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Tutorial

The Treatment of Tuberculosis

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Abstract

Tuberculosis (TB) remains a leading cause of infectious death worldwide, and poverty is a major driver. Clinically, TB presents as "latent" TB and active TB disease, and the treatment for each is different. TB drugs can display "early bactericidal activity (EBA)" and / or "sterilizing activity" (clearing persisters). Isoniazid is excellent at the former, and rifampin is excellent at the latter. Pyrazinamide and ethambutol complete the first-line regimen for drug-susceptible TB, each playing a specific role. Drug-resistant TB is an increasing concern, being met, in part, with repurposed drugs

(including moxifloxacin, levofloxacin, linezolid, clofazimine, and beta-lactams) and new drugs (including bedaquiline, pretomanid, and delamanid). One challenge is to select drugs without overlapping adverse drug reaction profiles. QTc interval prolongation is one such concern, but to date, it has been manageable. Drug penetration into organism sanctuaries, such as the central nervous system, bone, and pulmonary TB cavities remain important challenges. The pharmacodynamics of most TB drugs can be described by the area under the curve (AUC) divided by the minimal inhibitory concentration (MIC). The hollow fiber infection model (HFIM) and various animal models (especially mouse and macaque) allow for sophisticated pharmacokinetic / pharmacodynamic experiments. These experiments may hasten the selection of the most potent, shortest possible regimens to treat even extremely drug resistant TB. These findings can be translated to humans by optimizing drug exposure in each patient, using therapeutic drug monitoring and dose individualization.

Introduction

Tuberculosis (TB) remains a leading cause of infectious death worldwide, despite the availability of effective and inexpensive treatments.(1) Poverty is a major driver in sustaining TB globally. Some may consider it a social disease with medical consequences.(2) Because of its unique cellular construction and life cycle, the treatment of the disease caused by *Mycobacterium tuberculosis* (*Mtb*) is long, which in turn leads to nonadherence.(3) Incentives for the pharmaceutical industry to develop new drugs are few, and many companies choose not to develop TB drugs. When they do, considerable public support likely is involved.(4) Fortunately, new drugs have emerged recently for the treatment of drug-resistant TB, and research is focused on shortening the duration of treatment for all forms of TB.(5)

Since the vast majority of humans who become infected with *Mtb* are able to eliminate or contain it, clearly most humans already have the immune capacity to control *Mtb*. However, approximately 10% of the human population lacks this immunological capability, and because the immunology of TB is incompletely understood, transferring this immune capability to vulnerable populations via vaccine or immunotherapy remains a work in progress.(6-8) That immensely important topic is beyond the scope

of this tutorial. Instead, this tutorial focus on the pharmacology of TB drugs, their uses in TB patients, and currently available avenues for optimizing pharmacotherapy. A note about abbreviations: Among US *clinicians*, RIPE stands for Rifampin, Isoniazid, Pyrazinamide, and Ethambutol. Researchers and many non-US clinicians use HRZE for isoniazid (isonicotinic acid Hydrazide), Rifampin, pyraZinamide, and Ethambutol. Depending on context, P can stand for pyrazinamide (US clinicians) or rifaPentine (researchers and non-US clinicians). Let the reader beware.

Tuberculosis (TB)

Clinically, TB can be described in two general forms – "latent" TB and active TB disease.(3) This represents an oversimplification of a continuum from exposed but not infected, exposed and infected but cleared, infected but not clinically apparent (i.e. "latent"), to active TB disease with clinical manifestations.(3)

Latent TB infection (LTBI)

So called "latent" TB is a condition where skin or blood tests demonstrate that the immune system recognizes *Mtb*, but there are no signs or symptoms of active disease. Under these conditions, it is *estimated* that fewer than 1000 live bacilli reside within the host, largely or completely contained by the immune system. Patients with **latent TB infection (LTBI)** are not infectious because they do not have active pulmonary lesions.(1,3) LTBI presents an excellent opportunity, as well as a unique challenge, for "nipping TB in the bud." Chemotherapy during LTBI can reduce the lifetime risk of active disease in the host by over 90%.(3,9) Most treated patients with LTBI will never become sick with TB, and thus will never spread TB, breaking the cycle of new infections. The challenge comes from the need to convince people who feel perfectly well to take drugs with important toxicities for extended periods of time. Nevertheless, without a concerted global effort to reduce this reservoir of millions of cases of LTBI, the cycle of disease cannot be broken.

Historically, the main option for the treatment of LTBI had been isoniazid (INH) (9). George Comstock demonstrated the efficacy of INH with pioneering studies performed in Alaska, USA, during the 1960s.(10,11) INH 300 mg given daily for six months had considerable benefit, 9 months

even more benefit, and 12 months near-maximal benefit.(12) When used, 9 months of INH is the preferred duration.(9) The difficulties come with the fact that INH is not the best drug for the job – it is not considered a potent "sterilizing" drug, described later, and it carries a risk of **drug induced liver injury (DILI)**. So, while effective, better alternatives to INH are being sought.

Rifampin (RIF) is the best **"sterilizing" drug** (a drug that prevents post-treatment relapse in patients with active TB disease by eliminating so-called "persisters.") To the extent that the physiological state of a "latent" TB bacillus resembles the physiological state of a "persister" TB bacillus, RIF should be the preferred drug for LTBI. Studies have shown that RIF 600 mg is quite effective, even when given for only 4 months.(9,13)

Combination therapy also has been effective for LTBI. Some countries use 3 months of daily INH plus RIF, which now has entered the US guidance.(9) Alternatively, INH plus rifapentine (RPT, or cyclopentyl-rifampin) can be used. **3HP** is the abbreviation for 3 months of **once weekly** INH (shortened to H) 900 mg and RPT (shortened to P) 900 mg.(9) A newer modification is daily INH and RPT for one month has been studied in persons living with HIV.(14) A one month treatment clearly has the advantage of shortest duration (from 9 to 4 to 3 down to 1 month). Most patients could be engaged for that period of time, and observed for possible adverse effects. With further study, this can be scaled up to more patient populations, and could start to reduce the pool of future TB cases. Other agents are being considered for LTBI, including fluoroquinolones or the new drug bedaquiline (BDQ) which is described in detail below.(15) However, clinical data do not exist yet to comment on the role of BDQ for LTBI. Should that prove to be effective, it would be preferred in cases where the patient likely had been exposed to forms of TB that were resistant to the standard "first-line" TB drugs. Additional research is focused on long acting injectable dosage forms that would allow as little as one dose to block future transmission of TB.(16) Considerable research is needed, however, before that becomes a clinical reality.

