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

March 2025

AN ACTIVIST'S GUIDE TO SHORTER TREATMENT

FOR DRUG-RESISTANT TUBERCULOSIS

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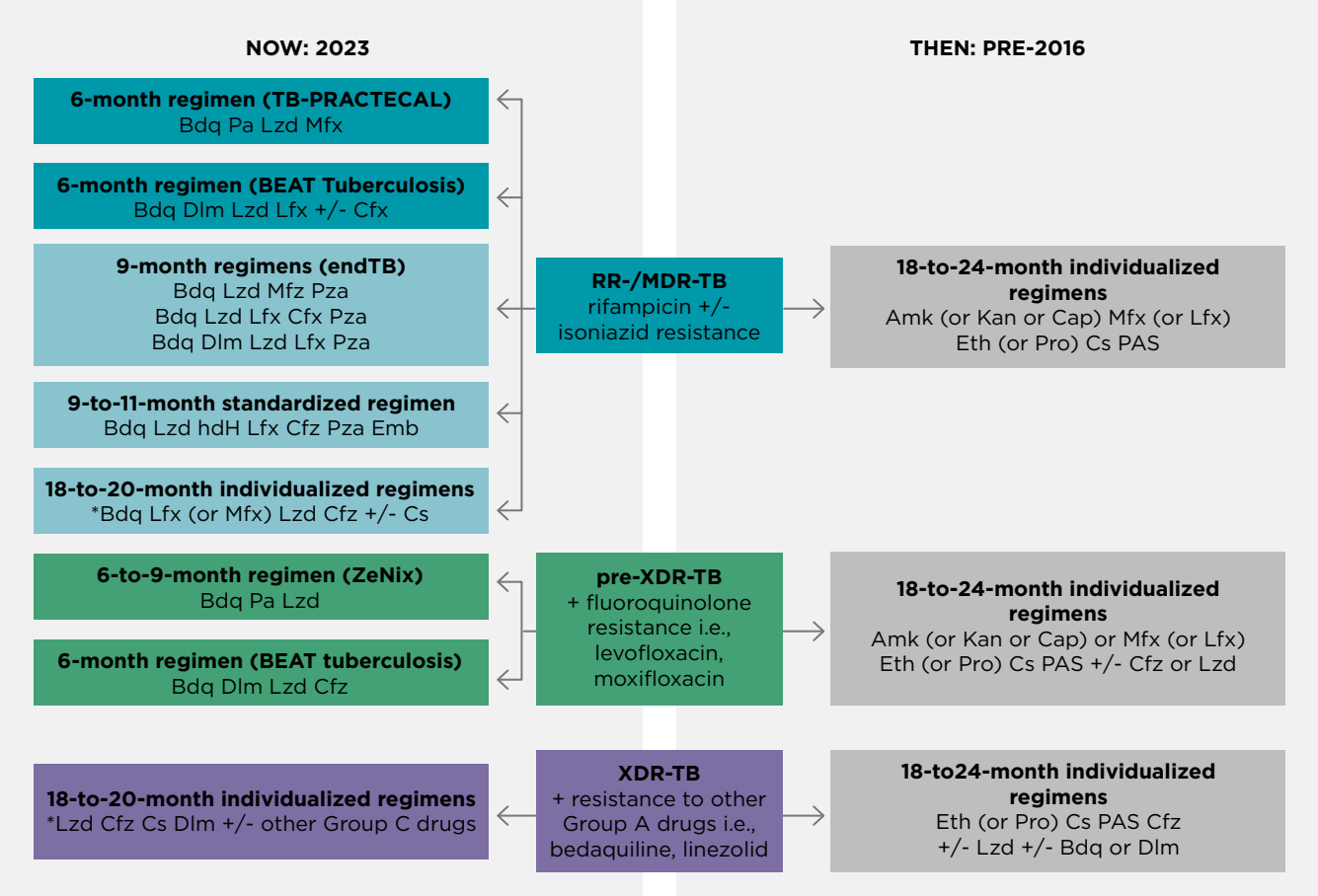
I. BACKGROUND AND INTRODUCTION

In 2025, 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 (DR-TB).[1] The updated recommendations expand the six- and nine-month regimens recommended for treating rifampicin- or multidrug-resistant TB (RR/MDR-TB), with or without additional resistance to fluoroquinolones (pre-XDR-TB). This Activist's Guide reviews the clinical trials behind the WHO recommendations — **TB-PRACTECAL, ZeNix, BEAT Tuberculosis, and endTB** — and provides information to support advocacy for access to the best available treatment regimens.

The WHO first introduced guidelines supporting the use of a standardized 9-to-11-month 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, replacing the injectable agent with bedaquiline and supporting the use of linezolid in place of ethionamide based on programmatic experience from South Africa.[3] In the 2022 iteration of its guidelines, the WHO endorsed 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) — remains the preferred treatment option for drug-resistant TB. The WHO's latest recommendation of pretomanid-sparing regimens, however, enables children, younger adolescents, pregnant women and persons, and other populations that are otherwise excluded from access to the six-month BPaL(M) regimen to benefit from shorter treatment regimens for drug-resistant TB.

