An Activist's Guide
to Tuberculosis Drugs

TREATMENT ACTION GROUP
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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 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 MDR-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 drug-resistant TB (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 approval was followed in 2014 by the European Medicines Agency's (EMA's) approval of another new drug, delamanid, for the treatment of DR-TB.

Bedaquiline, delamanid, and other new treatment options in development must be used in combination for the treatment of TB. They are currently being combined with existing drugs, for which significant knowledge and access gaps still exist. Research on the safety and efficacy of older drugs continues to be limited, especially in children and people with HIV. Issues beyond the sparsely populated research pipeline also impede effective treatment: patent restrictions, pricing issues, medication quality concerns, and poor supply management limit access to lifesaving drugs.

TB treatment must be 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, quality of medications, and access priorities. This guide provides a brief summary of safety and efficacy data for those drugs currently in use for TB (many 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' annual report, *DR-TB Drugs Under the Microscope* (complete citation listed under "Sources").

KEY DEFINITIONS AND ACRONYMS

Approved	Approved by a stringent regulatory authority for use against TB
DR-TB	Drug-resistant TB, or TB resistant to at least one TB drug
DS-TB	Drug-sensitive TB
EML	The World Health Organization (WHO) essential medicines list (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.
MDR-TB	Multidrug-resistant TB, or TB resistant to isoniazid and rifampin (group 1), the two most powerful existing TB drugs
Off-Label	Use of a drug for an indication other than the one for which it was approved
Pharmaceutical 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 (e.g., Hetero for linezolid). All drugs procured through the GDF are quality-assured.
TB	Tuberculosis
XDR-TB	Extensively drug-resistant TB, or MDR-TB also resistant to at least one second-line injectable drug (group 2) and one fluoroquinolone (group 3)

[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 five 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, MDR-TB, or XDR-TB (see figure 1).

Group 1 (first-line oral agents)	These drugs are agents used in the initial treatment of DS-TB.
Group 2 (injectable agents)	These drugs are delivered by injection, and could be avoided if effective all-oral regimens were developed and made available.
Group 3 (fluoroquinolones)	These drugs are broad-spectrum antibiotics currently used in the treatment of MDR-TB, and are being studied for use in simplifying and shortening DS-TB regimens.
Group 4 (oral bacteriostatic second-line agents)	These drugs are used in the treatment of MDR-TB. Although they do not have strong TB-killing activity, they can prevent the development of resistance to other drugs used in the regimen.
Group 5 (agents with unclear role in DR-TB treatment)	These drugs are deemed to be not well studied for use in DR-TB treatment, but may be used to support regimens for MDR-TB or XDR-TB that are resistant to other drugs.

How to Use This Guide

For convenience of reference, drugs are listed in alphabetical order. See “Drugs by Class” on page 27. 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.

