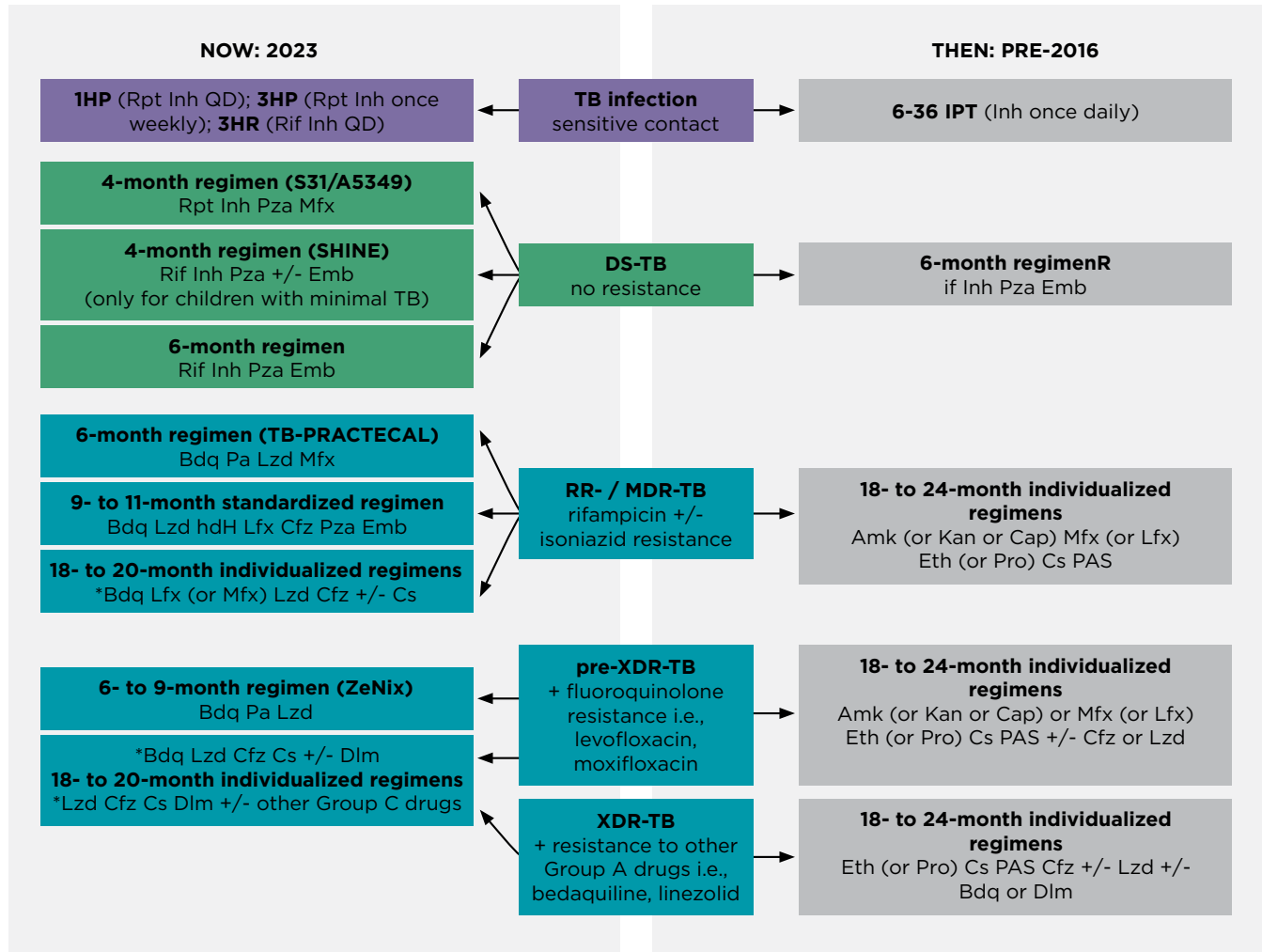
## I. BACKGROUND AND INTRODUCTION

In 2022, the World Health Organization (WHO) updated Module 4 of its *Consolidated Guidelines on Tuberculosis Treatment* with key changes to its recommendations for the treatment of drug-resistant tuberculosis.<sup>1</sup> The updated recommendations enable treatment shortening to just six months for rifampicin- or multidrug-resistant TB (RR/MDR-TB), with or without additional resistance to fluoroquinolones (pre-XDR-TB). This Activist's Guide reviews the two clinical trials behind the updated WHO recommendations on the six-month regimen: **TB-PRACTECAL** and **ZeNix**. The policy updates resulting from these trials round out more than two decades of research investments that have made it possible to treat most forms of drug-sensitive and drug-resistant TB in four and six months, respectively, and to treat TB infection in as little as one to three months.<sup>2</sup>

The WHO first introduced guidelines supporting the use of a standardized nine-to-11-month regimen for drug-resistant TB in 2016.<sup>3</sup> Over the course of several years, and in response to emerging evidence, the WHO modified the composition of the standardized shorter regimen it recommends, replacing the injectable agent with bedaquiline, and most recently replacing ethionamide with linezolid based on programmatic experience from South Africa.<sup>4</sup> In the latest iteration of its guidelines, the WHO also supports the use of a six-month regimen composed of bedaquiline (B), pretomanid (Pa), and linezolid (L), with or without moxifloxacin (M) depending on the presence of fluoroquinolone (i.e., moxifloxacin) resistance. This six-month regimen – known as BPaL(M) – is the preferred treatment option for drug-resistant TB. Compared with the 9- to 11-month regimen, the evidence is stronger, the duration is shorter, the pill burden is fewer, and the toxicity is less for the six-month regimen. But there are some important knowledge gaps that prevent certain populations from sharing in the benefits of these treatment advances, for now at least.

For more information on the WHO-recommended short-course regimens for drug-sensitive TB and TB prevention, see *An Activist's Guide to Shorter Treatment for Drug-Sensitive Tuberculosis* and *An Activist's Guide to Rifapentine for the Treatment of TB Infection*.

**FIGURE 1. TB TREATMENT REGIMENS: NOW AND THEN**



\*examples of individualized regimens containing 4-5 medicines selected according to the WHO table of priority medicines; composition will vary depending on the individual's profile of drug resistance and potentially other factors.