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

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

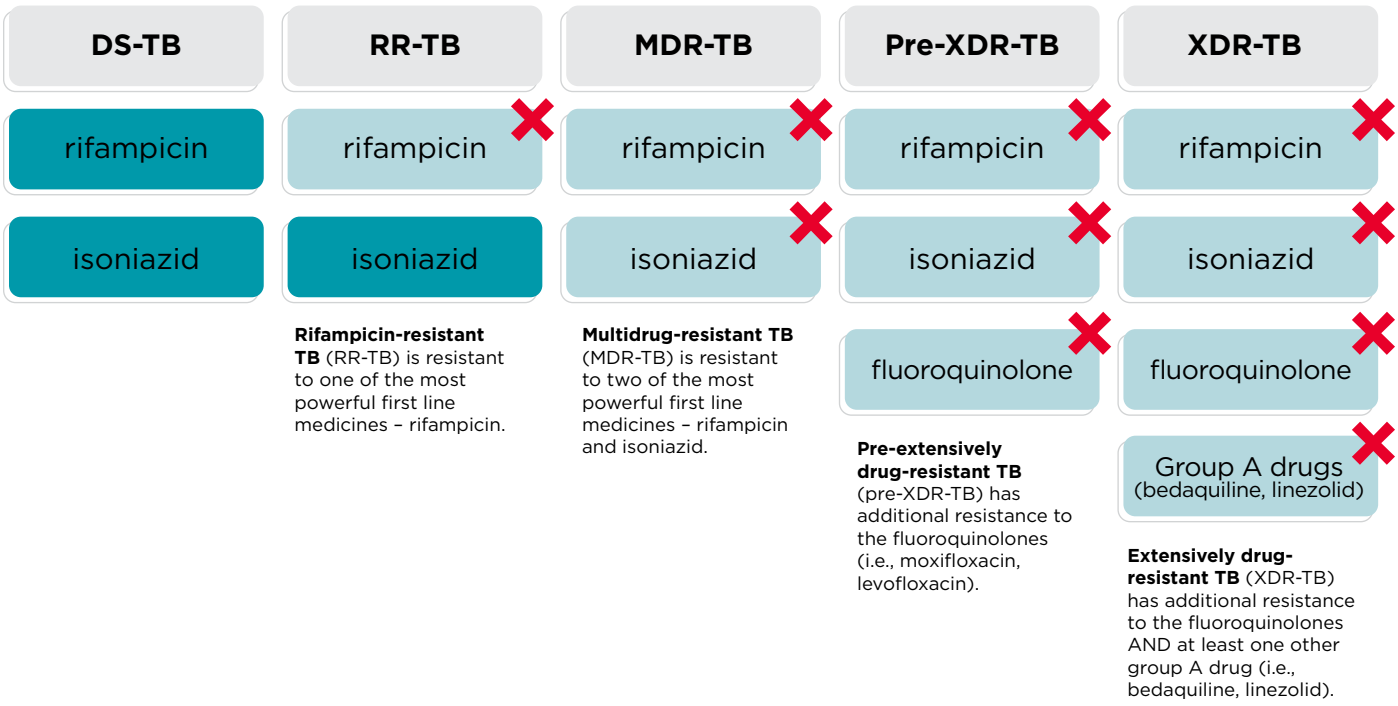
DEFINING DRUG-RESISTANT TUBERCULOSIS

Each of the medicines used to treat TB has a **mechanism of action** for disabling or killing TB bacteria. Certain bacterial changes (i.e., "mutations") can prevent a medicine from carrying out its intended 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% of these people are diagnosed and put on treatment. Global rates of treatment success among those diagnosed and treated range from 60% to 70%.[4] 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



*Many people are diagnosed with RR-TB because this is the only drug susceptibility their strain of TB is tested for. This is why WHO recommendations often group RR-TB and MDR-TB together — the treatment is the same.

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 for logistical reasons. The six-month BPaLM regimen was shown to be **non-inferior** to (no worse than) and **superior** to (better than) the 9-to-20-month 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

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.

fewer (16/138, 11.7%) than those observed among people randomized to receive the longer standard-of-care regimens (56/137, 40.9%).[5] The difference in unfavorable outcomes was driven by early treatment discontinuations in the control arm, primarily due to **adverse events**.[6] 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 3 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.

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.

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.[7] 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 at the originally prescribed dose of 1,200 mg daily. A total of 62 participants (57%) experienced adverse events of Grade 3 or higher during treatment. **Peripheral neuropathy** occurred in 88 participants (81%) and **myelosuppression** in 52 participants (48%).

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).

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/mm3 (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.[8] 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.

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.

BEAT Tuberculosis (NCT04062201)

The BEAT Tuberculosis study was a randomized controlled trial that evaluated the efficacy and safety of a six-month regimen composed of bedaquiline, delamanid, and linezolid given with levofloxacin and/or clofazimine depending on fluoroquinolone resistance (6BDLz + Lx or C) to people with RR-/MDR- and pre-XDR-TB. The study enrolled 402 participants from two sites in South Africa. Participants were randomized

to receive either the BEAT Tuberculosis regimen or the 9-to-11-month standard of care* for RR-/MDR-TB or a longer individualized regimen if fluoroquinolone resistance was detected among participants randomized to receive the standard of care. The study population included people living with HIV (50%).[9] Few participants (16%) had fluoroquinolone resistance, limiting the study's ability to draw firm conclusions about how the six-month BEAT Tuberculosis regimen performs against pre-XDR-TB. Another study focused explicitly on pre-XDR-TB, called endTB-Q, tested the same regimen (BDLzC) given for six or nine months and found that while the BDLzC regimen was safer and more tolerable, it did not perform as well as the longer regimens that made up the control arm.[10] The difference in performance was especially apparent in participants with more extensive disease. Data from endTB-Q have not yet been reviewed by the WHO.