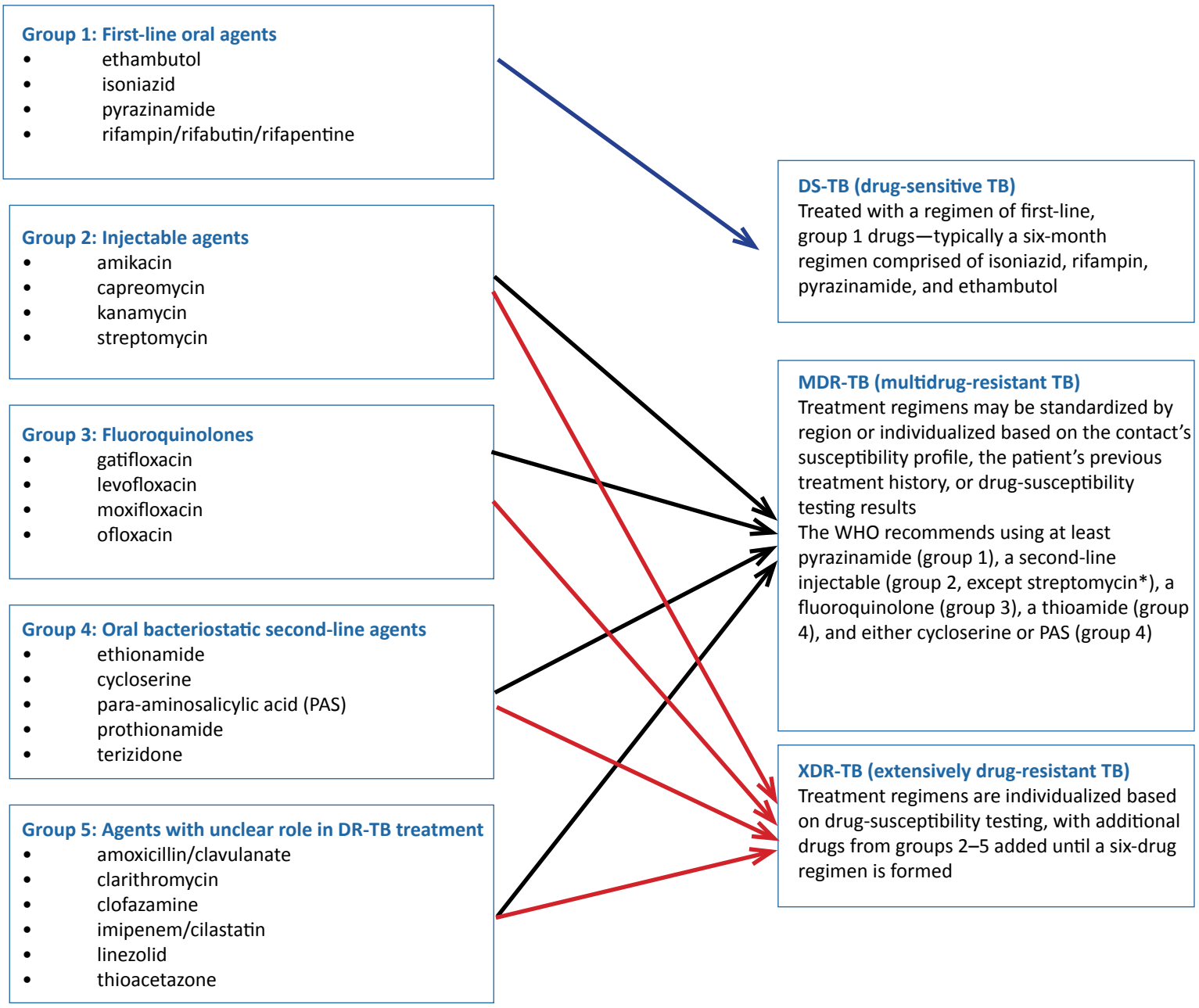
Each drug is listed as follows:

Drug Name (Drug Abbreviation[s])

WHO Grouping | Drug Class | Indication | Regulatory Status

Constructing a TB Drug Regimen

FIGURE 1



*Streptomycin is an injectable agent, but is not considered a second-line drug. Resistance to streptomycin does not qualify for XDR-TB diagnosis.

Drugs by Name

Amikacin (AMK, Am)

Group 2 | Aminoglycoside | DR-TB | Used Off-Label

Injectables like amikacin, when given with a fluoroquinolone, form the backbone of treatment for MDR-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. 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 adult and pediatric formulation

Amoxicillin/Clavulanate (AMC, Amx/Clv)

Group 5 | 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. It is also unclear how amoxicillin/clavulanate interacts with TB or HIV medications. Although generic sources are available, making it relatively inexpensive, amoxicillin/clavulanate has been subject to quality concerns in the past.

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, for adult formulation only

Bedaquiline (BDQ, B, J)

WHO Grouping Not Yet Identified (Recommended Use Similar to That of Group 5 Drugs)| Diarylquinoline | DR-TB | Approved for DR-TB

Bedaquiline was approved by the FDA (late 2012), the Russian regulatory authority (late 2013), and the EMA (early 2014) for the treatment of DR-TB, making it the first new TB drug from a new class of drugs to be approved for TB in over 40 years. However, many research and access gaps remain. To fill these gaps, activists must:

- hold drug sponsor, Janssen, accountable for completing a phase III trial, which is necessary to confirm bedaquiline's efficacy, optimal use, and, especially, safety, given the serious side effects and elevated risk of mortality demonstrated in a phase II trial;
- call for additional research to better understand how bedaquiline interacts with HIV medications, and to determine bedaquiline's effects in children, in people who use drugs or alcohol, and in people with hepatitis B or C;
- advocate for the inclusion of bedaquiline on the WHO EML to further improve wider in-country access and use;
- urge Janssen to file for approval in other countries, make the drug available for individual patients under compassionate use while filings are pending, and set fair and sustainable pricing for bedaquiline once it is approved;
- urge Janssen to provide bedaquiline via the GDF at a single fair and sustainable price regardless of country income classification or for Janssen to allow generic competition to do the same; and
- if bedaquiline's basic patent (which expires in 2023) creates barriers to accessible pricing, 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.

