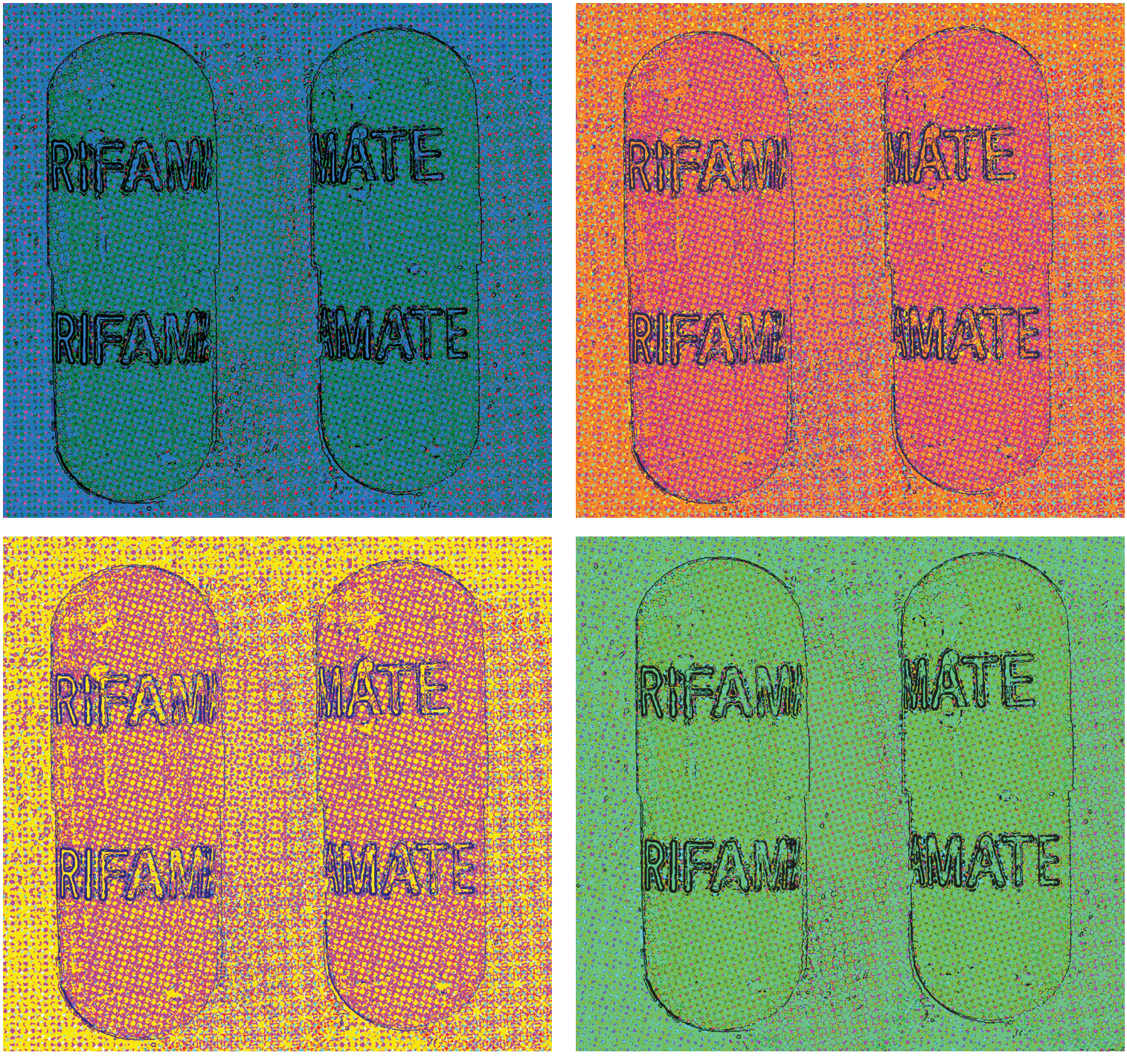
AN ACTIVIST'S GUIDE TO
Tuberculosis Drugs



2016 UPDATE

TAG
Treatment Action Group

This guide was updated by Lindsay McKenna.
An earlier edition, published in 2014, was written by
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ABOUT TAG

Treatment Action Group (TAG) is an independent AIDS research and policy think-tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information. We are science-based treatment activists working to expand and accelerate vital research and effective community engagement with research and policy institutions. TAG catalyzes open collective action on the part of all affected communities, scientists, and policy makers to end AIDS.

ABOUT THE TB/HIV PROJECT

Treatment Action Group's TB/HIV Project works to improve research, programs, and policy for people living with TB and HIV.

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AN ACTIVIST'S GUIDE TO TUBERCULOSIS DRUGS

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Introduction

Tuberculosis (TB) has been curable for decades, but a rise in the number of people living with drug-resistant TB (DR-TB) and TB/HIV coinfection challenges global targets of zero TB deaths, new infections, suffering, and stigma. Although TB and the people it affects have changed over the years, for the most part the drugs used against it have not. In 2012, bedaquiline, used to treat DR-TB, became the first new TB drug from a new class to be approved by the U.S. Food and Drug Administration (FDA) in over 40 years; its accelerated approval was followed in 2014 by the European Medicines Agency's (EMA's) conditional approval of bedaquiline and another new drug, delamanid, for the treatment of some forms of DR-TB.

All treatment options for TB disease must be used in combination. While knowledge on how to best use the new drugs is incomplete, and only two percent of those who could benefit from them have access, several ongoing studies may identify optimal combinations that could improve outcomes and allow for treatment shortening. Issues beyond knowledge gaps also impede effective treatment: lack of country registrations and program guidance, patent restrictions, pricing issues, medication quality concerns, inadequate or inappropriate formulations, and poor supply management limit access to lifesaving drugs.

Since *An Activist's Guide to Tuberculosis Drugs* was first published in 2014, updated guidelines, new findings, and other factors have shifted the research and access priorities for several TB drugs. Still, more research is needed to ensure that TB treatment becomes shorter, simpler, less toxic, and more tolerable, and affordable. Activists can contribute to the development and uptake of improved TB treatment by calling attention to research and access priorities. This guide provides a brief summary of safety and efficacy data for those drugs currently in use for TB (some of which have been approved for other diseases but are used off-label for TB), and suggests advocacy points for activists. For a comprehensive overview of drug patent and pricing information, refer to Médecins Sans Frontières' report, *DR-TB Drugs Under the Microscope* (complete citation listed under "Sources"). For a comprehensive overview of ongoing TB research and development work, refer to Treatment Action Group's annual *Pipeline Report* (complete citation listed under "Sources").

KEY DEFINITIONS AND ACRONYMS

Approved:	approved by a stringent regulatory authority for use against TB
Accelerated or conditional approval:	allows a drug to enter the market based on phase II data (surrogate endpoints), but requires the sponsor to conduct and submit data from a phase III trial (clinical endpoints) within a specified period of time in order to maintain their drug's approval
DR-TB:	drug-resistant TB, or TB resistant to at least one TB drug
DS-TB:	drug-sensitive TB
EML/ EMLc:	World Health Organization (WHO) model list of essential medicines (separate lists for adults and children)[1]—influences individual country essential medicines lists, which determine the drugs that country programs purchase
GDF:	The Global Drug Facility[2] is a global centralized procurement mechanism that offers quality-assured TB drugs at low prices
LTBI:	latent TB infection
MDR-TB:	multidrug-resistant TB, or TB resistant to isoniazid and rifampin, the two most powerful TB drugs
Off-label:	use of a drug for an indication other than the one for which it was approved
Quality Assurance (QA):	All activities and responsibilities required to ensure that the medicine that reaches the patient is safe, effective, and acceptable. A medication is deemed quality assured when the manufacturer has been approved by a stringent regulatory authority (i.e., the FDA or EMA) or by the World Health Organization's Prequalification of Medicines Program. Some manufacturers obtain temporary approval from the GDF/Global Fund Technical Review Panel. All drugs procured through the GDF are quality assured
RR-TB:	rifampin-resistant TB
TB:	tuberculosis
XDR-TB:	extensively drug-resistant TB, or MDR-TB also resistant to at least one second-line injectable drug and one fluoroquinolone

1. The current EMLs for adults and children are available at http://www.who.int/medicines/publications/essentialmedicines/en.