## HOW TO USE THIS GUIDE

We wrote this guide to provide activists with information about shorter treatment regimens for drug-resistant TB, including recent trial results, key considerations for special populations, and anticipated access barriers. The guide also equips activists with actions they can take and arguments they can use to advocate for access to shorter treatment regimens.

Throughout this guide, regimens are represented in short form where numbers represent the duration of treatment in months, letters represent the individual drugs that make up each regimen, and slashes are used to separate the intensive and continuation phases of treatment. For example, **6BPaLM** represents six months of bedaquiline, pretomanid, linezolid, and moxifloxacin. The cheat sheet below provides commonly used abbreviations for each TB medicine.

## TB MEDICINES ABBREVIATIONS CHEAT SHEET

<b>amikacin</b>	Am	<b>linezolid</b>	Lzd, Lz
<b>bedaquiline</b>	J, Bdq	<b>meropenem</b>	Mpm
<b>clofazimine</b>	C, Cfz	<b>moxifloxacin</b>	M, Mfx, Mx
<b>cycloserine</b>	Cs	<b>p-aminosalicylic acid</b>	PAS
<b>delamanid</b>	D, Dlm	<b>pretomanid</b>	Pa
<b>ethambutol</b>	E, Emb	<b>prothionamide</b>	Pto
<b>ethionamide</b>	Eto	<b>pyrazinamide</b>	Z, Pza
<b>high dose</b>	Hd	<b>rifampicin</b>	R, Rif
<b>imipenem-cilastatin</b>	Imp-Cln	<b>rifapentine</b>	P, Rpt
<b>isoniazid</b>	H, Inh	<b>streptomycin</b>	S
<b>levofloxacin</b>	L, Lfx, Lx	<b>terizidone</b>	Trd, Tzd

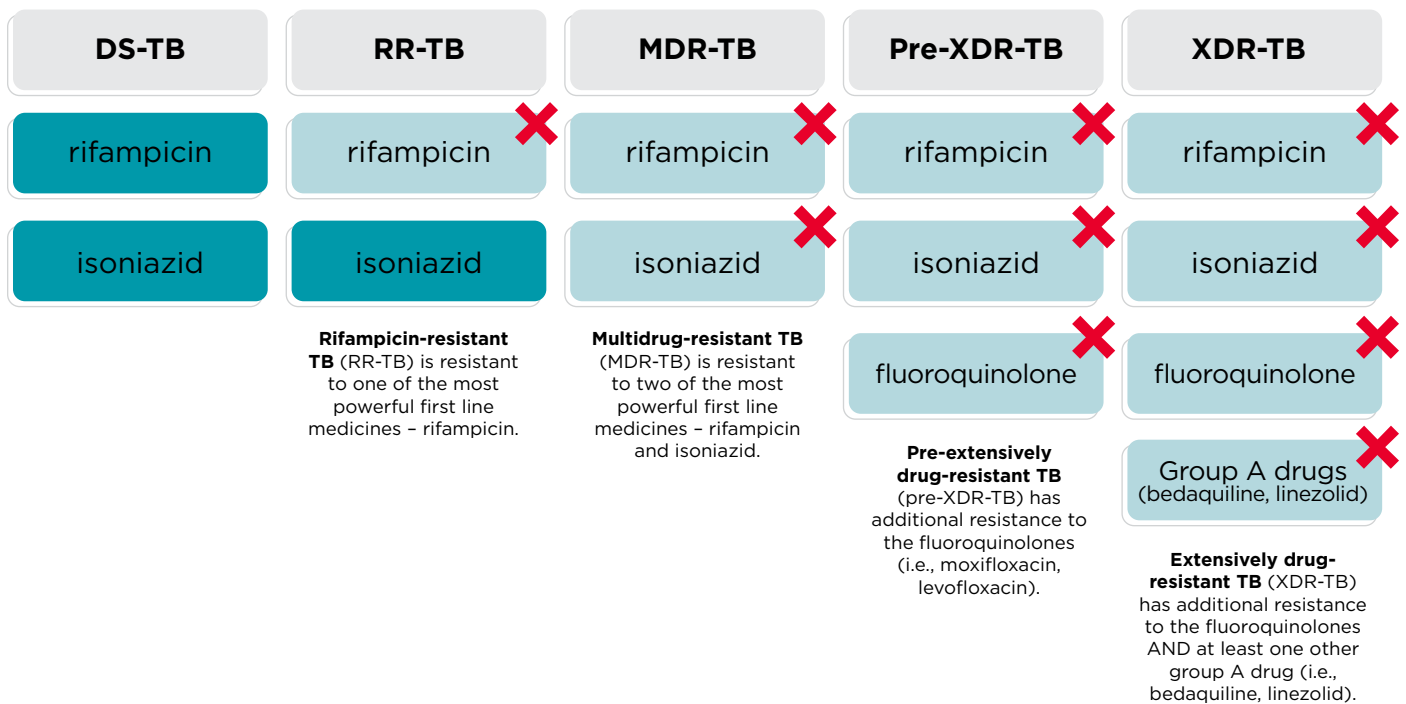
### DEFINING DRUG-RESISTANT TUBERCULOSIS

Each of the medicines used to treat TB has a **mechanism of action** for disabling or killing TB bacteria. Certain bacterial mutations can prevent a medicine from carrying out its mechanism of action by inactivating it or blocking it from entering or staying inside the TB bacterial cell. Mutations that confer resistance can occur naturally 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 inadequate treatment because of underdosing, malabsorption, or interrupted or incomplete TB treatment, referred to as acquired resistance.

An estimated 500,000 people become sick with drug-resistant TB each year, yet just 30 percent of these people are diagnosed and put on treatment. Global rates of treatment success among those diagnosed and treated range from 60 to 70 percent.<sup>5</sup> 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.