Active TB disease

LTBI presents with few live organisms, so the probability of selecting for drug resistance using monotherapy is considered very small. The situation changes dramatically with **active TB disease**. For active TB, monotherapy is unacceptable. Within **cavitary pulmonary lesions**, there can be 10^9 organisms or more, a number that exceeds typical wild-type mutation frequencies for many TB drugs. That is, there could be 10^3 or more pre-existing mutants at the onset of therapy, primed to survive any chosen monotherapy.(3) This was proven conclusively in the 1940s with the introduction of streptomycin (SM).(17,18) The lesson was learned quickly, but options were in short supply. Para-aminosalicylic acid (PAS) and eventually INH were added to SM by the early 1950s, producing the first effective 3 drug regimens. The duration was typically 18 months, toxicity was common, and success was good but not great. Pyrazinamide (PZA), ethionamide (ETA), cycloserine (CS) and ethambutol (EMB) were developed over the ensuing decade, making modest contributions at the time. The game-changer was RIF.(17,18)

Adding RIF to INH-containing regimens made it possible to cure TB in 9 months, half the prior duration. Adding PZA to INH and RIF made it possible to cure **drug-susceptible TB (DS-TB)** in 6 months, ushering in the so-called **"short course" era**.(17,18) Short, that is, compared to 18 months, but not short compared to 10 days of penicillin for strep throat. The current regimen, known as **RIPE**, is 2 months of RIF, INH, PZA, and EMB. EMB is added to protect RIF while clinicians await susceptibility data on the slow-growing *Mtb*. Currently, roughly 1 in 10 *Mtb* isolates in the US is resistant to INH, with that frequency varying by nation. Since **PZA is not effective at suppressing the development of resistance** (i.e., it does not protect RIF if the isolate is INH resistant), the 4th drug, EMB, serves that purpose. EMB can be stopped once the isolate is known to be INH susceptible, or after 2 months of effective treatment, whichever comes first. PZA also can be stopped after 2 months of effective treatment, because historical data suggest most of the benefit has been accrued by then.(3,17-19) RIPE then reduces to RI for an additional 4 months, assuming that the patient responds to treatment, and assuming the patient is not at an **elevated risk for treatment failure**. Patients who are substantially underweight, patients with large cavitary lung lesions, patients with bone or central nervous system disease typically are treated longer than 6 months.(19,20) Some

clinicians extend treatment in patients who are immunocompromised, depending on clinical circumstances.

Treatment gets much more complicated when the isolate is resistant to INH and RIF (so called **multidrug-resistant TB, or MDR-TB**).(21) Additional resistance to fluoroquinolones and aminoglycosides is called **extensively drug resistant TB (XDR-TB)**. For many years, the **"second-line" TB drugs** PAS, ETA, and CS were used in varying combinations with whatever other drugs showed *in vitro* susceptibility and / or had not been used in a given patient previously. This approach is called an **individualized, or optimized, MDR-TB regimen which will typically contain 5-7 drugs**. Typically, these regimens lasted 18-24 months.(17-22) The WHO has categorized drugs into groups based on preferred order of use (Fig. 1).(22) More recently, shortened standardized MDR-TB regimens have been tried, under selected conditions.(21-23) Such regimens can be as short as 9 months. Clofazimine (CLOF) is a leprosy drug that has found new life as a TB drug within such regimens.

New drugs have been tested, initially as add-ons to an **optimized background regimen (OBR)**. There is a desire to replace the most toxic older TB drugs, including the injectable drugs (aminoglycosides and capreomycin), since they can cause disabilities that last a lifetime. The TB Alliance has moved forward with trials using two new drugs, BDQ and pretomanid (PMD), along with the repurposed drug linezolid (LZD).(24) These regimens are only 6 months long, bringing the treatment duration of MDR-TB in line with the treatment duration of drug-susceptible TB. Work continues on optimizing the dose of linezolid, which is the most toxic of the 3 drug combination.(25,26) Delamanid (DLM) is another new TB drug that has some similarities to PMD.(27,28) No head-to-head trials comparing PMD to DLM exist, and clinical safety data for PMD are limited. Beta-lactam – beta-lactamase inhibitor combinations also are being evaluated as potential TB drugs, with clavulanic acid and avibactam showing good suppression of mycobacterial enzymes.(21,29) Additional drugs are at different stages of development (Fig. 2).

TB drug pharmacology

Extensive publications exist about the older TB drugs, with more limited data available for the newer drugs. Excellent resources include, but are not limited to, the 1988 book Anti-tuberculosis Drugs, edited by K. Bartmann,(30) the 1991 book Drug Susceptibility in the Chemotherapy of Mycobacterial Infections, edited by Leonid Heifets,(31) the 2000 book A Clinician's Guide to Tuberculosis, written by Michael D. Iseman,(19). There are many TB drug chapters in the 2005 book Antimicrobial Therapy and Vaccines, Volume II, 2nd edition: Antimicrobial Agents, edited by Victor Yu and colleagues (with subsequent on-line updates at antimicrobe.org),(32) and a complete description of TB in the 2020 book Clinical Tuberculosis, 6th edition, edited by Lloyd N. Friedman, Martin Dedicoat, and Peter D. O. Davies.(33) The authors of this Tutorial are the authors of the chapter *Clinical Pharmacology of the Anti-Tuberculosis Drugs* from the latter book, and we present a condensed summary here.(33) We give credit to these original publications, where full details and many more references may be found.(31-33) Figure 3 shows a depiction of the mechanisms of action for the TB drugs, from the NIAID.

Traditional first-line drugs

The majority of TB patients continue to be treated with the RIPE regimen, so it is important to understand the basic features of these 4 drugs.