The effectiveness and safety of the BEAT Tuberculosis regimen was comparable to the 9-to-11-month or longer standard of care, with a favorable treatment outcome observed among 86.1% of participants one year after the end of treatment (compared to 86% among participants receiving the standard of care).[11,12] Seventy-four (37%) and 63 (31.2%) participants in BEAT Tuberculosis and the control arm, respectively, experienced severe adverse events while on treatment, and 10 participants in each arm died.[13] A similar single-arm study conducted in India 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.[14]

Importantly, the BEAT Tuberculosis study conducted 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. These data enable pregnant people and children 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 (more on this later).

endTB (NCT02754765)

endTB was a randomized controlled trial designed to determine how to optimally combine new and **repurposed drugs** to shorten treatment for RR-/MDR-TB. The endTB trial compared five investigational nine-month bedaquiline- and/or delamanid-containing regimens to a control arm consisting mostly of participants that received treatment with 18-to-20-month regimens (the standard of care in most countries when the trial opened to enrollment in 2017). The study enrolled 754 participants from 12 sites in seven countries: Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa. The study population included adolescents down to 15 years old (3.6%), people living with HIV irrespective of CD4 cell count (14.1%), and people with cavitary disease (56.9%).

Three of the investigational regimens demonstrated noninferiority to the control arm — 9BLzMZ, 9BLzLxCZ, and 9BDLzLxZ (nine-month regimens composed of bedaquiline, linezolid, pyrazinamide, plus moxifloxacin or levofloxacin, with or without delamanid or clofazimine).[15] The three non-inferior endTB regimens performed comparably with favorable treatment outcomes ranging from 85% to 90% (compared to 81% for the control arm).[16] The three non-inferior endTB regimens were also comparable to the control regimen in terms of safety, with the number of participants experiencing any serious adverse events ranging from 14.3% to 15.8% (compared to 16.7% in the control) and any adverse events of Grade 3 or higher ranging from 54.8% to 61.4% (compared to 62.7% in the control). Hepatotoxicity was more common among participants receiving the endTB regimens compared to the control, ranging from 6.3% to 18.3% compared to 7.1% — this is likely attributable to the inclusion of pyrazinamide in the endTB regimens.

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

*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.

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, some of which may be asymptomatic. Several noteworthy treatment-related side effects are associated with the BPaL(M), BEAT Tuberculosis, and endTB regimens. 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;
- **optic neuropathy:** damage to the nerve that transfers visual information from the eye to the brain, which can cause eye pain and vision changes; and
- **skin hyperpigmentation:** darkening and other changes to the skin (associated with the use of clofazimine).[17]

It's important for people with TB to recognize the signs and 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 side effects are typically manageable using monitoring tests at the time treatment is started and at regular intervals over the course of treatment. The monitoring tests 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, liver function tests).[18] These routine tests can usually detect early signs of side effects that are developing and alert health care providers to take action 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 or lower 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., clofazimine, methadone, antimalarials), extra vigilance and monitoring with ECG is necessary. When linezolid is given alongside other serotonergic drugs (e.g., selective serotonin reuptake inhibitors used to treat depression, antipsychotics), there should be close monitoring for **serotonin syndrome**.[19] 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) or other bedaquiline-containing regimens because ritonavir-boosted protease inhibitors (e.g., lopinavir/ritonavir) increase bedaquiline levels and efavirenz decreases bedaquiline and pretomanid levels.[20] Aside from bedaquiline, other TB drugs in the BEAT Tuberculosis and endTB regimens do not interact with antiretroviral medications. There are not yet data on how DR-TB medicines interact with newer antiretroviral medicines, including those delivered via long-acting injectable formulations (e.g., cabotegravir).

TB drug side effects can also be worsened by certain behaviors and underlying conditions or comorbidities. For example, alcohol use can increase the risk for hepatotoxicity and/or peripheral neuropathy. People with underlying liver disease are at an increased risk of hepatotoxicity. People with diabetes are at an increased risk of peripheral neuropathy and optic neuritis given that diabetes can also affect these organ systems.

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

Any side effects of TB treatment should be managed as part of TB care and reported to the National TB Program (NTP) or Pharmacovigilance (PV) Unit 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)**.

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.

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^3, 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%) participants without HIV.[21]

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%)

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.

In the BEAT Tuberculosis and endTB trials, 98 (49%) and 98 (14.1%) participants, respectively, were PLHIV. The median CD4 cell count was 168 (85-298.5) and 296 (118-497) cells/mm^3, respectively. In both trials, treatment and safety outcomes were similar among people living with and without HIV. In BEAT Tuberculosis 82.9% of PLHIV had a favorable treatment outcome with the six-month regimen compared with 89.7% of participants without HIV.[22] In endTB, favorable treatment outcomes ranged from 70.6% to 100% for PLHIV treated with the nine-month regimen compared with 78% to 89.1% of participants without HIV.[23]

The 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 switch their HIV medications to integrase inhibitors (preferably) or be monitored closely while on treatment for drug-resistant TB, given the interactions between these drugs and bedaquiline. 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?

The WHO recommendation of the BPaL(M) regimen only applies to people aged 14 years or older because there are not yet data regarding the dose and safety of pretomanid in children.