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

**FIGURE 2. DEFINING DRUG-RESISTANT TB**



## II. THE EFFICACY AND SAFETY OF SIX-MONTH REGIMENS FOR DRUG-RESISTANT TB

### TB-PRACTECAL (NCT02589782)

The objective of the TB-PRACTECAL trial was to evaluate the safety and efficacy of three six-month bedaquiline-, pretomanid-, and linezolid-based regimens for the treatment of adults and adolescents with RR-/MDR-TB. The three experimental regimens were: 1. BPaL, 2. BPaL plus clofazimine (BPaLC), and 3. BPaL plus moxifloxacin (BPaLM). Each of the three investigational arms were compared with a control arm composed of participants who received a WHO-recommended 9- to 11- or 18- to 20-month standard-of-care regimen. TB-PRACTECAL enrolled 552 participants from seven sites in three countries: Belarus, South Africa, and Uzbekistan. Trial participants represented a diverse range of people with TB, including adolescents down to 15 years old (4%), people living with HIV irrespective of CD4 count (27.6%), and people with **cavitary disease** (60.7%).

The study was conducted in two phases. All three investigational regimens performed well in stage one, but only one (BPaLM) was taken forward in stage two. The six-month BPaLM regimen was shown to be **non-inferior** to (no worse than) and **superior** to (better than) the longer standard-of-care-regimens. Unfavorable treatment outcomes (i.e., a composite of death, treatment failure, treatment discontinuation, e.g., a change of two or more drugs, loss to follow-up, or recurrence of TB) observed among people randomized to receive the six-month BPaLM regimen were significantly fewer (16/138, 11.7%) than those observed among people randomized to receive the longer standard-of-care regimens (56/137, 40.9%).<sup>6</sup> The difference in unfavorable outcomes was driven by early treatment discontinuations in the control arm, primarily

**CAVITARY DISEASE** serves as a marker of TB disease severity — people with more extensive lung damage (cavitations measured by chest X-ray) typically have more severe disease.

**NON-INFERIOR** means that the intervention is no worse than the control by a pre-specified amount (called a non-inferiority margin).

**SUPERIOR** means the intervention was better than the control by a pre-specified margin.

due to **adverse events**.<sup>7</sup> The six-month BPaLM regimen was found to be safer than longer standard-of-care regimens, with 23% versus 48% of participants experiencing at least one serious adverse event or an adverse event of grade three or higher. Based on these data, the study was stopped by its data and safety monitoring board (DSMB) prior to being fully enrolled. This may impact the ability to fully assess how the regimen performs in subpopulations and other outcome measures such as mortality and treatment failure, since fewer people were enrolled than planned.

### **ZeNix (NCT03086486)**

The objective of the ZeNix trial was to optimize the safety and tolerability of the six-month BPaL regimen using different doses and durations of linezolid in adults and adolescents with pre-XDR-TB (MDR-TB with additional resistance to fluoroquinolones). ZeNix builds on a single-arm intervention study called Nix-TB (NCT02333799) that first established the efficacy of the six-month BPaL regimen for highly drug-resistant strains of TB, with successful treatment outcomes observed among 90% (98/109) of study participants.<sup>8</sup> In the Nix-TB trial, linezolid was administered at 1,200 mg daily for the full six months of treatment, but only 37 participants (34%) completed six months of linezolid without any interruption, and only 16 participants (15%) completed six months of linezolid without interruption at a total daily dose of 1,200 mg. A total of 62 participants (57%) experienced adverse events of grade three or higher during treatment. **Peripheral neuropathy** occurred in 88 participants (81%) and **myelosuppression** in 52 participants (48%).

To try to improve the safety and tolerability of the BPaL regimen, ZeNix evaluated it using four different approaches to the dose (1,200 vs. 600 mg daily) and duration (two vs. six months) of linezolid. ZeNix enrolled 181 participants from 11 sites in four countries: South Africa, Georgia, Moldova, and Russia. The study population included adults and adolescents 14 years of age or older and people living with HIV with a CD4 count of at least 100 cells/mm<sup>3</sup> (20%). The BPaL regimen with linezolid administered at 600 mg daily for six months demonstrated the best balance of safety and efficacy (most favorable risk-benefit profile), with 40 of 45 participants (89%) classified as having a favorable outcome and 6 of 45 participants (13%) requiring linezolid dose modifications.<sup>9</sup> Among participants randomized to receive BPaL with linezolid administered at 600 mg for six months, peripheral neuropathy of grade 3 or lower was reported in 11 of 45 participants (24%) and myelosuppression was reported in 1 of 45 participants (2%). Unlike with TB-PRACTECAL, the design of ZeNix did not include a standard-of-care **control arm**, limiting any direct comparison of ZeNix to other WHO-recommended 9- to-11- or 18- to 20-month regimens.

An **ADVERSE EVENT** is an unintentional, unfavorable clinical sign or symptom that occurs in association with the use of a drug or regimen. In clinical trials, adverse events are often “graded” using standard scales. The scale usually ranges from 1 to 5, with 1 being a mild event and 5 being death.

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

**MYELOSUPPRESSION** is 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).

**CONTROL ARMS** reduce the risk of bias in a study and enable researchers to directly compare how a new medication or regimen performs against the existing standard of care.

## Side Effects and Drug-Drug Interactions

These newer, shorter regimens represent a notable advance in the treatment of drug-resistant TB, but as with any treatment regimen, it is important to ensure people being treated are regularly monitored for side effects. Several noteworthy treatment-related side effects are associated with BPaL(M). These include:

- **myelosuppression:** 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);
- **hepatotoxicity:** drug-induced damage or injury to the liver;
- **cardiotoxicity (prolonged QTc interval):** a disturbance in the heart's electrical activity that can lead to serious (and sometimes fatal) rhythmic disturbances;
- **peripheral neuropathy:** nerve damage in the extremities, which can cause numbness and pain starting in the fingers and toes and spreading upwards; and
- **optic neuropathy:** damage to the nerve that transfers visual information from the eye to the brain, which can cause eye pain and vision changes.<sup>10</sup>

It's important for people with TB to recognize symptoms of these known treatment-related side effects (see Figure 3) and to alert their health care providers as soon as they develop so they can conduct an examination and any necessary tests and take appropriate action. These effects are typically manageable using monitoring tests at the time treatment is started and at regular intervals over the course of treatment. These include **electrocardiography (ECG)**, clinical assessments for peripheral neuropathy, visual acuity and color vision testing for optic neuropathy, and **blood profiles** (e.g., complete blood count) for anemia and other manifestations of myelosuppression.<sup>11</sup> These routine tests can usually find early any side effects that are developing so health care providers can make changes to protect people from harm.