Isoniazid

INH is a **pro-drug** which is activated within *Mtb* by the enzyme KatG. (33) A reactive intermediate of INH inhibits the synthesis of mycolic acids, which are needed for cell wall construction.(18,33) Resistance is conferred by mutations in katG (high-level) and/or inhA (low-level).(33) INH 300 mg daily has high oral bioavailability, which is modestly reduced by food.(33,34) Some RIPE regimens are given 3 times weekly, using INH 900 mg, although intermittent regimens have fallen out of favor. N-acetylation to inactive metabolites occurs through the polymorphic enzyme N-acetyl-transferase 2 (NAT2).(33,34) Fast (half-life, or $\mathbf{t_{1/2}}$, less than 2 hours), intermediate (i.e. heterozygous fast), and slow acetylators ($t_{1/2}$ greater than 2 hours) have been identified. Some Asian populations approach 80% fast genotype, while other populations trend towards 50% of each genotype. Some data suggest higher doses should be used in fast acetylators. Renal excretion accounts for up to 40% of INH, and it

has good cerebrospinal fluid penetration.(31-33) INH accumulates in epithelial lining fluid and in alveolar macrophages while concentrations in lesions are similar to plasma and may not extend into caseum.(33,35) INH can inhibit CYP1A2, 2A6, 3A4 and 2C19 to varying degrees.(33) Most clinically reported interactions involve CYP3A4 or 2C19, leading to higher plasma concentrations of the companion drugs, including anticonvulsants and benzodiazepines.

INH **pharmacodynamics (PD)** is driven by the area under the curve to MIC ratio (**AUC/MIC**).(33,34) Even a few days of INH is very effective at rapidly reducing the recoverable number of live *Mtb* in sputum, a phenomenon known as **early bactericidal activity (EBA)**.(17-20) The main toxicity of INH is **DILI**, affecting from <1% to about 2% of patients. Peripheral neuropathy and central nervous toxicity also occur, and these can be mitigated by the use of small doses of pyridoxine (vitamin B6). These adverse events may be more common in slow acetylators.

Rifampin

RIF currently is **the most important TB drug**. It binds to the beta subunit of mycobacterial DNA-dependent RNA polymerase enzyme, inhibiting transcription.(33) Resistance is conferred by mutations clustered in an 81-bp region of the *rpoB* gene, and this knowledge can be used to great effect within rapid **genotypic tests for RIF susceptibility**.(33) RIF is approximately 70% bioavailable; absorption is modestly affected by food.(33) Absorption increases non-linearly with dose through 40 mg/kg, with AUC higher than otherwise expected.(33,34) RIF has complex absorption involving the hepatic organic anion transporter SLCO1B1.(33,34) RIF is metabolized by hepatic esterases, possibly arylacetamide deacetylase (AADAC), primarily to the partially active 25-O-desacetyl-rifampin.(33) **Auto-induction of non-cytochrome P450 pathways** reduces RIF's AUC by 30-40% over the first 2 weeks of treatment. RIF and its metabolites are excreted in the bile, and may undergo **enterohepatic recirculation**. Concentrations in cerebrospinal fluid at doses of 10 mg/kg are very low.(31-33) Rif does accumulate in aveolar macrophages.(33) Penetration into caseum may be slow, but is good.(33,35)

RIF displays a modest EBA, but it is the most important **sterilizing drug** available for TB, meaning that the bacillary population is sufficiently reduced to prevent relapse. Until very recently, regimens

lacking RIF generally were 12-18 months, occasionally longer, and generally less effective.(17-19,33,34) This ability to act against what generally are termed **non-replicating persisters (NRP)** is the key feature of RIF and other rifamycins.(17-20,33,34) Importantly, the maximum effective RIF dose has never been defined in any PD model, with increasing AUC/MIC causing further reductions in the colony forming units (CFU). This has led to a renewed interest in **high-dose RIF therapy** for all forms of TB.(33,34,36,37)

Transient rises in bilirubin and/or transaminases are common, while true DILI is much less common.(19,20,33) RIF may cause cutaneous hypersensitivity or serious hypersensitivity reactions, especially with intermittent dosing.(19,20,33) A **flu-like syndrome**, or rarely, respiratory distress, hemolytic anemia, leucopenia and severe thrombocytopenia may occur. RIF should be permanently discontinued in the face of serious hypersensitivity reactions. RIF is a **strong inducer of multiple CYP isoforms** including CYP3A4, CYP2A6, CYP2B6, CYP2C9 and CYP2C19 but not CYP2D6 *in vitro*.(19,20,32,33) RIF also induced Phase 2 enzymes and various transporters, including Pgp. RIF therefore produces numerous **drug-drug interactions (DDI)** since the majority of prescription drugs are metabolized by one or more of these isoforms.

Pyrazinamide

Pyrazinamide (PZA) is a **pro-drug**, activated by human and mycobacterial amidases to form pyrazinoic acid (POA). It appears that protonated POA accumulates within *Mtb* and damages many important cellular processes.(32,33) Resistance primarily is associated with mutations in the *pncA* gene. Phenotypic and genotypic **resistance testing for PZA can be challenging**. The typical PZA dose is 25 mg/kg once daily, which is lower than the 35 mg/kg dose studied by the **British Medical Research Council (BMRC).**(17,18) A dose of 50-70 mg/kg three times per week occasionally is used when intermittent therapy is required.(20,33) PZA is well-absorbed and not affected by food or antacids. PZA is metabolized to pyrazinoic acid, and subsequently to 5-hydroxy-pyrazinoic acid.(31-33) Concentrations in the cerebrospinal fluid are similar to those in plasma.(31-33) PZA accumulates strongly in epithelial lining fluid but not in alveolar macrophages.(33) PZA does penetrate pulmonary lesions reasonably well.(33,35)

PZA has a weak EBA but is considered a key **sterilizing drug**, shortening the treatment for DS-TB from 9 to 6 months when combined with rifampin.(17,18,20) PZA appears to have a maximum impact within the first two months of treatment, targeting a subpopulation of *Mtb* within acidified portions of the lesions.(33) PZA's efficacy is predicted by AUC/MIC.(34) **DILI** is the main concern with PZA. Current guidelines do not recommend reintroducing PZA after a severe episode of DILI. Increased plasma uric acid, but very rarely gout, and gastrointestinal intolerance may occur. PZA is free of significant drug interactions.(20,32,33)

Ethambutol

The D-isomer of ethambutol (EMB) is an inhibitor of mycobacterial cell wall arabinosyltransferases, leading to depletion of arabinogalactan and lipoarabinomannan. Resistance primarily is associated with mutations in the *embB* gene, which codes for the major arabinosyltransferase enzyme.(32,33) Oral bioavailability is approximately 80%, with minimal effects of food or antacids.(33) 70% is excreted unchanged in the urine, and **elimination is related to renal function**.(31-33) Concentrations in CSF are typically 50% or less than those in plasma, generally less that 1 mcg/ml.(31-33) ETH does not accumulate in epithelial lining fluid but concentrates highly in alveolar macrophages and in pulmonary lesions.(33)