The BEAT Tuberculosis trial enrolled children as young as six years old and the endTB trial enrolled adolescents and children 14 years and older. Both regimens are expected to work as well in children as they do in adults, especially considering that children often present with **paucibacillary TB**. All medicines contained in the BEAT Tuberculosis and endTB regimens have been used to treat drug-resistant TB in children. As such, these regimens are recommended by the WHO for use in children of all ages. Pediatric formulations of all second-line medicines except pretomanid are available through the Stop TB Partnership **Global Drug Facility (GDF)**.[24]

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[25,26] and additional data from a reproductive safety study focused on sperm count (PaSEM; NCT04179500) suggest that pretomanid does not have negative effects on the reproductive function of male humans.[27] A multidose study will need to follow IMPAACT 2034 before children will be able to benefit from access to the six-month BPaL(M) regimen.

What About Pregnant Women/People?

Pregnancy was an exclusion criterion for the clinical trials that underpin the shorter regimens for drug-resistant TB, except for the BEAT Tuberculosis trial, which enrolled 10 pregnant women/people, 4 of whom were randomized to receive the six-month BEAT Tuberculosis regimen. All 10 pregnancies resulted in the delivery of healthy babies.[28] In the endTB trial, 8 of 10 participants who became pregnant while receiving treatment continued treatment. Among the seven of these participants with known pregnancy outcomes, there were two live births (including one set of pre-term twins), four elective abortions, and one spontaneous abortion.[29] Taken together with data available from small cohorts of pregnant individuals treated with bedaquiline- and delamanid-containing regimens,[30,31,32] and a mix of animal data, expert opinion/experience, and risk-benefit analysis,[33] the WHO suggests that these regimens can be safely used during pregnancy.

Data available on the use of pretomanid during pregnancy is more limited. In TB-PRACTECAL, 16 participants became pregnant while participating in the trial. Among the 14 of these participants with known pregnancy outcomes, there were 10 live births, 3 elective abortions, and 1 spontaneous abortion.[34,35] 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.[36] Animal data do not suggest **teratogenicity** or embryo fetal effects with the use of pretomanid during pregnancy,[37] but data in humans are still required.

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

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.

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.

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

What About People with Extrapulmonary TB?

People who have extrapulmonary forms of TB — that is, TB outside of the lungs — are generally not included in clinical trials like the ones described above. As such, we don't know how these regimens might work in people with extrapulmonary TB (EP-TB). People with EP-TB often have TB in places in their bodies that some drugs may not reach very well (for example, the spinal fluid or bones and joints). These forms of TB require 12 months of treatment even when drug sensitive. For these reasons, people with forms of TB outside the lungs are generally not eligible for these all-oral shorter regimens.

III. WORLD HEALTH ORGANIZATION TREATMENT GUIDELINES

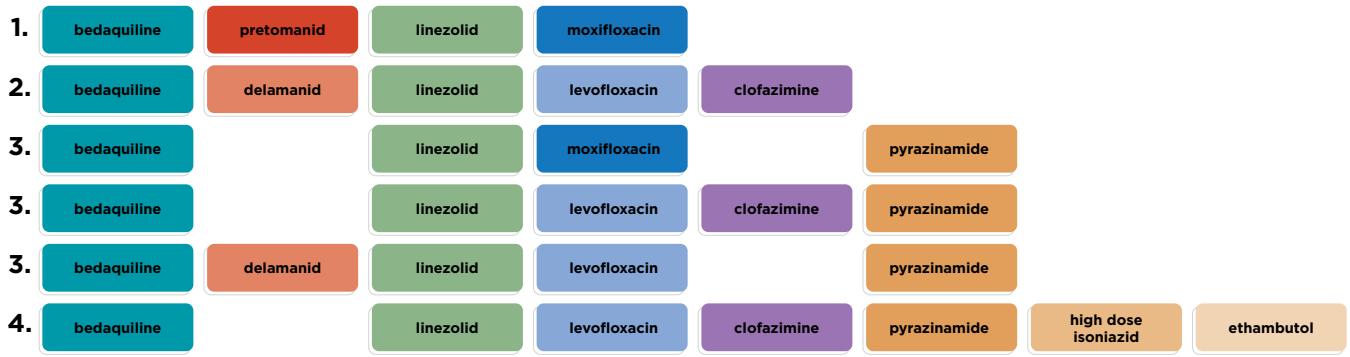
In August 2024, the WHO published *Rapid Communication: Key Updates to the Treatment of Drug-Resistant TB*.[38] The global standard of care for drug-resistant TB remains the six-month regimen composed of bedaquiline, pretomanid, and linezolid with or without moxifloxacin, BPaL(M), for adults and adolescents 14 years and older. In the rapid communication, however, the WHO also recommends the six-month BEAT Tuberculosis and nine-month endTB regimens for the treatment of drug-resistant TB, emphasizing their use to expand the shorter treatment options available to additional populations, namely children, adolescents, and pregnant women.