**ELECTROCARDIOGRAPHY (ECG)** is a test that measures the electrical activity in your heart to check for irregular rhythms.

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

### FIGURE 3. SYMPTOMS OF TREATMENT-RELATED SIDE EFFECTS



Symptoms of **MYELOSUPPRESSION** may include fatigue, weakness, dizziness, shortness of breath, and pale skin, lips, and nail beds.



Symptoms of **HEPATOTOXICITY** may include nausea, vomiting, fatigue, malaise, pruritus (itchy skin), fever, right upper abdominal pain (or sharp pain below your ribcage), and jaundice (yellowing of the skin and whites of the eyes).



**QTc INTERVAL PROLONGATION** is often asymptomatic, but severe instances may cause palpitations (fluttering in the chest), shortness of breath, chest pain, lightheadedness, near fainting, or fainting.



Symptoms of **OPTIC NEUROPATHY** may include eye pain, blurred vision, blind spots, reduced color vision (e.g., loss of red-green color distinctions), or complete loss of vision.



And symptoms of **PERIPHERAL NEUROPATHY** may include numbness and tingling in the feet or hands, burning, stabbing, or shooting pain in affected areas, and loss of balance and coordination.

Side effects of drugs can sometimes be exacerbated by other drugs. For example, two drugs may have the same side effect, increasing the risk and severity of the side effect they share when the two drugs are given together. Sometimes one drug can interfere with the way a person's body processes another drug, which may result in higher drug levels and increased risks for side effects (these are called drug-drug interactions). Because drug-drug interactions can exacerbate treatment-related side effects, extra vigilance and monitoring is necessary when certain drugs are given together. For example, when bedaquiline and moxifloxacin are administered alongside other QTc-prolonging drugs (e.g., methadone, antimalarials), extra vigilance and monitoring with ECG is necessary. When linezolid is given alongside other serotonergic drugs (e.g., selective serotonin reuptake inhibitors, antipsychotics), there should be close monitoring for **serotonin syndrome**.<sup>12</sup> In terms of antiretroviral medications, integrase inhibitor-based ART (i.e., dolutegravir) is preferable for people living with HIV while they are taking BPaL(M) as ritonavir-boosted protease inhibitors (e.g., lopinavir/ritonavir) increase bedaquiline levels and efavirenz decreases bedaquiline and pretomanid levels.<sup>13</sup>

Any side effects of TB treatment should be managed as part of TB care and reported to the National TB Program (NTP) so that the overall safety of TB drugs and regimens can be monitored at a higher level, something known as **active TB drug safety monitoring and management (aDSM)**.

**What About People Living with HIV?**

People living with HIV (PLHIV) participated in all three of the landmark trials that make up the evidence base for the WHO endorsement of the BPaL(M) regimens, though numbers were small. In Nix-TB, ZeNix, and TB-PRACTECAL, 56 (51%), 36 (20%), and 140 (27.6%) participants respectively were PLHIV. The median CD4 cell count was 343 (55-1023), 421 (122-1480), and 330 (209-547) cells/mm<sup>3</sup>, respectively. Treatment outcomes and safety (i.e., the frequency and severity of adverse events) were similar among people living with and without HIV who participated in Nix-TB and ZeNix. In ZeNix, 32/36 (89%) PLHIV had a favorable treatment outcome with BPaL compared with 126/145 (87%) of participants without HIV.<sup>14</sup>

In TB-PRACTECAL, treatment outcomes were still better among PLHIV randomized to receive BPaLM compared with the longer regimens in the control arm (see Table 1), but the difference was not as pronounced or statistically significant in a sub-analysis that evaluated whether the risk of an unfavorable treatment outcome was different for PLHIV in the trial, probably because the number of PLHIV included in the trial was small.

**TABLE 1. TB-PRACTECAL SUBGROUP ANALYSIS FOR PEOPLE LIVING WITH HIV**

Population	Unfavorable Outcomes		Risk Difference (Confidence Interval)
	BPaLM	Control	
HIV-positive	7/34 (20.6%)	9/38 (23.7%)	-3.1% (-23.8 to 17.6%)
HIV-negative	9/103 (8.7%)	47/99 (47.5%)	-38.7% (-50.9 to -26.6%)

**SEROTONIN SYNDROME**

is a potentially fatal drug-induced condition caused by too much serotonin in synapses in the brain.

**ACTIVE DRUG SAFETY MONITORING (ADSM)**

is 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.

**RISK DIFFERENCE**

is the difference between the risk of an outcome in the exposed group and the unexposed group. In this case, it's the difference between the risk of an unfavorable outcome among participants randomized to receive BPaLM vs. the longer regimens in the control arm.

A negative risk difference means the exposure (BPaLM) decreased the risk of an unfavorable outcome. In this case the protective effect of BPaLM against unfavorable outcomes is less pronounced in PLHIV.



BPaL(M) and the other regimens the WHO recommends for the treatment of drug-resistant TB are the same for people living with or without HIV, irrespective of CD4 cell count. However, some TB and HIV drug interactions and overlapping toxicities require careful attention and management. For example, PLHIV on protease inhibitors or efavirenz will have to be monitored closely or switch HIV medications to initiate treatment for drug-resistant TB, given the interactions described in the previous section. PLHIV may also require adjustments to their HIV and/or drug-resistant TB treatment regimens because of overlapping toxicities (e.g., some HIV medications also cause peripheral neuropathy and myelosuppression).

### **What About Children and Young People?**

Adolescents and children 14 years and older were included in Nix-TB, ZeNix, and TB-PRACTECAL. Therefore, the WHO recommendation of the BPaL(M) regimen applies to people aged 14 years or older. Bedaquiline, linezolid, and moxifloxacin have been used to treat drug-resistant TB in children of all ages, but there are not yet data regarding the dose and safety of pretomanid in children.

TB Alliance is working with the U.S. National Institutes of Health (NIH)-funded International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Network on a pediatric **pharmacokinetic (PK)** and safety study of pretomanid (IMPAACT 2034; NCT05586230). The study is currently only enrolling female children because reduced fertility was observed in male rats and mice treated with pretomanid. A meta-analysis of human male hormone data from pretomanid studies that has already been released<sup>15,16</sup> and additional data expected soon from a reproductive safety study focused on sperm count (PaSEM; NCT04179500) will help broaden the ability of researchers to include male children in future studies of pretomanid-containing regimens.