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 risk of 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, but clinical trial in children not yet initiated Limited data on risk during pregnancy and breastfeeding	**EML**: No; 2013 application was denied; Janssen can resubmit for 2015 WHO expert committee review **GDF**: Yes, but using a tiered-pricing structure

Capreomycin (CAP, Cm)

Group 2 | Polypeptide | DR-TB | Approved for TB

Capreomycin is a second-line drug used for DR-TB. Like the other group 2 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. Capreomycin is favored among the injectables, as the lower volume of liquid required per dose ensures a single injection (aminoglycosides such as amikacin may require two injections due to their volume per dose). While capreomycin is preferable to other injectables, as it requires fewer daily injections, cost remains a significant barrier. Capreomycin's sponsor, Eli Lilly, has been working with generics manufacturers to expand production and lower costs, but its supply is still considered vulnerable, since only two manufacturers produce quality-assured drug and only one produces quality-assured active ingredient.

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 adult and pediatric formulation

Clarithromycin (CLR)

Group 5 | Macrolide | DR-TB | Used Off-Label

Clarithromycin is an antibiotic used for DR-TB when few other treatment options remain, as its efficacy for TB has not been established. Macrolides like clarithromycin appear to kill TB bacteria in laboratory settings; however, clarithromycin is probably not highly effective against TB when taken by people. Other drug candidates from the macrolide class are in preclinical testing, and while they may prove to be more effective than clarithromycin for treating TB, they will not be approved or available for several years. In the meantime, clarithromycin is not included on the WHO EML for children, though the drug may be important for the treatment of DR-TB in children with complicated resistance patterns and few other treatment options.

- Activists should call for the inclusion of clarithromycin on the WHO EML for children.

Adverse Effects of Note	Potential TB and HIV Drug Interactions	Maternal/Pediatric Concerns	EML/GDF Inclusion
Gastrointestinal upset and distress; headache; hallucinations; dizziness; rash; jaundice; elevated liver enzymes; kidney damage; hearing loss; QT prolongation	**TB**: unknown **HIV**: non-nucleoside reverse transcriptase inhibitors: increased concentration of clarithromycin; protease inhibitors: increased concentration of clarithromycin; increased risk of QT prolongation	No pediatric formulations available Contraindicated during pregnancy (adverse effects on fetus were seen in animal studies); secreted in human milk (breastfeed with caution)	**EML**: Yes, for adults; listed as an antibacterial **GDF**: Yes

Clofazimine (CFZ, CLF)

Group 5 | Riminophenazine | DR-TB | Used Off-Label

Clofazimine is an anti-leprosy drug; while it has been recommended for use in patients with DR-TB, it has not been approved or well studied for the treatment of TB. However, recent trials for novel DS-TB and DR-TB regimens have incorporated clofazimine to see whether it might have a role in shortening treatment. Given clofazimine's potential to produce QT prolongation and skin discoloration, another riminophenazine with better activity and fewer side effects would be ideal. A new riminophenazine, discovered through a partnership of the Global Alliance for TB Drug Development and Institute of Materia Medica (IMM) in Beijing, has recently advanced into preclinical development. This new compound, named TBI-166, appears to be similarly effective to clofazimine at killing TB in mice, and may cause less skin discoloration. Novartis, the only source of quality-assured clofazimine, has declined to make the drug available for TB treatment, citing concerns over liability of off-label use and hindering both research and programmatic efforts to further study and use the drug for TB. 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 complete the research necessary to establish the efficacy and safety of clofazimine in DR-TB treatment 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 4 | 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. Although its high cost has hampered access since Eli Lilly's subsidized supply was exhausted, recent growth in production from generic manufacturers has lowered costs. Even as more manufacturers of quality-assured generics begin to produce cycloserine, its supply remains vulnerable, since only one manufacturer produces quality-assured active ingredient for it.