Similar to BPaL(M), the BEAT Tuberculosis regimen is indicated for the treatment of people with and without fluoroquinolone resistance. If fluoroquinolone resistance is detected, then the levofloxacin is stopped and clofazimine continued. If fluoroquinolone resistance is unknown, then both levofloxacin and clofazimine are continued. The endTB regimens, however, are only recommended for use in people in whom resistance to the fluoroquinolones has been ruled out. Though the regimens have never been directly compared, in the rapid communication, the WHO put the regimens in a ranked order considering duration, number of drugs, and cost. Among the three endTB regimens, the WHO recommends using BLzMZ over BLzLxCZ, and BLzLxCZ over BDLzLxZ. The WHO guidelines still include the 9-to-11-month standardized regimen and 18-to-20-month individualized regimens (constructed according to Table 2). The standardized regimen is ranked lowest among the regimens and is only recommended for people with fluoroquinolone-susceptible drug-resistant TB, and the longer individualized regimen is reserved for constructing salvage regimens for people with more complicated patterns of drug resistance (e.g., resistance to two or more group A drugs) and/or that are not doing well on treatment with the shorter regimens.

Factors to be considered in selecting a regimen include the individual's **drug-susceptibility profile**, previous exposure to key second-line TB medicines, type/site and severity of TB disease, age, pregnancy status, patient preference and treatment history, the presence of other coinfections, comorbidities, or conditions, and risk of adverse events.

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

FIGURE 3. SHORTER REGIMENS RECOMMENDED BY THE WHO



1. **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, or (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.

2. **6BDLz + Lx and/or C (the BEAT Tuberculosis regimen): six months of bedaquiline, delamanid, and linezolid given with levofloxacin for RR-/MDR-TB or clofazimine for pre-XDR-TB.** The regimen can be given with both levofloxacin and clofazimine if fluoroquinolone-resistance information is not available at the time of diagnosis. Treatment can be extended if sputum cultures are still positive at the end of the fourth month of treatment. In the BEAT Tuberculosis regimen, bedaquiline is given 400 mg daily for two weeks followed by 200 mg three times per week. Linezolid is given at 600 mg daily for the duration of treatment but can be temporarily stopped or permanently discontinued for adverse events.

3. **9BLzMZ, 9BLzLxCZ, 9BDLzLxZ (the endTB regimens in order): nine months of bedaquiline, linezolid, pyrazinamide given with moxifloxacin; or levofloxacin and clofazimine; or levofloxacin and delamanid.** Rapid DST should be performed to rule out fluoroquinolone resistance when starting one of these regimens. In the endTB regimens, bedaquiline is given 400 mg daily for two weeks followed by 200 mg three times per week and linezolid is given 600 mg daily for at least four months and, depending on tolerability, can then be reduced to 300 mg daily or three times per week.

4. **9-11 Bdq Lzd hdH Lfx Cfz Z E: 9 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 because 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.

5. **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 be used. 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.

TABLE 2. 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	Lfx M, Mfx
	bedaquiline	B, Bdq
	linezolid	L, 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

THE IMPORTANCE OF DRUG SUSCEPTIBILITY TESTING

Drug-susceptibility testing (DST) is used to detect resistance to TB drugs. Testing 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 and in development for bedaquiline.[39] 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 typically performed via genotypic **line probe assay (LPA)** or culture to determine further drug resistance and the necessity for any corresponding regimen adjustments. In 2023, the WHO also endorsed the use of **targeted next-generation sequencing (tNGS) technologies**.[40] However, due to limited data regarding resistance-conferring mutations for new and repurposed drugs (e.g., bedaquiline, linezolid, and pretomanid)[41] 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, levofloxacin, 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. There are also pediatric formulations available. If purchased through the GDF, regimen costs are as follows:[42]

- $357 – $382 for the six-month BPaL(M) regimen;
- $1,091 – $1,170 for the six-month BEAT Tuberculosis regimen;
- $224 – $1,767 for the nine-month endTB regimens;
- $309 for the standardized 9-to-11-month regimen; and
- $488 (or more) for the 18-to-20-month individualized regimen, depending on duration and drug composition.

Using pediatric formulations available through the GDF, the regimen costs are as follows:[43]

- $787 – $1,286 for the six-month BEAT Tuberculosis regimen;
- $447 – $2,087 for the nine-month endTB regimens;
- $627 – $900 for the standardized 9-to-11-month regimen; and
- $745 (or more) for longer individualized regimens, depending on weight, 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.

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

Drug	Suppliers	Price	Geographic Scope
Bedaquiline	Johnson & Johnson	$130*	Global (including Pharmstandard via GDF; minus Pharmstandard via other procurement mechanisms)
	Pharmstandard	$1,650†	Russia, Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Kazakhstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan
	Lupin	$90*	All LMICs‡
	Macleods	$90*	All LMICs‡
	MSN Labs India	Unknown	All LMICs‡
Pretomanid	Viatris	$224*	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
Delamanid	Otsuka	$1,190	Global minus 10 countries exclusive to Viatris$^{\Phi}$
	R-Pharm	$1,488†	Russia, Armenia, Azerbaijan, Belarus, Georgia, Kyrgyzstan, Kazakhstan, Moldova, Tajikistan, Turkmenistan, Ukraine, Uzbekistan
	Viatris	$800	Global minus 32 countries exclusive to Otsuka$^{\Phi}$

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.
†This is the price available to Russia.
‡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.
$^{\Phi}$The list of high TB burden countries exclusive to Otsuka includes Azerbaijan, Belarus, Kyrgyzstan, Moldova, Tajikistan, Ukraine, and Uzbekistan. South Africa is the only high TB burden country exclusive to Viatris.[44]