Until pediatric PK and safety data are available for pretomanid, the WHO recommends that children below 14 years of age be treated with WHO-recommended regimens for drug-resistant TB that do not include pretomanid, e.g., the 9- to 11-month standardized all-oral regimen (see section III). Experts in the field have made the case for children to be treated with simplified, four- to five-drug regimens with duration tailored to disease severity.<sup>17</sup> Pediatric formulations of all second-line medicines except pretomanid are available through the Stop TB Partnership Global Drug Facility (GDF).<sup>18</sup>

### **What About Pregnant People?**

Pregnant people were excluded from Nix-TB, ZeNix, and TB-PRACTECAL. However, 16 participants became pregnant while participating in TB-PRACTECAL. Among the 14 of these participants with known pregnancy outcomes, there were 10 live births, three elective abortions, and one spontaneous abortion.<sup>19</sup> Four participants became pregnant while participating in Nix-TB and ZeNix with the following pregnancy outcomes: one healthy baby, one medical termination, one ectopic pregnancy, and one miscarriage.<sup>20</sup> Given these limited data, the WHO guidelines suggest that pregnant people be treated with the 9- to 11-month standardized all-oral regimen (see section III) until data on the use of pretomanid during pregnancy is available. Pregnant individuals may receive treatment with an individualized regimen, the composition

**PHARMACOKINETICS (PK)** is the study of how the body interacts with a drug. Understanding how the drug is absorbed, metabolized, and eliminated informs overall drug exposure and appropriate dosing.

of which is informed by a mix of animal and human data, expert opinion/ experience, and risk-benefit analysis.<sup>21</sup> Data from small cohorts of pregnant individuals from South Africa treated with bedaquiline- and delamanid-containing regimens suggest that these drugs can be safely used during pregnancy.<sup>22,23</sup>

Animal data do not suggest **teratogenicity** or embryo fetal effects with the use of pretomanid during pregnancy,<sup>24</sup> but data in humans are still required. PRISM-TB, a study to evaluate a **stratified medicine approach** to the BPaL(M) regimen sponsored by the USAID-funded SMART4TB Project, will allow people who become pregnant during the study to decide whether to continue treatment with BPaL(M).

### What About Other Six-Month Regimens?

Two USAID-funded studies, BEAT Tuberculosis (NCT04062201), conducted in South Africa, and BEAT TB India (CTRI/2019/01/017310) evaluated a six-month regimen composed of bedaquiline, delamanid, and linezolid with levofloxacin or clofazimine (depending on fluoroquinolone resistance) for RR-/MDR- and pre-XDR-TB. The study in India was a single-arm study that found the six-month bedaquiline- and delamanid-containing regimen safe and efficacious, with a favorable treatment outcome observed among 86% of participants six months after the end of treatment.<sup>25</sup> The study in South Africa was a randomized controlled trial that found the efficacy and safety of the six-month bedaquiline- and delamanid-containing regimen comparable to the 9- to 11-month regimen, with a favorable treatment outcome observed among 87% of participants six months to one year after the end of treatment.<sup>26</sup> At the time of writing, the WHO had not yet convened a Guideline Development Group (GDG) to review these and other data for six-month regimens<sup>27</sup> (or data for nine-month regimens with the potential to define a new role for delamanid as part of shorter treatment regimens for drug-resistant TB).<sup>28,29</sup>

Importantly, BEAT Tuberculosis in South Africa included pregnant people and children as young as six years old, populations currently ineligible to access the benefits of the six-month BPaL(M) regimen. Depending on the outcome of the WHO GDG review of these data, pregnant people and children may finally be able to benefit from access to a six-month, four-drug regimen, even while data gaps on the use of pretomanid in these populations are still being filled.

## III. WORLD HEALTH ORGANIZATION TREATMENT GUIDELINES

The 2022 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 by recommending a six-month regimen composed of bedaquiline, pretomanid, and linezolid with or without moxifloxacin. For the treatment of drug-resistant TB, the WHO guidelines now include six-month and nine- to 11-month standardized regimens and 18- to 20-month individualized regimens (constructed according to Table 2). All regimens are bedaquiline based, with the other drugs and duration dependent on the extent of drug resistance and other factors. The WHO Guidelines prioritize the use of the six-month treatment regimen over longer regimens.

**TERATOGENICITY** is the ability to cause defects in a developing fetus.

**STRATIFIED MEDICINE** refers to an approach that tailors treatment duration (and/or regimen composition) based on risk factors that are associated with poor treatment outcomes.

Factors to be considered in selecting a regimen include the individual's **drug susceptibility profile**, previous exposure to key second-line TB medicines, type and severity of TB disease, age, and the presence of other coinfections, comorbidities, or conditions.

**6BPaL(M): six months of bedaquiline, pretomanid, and linezolid given with moxifloxacin for RR-/MDR-TB and without moxifloxacin for pre-XDR-TB.** Treatment extension to a total of nine months can be considered if sputum cultures are still positive between months four and six of treatment. If doses are missed, treatment duration can also be extended to make up for the number of missed doses (up to one month). There are two recommended dosing options for bedaquiline: (1) 400 mg daily for two weeks followed by 200 mg three times per week; and (2) 200 mg daily for eight weeks followed by 100 mg daily. Pretomanid and moxifloxacin are administered at 200 and 400 mg daily, respectively. The recommended dose of linezolid in the BPaL(M) regimen is 600 mg daily. Dose modifications are allowed for linezolid – but only after the first nine weeks of treatment – to manage toxicity and adverse events such as peripheral neuropathy, optic neuritis, and myelosuppression. There are currently no data on the substitution of levofloxacin for moxifloxacin.