2. The GDF online product catalogue is available at http://www.stoptb.org/gdf/drugsupply/pc2.asp.

WHO GROUPINGS

WHO groupings refer to the way the World Health Organization categorizes existing TB drugs. The WHO classifies TB drugs into groups based on drug efficacy, potency, class, and frequency of use against TB. Regimens are constructed from these groups according to whether the strain of bacteria is DS-TB, RR/MDR-TB, or XDR-TB (see Constructing a Regimen, figures 1, 2, and 3).

First-line agents:	These drugs are used in the initial treatment of DS-TB.
Group A, fluoroquinolones:	These drugs are broad-spectrum antibiotics, considered to be the most important component of the WHO-recommended standard and shortened regimens for DR-TB, and under evaluation as a component of other regimens for simplifying and shortening TB treatment.
Group B, second-line injectable agents:	These drugs are delivered by injection and contribute to the WHO-recommended standard and shortened regimens for DR-TB, but could be avoided if effective all-oral regimens were developed and made available.
Group C, other core second-line agents:	At least two drugs from this group are necessary to build the standard WHO-recommended five-drug core regimen for DR-TB and this group contains drugs included in the WHO-recommended shortened regimen.
Group D, add-on agents:	These drugs may be used to further strengthen the standard WHO-recommended five-drug core regimen for DR-TB, to substitute in situations of drug toxicity or intolerance, or when, due to resistance or access issues, a five-drug regimen cannot be constructed using drugs from groups A, B, and/or C.

How to Use This Guide

For convenience of reference, drugs are listed in alphabetical order. See “Drugs by Class” on page 32. A glossary is provided at the end of the text for further explanations of scientific terminology included in the adverse effects and TB/HIV drug interactions categories. When evaluating treatment options for pregnant women, please consider the risk benefit ratio of using each drug and available options: while many drugs have limited evidence to guide their use in this population, leaving the mother’s TB untreated can cause considerable harm to both mother and fetus.

Each drug is listed as follows:

Drug Name (Drug Abbreviation[s])

WHO Grouping | Drug Class | Indication | Regulatory Status

Constructing a Regimen

Figure 1. Standard "short-course" regimen for drug-sensitive TB

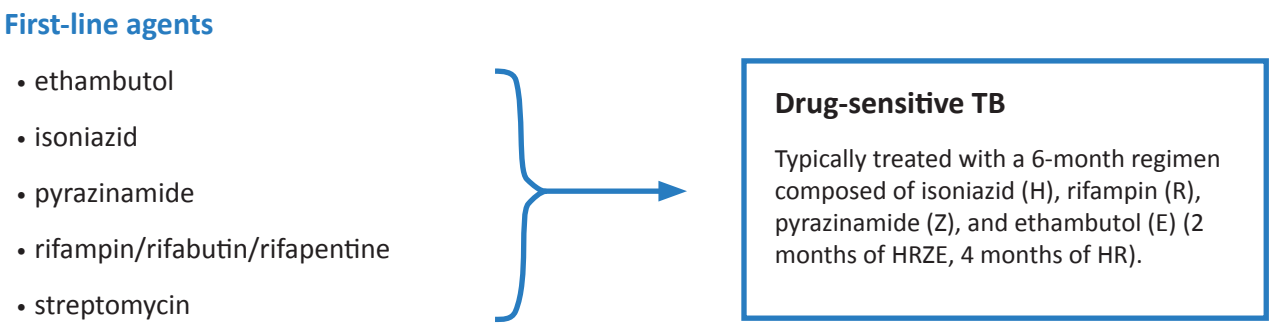
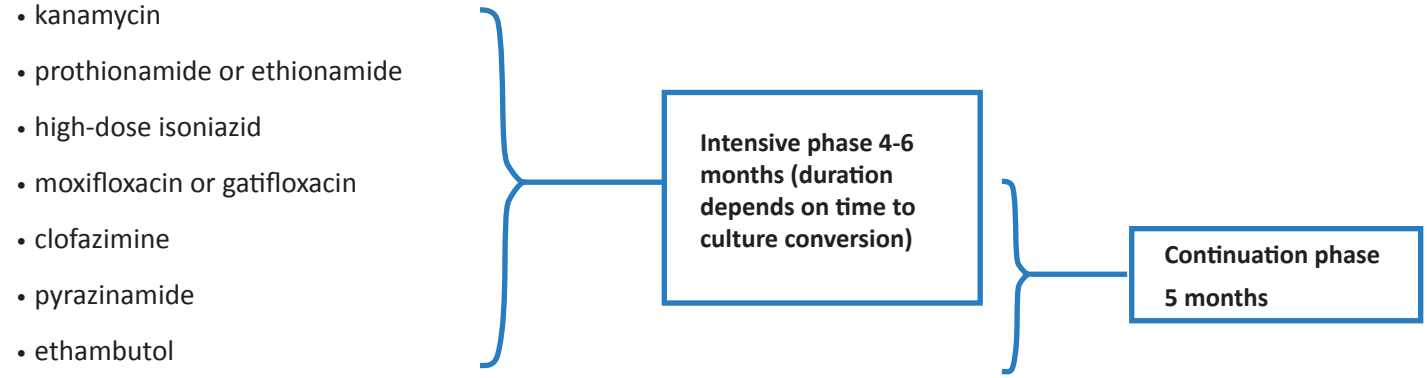