Academics from the University of Liverpool estimated that the newer TB drugs could be produced and sold by generics for $8 – $17 per month for bedaquiline, $11 – $34 per month for pretomanid, and $5 – $16 per month for delamanid.[45] These estimates were made assuming annual volumes of 108,000 courses of treatment. These target prices have only been achieved for bedaquiline, now $15 per month,[46] following a successful campaign to get Johnson & Johnson to commit to not enforcing its secondary patents, enabling market entry of multiple generics. For the other medicines, the lowest prices listed in Table 3 are $37 per month for pretomanid and $133 per 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 price of pretomanid and what academics estimated it could be produced for 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, and competitive tenders have since reduced the price to $224. 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 (58%) 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 enabled the market entry of a completely in-house generic version of delamanid, but the price remains relatively high. A price reduction is expected with the market entry of a second generic supplier in 2025. The recent shift in the role of delamanid in treatment regimens for drug-resistant TB (and a resulting increase in demand and volumes) will be critical to achieving a more substantial price reduction for delamanid. Increased volumes and competitive drug tenders will be important tools for reducing the price of pretomanid too.

ACTIVE PHARMACEUTICAL INGREDIENT (API) is the component of a medication that produces its effect(s).

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*.[47]

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 offered 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.[48] 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 NTP. Other facets might include community awareness campaigns, especially to address stigma;[49] mental health and psychosocial support; community health care worker- and/or peer-led treatment literacy and adherence counseling 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.[50]

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 including by developing interactive educational materials (e.g., videos, infographics) to explain the trial results, regimens, and side effects in accessible ways. Facilitate community dialogues to discuss the implications of the results and address concerns. Partner with local media to amplify these messages. 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 in-person and virtual 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 monitor implementation.** Contact your NTP to sensitize them to the results of the TB-PRACTECAL, ZeNix, BEAT Tuberculosis and endTB trials and the corresponding updates to WHO treatment guidelines. Ask when your national program plans to update its guidelines and make the new six- and nine-month regimens available. Push your national program to be ambitious with its timeline and approach. Anticipate barriers to efforts to change and implement national and subnational guidelines and identify allies and strategies for overcoming them. Monitor the implementation of updated guidelines and document any discrepancies between policy and practice, including any drug stock outs. Facilitate dialogues, roundtables, or workshops that bring together the NTP, health care providers, and other stakeholders to discuss implementation and to share best practices and other learnings, including from other countries or regions.

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. Activists should also track local TB drugs and diagnostics pricing to document any instances of price gouging and mobilize affected communities, TB survivors, and civil society organizations to pressure decision-makers and raise awareness about access barriers through media campaigns and public advocacy.

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 shorter regimens for drug-resistant TB 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. Evidence to support advocacy for additional resources can be collected via community-led monitoring systems that track national rollout of shorter TB treatment regimens, access challenges, and patient needs.

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.[51] 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.msfaccess.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.[52] This reduction is a significant step forward that will help increase access. The Global Fund estimated that the price reduction would enable the procurement of an additional 3.6 million Xpert TB tests per year (valued at US$32 million).[53] 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 fluroquinolones should not delay treatment initiation with BPaLM or the BEAT Tuberculosis regimens. You can start with BPaLM or BDLzLxC, and when results of the test are available, they can be used to determine whether moxifloxacin should be retained or dropped from the BPaLM regimen and whether levofloxacin or clofazimine should be dropped from the BEAT Tuberculosis regimen. It is easier from a logistics, supply, and patient/provider perspective to switch from BPaLM to BPaL or from BDLzLxC to BDLzC in the presence of fluoroquinolone resistance than it would be to switch from the 9-to-11-month regimen to BPaL, BDLzC, 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.

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.[54] 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.[55] But pyrazinamide is not a part of the BPaL(M) regimen, so this isn't a concern. In TB-PRACTECAL, the rate of liver toxicity reported for the BPaL(M) regimen was no different from that of the regimens in the control arm (4% vs 11%). Results from male hormone and semen studies of humans have allayed concerns about the pretomanid reproductive toxicity reported in rats.

EXCUSE: There are too many regimens recommended now. Why can't there be just one?

RESPONSE: The WHO recommends six different shorter regimens for the treatment of drug-resistant TB, which perform similarly but differ in terms of their duration, pill burden, frequency of clinic visits, monitoring tests, side effects, drug interactions, contraindications, and cost. Importantly, not every regimen is recommended for everyone, which is why having multiple regimens available is critically important. The decision about which treatment regimen to use should be a shared decision that considers the medical risks and benefits of the different regimens as well as the preferences and needs of the person undergoing treatment. It's important to maintain access to individualized longer regimens too because they are still used in situations in which there has been prior exposure to the drugs in or 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, or severe disease, including certain types of extrapulmonary TB.

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.

EXCUSE: New TB drugs must be "protected."

RESPONSE: Clinicians and programs should be more concerned with protecting the people with TB 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 people with TB 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.

EXCUSE: There were not very many children included in the studies, so it is better to use the older regimens.

RESPONSE: There may be more experience with the older regimens because they have been around and used for a longer period, but they never underwent any careful evaluation in pediatric populations. Well-controlled studies show that the six-to-nine-month regimens are not only as effective as the older, longer regimens but they are also safer. The newer drugs have fewer side effects than some of the older drugs, like the injectable agents that cause hearing loss and ethionamide, which causes nausea and vomiting. The newer drugs that make up the six-to-nine-month regimens have been studied in children, are available in pediatric formulations, are recommended by the WHO for use in children of all ages, and have been used to treat thousands of children already. It is not evidence-based or good practice to continue using the older regimens in children.