**9-11 Bdq Lzd hdH Lfx Cfz Z E: nine to 11 months of levofloxacin, clofazimine, pyrazinamide, and ethambutol; supplemented by bedaquiline for the first six months, linezolid for the first two months, and high-dose isoniazid for the first four to six months for RR-/MDR-TB.** If sputum cultures are still positive at the end of the fourth month of treatment, the overall treatment duration can be extended to a total of 11 months and the use of bedaquiline can be extended from six to nine months. Bedaquiline is administered at 200 mg daily for eight weeks followed by 100 mg daily. Linezolid is given at 600 mg daily. Dose modifications are not allowed for linezolid in this regimen, as it is only given for the first two months of treatment. Either levofloxacin or moxifloxacin can be used in the 9- to 11-month regimen, with levofloxacin associated with a lower risk of QT interval prolongation. This regimen is only recommended for RR-/MDR-TB. If fluoroquinolone resistance is detected, patients should be switched to a longer individualized regimen.

**18- to 20-month individualized regimen: at least four medicines selected according to an individual's drug-susceptibility profile and the grouping of medicines in Table 2.** For example, all three group A agents and at least one group B agent. Or two group A agents and both group B agents. Group C agents are added when the regimen cannot otherwise be composed with agents from groups A and B alone. The agents in group C are ranked by the relative balance of benefit and harm, so medicine selection should be made from top to bottom. The 18- to 20-month regimen should only be used when the shorter regimens cannot. This includes situations where there is a lack of response to the shorter regimens, or where there is additional resistance to fluoroquinolones and other group A medicines (i.e. XDR-TB), intolerance to key medicines used in shorter regimens, severe disease, including certain types of extrapulmonary TB, or other complications needing an individualized approach.

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

**TABLE 2. GROUPINGS OF MEDICINES RECOMMENDED FOR USE IN INDIVIDUALIZED REGIMENS**

<b>Group</b> [steps for composing an individualized regimen]	<b>Medicine(s)</b>	<b>Abbreviation(s)</b>
<b>Group A</b> [include all three medicines]	levofloxacin or moxifloxacin	Lfx M, Mfx
	bedaquiline	B, Bdq
	linezolid	L, Lzd
<b>Group B</b> [add one or both medicines]	clofazimine	Cfz
	cycloserine or terizidone	Cs Trd
<b>Group C</b> [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

**Pretomanid-sparing shorter regimens for children**

Until pediatric data on pretomanid become available, the WHO recommends that children with drug-resistant TB be treated with the 9- to 11-month standardized or 18- to 20-month individualized regimens. Individualized regimens of shorter duration are also an option for children given that they often present with **paucibacillary TB**. The *WHO Consolidated Guidelines on Tuberculosis: Module 5: Management of Tuberculosis in Children and Adolescents* suggests that treatment duration depend on the extent and severity of disease, as well as the response to treatment, and that shortening the total duration of treatment to less than 18 months may be considered in children without extensive disease.<sup>30</sup>

**PAUCIBACILLARY TB** is TB caused by a smaller number of TB bacteria.

**THE IMPORTANCE OF DRUG SUSCEPTIBILITY TESTING**

**Drug susceptibility testing (DST)** is used to detect resistance to TB drugs and inform regimen selection. Being able to test for drug susceptibility is crucial to informing regimen selection, improving treatment outcomes, preventing further drug resistance, and guarding against unnecessary potential risks of treatment-related toxicities.

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

Depending on the drug of interest, DST can be performed using **genotypic tests** or phenotypic **culture-based tests**. Rapid genotypic tests (also referred to as molecular tests) are available for detecting rifampicin, isoniazid, and fluoroquinolone resistance. Rapid molecular tests are generally placed in decentralized labs near the point of care and can turn around results in less than two hours. **High-throughput molecular testing platforms** are also available to test for rifampicin and isoniazid resistance in centralized labs, but they often rely on sample referral and transport systems that can significantly delay the turnaround time for results. Additional DST for drugs not covered by rapid or high-throughput molecular testing is then typically performed via genotypic **line probe assay (LPA)** or culture to determine further drug resistance and whether any corresponding regimen adjustments are necessary. In 2023, the WHO also endorsed the use of **targeted next-generation sequencing (tNGS) technologies**.<sup>31</sup> However, due to limited data regarding resistance-conferring mutations for new and repurposed drugs (e.g., bedaquiline, linezolid, and pretomanid)<sup>32</sup> needed to inform molecular targets, culture is still required to rule out resistance to these drugs.

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*.

#### IV. PRICE AND ACCESS INFORMATION

The regimens recommended by the WHO for the treatment of drug-resistant TB require a combination of newer (e.g., bedaquiline, pretomanid, delamanid) and **repurposed** (e.g., moxifloxacin, linezolid) medicines. In contrast to the situation several years ago, there are now multiple suppliers of the newer TB drugs (see Table 3). As a result, the price of newer TB medicines and the cost of treatment regimens have improved dramatically. If purchased through the Stop TB Partnership **Global Drug Facility (GDF)**, regimen costs are as follows:<sup>33</sup>

- \$458 for the six-month BPaL(M) regimen;
- \$409 for the standardized 9- to 11-month regimen; and
- \$645 – \$1500 (or more) for the 18- to 20-month individualized regimen, depending on duration and drug composition.

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

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

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

**LINE PROBE ASSAYS (LPAS)** are 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).

**TARGETED NEXT-GENERATION SEQUENCING TECHNOLOGIES** are rapid genotypic tests capable of comprehensive resistance testing for up to 15 TB drugs, including rifampicin, isoniazid, moxifloxacin, bedaquiline, and linezolid. This technology is considered most appropriate for use in centralized labs.

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

**THE GLOBAL DRUG FACILITY (GDF)** is a one-stop bundled procurement and supply mechanism that provides a package of services that combine strategic procurement of TB products and coordination of market activities, with technical assistance and capacity-building for TB programs.