EMB has a modest EBA.(33) EMB's current first-line use is intended to **prevent emergence of RIF resistance**. EMB is dosed at 15-25 mg/kg daily or 50 mg/kg thrice weekly. EMB's efficacy is predicted by Cmax/MIC and by AUC/MIC.(34) The most serious toxicity of EMB is **optic neuritis** and is dose-related, and which is consistent with EMB delivery to the CNS.(20,31-33) Screening of acuity and color vision prior to and during treatment is essential, and EMB should be discontinued as soon as this complication is suspected. EMB is free of significant drug interactions. The half-life of EMB is **prolonged in renal failure** and EMB is minimally removed by dialysis (~1%).(32-34) Three-times weekly dosing post-dialysis is recommended with **therapeutic drug monitoring (TDM)** to ensure 24-hour trough concentrations are less than 1 mcg/mL.(32-34) Anecdotal experience shows EMB should be avoided in patients receiving peritoneal dialysis.

Alternative drugs

Under certain circumstances, one cannot or should not use the standard RIPE regimen. These include known allergy or intolerance, extensive DDI, or known drug resistance. Under these conditions, and **in consultation with experienced TB clinicians**, one can derive an effective alternative regimen to meet most clinical situations. Every effort should be made to include a rifamycin in the regimen. The reader is referred to **recently published guidelines** and their supplements for further details.(3,19-22)

Rifabutin

Rifabutin (RBN) is a lipophilic, synthetic spiro-piperidyl derivative of RIF, with a similar mechanism of action. Most mutations in the *rpoB* gene associated with RIF resistance also produce RBN resistance.(20,31-34) Some controversy exists as to whether "RIF-resistant, RBN-susceptible" isolates can be effectively treated with RBN, since clinical experience is severely limited. RBN absorption is not significantly affected by food.(32,33) The primary metabolite is the partially active 25-O-desacetyl-RBN.(32,33) Like RIF, RBN shows concentration-dependent killing. C_{max} values with the typical 300 mg daily dose above 0.45 mcg/ml are associated with better clinical outcomes.(32-34) RBN does accumulate in aveolar macrophages.(33) Penetration data into caseum are not available.

Like RIF, RBN may occasionally cause DILI. RBN also may cause reversible **anterior uveitis**, typically with combined C_{max} values of the parent plus des-acetyl metabolite above 1 mcg/ml, usually as the result of DDI.(31-33) Arthralgia, skin discoloration and leucopenia also have been reported. **RBN is a less potent inducer of CYP isoforms than RIF**, and this is why it is used.(20,31-34) However, unpredictable bi-directional interactions may occur, because RBN is a substrate for CYP3A4, as well as an inducer.

Rifapentine

Like RIF, RPT is an inhibitor of DNA-dependent RNA-polymerase.(31-33) Complete cross-resistance with RIF is expected. **High-fat meals increase the AUC** by 30-80%.(20,32,33) **Plasma protein**

binding is around 99%, and this may reduce penetration into cavitary TB lesions.(33) RPT is primarily metabolized to the partially active 25-desacetyl-RPT.(32,33) Like RIF, RPT shows concentration-dependent killing.(33,34). Initially, RPT was dosed at 600 mg, but more recent studies have used 1200 mg daily, with food, for active TB disease. Dosing for LTBI is noted above. RPT does accumulate in aveolar macrophages.(33) Penetration into caseum is very limited.(33,38)

Like RIF, RPT may be associated with DILI, and RPT may cause serious **rifamycin hypersensitivity syndromes**. **RPT strongly induces CYP3A4**, especially with daily doses. Unlike RBN, **RPT has no advantage over RIF regarding DDI**.(20,32,33)

Fluoroquinolones

Some of the fluoroquinolones have established roles as TB drugs, even though they have not been approved by regulatory agencies for that indication.(20,33,34) Moxifloxacin (MFX) and levofloxacin (LFX) are most commonly used. Limited head to head comparisons in humans with TB have been conducted, and debate continues regarding the correct dose for each. Both MFX and LFX concentrate in alveolar macrophages and in pulmonary lesions, as measured by microdialysis and MALDI-ToF imaging.(33) Early on, it was hoped that fluoroquinolones could approach the sterilizing activity of the rifamycins, but they do not appear to be as potent. Nevertheless, meta-analyses show fluoroquinolones are key drugs in the treatment of MDR-TB.(28,29,34,39)

Moxifloxacin

MFX and other fluoroquinolones inhibit the enzymes DNA gyrase and topoisomerase IV, although the latter is lacking in *Mtb*. This blocks the supercoiling of DNA. Mutations in both the *gyrA* and less commonly *gyrB* genes confer resistance.(21,22,32,33)

Oral bioavailability of MFX is greater than 90%, and it has good CNS penetration.(32,33) Elimination involves N-sulfo conjugation and glucuronidation. The $t_{½}$ of MFX is 11-15 hours in healthy volunteers, but is shorter, around 7 hours, in TB patients.(33,34) MFX's efficacy is predicted by

AUC/MIC (34). MFX concentrates in epithelial lining fluid, alveolar macrophages, and pulmonary lesions (33,34A). MFX 400 mg daily has a moderate EBA and modestly accelerated culture conversion in several Phase IIB studies in DS-TB.(21,22,33,34) *Preliminary results* show that a **4 month regimen** including RPT 1200 mg and MFX 400 mg was non-inferior to the standard 6 month regimen.(40)

MFX **prolongs the QT_c interval** and should be used with caution in conjunction with other QT_c prolonging agents, and in patients with pro-arrythmic conditions.(32,33,34) Like other fluoroquinolones, MFX also is associated with psychiatric disturbance, tendinopathy, and increases in transaminases. **RIF reduces the MFX AUC** by 27-32%, with RPT expected to do the same.(33,34) Co-administration of di- or trivalent cations should be avoided.