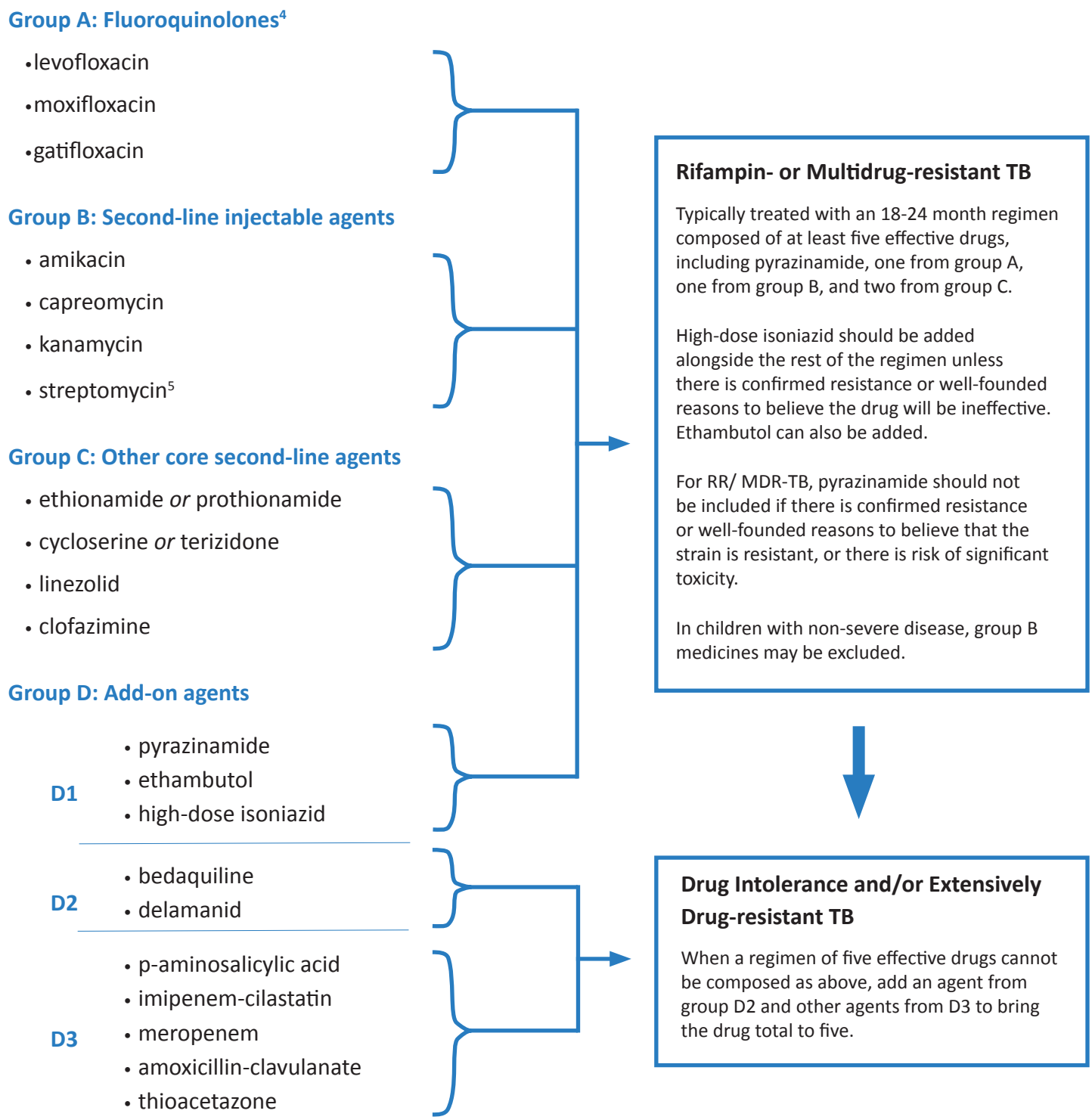
Figure 2. Shortened regimen for some forms of drug-resistant TB

In patients with rifampin-resistant or multidrug-resistant TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shortened regimen of 9-12 months may be used instead of the standard 18-24 month DR-TB regimen, according to a 2016 conditional recommendation by the WHO.[3]



3. The 2016 update to the WHO treatment guidelines for drug-resistant tuberculosis is available at http://www.who.int/tb/MDRTBguidelines2016.pdf.

Figure 3. Standard regimen(s) for drug-resistant TB



4. Drugs are shown in order of preference.
5. Streptomycin is not usually considered a group B drug, but it can be used to treat multidrug-resistant TB if no other injectable agent in this group is available; resistance to streptomycin does not qualify for extensively drug-resistant TB diagnosis.

Amikacin (AMK, Am)

Group B | Aminoglycoside | DR-TB | Used Off-Label

Injectables like amikacin, given with a fluoroquinolone and pyrazinamide, form the backbone of the standard WHO-recommended five-drug core regimen for DR-TB. Because aminoglycosides cannot be absorbed by the body when taken orally, they must be administered by injection, which is uncomfortable for patients and burdensome for health care workers, and could be avoided if all-oral regimens become a reality. Given the potential for harm– including hearing loss– associated with injectable agents to outweigh their benefits, they may be excluded from regimens given to children with non-severe disease. Generic sources of quality-assured amikacin are available, making it a relatively inexpensive drug within its class.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Hearing disturbances and loss; dizziness; reversible kidney damage; electrolyte abnormalities	**TB:** other aminoglycosides and capreomycin: increased risk of kidney toxicity **HIV:** tenofovir: increased risk of kidney toxicity	Pediatric formulation available; use with caution in newborns and premature infants (risk of kidney damage) May cause fetal hearing loss and kidney damage during pregnancy (other aminoglycosides cause hearing loss); secreted in human milk in trace amounts, but not absorbed orally (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Amoxicillin/Clavulanate (AMC, Amx/Clv)

Group D3 | Penicillin | DR-TB | Used Off-Label

Amoxicillin/clavulanate is an antibiotic that is used as a last resort for DR-TB, as it has not been validated for efficacy or safety in treating TB. Though it does not have anti-TB activity of its own, clavulanic acid (currently only available in combination with amoxicillin), is important when using carbapenems like imipenem or meropenem because it aids their anti-TB activity. It is unclear how amoxicillin/clavulanate interacts with TB or HIV medications. Generic sources are available, making it a relatively inexpensive drug.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; skin allergies	**TB:** unknown **HIV:** unknown	Pediatric formulations available, but not through the GDF; may not be safe for long-term use in children No known risk during pregnancy; secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children; listed as an antibacterial **GDF:** Yes, only for adult formulation

Bedaquiline (BDQ, B, J)

Group D2 | Diarylquinoline | DR-TB | Accelerated approval for DR-TB

Bedaquiline was granted accelerated approval for the treatment of DR-TB by the FDA in late 2012, making it the first new TB drug from a new class of drugs to be approved for TB in over 40 years. Bedaquiline has since been conditionally approved by the EMA and registered in nine of 27 high MDR-TB burden countries, including Russia, India, South Africa, Philippines, Peru, South Korea, Turkmenistan, Armenia, and Uzbekistan, and filed for registration in several more. After significant delays, Janssen's pediatric study, its phase III trial, and a study to evaluate the safety of co-administering bedaquiline and delamanid each opened to enrollment in 2016. However, many research and access gaps remain. To fill these gaps, activists must:

- encourage ministries of health and country programs to incorporate bedaquiline into treatment programs;
- urge Janssen to continue to file for approval in other countries;
- call for Janssen to expand the eligibility criteria for accessing bedaquiline through the GDF to include all countries;
- urge Janssen to lower the price of bedaquiline for all low- and middle-income countries when the donation program ends in 2019;
- if pricing barriers remain, press Janssen to voluntarily license the drug to generic drug manufacturers, or urge governments to exercise compulsory licensing to allow the manufacturing of more affordable generic versions; and
- call for additional research to better understand how bedaquiline interacts with HIV medications, and to determine bedaquiline's effects in people who use drugs or alcohol, and in people being treated for hepatitis B or C.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
QT prolongation; hyperuricemia; phospholipidosis; elevated liver enzymes; nausea; joint pain; headache; chest pain; coughing up blood	**TB:** rifampin, rifabutin, and rifapentine: increased concentration of bedaquiline; clofazimine, delamanid,* and fluoroquinolones: increased QT prolongation HIV: ketoconazole and protease inhibitors, e.g., lopinavir/ritonavir: increased concentration of bedaquiline; non-nucleoside reverse transcriptase inhibitors, e.g., efavirenz: decreased concentration of bedaquiline	Dispersible tablet developed; clinical trial in children underway Limited data on risk during pregnancy and breastfeeding	EML: Yes, for adults GDF: Yes, only for adult formulation

* Not yet known; AIDS Clinical Trials Group (ACTG) study to evaluate the safety of co-administered delamanid and bedaquiline underway.