**TABLE 3. THE ACCESS LANDSCAPE FOR QUALITY-ASSURED NEWER TB MEDICINES IN LMICS**

Drug	Suppliers	Price	Geographic Scope
<b>Bedaquiline</b>	Johnson & Johnson	\$130*	Global (including Pharmstandard via GDF; minus Pharmstandard via other procurement mechanisms)
	Pharmstandard	\$1,650 <sup>†</sup>	Russia, Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Kazakhstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan
	Lupin	\$194*	All LMICs <sup>‡</sup>
	Macleods	\$190*	All LMICs <sup>‡</sup>
<b>Pretomanid</b>	Viartis	\$240*	214 countries (70 exclusive) – see medspal.org
	Macleods	\$238*	143 countries – see medspal.org
	Lupin	Unknown	140 countries – see medspal.org
	Hongqi	Unknown	China
	Remington	Unknown	Pakistan
<b>Delamanid</b>	Otsuka	\$1,190	89 LMICs
	R-Pharm	\$1,488 <sup>†</sup>	Russia, Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Kazakhstan, Moldova, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
	Viartis	\$1,242	Global (minus Otsuka + R-Pharm)

Geographic scope refers to territories where patent holders retained or licensed rights to commercialize products, not territories where patents are granted, pending, or filed.  
**Price is listed in USD per six-month course and only for low- and middle-income countries.**  
 \*This is the price available through the GDF. Countries procuring directly from companies may pay a different price.  
<sup>†</sup>This is the price available to Russia.  
<sup>‡</sup>In September 2023, Johnson & Johnson publicly committed to not enforcing its secondary patents on bedaquiline in the treatment of drug-resistant tuberculosis (DR-TB) in 134 low- and middle-income countries.

Academics from the University of Liverpool estimated that the newer TB drugs could be produced by generics for \$8-\$17/month for bedaquiline, \$11-\$34/month for pretomanid, and \$5-\$16/month for delamanid.<sup>34</sup> These estimates were made assuming annual volumes of 108,000 courses of treatment. These prices have not been achieved for any medicine yet. The lowest prices listed in Table 3 are \$22/month for bedaquiline, \$40/month for pretomanid, and \$200/month for delamanid. For comparison, repurposed, off-patent medicines, for which there are additional uses outside of TB and multiple suppliers, linezolid and moxifloxacin each cost ~\$5/month.

While the gap between the prices of bedaquiline and pretomanid and what academics estimated they could be produced for by generics has narrowed recently, there is still room for improvement.

Pretomanid first entered the market at \$364 per six-month course of treatment. A volume guarantee later lowered the price by 34% to \$240. Pretomanid’s development was sponsored by a non-profit product development partnership, TB Alliance, and funded entirely by public and philanthropic donors. Though there are multiple generic suppliers with licenses from the TB Alliance to manufacture and commercialize pretomanid, the price of the drug remains high, constituting more than half (56%) of the cost of the BPAL(M) regimen. This is expected to change as the other generic suppliers listed in Table 3 enter the market and as volumes increase as more countries implement BPAL(M).

The price of delamanid has always been egregiously high – even after Otsuka granted voluntary licenses to generics companies in 2017. This is in part because generics companies were reliant on Otsuka for the **active pharmaceutical ingredient (API)** required to make delamanid. The delamanid technology transfer between Otsuka and Viatris is finally expected to result in the market entry of a completely in-house generic version of delamanid by the end of 2023. A price reduction is expected, but details of the agreement between Otsuka and Viatris are not public, leaving concerns that there might be restrictions on Viatris even beyond the expiration of Otsuka’s primary patent on delamanid (October 2023) and tempering expectations for a major price reduction. A shift in the role of delamanid in treatment regimens for drug-resistant TB (and a resulting increase in demand and volumes) and the market entry of additional generics will be critical to achieving a more substantial price reduction for delamanid. Increased volumes and competitive drug tenders will be tools important to reducing the prices of pretomanid and delamanid.

There are several other factors beyond **intellectual property barriers** and price that impact access to treatment for drug-resistant TB. These include whether WHO guideline updates have been translated at the country level into national guidelines; whether new drugs and regimens have been incorporated into national strategic plans and funding proposals; and whether there are any local regulatory barriers, especially for new generic formulations that may be **quality assured** through the Global Fund Expert Review Panel or the WHO Prequalification Program but have not yet been registered with national regulatory authorities. Other important issues that are primarily impacting communities in countries shifting to national procurement with domestic resources include drug stockouts due to failed national tenders and/or the inability of local suppliers to deliver when needed, and the use of non-adapted products (e.g., single tablets when fixed-dose combinations should be available, modified adult formulations when pediatric formulations should be available, etc.) or medicines of unknown quality. Additionally, access to TB screening, diagnosis, and DST is critically important, as without it people are not diagnosed and linked to treatment or put on the right treatment regimen. For a comprehensive overview of TB medicines access issues, refer to the Médecins Sans Frontières *DR-TB Drugs Under the Microscope* report.<sup>35</sup>

#### **ACTIVE PHARMACEUTICAL INGREDIENT (API)**

is the component of a medication that produces its effect(s).

#### **INTELLECTUAL**

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

#### **QUALITY-ASSURED**

drugs have been evaluated and approved by a stringent regulatory authority (e.g., the Food and Drug Administration, the European Medicines Agency) or the WHO prequalification program, or the Global Fund Expert Review Panel (ERP).

## **COMPREHENSIVE AND PATIENT-CENTERED PACKAGES OF CARE**

The inclusion of treatment support as part and parcel of shorter regimen rollout is vital. Treatment support packages should include a variety of needs-based measures and interventions to support adherence, retention in care, and favorable treatment outcomes. Support packages and interventions should address the aspects of TB treatment that are most challenging for affected individuals and their families, such as stigma and discrimination, economic and housing insecurity, and nutrition. Support should be provided through differentiated models of care on offer in-person in the community or virtually with the assistance of digital health technologies.

Digital adherence technologies (DATs) like smart pill boxes or video-supported treatment are designed to monitor and support treatment adherence.<sup>36</sup> Data collected through DATs can be leveraged to identify people who may need additional support to complete treatment. DATs should be one part of a multifaceted patient-centered support package provided by the National TB program. Other facets might include community awareness campaigns, especially to address stigma;<sup>37</sup> mental health and psychosocial support; community health care worker- and/or peer-led treatment literacy and adherence counselling and support; timely, effective treatment of side effects; patient involvement in decision-making about their care; and financial assistance through provision of food, housing, transport stipends, and/or social insurance schemes.<sup>38</sup>

## V. TAKE ACTION

There are several actions activists can take to overcome the barriers discussed in the previous sections and to promote equitable access to shorter treatment regimens for TB.