Levofloxacin

Levofloxacin shares many of the characteristics described above for MFX. Oral bioavailability of LFX is 99-100 % with minimal food effect.(32-34) Nearly 90% of the parent drug is **excreted unchanged in the urine**. The $t_{½}$ of LFX is about 7 hours, and CSF penetration is about 74%.(32-34) LFX's efficacy is predicted by AUC/MIC.(34) LFX concentrates in epithelial lining fluid, alveolar macrophages, and pulmonary lesions.(33)

At a dose of 1000 mg, LFX had a slightly higher EBA than MFX.(33) LFX typically is dosed at 750-1000 mg once daily for TB, although higher doses are being investigated. LFX can prolong the QTc interval.(32-34) It shares other potential adverse drug effects with MFX. LFX does not depend upon, or interfere with, metabolizing enzymes.

Newer replacement regimens

When RIPE or single drug modifications cannot be used, novel regimens must be considered. Newer regimens are displacing the older second-line drugs, with the "BPaL" regimen, BDQ, PMD, and LZD currently of interest. Other regimens can be built around these drugs, especially BDQ, to eliminate

injectables, and keep the duration at 9 months, and possibly less. Various combinations of new and investigational drugs will continue to be studied.(28,29,33,34,39)

Bedaquiline

Bedaquiline (BDQ) is a synthetic diarylquinoline that inhibits mycobacterial ATP synthase.(28,29,33,34,39) Mutations in the *atpE* gene selected *in vitro* are clearly associated with high-level resistance.(33) **Bioavailability is increased 2-fold by food**, and plasma protein binding is >99%.(33,34) BDQ is metabolized by CYP3A4, CYP2C8 and 2C19 to N-monodesmethyl-BDQ and further demethlyated metabolites, which are excreted in the feces.(33) A loading dose of 400 mg daily is administered for 2 weeks, followed by a maintenance dose of 200 mg three times a week with food. BDQ's Cmin and AUC have a significant effect on response.(34) In mouse models, BDQ preferentially accumulated within the highly cellular regions in the lungs, with lower concentrations within the central caseum.(41)

BDQ exhibits a modest and delayed EBA. Culture conversion at 8 weeks was improved by the addition of BDQ in a Phase II trial in MDR-TB.(28,29,33,34,39) Also, there was evidence of a mortality benefit from observational data in South Africa. BDQ at steady state **prolongs the QT_c interval**, but has not been clearly associated with serious dysrhythmias.(28,29,33,34,39) It may cause gastrointestinal disturbance, arthralgia, headache and dizziness. Phospholipidosis seen in preclinical models has not been observed in humans to date.(33) Since it is principally metabolized by CYP3A4, BDQ plasma concentrations may be significantly decreased by inducers of the enzyme (rifamycins, 75% or more for RIF and RPT) and increased by inhibitors (ritonavir, ketoconazole and clarithromycin).(33,34)

Pretomanid

Pretomanid (PMD) is a **pro-drug** that gained FDA approval in late 2019, in combination with BDQ and linezolid (BPaL), for the treatment of highly-resistant tuberculosis.(28,29,34,39,42) It is a nitroimidazole that inhibits mycolic acid synthesis in actively multiplying bacilli, with additional affects against NRP likely based on the release of intracellular nitric oxide.(28,42) Like delamanid

below, it appears that mutations in F420 coenzymes Rv3547, FGD, FbiA, FbiB and FbiC are associated with *in vitro* resistance.(43) **Food increases pretomanid absorption**.(28,34) Pretomanid is metabolized by multiple reductive and oxidative pathways, with CYP3A4 responsible for approximately 20%.(44) Efavirenz reduces the AUC of pretomanid by 35%, and rifampin by 66%.(28,34) PMD's Cmin and AUC have a significant effect on response in murine models.(45) Detailed tissue penetration studies have yet to be published. The most common adverse events observed during pretomanid therapy included peripheral neuropathy, anemia, GI upset, and elevated liver enzymes.(28,34) Monitoring the latter is very important, and studies continue regarding effects on male fertility.

Linezolid

Linezolid (LZD) has been used for drug-resistant Gram-positive infections since 2000.(32) It is a synthetic inhibitor of ribosomal translation, binding to the 23S subunit and formation of the initiation complex.(32,33) Resistance is associated *in vitro* with point mutations in the peptidyl transferase domain of the 23S Rrna (*rrs* gene). Oral bioavailability is approximately 100% and is not affected by food.(32,33) Biotransformation occurs by non-enzymatic oxidation of the morpholine ring, and renal elimination of parent drug plus metabolites.(32-34) Concentrations in lesions determined by *ex vivo* dialysis were 49% of serum, with good distribution by lesion type.(33,35) CSF exposure is 57% of plasma.(33) While twice daily dosing is common for Gram-positive infections, **600 mg once daily is the most frequently used dose for TB**. Higher doses are being explored, but appear to be more toxic.(21,22,25) AUC appears to be the main driver of efficacy, especially with combination therapy.(34) Trough appears closely associated with mitochondrial toxicity.(34)

LZD monotherapy achieved 87% culture conversion at six months in a small trial of patients with XDR-TB.(33) LZD inhibits protein synthesis in human mitochondria resulting in clinically significant toxicities including lactic acidosis, **myelosupression, and peripheral and optic neuropathy** with chronic dosing, as is required for TB.(26,28,32) Trough concentrations of LZD correlate with mitochondrial dysfunction and risk of toxicity, and therapeutic drug monitoring may be useful.(26,34) LZD does not depend heavily upon, or interfere with, metabolizing enzymes. However, RIF can

reduce LZD plasma exposure by about a third.(33) LZD is a weak inhibitor of monoamine oxidase and should usually not be used with MAOIs, SSRIs or triptans due to reports of serotonergic syndrome.(33)

Clofazimine

Clofazimine (CFZ) is a semi-synthetic riminophenazine.(21,22,33,34. The mechanism of action has been postulated to be disruption electron transport and generating reactive oxygen species.(33) Additional mechanisms have also been suggested, including disruption of the membrane potential through inhibition of potassium uptake channels.(33) Resistance mutations and the PK/PD driver for CFZ have not been clearly identified.(33,34) Since CFZ has a very long half-life, like BDQ, one can posit that Cmin and AUC will correlate with activity. Oral bioavailability is 45-62% and is **increased 45% by a high fat meal**.(33,34) Though the initial $t_{½}$ is 7.8-15.9h this reflects distribution and the terminal elimination $t_{½}$ is 70 days.(29,33,34) CFZ concentrations in the rim of lesions are 10 times higher than in plasma, though lower in caseum.(33,35)