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, stavudine: increased risk of peripheral neuropathy	No pediatric formulations available 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)

WHO Grouping Not Yet Identified (Recommended Use Similar to That of Group 5 Drugs) | Nitroimidazole| DR-TB | Approved for DR-TB

Delamanid is a novel drug that was approved by the EMA in early 2014 for the treatment of DR-TB. However, delamanid is not widely available to patients outside of the European Union or clinical trials. Delamanid's sponsor, Otsuka, has been slow to make it available for pre-approval access under its compassionate use program, which is being piloted using Médecins Sans Frontières sites. Advocates should:

- demand that Otsuka rapidly implement and expand its compassionate use program and provide pricing and registration plans as well as ensure that it files for registration of the drug in key high-burden countries and where it has conducted clinical trials;
- advocate for the inclusion of delamanid on the WHO EML and in the GDF catalogue to further improve wider in-country access and use as the drug is registered in more countries;
- call for expedited additional research to determine delamanid's safety when used in combination with bedaquiline[3] or drugs like clofazimine, moxifloxacin, and methadone, as these drugs can cause QT prolongation; and
- call for additional research on how delamanid can optimize DR-TB treatment, either by replacing more toxic, less efficacious, and injectable drugs, or by shortening treatment duration.

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	Pediatric formulation under development (dispersible minitablet developed for clinical trial enrolling in Philippines and South Africa) Limited data on risk during pregnancy and breastfeeding	**EML**: No; approved in 2014; eligible to submit application for 2015 WHO expert committee review **GDF**: No

[3] The U.S. National Institutes of Health is developing a study protocol to answer this question.

Ethambutol (ETH, EMB, E)

Group 1 | Ethylenediamine | DS-TB | Approved for TB

Ethambutol is part of the standard six-month, four-drug regimen for the initial treatment of DS-TB. Although numerous sources of quality-assured, generic ethambutol exist globally, supply-chain issues continue to disrupt 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 or red-green color blindness); gastrointestinal upset and distress; rash; neuropathy; elevated liver enzymes (very rare); low white blood cell 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 adult and pediatric formulation

Ethionamide (Eto)

Group 4 | 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 now exist, resulting in improved supply and pricing compared to past years. 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;[4] 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; delavirdine, nevirapine: increased risk of elevated liver enzymes; didanosine, stavudine: increased risk of peripheral neuropathy	No pediatric formulations yet available; 125 mg formulation under evaluation by GDF/ Global Fund Technical Review Panel Contraindicated during pregnancy (damage to fetus was seen in animal studies); limited risk data for breastfeeding	**EML**: Yes, for adults and children **GDF**: Yes

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

Gatifloxacin (GAT)

Group 3 | Fluoroquinolone | DS-TB | Used Off-Label

Gatifloxacin was an approved broad-spectrum antibiotic in the fluoroquinolone class often used for DR-TB therapy; however, concerns about its significant adverse effects led to its withdrawal from markets in 2006. Gatifloxacin is believed to be a better drug than ofloxacin or PAS, but inferior to moxifloxacin. A regimen containing gatifloxacin was studied for its potential to shorten DS-TB treatment, but was found inferior to the standard treatment course. Results from past research studies involving gatifloxacin may still help inform the role of fluoroquinolones such as moxifloxacin in shortening TB therapy.

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 was seen in animal studies); limited risk data for breastfeeding	**EML**: No **GDF**: No

Imipenem/Cilastatin (Imi, Imi/Cls)

Group 5 | 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 anti-bacterial **GDF**: Yes, for adult and pediatric formulation

Isoniazid (INH, H)

Group 1 | Pyridine | DS-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. 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. Further research is required to determine the efficacy, safety, and optimal dose of high-dose isoniazid for the treatment of DR-TB. In addition, a rapid test that determines whether people clear isoniazid from their bodies quickly or slowly could better inform optimal dose selection.

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); vision impairment (decreased visual acuity or red-green color blindness)	**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 adult and pediatric formulation

Kanamycin (KAN, Km, K)

Group 2 | Aminoglycoside | DR-TB | Used Off-Label

Kanamycin is a drug used for DR-TB. Like amikacin and capreomycin, it cannot be absorbed orally and must be delivered by injection. However, even though patients report that kanamycin is particularly painful, even among the injectables, it is the least expensive second-line drug. 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 adult and pediatric formulation

Levofloxacin (LVX, LEV, Lfx)

Group 3 | Fluoroquinolone | DR-TB | Used Off-Label

Levofloxacin is a relatively inexpensive, widely available broad-spectrum antibiotic used for DR-TB. It is one of the preferred drugs among the fluoroquinolones, demonstrating stronger activity against TB than gatifloxacin or ofloxacin, 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:

- call for the additional research necessary to understand the effects of using levofloxacin for extended periods of time in children and how it interacts with HIV medications.