Capreomycin (CAP, Cm)

Group B | Polypeptide | DR-TB | Approved for TB

Capreomycin is a second-line drug that, given with a fluoroquinolone and pyrazinamide, forms the backbone of the standard WHO-recommended five-drug core regimen for DR-TB. Like the other group B drugs, capreomycin cannot be absorbed by the body when taken orally, and as such requires burdensome and painful daily injections, which could be avoided with all-oral regimens. Just like with amikacin, this agent may be excluded from regimens given to children with non-severe disease. Even with five quality-assured sources of capreomycin, cost remains a significant barrier

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Hearing disturbances and loss; dizziness; reversible kidney damage (which can lead to nausea and vomiting); eosinophilia; electrolyte abnormalities	**TB:** aminoglycosides: increased risk of kidney toxicity **HIV:** tenofovir: increased risk of kidney toxicity	Pediatric formulations available May cause fetal hearing loss; no risk information for breastfeeding	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Clarithromycin (CLR)

No longer recommended | Macrolide | DR-TB | Used Off-Label

Given a lack of evidence of effectiveness against TB, clarithromycin and other macrolides are no longer included among medicines recommended by the WHO for the treatment of DR-TB.

Clofazimine (CFZ, CLF)

Group C | Riminophenazine | DR-TB | Used Off-Label

Clofazimine is an anti-leprosy drug that has cross-resistance with bedaquiline. While clofazimine has been recommended for use in patients with DR-TB and is a component of the WHO-recommended shortened regimen for DR-TB, it has not been approved for the treatment of TB. However, ongoing or planned studies will formally evaluate clofazimine's efficacy, safety, optimal dose, and role in treatment shortening. Given clofazimine's potential to produce QT prolongation and skin discoloration, another riminophenazine with better activity and fewer side effects would be ideal. Novartis, the only source of quality-assured clofazimine, has hindered access to clofazimine for researchers and programs in the past, but is now planning to formally study the drug for TB. Quality-assured generic manufacturers of clofazimine are urgently needed, as is registration of the drug for a TB indication as soon as sufficient data are available. Activists should:

- call for Novartis to ensure a stable and affordable supply of clofazimine for use in DR-TB treatment and/or for alternative manufacturers to enter the market with quality-assured generic versions;
- call for Novartis to complete the research necessary to establish the efficacy and safety of clofazimine for TB and to register the drug for a TB indication, or make clofazimine available to others interested in doing this work; and
- advocate for research to determine how clofazimine interacts with HIV medications, and to understand clofazimine's effects in pediatric populations.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; discoloration of the skin, eyes, and body fluids; abdominal pain; QT prolongation; elevated liver enzymes; elevated blood sugar; fever; headache; photosensitivity; depression	**TB:** bedaquiline, delamanid, fluoroquinolones: increased risk of QT prolongation; rifampin: in patients with leprosy, clofazimine has been shown to decrease the rate at which the body absorbs rifampin **HIV:** protease inhibitors: increased concentration of protease inhibitors and risk of QT prolongation; efavirenz, ketoconazole: increased risk of QT prolongation; etravirine: increased concentration of etravirine	No pediatric formulations available Contraindicated during pregnancy; secreted in human milk; risk of skin discoloration in breastfeeding infants	**EML**: Yes, for adults and children; listed as anti-leprosy drug **GDF**: Yes

Cycloserine (Cs)

Group C | D-alanine Analogue | DR-TB | Approved for TB

Cycloserine is a second-line drug used for DR-TB. However, its well-documented and significant adverse effects, including psychosis, make it unpopular with patients and clinicians alike. Data are lacking on how the body processes cycloserine, how it interacts with HIV medications, and its effects in children; however, given the known tolerability issues, it is not an ideal drug for further research. Nevertheless, cycloserine is still used in TB treatment because of the paucity of other treatment options and cycloserine's gastrointestinal acceptability. Recent growth in the number of quality-assured sources of the active pharmaceutical ingredient and finished product have improved supply stability and lowered the cost of cycloserine-containing regimens.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Neurological and psychiatric disturbances; seizures (risk exacerbated by alcohol use); irritability; headaches; skin allergies (ranging in severity from rash to Stevens–Johnson syndrome, a severe allergic skin reaction); vision disturbances (rare); peripheral neuropathy	**TB:** prothionamide, ethionamide, isoniazid: increased risk of neurological disturbances **HIV:** efavirenz: increased risk of Stevens–Johnson syndrome and psychiatric problems; nevirapine: increased risk of Stevens–Johnson syndrome; didanosine (ddI), stavudine (d4T): increased risk of peripheral neuropathy	No pediatric formulations available; mini-capsule under development No known risk during pregnancy, but recommended only when no alternatives exist; secreted in human milk (breastfeeding not recommended)	**EML:** Yes, for adults and children **GDF:** Yes

Delamanid (DLM, D)

Group D2 | Nitroimidazole| DR-TB | Conditionally approved for DR-TB

Delamanid is a novel drug that was approved by the EMA in early 2014 for the treatment of DR-TB. Delamanid's sponsor, Otsuka, has completed investigations in adolescents and children down to six years old, and WHO guidelines have been extended to recommend delamanid's use in this population. Otsuka is currently investigating delamanid's use in younger children. Otsuka's phase III trial results are expected in 2018, and studies to optimize the combination of delamanid with other new and existing TB drugs and to investigate its potential for the prevention of DR-TB are planned or underway. However, delamanid remains widely inaccessible to patients under program conditions; uptake is much lower than that of bedaquiline despite having a broader application for use per WHO guidance. While delamanid is available to Global Fund-eligible countries through the GDF, delamanid is only registered in European Union countries, Hong Kong, Japan, and South Korea, limiting access. Advocates should:

- demand that Otsuka rapidly file for registration in all high DR-TB burden countries and where it has conducted clinical trials;
- urge Otsuka to expand the eligibility criteria for accessing delamanid through the GDF to include all countries;
- urge country programs to procure delamanid through the GDF using import waivers where necessary;
- call on Otsuka to lower the price of delamanid for all low- and middle-income countries; and
- advocate for Otsuka to submit already available data on delamanid for adolescents and children to the EMA, submit future data from younger cohorts to the EMA and WHO as they become available, and apply for the addition of delamanid to the WHO EMLc.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
QT prolongation; gastrointestinal upset and distress; neurological disturbances; hyperuricemia; hemolytic anemia	**TB:** no existing data on whether delamanid is safe to use with other QT-prolonging drugs (bedaquiline,* clofazimine, moxifloxacin) **HIV:** lopinavir/ritonavir: increased concentration of delamanid	Dispersible mini-tablet developed; clinical trial in children underway Limited data on risk during pregnancy and breastfeeding; pregnant women may be eligible for access under compassionate use program	**EML:** Yes for adults, eligible to submit application for children to expert committee meeting in 2017 **GDF:** Yes, only for adult formulation

* Not yet known; AIDS Clinical Trials Group (ACTG) study to evaluate the safety of co-administered delamanid and bedaquiline underway.