CFZ is usually dosed at 100 mg daily with food, though 200 mg may be used for short periods in severe disease.(20,21,33,34) CFZ crystals are deposited throughout the body during treatment, and may be associated with epithelial and body fluid discoloration, dry skin, photosensitivity and corneal deposits. The discoloration is reversible, but only after six months or more off treatment. Gastrointestinal discomfort also is common, and gastrointestinal obstruction and bleeding have been reported. CFZ has not been shown to provoke drug-drug interactions. However, CFZ may significantly **prolong the QT_c interval,** and could potentiate this effect by other drugs.(20,21,33,34)

Delamanid

Delamanid (DLM) is the R-enantiomer of a synthetic nitro-dihydro-imidazo-oxazole derivative, a chemical relative of pretomanid. It is a **prodrug** activated by the F_{420} dependent nitro-reductases, and resistance is associated with mutations in the genes coding for these coenzymes.(33) DLM inhibits mycolic acid synthesis and releases reactive oxygen species in mycobacteria.(27,33) Oral bioavailability is estimated to be 25-47% and is increased 3-4 fold by food.(27,33,34) Plasma protein

binding >99.5% to albumin and lipoproteins.(33) The **metabolism** of DLM is complex, **initiated by albumin**, with subsequent oxidation by CYP3A4 and possibly other enzymes.(33) DLM is dosed at 100 mg twice daily for two months and then 200 mg daily with food.(27-29,33,34) DLM's PK/PD driver is not well described. It may be reasonable to expect Cmin and AUC have a significant effect on response, based on PMD.(43)

DLM **prolongs the QT_c interval**. Caution should be exercised in patients with hypoalbuminaemia. DLM also may cause nausea, vomiting, tremor, anxiety and paraesthesia. RIF reduces the DLM AUC 47%, while ritonavir increases AUC by 25%.(33) Use cautiously with other inducers and inhibitors of CYP3A4.

Beta-lactams

Imipenem, Meropenem, Ceftazidime

Imipenem (IMP) and Meropenem (MRP) are synthetic carbapenems, and ceftazidime (CTZ) is a 3rd generation cephalosporine.(32,33) They target multiple transpeptidases (penicillin-binding proteins) involved in bacterial cell-wall synthesis .(32,33) Resistance occurs by enzymatic degradation. Specifically, ***Mtb* possesses an extended spectrum class A β-lactamase (BlaC)**, which must be inactivated.(33) **Clavulanic acid and avibactam** are candidates for this role.(29,33,34,46) Clavulanic acid can be given orally (only in combination with amoxicillin); the other drugs are given intravenously. Dosing has been empiric, and is not a settled matter. For rapidly multiplying bacteria, time above MIC is the PK/PD driver. For slow-growing TB, clinical proof is pending.(34) To date, most experience has been with IMP dosed at 1000 mg 12 hours and MRP dosed at 1000 mg 8 hours, intravenously – a route of administration that limits widespread application in outpatient clinics.(33) Most of the drugs are excreted unchanged in the urine.(32-34) No data are available on penetration of lesions. Concentrations in CSF are 10-30% of plasma.(32,33) No comparative or controlled clinical studies have been reported, though a meta-analysis of observational studies in MDR-TB observed more favorable response rates with MRP than with IMP.(29,33) Adverse effects include hypersensitivity reations, abnormal liver enzymes, and DILI. CNS side-effects including seizures may

occur, especially with renal dysfunction.(32,33) Beta-lactams do not depend upon, or interfere with, metabolizing enzymes.

Reserve Drugs

A number of older TB drugs can be used in certain situations. These drugs tend to have weaker activity against TB, higher rates of adverse drug reactions, or both. Therefore, these drugs are used out of necessity, to round out regimens that otherwise are lacking. With the advent of newer agents, these drugs likely will be used less. A brief summary is provided.

Aminoglycosides

Streptomycin (SM), kanamycin (KM), and amikacin (AK) all have been used for TB, usually at a dose of 15 mg/kg once daily. Currently, amikacin appears to be the preferred drug, although **treatment is moving away from the use of injectable agents**. Clearance is highly dependent on renal function. Aminoglycoside Cmax and AUC have a significant effect on response.(34) SM and AK have weak EBA but the clinical efficacy of aminoglycosides in both DS and MDR- TB is supported by clinical trial and observational data.(17-19,30,32,33) Penetration into human lung lesions was poor.(35)

Aminoglycosides are associated with ototoxicity (**hearing loss or vestibular effects**) which are related to the duration of dosing, but not to dose size or interval.(30-34) Nephrotoxicity is less common and usually reversible. Hypokalemia and hypomagnesemia also occur.(30-33)

Capreomycin

Capreomycin (CM) is an **injectable macrocyclic polypeptide**. Cross-resistance with KM / AK is common but not with SM. It is excreted unchanged in the urine.(30-33) The typical dose is 15 mg/kg daily IM or IV. Overall, CM is similar to aminoglycosides regarding dose, pharmacokinetics, and adverse effects. It is assumed that the PK/PD drivers also are similar. Based on recent meta-analyses, its use has fallen out of favor.(20-22)

Para-aminosalicylic acid

Para-aminosalicylic acid (PAS) is a synthetic analogue of para-aminobenzoic acid.(17-19,30-34) Absorption of the **sustained release dosage forms** is improved by food.(32,33) The usual dose is 4000 mg twice daily. The major metabolite is N-acetyl PAS, produced by NAT1. PAS has a modest EBA that may be dose dependent.(30-34) PAS granules usually are given as 4 grams twice daily, with food. The PK/PD drivers for PAS are not certain. Based on limited *in vitro* activity, time above MIC can be suggested.(47) In contrast, limited clinical data suggest high peaks may produce better effects.(48) Penetration into human lung lesions is unknown. GI upset and diarrhea are the main adverse effects. PAS has been associated with **hypothyroidism** and goiter, especially when used with thioamides.(30-34)

Thioamides

Ethionamide, Prothionamide

Ethionamide (ETA) and Prothionamide (PTA) are synthetic structural analogues of nicotinamide. Both are **prodrugs** activated by the mycobacterial mono-oxygenase EthA and target the same enoyl-acyl reductase enzyme InhA as INH, disrupting mycolic acid synthesis.(30-34) Oral bioavailability is nearly complete and is not significantly affected by food.(32,33) Clearance involves sulphoxidation, desulphuration and deamination followed by methylation. The **sulphoxide metabolites are active**. AUC has been suggest as the driver of efficacy, similar to that seen with INH (34). Penetration into human lung lesions is unknown.