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	Pediatric formulation specific to TB is under development Limited data on risk during pregnancy (adverse effects on fetus were 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, for adult formulation only

Linezolid (LZD, LNZ)

Group 5 | Oxazolidinone | DR-TB | Used Off-Label

Linezolid is an antibiotic used for DR-TB when few other options exist. Although linezolid is not approved to treat TB, a recent trial showed linezolid's efficacy against XDR-TB, though it did cause serious side effects. Although linezolid is currently the only approved drug of its class (being used off-label for TB treatment), other oxazolidinones in the pipeline such as Sequella's sutezolid and AstraZeneca's AZD5847 are being studied for their promise against DR-TB in humans. Despite linezolid's importance as a last-resort drug and as a potential component of background regimens required for pre-approval access to novel drugs like delamanid and bedaquiline, it is often not a treatment option for XDR-TB patients due to its lack of availability and prohibitive cost, which is determined by Pfizer, previously the only manufacturer of quality-assured linezolid. A generic, quality-assured, and more affordable version produced by Hetero of India has since been approved, and is available through the GDF in countries where Pfizer does not have patent protections over the drug. Four additional manufacturers are expected to enter the market as quality-assured sources in November 2014, when Pfizer's basic patent expires in the United States; however, secondary patents and the threat of litigation may continue to impede access to an affordable generic in many countries. Activists should:

- call on Pfizer to develop nonassertion agreements in countries that procure TB drugs through the GDF where secondary patents for linezolid are registered; and
- call for the additional research necessary to establish the timing and dosage of linezolid in TB treatment, to understand the effects of linezolid's extended use, and to determine how linezolid interacts with HIV medications.

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) Contraindicated for pregnant women (adverse effects on mother and fetus were seen in animal studies); secreted in human milk (breastfeed with caution)	**EML**: No **GDF**: Yes, for adult formulation only

Moxifloxacin (MXF, Mox, Mfx)

Group 3 | Fluoroquinolone | DR-TB | Used Off-Label

Moxifloxacin is a broad-spectrum antibiotic used for DR-TB. It is one of the preferred drugs among the fluoroquinolones, since it lasts longer in the body, requires lower dosages, and is more effective against persistent TB than levofloxacin. However, as with most TB drugs, tolerability may vary substantially between patients. While moxifloxacin has traditionally been used in DR-TB regimens, it has recently also been incorporated into trials for DS-TB to see whether fluoroquinolones might have a role in simplifying and shortening DS-TB treatment. An increasing number of generic sources of moxifloxacin are available, and while historically the high price of moxifloxacin weighed heavily on the cost of DR-TB regimens, the price has already come down and is expected to decrease further as Bayer's patents expire (2019 in the United States). Activists should:

- call for the additional research necessary to determine how moxifloxacin interacts with HIV medications, and to understand moxifloxacin's effects in pediatric populations, especially given recent evidence that quinolones may damage the cells of tendons, cartilage, and other connective tissues in children.

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, unboosted atazanavir: increased concentration of moxifloxacin; buffered didanosine: reduced absorption of moxifloxacin	No pediatric formulations available 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)

Group 3 | Fluoroquinolone | DR-TB | Used Off-Label

Ofloxacin was the earliest-developed fluoroquinolone used for TB treatment; however, ofloxacin's inferior efficacy has led to its replacement with levofloxacin or moxifloxacin in current DR-TB regimens. Nevertheless, its low cost means that ofloxacin retains a place in drug-resistant TB regimens. Additional research in this class generally focuses on levofloxacin and moxifloxacin; recent research on ofloxacin has generally focused on dosing.