Ethambutol (ETH, EMB, E)

Group D1 | Ethylenediamine | DS-TB | Approved for TB

Ethambutol is part of the standard six-month, four-drug regimen for the initial treatment of DS-TB and a component of the WHO shortened regimen for DR-TB. Although numerous sources of quality-assured, generic ethambutol exist globally, in the past, supply-chain issues have disrupted regular access to the drug, leading to dangerous programmatic stock-outs. Because its primary role in drug regimens is to prevent the emergence of rifampin-resistant TB, rather than to directly eliminate the TB itself, other drugs are frequently substituted for it when pricing or access becomes an issue.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Vision impairment (decreased visual acuity and/or red-green color blindness); gastrointestinal upset and distress; rash; neuropathy; elevated liver enzymes (very rare); low white blood count and low platelets; bone marrow suppression and aplastic anemia; hyperuricemia (very rare)	**TB:** unknown **HIV:** unknown	Pediatric formulations available May cause vision disturbances; may cause damage to fetus during pregnancy; secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Ethionamide (Eto)

Group C | Thioamide | DR-TB | Approved for TB

Ethionamide is a second-line drug used interchangeably with prothionamide for DR-TB. Four sources of quality-assured drug exist, resulting in improved supply and pricing. Additional research is necessary to determine how ethionamide interacts with HIV medications, and to understand ethionamide's effects in pediatric populations. Approximately one-third of patients whose TB is resistant to isoniazid also have cross-resistance to ethionamide;[1] this raises concern about subjecting patients to numerous adverse effects when ethionamide may be ineffective against certain strains of DR-TB.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; loss of appetite; neurological impairment; elevated liver enzymes; jaundice; vision disturbances; photosensitivity; low blood pressure; depression; endocrine effects (including hypothyroidism, gynecomastia, hair loss, and menstrual irregularity)	**TB:** cycloserine: increased risk of neurological disturbances; isoniazid: increased concentration of isoniazid **HIV:** protease inhibitors: increased risk of elevated liver enzymes; efavirenz: increased risk of elevated liver enzymes and psychiatric symptoms; nevirapine: increased risk of elevated liver enzymes; didanosine, stavudine: increased risk of peripheral neuropathy	Dispersible tablet approved by the GDF/ Global Fund Expert Review Panel in July 2015 Contraindicated during pregnancy (damage to fetus was seen in animal studies); limited risk data for breastfeeding	**EML:** Yes, for adults and children **GDF:** Yes

1. Ethionamide and isoniazid have similar chemical structures and target the same enzyme, leading to high rates of cross-resistance.

Gatifloxacin (GAT)

Group A | Fluoroquinolone | DR-TB | Used Off-Label

Gatifloxacin is a broad-spectrum antibiotic in the fluoroquinolone class. Concerns about adverse effects led to its withdrawal from most markets in 2006, but its inclusion in the "Bangladesh regimen," upon which the WHO-recommended shortened DR-TB regimen is based, and its lack of association with severe adverse events in a four-month DS-TB trial, renewed interest in this drug and led to its reinstatement as a WHO-recommended drug for DR-TB. While gatifloxacin has better anti-TB activity than ofloxacin or PAS, and has less association with QT prolongation than moxifloxacin, levofloxacin and moxifloxacin still have better anti-TB activity and more compelling safety profiles. No quality-assured gatifloxacin products currently exist.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Neurological and psychiatric disturbances; gastrointestinal upset and distress; elevated liver enzymes; low blood sugar; QT prolongation	**TB:** bedaquiline, clofazimine, delamanid; other fluoroquinolones: increased risk of QT prolongation **HIV:** protease inhibitors: increased risk of QT prolongation and elevated liver enzymes; efavirenz: increased risk of QT prolongation, psychiatric symptoms, and elevated liver enzymes; nevirapine: increased risk of elevated liver enzymes; ketoconazole: increased risk of QT prolongation; buffered didanosine: reduced absorption of gatifloxacin	No pediatric formulations available Contraindicated during pregnancy (damage to fetus seen in animal studies); limited risk data for breastfeeding	**EML:** No **GDF:** No

Imipenem/Cilastatin (Imi, Imi/Cls)

Group D3 | Carbapenem | DR-TB | Used Off-Label

Imipenem/cilastatin is a drug used as a last resort for DR-TB, since its twice-daily injection routine is complicated for both patients and providers, and limited data are available on its use for TB.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; neurological and psychiatric disturbances; irregular heartbeat; risk of seizure	**TB:** unknown **HIV:** unknown	Pediatric formulations available No known risk during pregnancy; may require dose adjustment; secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children; listed as antibacterial **GDF:** Yes, for adults and children

Isoniazid (INH,H)

First-line agent/ Group D1 | Pyridine | DS/DR-TB | Approved for TB

Isoniazid is one of the primary drivers of TB-killing activity in the standard six-month, four-drug regimen for DS-TB treatment and is used as TB preventive therapy (to treat LTBI). While numerous manufacturers of quality-assured isoniazid exist globally, and the generics are very cheap, there is only one source of quality-assured active pharmaceutical ingredient for it. As such, supply chain issues continue to disrupt regular access to isoniazid, leading to dangerous programmatic stock-outs. While isoniazid is relatively safe and tolerable, higher doses have been shown to increase toxicity. While MDR-TB is by definition resistant to isoniazid, some research indicates that high doses of isoniazid may work against some strains of MDR-TB–this is the rationale behind its inclusion in the WHO-recommended shortened DR-TB regimen and as a group D1 drug for the WHO-recommended standard DR-TB regimen.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Elevated liver enzymes; jaundice; peripheral neuropathy (vitamin B6 can compensate); rash; fever; joint pain; stomach upset and distress; trouble sleeping; psychiatric disturbances (e.g., depression, irritability); drug-induced lupus syndrome (bone marrow suppression or joint aches and pain; fluid build-up around heart and lungs; blood abnormalities); optic neuropathy (same as ethambutol)	**TB:** cycloserine, terizidone: increased risk of neurological disturbances; linezolid: increased risk of peripheral neuropathy; rifampin, thioacetazone: increased risk of elevated liver enzymes; ethionamide: increased concentration of isoniazid **HIV:** None	Pediatric formulations available Can be used during pregnancy and while breastfeeding	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Kanamycin (KAN, Km, K)

Group B | Aminoglycoside | DR-TB | Used Off-Label

Kanamycin is a second-line drug that is a component of the WHO shortened regimen for DR-TB and when given with a fluoroquinolone and pyrazinamide forms the backbone of the standard WHO-recommended five-drug core regimen for DR-TB. Like amikacin and capreomycin, it cannot be absorbed orally and must be delivered by injection and may be excluded from regimens given to children with non-severe disease. Patients report that kanamycin is particularly painful, even among the injectables. The supply of kanamycin is considered vulnerable, since only two manufacturers of quality-assured drug exist, and production of quality-assured active ingredient remains a challenge.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Hearing disturbances and loss; dizziness; reversible kidney damage; electrolyte abnormalities	**TB:** other aminoglycosides, capreomycin: increased risk of kidney toxicity **HIV:** tenofovir: increased risk of kidney toxicity	Pediatric formulations available May cause fetal hearing loss; secreted in human milk in trace amounts (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Levofloxacin (LVX, LEV, Lfx)

Group A | Fluoroquinolone | DR-TB | Used Off-Label

Levofloxacin is a relatively inexpensive, widely available broad-spectrum antibiotic that, with pyrazinamide and a second-line injectable agent, forms the backbone of the standard WHO-recommended five-drug core regimen for DR-TB. It is one of the preferred drugs among the fluoroquinolones, demonstrating stronger activity against TB than gatifloxacin, and causing fewer side effects than moxifloxacin. It is also one of few drugs used for DR-TB that has been studied and approved in pediatric populations, though only for acute infections with treatment lasting less than 14 days. As such, pediatric formulations exist, but are not widely available or necessarily made in ideal doses for treating DR-TB in children. Given its safety, it is also under investigation for the prevention of MDR-TB. Activists should:

- encourage Macleods and other quality-assured sources of levofloxacin to expedite the development and market entry of pediatric formulations.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; loss of appetite; sensitivity of tendons to damage; dizziness; headache; mood changes; caffeine-like effect; photosensitivity; QT prolongation; peripheral neuropathy	**TB:** other fluoroquinolones: increased risk of QT prolongation **HIV:** buffered didanosine: reduced absorption of levofloxacin; protease inhibitors, efavirenz: increased psychiatric irritability, strange dreams, and elevated liver enzymes	Dispersible tablet under development Limited data on risk during pregnancy (adverse effects on fetus seen in animal studies; may cause cartilage damage); secreted in human milk in trace amounts (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, only for adult formulation

Linezolid (LZD, LNZ)

Group C | Oxazolidinone | DR-TB | Used Off-Label

Linezolid is an antibiotic used off-label for DR-TB that can be a component of the standard WHO-recommended five-drug regimen for DR-TB. Ongoing or planned studies will formally evaluate linezolid's efficacy, safety, optimal dose, and role in treatment shortening. Other oxazolidinones in the pipeline such as Sequella's sutezolid and Merck's tedizolid are also being studied for their promise against DR-TB. Linezolid is an important potential component of the standard WHO-recommended regimen for DR-TB and for building adequate background regimens for the use of new drugs like delamanid and bedaquiline. Hetero's generic quality-assured and, when purchased through the GDF, more affordable version of Pfizer's linezolid has improved access. Additional manufacturers are expected to enter the market and further improve accessibility. In the meantime, activists should:

- call on manufacturers of quality-assured linezolid to develop 600-mg scored or 300-mg strength tablets to facilitate dose adjustments in adults, and a 150-mg dispersible tablet for children;
- advocate for Pfizer to register linezolid for a TB indication (including conducting any research necessary to support doing so), or make existing linezolid data available to others interested in doing this work; and
- call on Sequella and Merck to rapidly advance the evaluation and development of sutezolid and tedizolid for TB, respectively, as potential safer alternatives to linezolid.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Bone marrow suppression; gastrointestinal upset and distress; neurological disturbances; rhabdomyolysis; insomnia; taste alteration; tongue discoloration; oral thrush; yeast infection; serotonin syndrome; peripheral neuropathy; thrombocytopenia	**TB:** isoniazid, cycloserine, terizidone: increased risk of peripheral neuropathy; clarithromycin: increased concentration of linezolid **HIV:** nucleoside reverse transcriptase inhibitors, e.g., didanosine, stavudine: increased risk of rhabdomyolysis and peripheral neuropathy; zidovudine: increased risk of rhabdomyolysis and bone marrow toxicity	Pediatric formulations available (liquid suspension); dispersible tablet under development Contraindicated for pregnant women (adverse effects on mother and fetus seen in animal studies); secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, only for adult formulation

Meropenem (MEM, Mrp)

Group D3 | Carbapenem | DR-TB | Used Off-Label

Meropenem is a drug used as a last resort for DR-TB, since its thrice-daily injection routine is complicated for both patients and providers, and limited data are available on its use for TB. In a recent two-week study, meropenem demonstrated anti-TB activity when given with amoxicillin/clavulanate. Meropenem and other carbapenems are being further explored for their potential against DR-TB.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; neurological and psychiatric disturbances; risk of seizure; thrombocytopenia; elevated liver enzymes; skin allergies (ranging from rash to severe allergic reaction)	**TB:** unknown **HIV:** unknown	Pediatric formulations available No known risk during pregnancy; secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children; listed as antibacterial alternative to imipenem/cilastatin **GDF:** Yes, for adults and children

Moxifloxacin (MXF, Mox, Mfx)

Group A | Fluoroquinolone | DR-TB | Used Off-Label

Moxifloxacin is a broad-spectrum antibiotic, and a component of both the WHO-recommended shortened and standard regimens for DR-TB. Among the fluoroquinolones, moxifloxacin is preferred only second to levofloxacin given moxifloxacin's pronounced QT prolonging effects. However, as with most TB drugs, tolerability may vary substantially between patients and availability may vary by setting. Several trials to evaluate whether fluoroquinolones could shorten treatment for DS-TB have failed, but a number of new studies will see whether moxifloxacin might still have a role in simplifying and shortening DS-TB treatment when given as part of new combinations. An increasing number of generic sources of quality-assured moxifloxacin have helped to secure the supply and reduce prices. Activists should:

- call for the additional research necessary to determine how moxifloxacin interacts with HIV medications, and to understand moxifloxacin's effects in young children; and
- call for Macleods and other sources of quality-assured moxifloxacin to expedite the development and market entry of pediatric formulations.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; loss of appetite; sensitivity of tendons to damage; joint pain; elevated liver enzymes; QT prolongation; low or high blood sugar; headache; dizziness; mood changes; caffeine-like effect; peripheral neuropathy	**TB:** bedaquiline, clofazimine, delamanid, other fluoroquinolones: increased risk of QT prolongation; decreased concentration of rifampin **HIV:** protease inhibitors: increased risk of QT prolongation and elevated liver enzymes; efavirenz: increased risk of QT prolongation, psychiatric symptoms, and elevated liver enzymes; nevirapine: increased risk of elevated liver enzymes; ketoconazole: increased risk of QT prolongation; ritonavir: reduced concentration of moxifloxacin; atazanavir: increased concentration of moxifloxacin buffered didanosine: reduced absorption of moxifloxacin	No pediatric formulations available; dispersible tablet under development Limited data on risk during pregnancy (adverse effects on fetus were seen in animal studies; may cause cartilage damage); limited risk data for breastfeeding	**EML:** Yes, listed as alternative for levofloxacin for adults and children **GDF:** Yes

Ofloxacin (Ofx)

No longer recommended | Fluoroquinolone | DR-TB | Used Off-Label

Ofloxacin was the earliest-developed fluoroquinolone used for TB treatment; however, limited evidence of ofloxacin's effectiveness has led to its replacement with later-generation fluoroquinolones levofloxacin and moxifloxacin in current DR-TB regimens. Ofloxacin is no longer included among medicines recommended by the WHO for the treatment of DR-TB.

Para-Aminosalicylic Acid (PAS)

Group D3 | Salicylic Acid Antifolate | DR-TB | Approved for TB

Para-aminosalicylic acid (PAS) is used as a last resort for DR-TB and largely to prevent the development of resistance to other drugs in the regimen. Although it is recommended for treating DR-TB, its efficacy is limited, and it is poorly tolerated. PAS often requires divided doses, and in some patients has caused diarrhea so severe it led to incontinence. Because there is only one manufacturer of quality-assured PAS and two manufacturers of quality-assured PAS-sodium—formulations that are not easily interchangeable—the drug is both expensive and vulnerable to supply disruption. In addition, PAS must be stored in a cold-chain environment, which requires investment and infrastructure. While PAS-sodium does not require any special storage conditions, it is presented in a different formulation and dose, which can be complicated and confusing for programs and providers.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; loss of appetite; allergic reactions, fever; rash; hypothyroidism; malabsorption; elevated liver enzymes; electrolyte abnormalities; thrombocytopenia; anemia; fluid retention	**TB:** rifampin: reduced absorption of rifampin **HIV:** protease inhibitors, efavirenz, nevirapine: increased risk of elevated liver enzymes	Spoon and scoop for pediatric dosing of adult granular formulations available Limited data on risk during pregnancy (damage to the fetus was seen in animal studies); secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Prothionamide (Pto)