No EBA data are available for ETA or PTA. ETA and PTA are dosed at 15-20 mg/kg per day up to a maximum of 1g. To improve tolerability, the drugs are usually dose-escalated over several days. Gastrointestinal tolerability of ETA and PTA is poor.(30-34) **Hypothyroidism** may occur in up to 30% of patients on ETA (32,33). Gynaecomastia also may occur.

Cycloserine and Terizidone

D-Cycloserine (CS) is a small, water-soluble weak acid.(30-33) Terizidone (TZ) is a condensation product of two cycloserine molecules with terephtalaldehyde, which acts as a pro-drug. **CS is a**

natural product analogue of D-Alanine. It is a competitive inhibitor of alanine racemase and D-alanine:D-alanine ligase, disrupting peptidoglycan synthesis.(33) CSF concentrations are 80-100% of plasma in meningitis.(14) Analogous to beta-lactams, Cmin/MIC or time above MIC have been suggested as the driver of efficacy.(34) Penetration into human lung lesions is unknown.

No EBA studies of CS or TZ are available. Weak evidence for their efficacy derives from combination studies in retreatment from the 1960s.(30-34).The usual starting dose of CS and TZ is 250 mg once daily, increased by 250 mg every few days to a maximum of 500 mg twice daily, though many patients tolerate less than that. The therapeutic index of CS is low. **Neuropsychiatric side-effects** are common (~6%) including drowsiness, anxiety, mood disturbance, psychosis and seizures.(30-34) Pyridoxine 50-100 mg is suggested to counteract neurotoxicity, but proof of efficacy is lacking.(33) Dosing should be guided by therapeutic drug monitoring.

Problems and Solutions

Heteroresistance and multiple isolates

Knowing what you are treating is one key to success. It is well known that patients can have more than one *Mtb* isolate infecting them at the same time. This might occur due to more than one infectious event, or generated within the host due to variable growth conditions or gradients of drug exposure. Molecular approaches can detect heteroresistance, i.e. the presence of a resistant subpopulation in otherwise phenotypically drug susceptible mycobacteria.(49,50) This is an active area of research focused on refining tests to be both sensitive and highly specific.

Drug Penetration into cavitary lesions

It is widely recognized that *Mtb* provokes an immune response that can seriously damage the lung parenchyma.(3,6,19,33) Cavitary lesions can wax and wane over the course of the disease, and can provide sanctuary to organisms, especially those in the acidified areas and in the caseum. Drug delivery into these areas is needed, but must rely on passive diffusion and the chemical properties of the drug.(33) Several models have been evaluated, including in vivo and ex vivo animal models, and ex vivo human models. It appears that the drug with the most favorable penetration profile is

rifampin.(34A,36A,51,52) Information of this type can assist in the design of next-generation TB drugs.

Drug Penetration into the central nervous system

The deadliest form of TB in central nervous system TB, most often meningitis but sometimes tuberculoma.(3,19,33) As with other central nervous system infections, CNS penetration is limited for some important drugs, including rifampin and ethambutol.(31-33,53-56) Treatment typically is extended up to a year.(3,19,20) Higher doses, and alternative agents, including fluoroquinolones and linezolid, are being studied for this condition.(33,53-56) Advances for this condition can contribute significantly to lowering TB morbidity and mortality.

Drug Penetration into bone

TB osteomyelitis is another condition frequently requiring extended treatment.(3,19,33) Because of the limited vascular supply to parts of various bones, drug penetration can be limited as well as difficult to study.(19,31-33,57-59) This is an area where alternative dosage forms might be able to expedite the elimination of Mtb within bone lesions.

Inhaled drug therapy

Given that TB typically presents as a chronic pneumonia, it is tempting to consider direct chemotherapy in the lungs, thus sparing systemic toxicity.(19,32) Several drugs have been prepared as inhaled dosage forms.(60-64) The challenges to this approach include delivery into the damaged areas of the lung, extra-pulmonary organisms, patient acceptance, adherence, and proper technique, and cost. All of these problems can be overcome, some more easily than others. It will remain true that TB is not confined to the lungs.(3,19) Therefore, inhaled therapy may be an add-on component of therapy, potentially rendering patients non-infectious more quickly, and potentially shortening the duration of treatment.

Are there biological barriers to shortening regimens?

It is only with immense difficulty that randomized clinical trials have been able to show reasonable success (non-inferiority) with a standardized 4 month regimen.(38) Many other potentially good regimens were not able meet this goal.(65-67) Part of the puzzle lies with the heterogeneity among patients, some having new disease, others well-entrenched or recurrent, some having minimal lesions, others having large cavities. Another part of the puzzle is that there is no good way, currently, to assess the degree of immune function specifically against TB, and no good way to enhance it. Yet another piece lies in standardized dosing – one size fits all – even though wide interpatient pharmacokinetic variability is known to exist.(34,68) Finally, it is not known if the pathogen within the host, especially acid-phase and NRP *Mtb*, might have defense mechanisms that simply require months of chemotherapy to effectively overcome. In other words, are there biological barriers to shortening regimens, such as phenotypic antibiotic tolerance, that prevent further shortening of regimens until they are understood and overcome?

Understanding drugs and doses

Preclinical models allow for explorations that would not be possible in humans. Several animal species have been used for TB drug development, each with advantages and disadvantages. These include various types of mice, Guinea pigs, rabbits, and non-human primates.(69-74) *In vitro* systems, including Hollow Fiber Infection Model (HFIM), allow one to control drug exposure, and one can mimic either animal or human pharmacokinetics.(75-77) Through this process, important insights have been learned. A few of these are shared here, reflecting our experience with an NIH-funded program project grant for TB regimen development, based at the University of Florida. This is one example of such an approach. The interested reader also can evaluate TB research programs at other institutions, including Johns Hopkins University, Colorado State University, Hackensack Meridian Health, the University of California, San Francisco, and several others outside of the United States, including the University of Liverpool, Radboud University, the University of Cape Town, and Stellenbosch University.