- 1. Share the trial results with your communities.** Break down the information included in this document for sharing at the community level. Translate this information into local languages and facilitate its dissemination among your civil society and community networks. Identify opportunities to raise awareness about the shorter regimens at community forums. Note the questions from members of your networks that are not answered in this document and share these with TAG (so we can help get you the information you need).
- 2. Advocate for national guidelines updates and implementation.** Contact your national TB program to sensitize them to the results of TB-PRACTECAL and ZeNix-TB and the corresponding updates to WHO treatment guidelines. Ask when your national program plans to update its guidelines and make six-month regimens available. Push your national program to be ambitious with its timeline and approach. Anticipate barriers to national and subnational guidelines change and implementation and identify allies and strategies for overcoming them.
- 3. Push research funders to fill data gaps so that everyone can benefit from access to shorter treatment regimens.** For example, additional research is necessary to determine the dose and safety of pretomanid for children and pregnant people.
- 4. Call for lower prices of medicines and diagnostics.** Newer TB drugs are driving the cost of treatment regimens, and molecular diagnostics tests remain too expensive for implementation at the scale required to end TB. Activists should hold drug and diagnostics sponsors and manufacturers, as well as the donors and projects that supported the introduction and scale-up of these products, and country governments accountable for taking actions necessary to expand and enable global equitable access to essential TB medicines and diagnostic tools.
- 5. Advocate for country governments and finance mechanisms to allocate additional resources** to scale up TB screening and diagnosis and to support national rollout of the six-month regimen within a comprehensive package of care. Additional financial resources will be necessary to support access to rapid molecular drug susceptibility testing, and to fund guidelines updates, trainings, and other activities associated with introducing new interventions to TB programs.





## THE TIME FOR \$5 CAMPAIGN

Time for \$5 is a campaign calling on the diagnostics company Cepheid and its parent corporation Danaher to reduce the price of the GeneXpert test cartridge to \$5. According to an independent cost of goods sold (COGS) analysis, it costs Cepheid less than \$5 to produce one GeneXpert test.<sup>39</sup> But Cepheid charged low- and middle-income countries \$10 per test for TB and resistance to rifampicin for a decade (a markup of at least 100%) and \$15 per test for resistance to isoniazid and fluoroquinolones (a markup of at least 200%). This

price gouging made it too expensive to implement rapid molecular testing at the scale required to reach all people in need. Open letters sent to Cepheid and other campaign materials, including an analysis of public investments in the development of GeneXpert molecular diagnostic technologies, are available here: <https://www.msfaaccess.org/time-for-5>.

Following intense pressure from TB-affected communities and civil society, the price of Cepheid's test for TB and rifampicin resistance was recently reduced from \$10 to \$8.<sup>40</sup> This reduction is a significant step forward that will help increase access. However, this 20% price reduction falls short of community and civil society demands for \$5 TB tests and doesn't apply to Cepheid's test for resistance to isoniazid and fluoroquinolones (needed to scale up access to the shorter regimens for drug-sensitive and drug-resistant TB) or assays for other diseases. Lowering the price of TB tests and breaking Cepheid's decade-long monopoly on the TB diagnostics market through competition and the introduction of new rapid molecular tests will be critical to expanding access to TB testing and diagnosis at the scale necessary to end TB.

## VI. OVERCOMING OPPOSITION TO IMPLEMENTING SHORTER REGIMENS

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

**EXCUSE: We don't have access to rapid fluoroquinolone resistance testing.**

**RESPONSE:** Access to rapid drug-susceptibility testing for fluoroquinolones should not delay treatment initiation with BPaLM. You can start with BPaLM, and when results of the test are available, they can be used to determine whether moxifloxacin should be retained or dropped from the regimen. It is easier from a logistics, supply, and patient/provider perspective to switch from BPaLM to BPaL in the presence of fluoroquinolone resistance than it would be to switch from the 9- to 11-month regimen to BPaL or an 18 to 20-month individualized regimen.

**EXCUSE: The medicines in the six-month regimen are too expensive.**

**RESPONSE:** The new shorter regimens cost less than older, longer regimens. What we can't afford are the costs of treating drug-resistant TB with suboptimal regimens. 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 will support manufacturing efficiencies that can lead to further price reductions. Governments can negotiate with drug companies directly and have other tools at their disposal that they can use to provide access to essential medicines that are priced out of reach or otherwise inaccessible (e.g., compulsory licensing), especially considering the amount of public investment that has gone into the development and introduction of these drugs and regimens.

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**EXCUSE: Linezolid and the BPaL(M) regimen are too toxic/are not tolerable.**

**RESPONSE:** The overall toxicity of the BPaL(M) regimen is far less than what is observed with other WHO-recommended regimens for drug-resistant TB. Lowering the dose of linezolid from 1,200 mg to 600 mg daily has greatly improved the tolerability of the BPaL(M) regimen without reducing its efficacy. In ZeNix, among participants who received linezolid dosed at 600 mg daily for six months, the treatment success rate was 90%. Additionally, in ZeNix when linezolid was administered at 600 mg daily, just 13% of participants required dose adjustments or interruptions (compared with 85% of participants in the Nix-TB study exposed to 1,200 mg linezolid daily). By design in TB-PRACTECAL the linezolid dose was reduced from 600 mg to 300 mg after 16 weeks of treatment; only 1.1% of participants required linezolid treatment interruptions with this approach.<sup>41</sup> Clinicians have reported linezolid side effects as being manageable using appropriate tests for monitoring for adverse drug reactions. Pretomanid has been associated with liver toxicity when studied in combination with pyrazinamide for drug-sensitive TB.<sup>42</sup> But pyrazinamide isn't a part of the BPaL(M) regimen so this isn't a concern. In TB-PRACTECAL, the rate of liver toxicity reported for the BPaLM regimen was no different from that of the regimens in the control arm (4% vs 11%). Results from male hormone and semen studies to assess in humans the pretomanid reproductive toxicity reported in rats are expected in the coming months.

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**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. WHO guidelines are meant to apply globally.

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**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 right to health and to benefit from scientific progress. The best way to protect new drugs is to optimize the regimens within which they are given and ensure that patients have uninterrupted access to quality assured medicines and 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.

**WANT MORE INFORMATION?**

Write to [communications@treatmentactiongroup.org](mailto:communications@treatmentactiongroup.org)

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