Group C | Thioamide | DR-TB | Approved for TB

Prothionamide, a component of the WHO-recommended shortened regimen for DR-TB, is used interchangeably with ethionamide for DR-TB. Four manufacturers of quality-assured drug currently exist, and approvals for additional generics manufacturers are expected in the near future. As such, supply and pricing are expected to improve. Additional research is necessary to establish prothionamide's efficacy and safety in DR-TB treatment, to determine how prothionamide interacts with HIV medications, and to understand prothionamide's effects in pediatric populations.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; loss of appetite; neurological impairment; jaundice; elevated liver enzymes; endocrine effects (including hypothyroidism, menstrual disturbances)	**TB:** cycloserine: increased risk of neurological disturbances; rifamycins: increased risk of elevated liver enzymes and jaundice **HIV:** protease inhibitors, nevirapine: increased risk of elevated liver enzymes; efavirenz: increased risk of elevated liver enzymes and psychiatric symptoms; didanosine, stavudine: increased risk of peripheral neuropathy	No pediatric formulations available Contraindicated during pregnancy; damage to the fetus was seen in animal studies); limited risk data for breastfeeding	**EML:** Yes, for adults and children; listed as alternative to ethionamide **GDF**: Yes

Pyrazinamide (PZA, PYR, Z)

First-line agent/ Group D1 | Pyrazine | DS-TB, DR-TB | Approved for TB

Pyrazinamide is used for DS-TB and as a component of both the WHO-recommended shortened and standard regimens for DR-TB. Given its inclusion in existing regimens and as a key component of new shortened regimens under investigation, a rapid test to diagnose resistance to pyrazinamide is urgently needed. Additional research is required to determine optimal treatment duration and dose in non-rifampin-containing regimens. Numerous generic sources of quality-assured pyrazinamide exist globally, although supply-chain issues continue to disrupt regular access to the drug and lead to dangerous programmatic stock-outs. Activists should:

- call for the additional research required to determine optimal treatment duration and dose of pyrazinamide in non-rifampin-containing regimens; and
- call for expedited development of a rapid test to diagnose pyrazinamide resistance.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Hyperuricemia; joint pain; jaundice; elevated liver enzymes; skin allergies; photosensitivity; gastrointestinal upset and distress	**TB:** unknown **HIV:** unknown	Pediatric formulations available Limited data in humans, but can be used during pregnancy; secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Rifabutin (RFB, RBT)

First-line agent | Rifamycin | DS-TB | Used Off-Label

Rifabutin, like rifampin (see below) is from the rifamycin class and is used for DS-TB. Rifabutin is preferred for use with HIV medicines, since it has fewer drug-drug interactions than rifampin. Although Pfizer's patent has expired and generic sources are available in some countries, demand has yet to drastically increase despite rifabutin's inclusion in HIV treatment guidelines, in which the WHO recommends that all people with HIV and active TB immediately start treatment including a rifamycin, preferably rifabutin. Activists should:

- call for the research to determine any dosing adjustments needed as a result of rifabutin's interactions with HIV medications, and to understand rifabutin's effects in pediatric populations.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Skin and body fluid discoloration; bone marrow suppression; skin allergies; jaundice; elevated liver enzymes; severe headache; muscle aches; chest pain; joint pain; uveitis; vision disturbances	**TB:** unknown **HIV:** non-nucleoside reverse transcriptase inhibitors, nevirapine, efavirenz: decreased concentration of rifabutin; saquinavir, protease inhibitors: increased concentration of rifabutin; integrase inhibitors: decreased concentration of raltegravir and elvitegravir	No pediatric formulations available; no information on pediatric dosing with HIV medications Limited data on risk during pregnancy (adverse effects on fetus seen in animal studies); limited risk data for breastfeeding	**EML:** Yes, for adults **GDF:** Yes

Rifampin or Rifampicin (RIF, RMP, R)

First-line agent | Rifamycin | DS-TB | Approved for TB

Rifampin is one of the primary drivers of TB-killing activity in the standard six-month, four-drug regimen for treatment of DS-TB. Dose optimization studies are ongoing. Rifampin interacts with many other medications, notably protease inhibitors, making rifabutin a more suitable candidate for people on HIV medicines. Although numerous generic sources of quality-assured rifampin exist globally, supply-chain issues continue to disrupt regular access to the drug, leading to dangerous programmatic stock-outs. Several studies are currently examining the efficacy and safety of higher doses of rifampin, and its potential for shortening TB treatment.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Body fluid discoloration; skin allergies; flu-like symptoms; gastrointestinal upset and distress; jaundice; elevated liver enzymes; kidney failure; hemolytic anemia; thrombocytopenia; neutropenia	**TB:** bedaquiline: decreased concentration of bedaquiline; clarithromycin: decreased concentration of clarithromycin; isoniazid and pyrazinamide: increased risk of elevated liver enzymes **HIV:** protease inhibitors (PIs): decreased concentrations of PIs; non-nucleoside reverse transcriptase inhibitors (NNRTIs), except efavirenz: decreased concentrations of NNRTIs; integrase inhibitors: decreased concentrations of integrase inhibitors; ketoconazole: decreased concentrations of both ketoconazole and rifampin	Pediatric formulations available Limited data on risk during pregnancy (damage to fetus was seen in animal studies; bleeding in infant and mother post delivery reported when given with isoniazid in last weeks of pregnancy); secreted in human milk (breastfeed with caution)	**EML:** Yes, for adults and children **GDF:** Yes, for adults and children

Rifapentine (RFP, RPT, P)

First-line agent | Rifamycin | DS-TB | Approved for TB and LTBI

Rifapentine is another DS-TB drug in the same class of drugs as rifampin (rifamycins); it stays in the body longer than rifampin and therefore may have the potential to shorten the treatment of active TB. Rifapentine is approved for LTBI in children two years and older as part of a regimen that shortens LTBI treatment from nine months of daily isoniazid to just 12 once-weekly doses of isoniazid and rifapentine, substantially reducing the burden of TB treatment for patients and providers alike. For active DS-TB, rifapentine has been shown to allow for once- (when given with moxifloxacin) or twice-weekly dosing in the continuation phase of DS-TB treatment and is approved for use in those 12 years and older. However, despite studying rifapentine in several high–TB burden countries and its importance for the treatment of LTBI, Sanofi-Aventis has registered the drug only in the United States. Activists should:

- urge Sanofi-Aventis to expedite wider registration, especially in countries where the drug was studied; and
- while country registrations are pending, push TB programs that want to use rifapentine for LTBI to procure through the GDF using import waivers.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Skin allergies; fever; jaundice; elevated liver enzymes; irregular heartbeat; gastrointestinal upset and distress; neutropenia	**TB:** bedaquiline: decreased concentration of bedaquiline **HIV**: PIs: decreased concentrations of PIs; integrase inhibitors: increased concentration of raltegravir	Dispersible tablet developed; clinical trial in children planned Limited data on risk during pregnancy (damage to fetus was seen in animal studies; bleeding in infant and mother post delivery reported when other rifamycins given with isoniazid in last weeks of pregnancy); limited risk data for breastfeeding	**EML:** Yes, for adults and children GDF: Yes

Streptomycin (STR, S)