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, 2025 update. Geneva: World Health Organization; 2025. https://iris.who.int/handle/10665/380799
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. WHO consolidated guidelines on tuberculosis. Module 4.
4. World Health Organization. Global tuberculosis report 2022. Geneva: World Health Organization; 2022. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022.
5. Bern-Thomas Nyang'wa. TB-PRACTECAL final efficacy and safety results. Presented at: 27th Annual Conference of the Union–North America Region. 2023 February 22-25; Vancouver, BC, Canada. https://bclung.ca/sites/default/files/4.%20220_Nyang%27wa.pdf.
6. Nyang'wa BT, Berry C, Kazounis E, et al. A 24-week, all-oral regimen for rifampin-resistant tuberculosis. N Engl J Med. 2022 Dec 22;387:2331–2343. doi: 10.1056/NEJMoa2117166.
7. Conradie F, Diacon A, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. 2020 March 5. N Engl J Med; 382:893–902. doi: 10.1056/NEJMoa1901814
8. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis. N Engl J Med. 2022 Sep 1;387:810–823. doi: 10.1056/NEJMoa2119430.
9. Conradie, Francesca (University of Witwatersrand, Johannesburg, South Africa). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2025 February 10.
10. Guglielmetti L, Patil S, Panda S, et al. endTB-Q: Interim results of a randomised controlled trial testing a shorter treatment strategy for pre-XDR TB [LB02-1213-13]. Oral abstract presented at: Union Conference during the Union-CDC late-breaker. 2024 November 13; Bali, Indonesia. https://unionconf2024.abstractserver.com/programme/#/details/presentations/2023.
11. Conradie F, Phillips P, Badet T, et al. High rate of successful outcomes treating RR-TB with a delamanid-bedaquiline regimen in BEAT Tuberculosis: an interim analysis. Presented at: Union World Conference on Lung Health during LBTB The Union/CDC late-breaker session on TB. 2022 November 11; virtual. https://theunion.floq.live/event/worldconf2022/dailyprogramme?objectClass=timeslot&objectId=62fb512decb44417ab3bf64b&type=detail.
12. Conradie, Francesca (University of Witwatersrand, Johannesburg, South Africa). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2025 February 10.
13. Conradie, Francesca (University of Witwatersrand, Johannesburg, South Africa). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2025 February 10.
14. Padmapriyadarsini C, Vohra V, Bhatnagar A, et al. Bedaquiline, delamanid, linezolid and clofazimine for treatment of pre-extensively drug-resistant tuberculosis. Clin Infect Dis. 2022 Jun 29:ciac528. doi: 10.1093/cid/ciac528.
15. Mitnick C, Khan U, Guglielmetti L, et al. SP01 Innovation to guide practice in MDR/RR-TB treatment: efficacy and safety results of the endTB trial. Presented at: Union World Conference on Lung Health. 2023 November 15; Paris, France. https://theunion.floq.live/event/worldconf2023/symposia?objectClass=timeslot&objectId=64ef5819e0400915b209e22f&type=detail.
16. Guglielmetti L, Khan U, Velásquez G, et al. Nine-month, all-oral regimens for rifampicin-resistant tuberculosis. medRxiv preprint. 2024 January 29. doi: 10.1101/2024.01.29.24301679.
17. World Health Organization. WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. https://www.who.int/publications/i/item/9789240065116.
18. Ibid.
19. Ibid.
20. University of Liverpool. HIV Drug Interactions [Internet]. https://www.hiv-druginteractions.org/checker. [Cited 2023 August 25].
21. Conradie F, Bagdasaryan TR, Borisov S, et al. Bedaquiline-pretomanid-linezolid regimens for drug-resistant tuberculosis.
22. Phillips, Patrick (University of California, San Francisco, CA). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2025 February 11.
23. Guglielmetti L, Khan U, Velásquez GE, et al. Oral regimens for rifampin-resistant, fluoroquinolone-susceptible tuberculosis [Supplementary Appendix]. N Engl J Med. 2025 Jan 30;392(5):468-482. doi: 10.1056/NEJMoa2400327.
24. Stop TB Partnership Global Drug Facility. Medicines catalogue. Geneva: Stop TB Partnership Global Drug Facility; 2023 September. https://www.stoptb.org/global-drug-facility-gdf/gdf-product-catalog.
25. Burke A, Alffenaar J, Denholm J. Evidence of safety for pretomanid and male reproductive health. Int J Tuberc Lung Dis. 2022;26(6):473–474.
26. Boekelheide K, Olugbosi M, Nedelman J, et al. Male reproductive hormones in patients treated with pretomanid. Int J Tuberc Lung Dis. 2022;26(6):558–565.
27. Howell, P. Results of studies on pretomanid: side effects on male fertility and PK/PD in female children. Presented during: WHO BPaLM Accelerator Call. 2024 May 28.
28. Conradie, Francesca (University of Witwatersrand, Johannesburg, South Africa). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2025 February 10.
29. Mitnick, Carole (Harvard Medical School, Boston, MA). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2025 February 11.
30. 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. 2021 Apr 1;72(7): 1158–1168. https://doi.org/10.1093/cid/ciaa189.
31. Acquah R, Mohr-Holland E, Daniels J, et al. Outcomes of children born to pregnant women with drug-resistant tuberculosis treated with novel drugs in Khayelitsha, South Africa: a report of five patients. Pediatr Infect Dis J. 2021 May 1;40(5):e191–e192. doi: 10.1097/INF.0000000000003069.
32. Farrukh IL, Lachenal N, Adenov MM, et al. Pregnancy and birth outcomes in patients with multidrug-resistant tuberculosis treated with regimens that include new and repurposed drugs. Clin Infect Dis. 2024 Jan 15;78(1):144–148. doi: https://doi.org/10.1093/cid/ciad445.