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; QT prolongation; peripheral neuropathy; photosensitivity; headache; dizziness; mood changes; caffeine-like effect	**TB**: other fluoroquinolones: increased risk of QT prolongation **HIV**: protease inhibitors: increased risk of 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 ofloxacin; atazanavir, lopinavir: increased risk of QT prolongation and increased concentration of ofloxacin	No pediatric formulations available Limited data on risk during pregnancy (adverse effects on fetus were seen in animal studies; may cause cartilage damage); secreted in human milk (breastfeed with caution)	**EML**: Yes; listed as alternative for levofloxacin for adults and children **GDF**: Yes

Para-Aminosalicylic Acid (PAS)

Group 4 | Salicylic Acid Antifolate | DR-TB | Approved for TB

Para-aminosalicylic acid (PAS) is used for DR-TB most often when ethionamide or cycloserine are unavailable or intolerable, and largely to prevent the development of resistance to other drugs in the regimen. Although it is recommended for treating MDR- and XDR-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 extremely 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. Additional research is necessary to establish the safety of PAS, to determine how PAS interacts with HIV medications, and to understand PAS'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; 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 fetus was seen in animal studies); secreted in human milk (breastfeed with caution)	**EML**: Yes, for adults and children **GDF**: Yes, adult and pediatric formulation

Prothionamide (Pto)

Group 4 | Thioamide | DR-TB | Approved for TB

Prothionamide is a DR-TB drug used interchangeably with ethionamide. Three 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 of Note	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, delavirdine, 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 fetus was seen in animal studies); limited risk data for breastfeeding	**EML**: Yes, listed as alternative for ethionamide for adults and children **GDF**: Yes

Pyrazinamide (PZA, PYR, Z)

Group 1 | Pyrazine | DS-TB, DR-TB | Approved for TB

Pyrazinamide is used for DS-TB and DR-TB; its primary role in DS-TB treatment is to reduce treatment time. Given its inclusion in many DR-TB regimens and as a key component of planned new shortened regimens, 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 of Note	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, as single formulation for adults and as part of fixed-dose combination for children

Rifabutin (RFB)

Group 1 | 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 recent 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. These guidelines are expected to increase demand for the drug. 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 of Note	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, delavirdine, 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 were seen in animal studies); limited risk data for breastfeeding	**EML**: Yes, for adults **GDF**: Yes

Rifampin or Rifampicin (RIF, R)

Group 1 | 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. 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 of Note	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, as part of fixed-dose combination for adults and children

Rifapentine (RFP, RPT, P)

Group 1 | Rifamycin | DS-TB | Approved for TB

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 shortens latent TB 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. However, despite studying rifapentine in several high–TB burden countries, 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
- encourage TB programs to include nutritional support with treatment, as studies have found that rifapentine works best when given with food.

Adverse Effects of Note	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	Pediatric formulation under development (dispersible tablet) Limited data on risk during pregnancy (damage to fetus was seen in animal studies; bleeding in infant and mother postdelivery reported when other rifamycins given with isoniazid in last weeks of pregnancy); limited risk data for breastfeeding	**EML**: No **GDF**: No

Streptomycin (STR, S)

Group 2 | Aminoglycoside | DR-TB | Approved for TB

Streptomycin was the first drug to be approved for TB treatment (in 1947), and is today used in the treatment of DR-TB. Like amikacin, capreomycin, and kanamycin, it cannot be absorbed by the body when taken orally and must be delivered by injection. Although streptomycin is an injectable drug, it is not considered a second-line drug, and 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 "cat 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 be reserved for use in patients only after drug-susceptibility testing is conducted.

Adverse Effects of Note	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 4 | D-alanine Analogue | DR-TB | Approved for TB

Terizidone is used as a last-resort drug for treating DR-TB and primarily in South Africa; it is derived from cycloserine, and works in a similar way. Only one source of quality-assured terizidone exists. Terizidone is poorly understood, but given its tolerability issues, may not merit further study.

Adverse Effects of Note	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**: No **GDF**: Yes, for adult formulation only

Thioacetazone (Thz)

Group 5 | Thiosemicarbazone | DR-TB | Used Off-Label

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 of Note	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

Drugs by Class

Aminoglycosides	amikacin, kanamycin, streptomycin
Carbapenem	imipenem
D-alanine analogues	cycloserine, terizidone
Diarylquinoline	bedaquiline
Ethylenediamine	ethambutol
Fluoroquinolones	gatifloxacin, levofloxacin, moxifloxacin, ofloxacin
Isoniazid	pyridine
Macrolide	clarithromycin
Nitroimidazole	delamanid
Oxazolidinone	linezolid
Penicillin	amoxicillin
Polypeptide	capreomycin
Pyrazines	pyrazinamide
Rifamycins	rifabutin, rifampin, rifapentine
Riminophenazine	clofazimine
Salicylic acid antifolate	para-aminosalicylic acid (PAS)
Thioamides	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, 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 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 build-up 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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