Group B | Aminoglycoside | DR-TB | Approved for TB

Streptomycin was the first drug to be approved for TB treatment (in 1947), and is still sometimes used in the treatment of DR-TB when no other drug from group B is available. However, unlike with resistance to the other injectable agents (amikacin, capreomycin, and kanamycin), resistance to streptomycin does not qualify an isolate as XDR-TB. Some country programs recommend adding streptomycin to the regimens of patients failing treatment for DS-TB; this practice, referred to as "category II treatment," is often ineffective and further delays appropriate treatment, which can foster the development of additional drug-resistance—a single drug should never be added to a failing regimen. In addition, resistance to streptomycin is widespread; it should only be used after drug-susceptibility testing is conducted.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Hearing impairment and loss; electrolyte abnormalities; kidney damage; decreased urine output; dizziness; skin allergies; perioral numbness; oral thrush	**TB:** unknown **HIV:** unknown	Pediatric formulations available May cause fetal hearing loss; secreted in human milk; not recommended while breastfeeding	**EML:** Yes, for adults and children **GDF:** Yes

Terizidone (Trd)

Group C | D-alanine Analogue | DR-TB | Approved for TB

In some settings terizidone is used interchangeably with cycloserine to treat DR-TB; it is derived from cycloserine, and works in a similar way. Only one source of quality-assured terizidone currently exists. Terizidone is poorly understood, but given its tolerability issues, may not merit further study.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Neurological and psychiatric disturbances; gastrointestinal upset and distress; skin allergies	**TB:** ethionamide, prothionamide, isoniazid: increased risk of neurological disturbances **HIV:** efavirenz: increased risk of Stevens–Johnson syndrome and psychiatric problems; nevirapine: increased risk of Stevens–Johnson syndrome; didanosine, stavudine: increased risk of peripheral neuropathy	No pediatric formulations available Limited data on risk during pregnancy and breastfeeding	**EML**: Yes, for adults; listed as an alternative to cycloserine **GDF:** Yes

Thioacetazone (Thz)

Group D3 | Thiosemicarbazone | DR-TB

Thioacetazone is another drug used as a last resort for treating DR-TB as it has severe and numerous side effects. Thioacetazone should not be used in people with HIV, due to an elevated risk of a severe adverse skin reaction. Thioacetazone's effects on children are not well researched. While thioacetazone is the only thiosemicarbazone widely used for TB treatment, another drug purportedly of that class, perchlozone, has recently been approved in Russia for treating MDR-TB. However, JSC Pharmasyntez's substandard clinical trial design and failure to publish externally validated data on the drug raise significant concerns about the use of perchlozone, or even confidence in whether it is indeed of the drug class claimed.

Adverse Effects	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Bone marrow suppression; gastrointestinal upset and distress; loss of appetite; neurological impairment; vision disturbances; mood changes; clumsiness; aches; jaundice; elevated liver enzymes; skin allergies (ranging from rash to severe allergic reaction)	**TB:** isoniazid: increased risk of elevated liver enzymes **HIV:** contraindicated in people with HIV due to risk of Stevens–Johnson syndrome	No pediatric formulations available Limited data on risk during pregnancy and breastfeeding	**EML:** No **GDF:** No

Appendix A: Drugs by Class

Aminoglycoside	amikacin, kanamycin, streptomycin
Carbapenem	imipenem, meropenem
D-alanine analogue	cycloserine, terizidone
Diarylquinoline	bedaquiline
Ethylenediamine	ethambutol
Fluoroquinolone	gatifloxacin, levofloxacin, moxifloxacin, ofloxacin
Pyridine	isoniazid
Macrolide	clarithromycin
Nitroimidazole	delamanid
Oxazolidinone	linezolid
Polypeptide	capreomycin
Pyrazine	pyrazinamide
Rifamycin	rifabutin, rifampin, rifapentine
Riminophenazine	clofazimine
Salicylic acid antifolate	para-aminosalicylic acid (PAS)
Thioamide	ethionamide, prothionamide
Thiosemicarbazone	thioacetazone

Glossary

Aplastic anemia	very low levels of red blood cells due to failure of bone marrow to produce them; can lead to fatigue
Bone marrow suppression	a reduction in the production of blood cells from the bone marrow. This can manifest as **anemia**, **neutropenia**, or **thrombocytopenia**
Caffeine-like effect	a range of symptoms including jitteriness, difficulty concentrating or focusing on tasks, difficulty sleeping, irritability, and increased activity
Contraindicated	inadvisable to take drug or treatment
Electrolyte abnormalities	abnormal levels of chemicals essential for many body functions, including skeletal and heart muscle contraction; typically refers to low levels of calcium, potassium, and/or magnesium
Elevated liver enzymes	increased liver enzymes in the blood, which indicates potential liver damage
Eosinophilia	high levels of eosinophils in the blood; eosinophils belong to the white blood cell group and, when elevated, suggest possibly allergic reactions or parasites
Gastrointestinal upset and distress	a general term used here to denote a common group of adverse effects including nausea, vomiting, diarrhea, and bloating
Gynecomastia	growth of atypically large breasts in males
Gout	the deposit of uric acid crystals, which leads to painful, swollen joints
Hemolytic anemia	abnormal breakdown of red blood cells, which can lead to fatigue
Hypothyroidism	a condition in which the thyroid gland doesn't produce enough thyroid hormone, leading to decreased energy, increased weight gain, sluggishness, hair loss, and if severe, coma; can be treated with thyroid hormone replacement therapy
Hyperuricemia	increased levels of uric acid in the blood, which in rare cases can lead to **gout**. Universally noted in treatment with pyrazinamide, but usually without progression to gout; therefore, there is no need for treatment
Jaundice	yellowing of the skin due to elevated levels of bilirubin in the bloodstream; indicates potential liver disease

Malabsorption	the inability to fully absorb orally ingested nutrients or medications through the GI tract during digestion
Neurological disturbances	a general term used here to denote a group of serious neurological adverse effects, commonly including the central nervous system and the peripheral nervous system (see **peripheral neuropathy,** below). Includes symptoms such as confusion, weakness, numbness, and seizures
Neutropenia	low levels of neutrophils, a member of the white blood cell class, which can lead to an increased risk of severe infection
Oral thrush	a yeast infection in the mouth, which appears as white lesions, usually on the tongue or inner cheeks
Perioral numbness	numbness around the mouth; a common side effect of streptomycin that is notably not indicative of an allergic reaction
Peripheral neuropathy	nerve damage in the extremities, which can cause numbness and pain starting in the fingers and toes, spreading upwards
Phospholipidosis	the buildup of fats in the body's tissues, the significance of which is currently unknown
Photosensitivity	sensitivity to light, which can manifest as sunburn or allergic reactions in the skin with exposure
Psychiatric disturbances	a general term used here to denote a group of serious psychiatric adverse effects, including agitation, hallucinations, psychosis, and thinking about suicide
QT prolongation	a disturbance in the heart's electrical activity that could potentially lead to serious (and sometimes fatal) rhythmic disturbances
Rhabdomyolysis	the breakdown of skeletal muscle, which can lead to kidney failure
Serotonin syndrome	the buildup of serotonin in the body, which can lead to fever, severe muscle contraction, and difficulty breathing; usually caused by the use of multiple drugs that affect serotonin levels in the body
Stevens–Johnson syndrome	a severe allergic skin reaction
Thrombocytopenia	low levels of platelets, which can lead to easy bruising or bleeding
Uveitis	inflammation of the middle part of the eye, which can cause swelling, redness, and pain; thought to be caused by the high dosing of rifabutin

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