33. Maugans C, Loveday M, Hlangu S, et al. Best practices for the care of pregnant people living with TB. Int J Tuberc Lung Dis. 2023 May 1;27(5):357–366. doi: 10.5588/ijtld.23.0031.
34. Ahmed S, Lachenal N, Moodliar R, et al. Pregnancy outcomes for patients treated with new and repurposed drugs for drug-resistant tuberculosis (OA 10-268-08). Presented at: Union World Conference on Lung Health. 2022 November 11; virtual.
35. Crocker-Buque T, Lachenal N, Narasimooloo C, et al. Pregnancy outcomes in multidrug-resistant tuberculosis in TB-PRACTECAL. Clin Infect Dis 2024 Aug 15;79(2): 569–570. doi: https://doi.org/10.1093/cid/ciad767.
36. Stephanie Seidel (TB Alliance, New York, NY). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2023 September 14.
37. U.S. Food and Drug Administration. Pretomanid label. 2019 August. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212862s000lbl.pdf.
38. World Health Organization. Key updates to the treatment of drug-resistant tuberculosis. Rapid Communication, June 2024. Geneva: World Health Organization; 2024. https://www.who.int/publications/i/item/B09123.
39. Dharmapuri Vachaspathi, T. 2024 TB diagnostics pipeline report. New York: Treatment Action Group; 2024 November. https://www.treatmentactiongroup.org/wp-content/uploads/2025/02/2024_pipeline_tb_diagnostics_final.pdf.
40. World Health Organization. Use of targeted next-generation sequencing to detect drug-resistant tuberculosis. Rapid Communication. Geneva: World Health Organization; 2023 July. https://www.who.int/publications/i/item/9789240076372.
41. World Health Organization. Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance. Geneva: World Health Organization; 2021 June. https://www.who.int/publications/i/item/9789240028173.
42. Stop TB Partnership. Plan an order. GDF estimated prices for select drug-resistant TB treatment regimens. https://www.stoptb.org/buyers/plan-order. [Cited 2025 February 6].
43. Stop TB Partnership. Plan an order. [Cited 2025 February 28].
44. Stop TB Partnership. Results of the Global Drug Facility's 2024 tender for delamanid: Frequently Asked Questions (FAQ). https://www.stoptb.org/faq-results-global-drug-facilitys-2024-tender-delamanid. [Cited 2025 February 6].
45. Gotham D, Fortunak J, Pozniak A, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother. 2017 Apr 1;72(4):1243–1252. doi: 10.1093/jac/dkw522.
46. Stop TB Partnership. Bedaquiline is accessible through GDF at new updated pricing. https://www.stoptb.org/what-we-do/facilitate-access-tb-drugs-diagnostics/global-drug-facility-gdf/new-tools/bedaquiline. [Cited 2025 February 7].
47. Médecins Sans Frontières Access Campaign. DR-TB drugs under the microscope. https://msfaccess.org/drtb-drugs-under-microscope.
48. TB Digital Adherence. Using digital technologies to support TB treatment. https://tbdigitaladherence.org/.
49. KNCV TB. TB stigma and discrimination. https://www.kncvtbc.org/en/tb-stigma/.
50. U.S. Agency for International Development. Delivering comprehensive supportive care to people with drug-resistant tuberculosis. 2019 February. https://pdf.usaid.gov/pdf_docs/PA00TNZK.pdf.
51. Médecins Sans Frontières Access Campaign. Technical brief: Time for $5: GeneXpert diagnostic tests. 2019 December. https://msfaccess.org/time-for-5-brief.
52. Global Fund. Global Fund, Stop TB Partnership and USAID announce new collaboration with Danaher to reduce price and increase access to Cepheid's TB test [Press Release]. 2023 September 19. https://www.theglobalfund.org/en/news/2023/2023-09-19-global-fund-stop-tb-partnership-and-usaid-announce-new-collaboration-with-danaher-to-reduce-price-and-increase-access-to-cepheids-tb-test/.
53. Médecins Sans Frontières Access Campaign, Partners In Health, Treatment Action Group. Technical brief: hidden costs: GeneXpert tests and Danaher's delayed audit. 2024 September. https://www.msfaccess.org/hidden-costs-genexpert-tests-and-danahers-delayed-audit.
54. Bern-Thomas Nyang'wa (Médecins Sans Frontières, Amsterdam, NL). Personal communication with: Lindsay McKenna (Treatment Action Group, New York, NY). 2023 October 23.
55. Eristavi M, Variava E, Haraka F, et al. SimpliciTB results and hepatic safety of pretomanid regimens +/1 Pyrazinamide [OA-109]. Presented at: 2023 Conference on Retroviruses and Opportunistic Infections during Oral Abstracts Session-02 TB and Hepatitis. 2023 February 20; Seattle, Washington.

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