Preclinical animal models of infection are employed to develop new agents, but also to screen among molecules to rank them.(78,79) Limitations include variable natural susceptibility to TB, different

immune responses, different lesion pathology, and so forth. Also, animal models of infection may have very different pharmacokinetics compared to humans, leading to substantial differences in efficacy.(78,79) Otherwise useful drugs could be discarded if a particular model does not look favorable. The HFIM can be used to evaluate the impact of different pharmacokinetic profiles on bacterial cell kill, as well as resistance suppression.(78,79) Then, the *in vitro* results are examined with mathematical modeling, allowing one to establish links between HFIM reproductions of plasma and bronchoaveolar lavage (BAL) concentrations from animals or humans, and the pharmacodynamics of test drugs.(78,79) This information allows one to select the dose and frequency needed to optimize therapy.

As more repurposed drugs and new agents are considered, how does one prioritize among the hundreds of potential regimens to explore? Even 6-8 potential agents translate into 64-256 possible 2-drug combinations.(80) There is neither time nor resources to give an extensive evaluation for all combinations.(80) A screening procedure is needed to identify combinations with a high likelihood of achieving good bacterial burden decline.(80) The University of Florida research team examined pretomanid, moxifloxacin, linezolid and bedaquiline in Log-phase growth, Acid-phase growth and non-replicating persister (NRP)-phase, using the Greco interaction model.(80) The primary metric was bacterial kill.(80) The combination of pretomanid plus moxifloxacin emerged as the clear frontrunner, as the largest bacterial declines were seen in Log-phase and Acid-phase with this regimen and it was second best in NRP-phase, while bedaquiline also produced good kill.(80) This screening process may identify optimal combinations that can be further evaluated in both the HFIM and in animal models of Mycobacterium tuberculosis infection.(80)

The next phase is to develop multidrug regimens, combining the best candidates from the initial steps.(81) First, 2-drug regimens with a synergistic or additive interaction are determined, using a full factorial study design.(81) Next, optimal 3-drug regimens are explored. Total bacterial burdens and the less-susceptible or resistant subpopulations can be examined.(81) Once again, mathematical models are fit to the data, followed by Monte Carlo simulations. The time and conditions needed to drive the total bacterial burden to extinction with multidrug regimens can be determined.(81) This

model-based system approach to evaluating combinations of 3 agents shows promise to rapidly identify the most promising combinations to take forward in human trials.(81)

We may look at the combination of these three citations (78-81) and recognize that, taken together, they lay out an algorithm to identify potential high value multi-drug combinations. As more and more agents are discovered or repurposed, this algorithm will be increasingly useful.

Conclusions

This tutorial should provide the reader with a concise summary of major trends in the area of TB treatment. We attempted to be judicious in our selection of topics, and this tutorial should not be considered encyclopedic. We do hope that the references provided offer the reader an opportunity to examine the past and to look into the future of TB treatment.

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FIGURE LEGEND

Figure 1. WHO grouping of medications for multidrug-resistant TB. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2019. License: CC BY-NC-SA 3.0 IGO. Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris. The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

Figure 2. Working Group on New TB Drugs 2021 pipeline of TB drugs. Credit: Stop TB Partnership's Working Group on New TB Drugs (Pipeline as of March 2021).

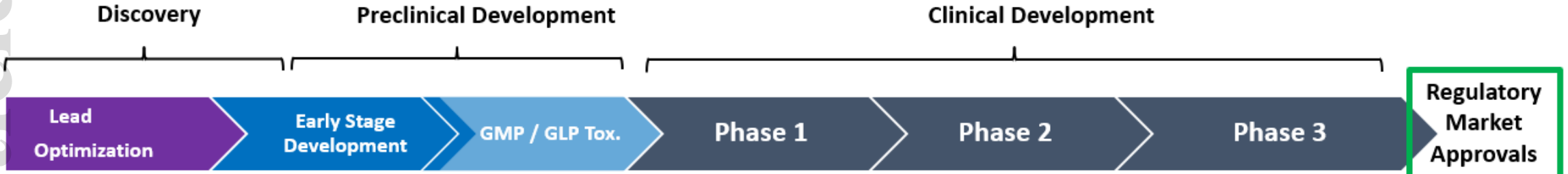
Figure 3. NIH depiction of TB drug mechanisms of action. The photo of *Mycobacterium tuberculosis* is from the Centers for Disease Control and Prevention (http://wayback.archiveit.org/7761/20160909192435/http://phil.cdc.gov/phil/home.asp), CDC/Dr. Ray Butler, Janice Carr. This illustration is in the public domain. Credit: the National Institute of Allergy and Infectious Diseases (NIAID).

Table 2.1. Grouping of medicines recommended for use in longer MDR-TB regimens[1]

Groups & steps	Medicine	
Group A: **Include all three medicines**	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: **Add one or both medicines**	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: **Add to complete the regimen and when medicines from Groups A and B cannot be used**	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

1. This table is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized; *see* Section 4). Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 IPD-MA for longer regimens included no patients on thioacetazone and too few patients on gatifloxacin and high-dose isoniazid for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies (*see* online Annex 9).
2. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and below the age of 6 years was insufficient for review. Use of bedaquiline beyond these limits should follow best practices in "off-label" use *(48)*.
3. Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review.
4. Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using linezolid for the whole duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for more than 6 months and 30% for 18 months or the whole duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.
5. Evidence on the safety and effectiveness of delamanid beyond 6 months and below the age of 3 years was insufficient for review. Use of delamanid beyond these limits should follow best practices in "off-label" use *(48)*.
6. Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.
7. Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.
8. Amikacin and streptomycin are to be considered only if DST results confirm susceptibility and high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.
9. These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

2021 Global New TB Drug Pipeline [1]



PanD inhibitors
Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Macrolides
Mycobacterial Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase
Oxazolidinones

JSF-3285*
MPL-446, 447*
CPZEN-45*
NTB-3119*
TB-47*
TZY-5-84
FNDR-20081*
Spectinamide – 1810*

GSK-839*
OTB-658
Sanfetrinem

BVL-GSK098*
GSK-286*
TBAJ-587
TBAJ-876
TBI-223
Macozinone* (PBTZ-169)
TBI-166

SPR720*
BTZ-043*
TBA-7371*
GSK-656* (070)
OPC-167832*
Delpazolid
Sutezolid
Telacebec* (Q203)
SQ-109*
Macozinone*

Bedaquiline*
Delamanid*
Pretomanid*

Rifapentine / Moxifloxacin (4-month regimen)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical. Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2020

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: March 2021

Mechanisms of Action of Current TB Drugs