

Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis (Nahid et al, CID 2016)

APPENDIX C:

DRUGS IN CURRENT USE

The U.S. Food and Drug Administration (FDA) has approved 11 drugs for treating tuberculosis. Several other drugs, including levofloxacin and moxifloxacin, are not FDA approved for tuberculosis, but are used in selected populations. Rifabutin, approved for disseminated *Mycobacterium avium* complex disease, can be used to minimize drug-drug interactions. Amikacin and kanamycin are aminoglycosides used for drug-resistant organisms. Clofazimine, linezolid, and selected beta-lactam – beta-lactamase inhibitor combinations have been used in patients with drug resistant tuberculosis. The precise role of these additional drugs in the treatment of tuberculosis is a subject for further research.

Isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB) are considered first-line antituberculosis agents and form the core of initial treatment regimens. Rifabutin (RBT) and rifapentine (RPT) also may be used under certain circumstances. RBT is used predominantly to minimize drug interactions, as the current available evidence does not otherwise support the replacement of RIF by RBT for first-line treatment of tuberculosis [432]. RPT is currently used for latent tuberculosis infection, and may have an increasing role in the management of drug-susceptible tuberculosis pending ongoing randomized clinical trials. INH has excellent early bactericidal activity (EBA, meaning it is capable of causing a rapid drop in the number of actively multiplying bacilli within days), while rifamycins and PZA have excellent sterilizing activity, functioning to prevent post-treatment relapses). Streptomycin currently is seldom used. The remaining drugs are reserved for special situations, such as drug intolerance or mycobacterial resistance.

Basic antimicrobial pharmacology is predicated upon achieving adequate drug exposure. This exposure generally is quantified as the area under the curve (AUC) in a plot of unbound (protein-free, f) serum drug concentration versus time divided by the minimal inhibitory concentration (MIC) (i.e., the fAUC/MIC). For certain antimicrobials, peak concentration (fC_{max}/MIC) or time above MIC (f%Time>MIC) are more predictive of efficacy in the models or the patients studied. When fAUC/MIC or fC_{max}/MIC are most predictive of microbial killing, antimicrobials are considered “concentration-dependent.” Otherwise, when time above MIC (f%Time>MIC) is they are considered “time-dependent.” The use of such pharmacokinetic / pharmacodynamic (PK/PD) data allow for the most effective employment of antimicrobials, achieving maximum pathogen killing in the shortest time possible. Historically, these measures of drug effect have not been quantified routinely in tuberculosis patients. Drug exposure (i.e., AUC) has been assumed to be “adequate” in all treated patients, regardless of their weight or condition, and this has led to some uncertainties in terms of optimal dosing of first-line drugs. Instead of an MIC, isolates only have been characterized as “susceptible or resistant” at a “critical concentration”. In some locations, susceptibility data have not been used at all. Therefore, clinicians generally have not known how close serum drug concentrations were to achieving sub-MIC exposures in their patients. Even with weight adjustment, optimal dosing of PZA, for example, has yet to be determined. In prior guidance, PZA was recommended at 20 mg/kg/day (20-25 mg/kg/day); international guidelines recommend 25 mg/kg/day (20-30 mg/kg), however, the British Medical Research Council (BMRC) short-course clinical trials used PZA at 36 mg/kg/day [433-436]. Further research is needed to establish the optimal dosing of PZA in terms of efficacy, safety and tolerability.

Drug exposure is determined by the magnitude and the frequency of the dose. Drug exposure also is determined by the size of the patient, and the patient’s ability to clear the drug through the liver and/or kidneys. Inadequate drug exposure has been shown to produce delayed treatment responses and failures, as well as drug resistance [9, 249]. Conversely, high drug exposures have been correlated with more rapid clearance of

tuberculosis [418]. Thus, drug exposure is a key driver of efficacy in tuberculosis patients, and fixed doses (INH 300 mg, RIF 600 mg) and “maximum” doses may not be appropriate for heavier patients. This document removes the term “maximum” dose.

Isoniazid (INH)

- *Role in treatment regimen:* INH is a first-line agent for treatment of all forms of tuberculosis caused by organisms known or presumed to be susceptible to the drug. It has strong early bactericidal activity against rapidly dividing organisms [105, 437].
- *Dose:* (See **Table 2**).
 - Adults: typically 300 mg daily, or 15 mg/kg (typically 900 mg) once, twice, or three times weekly.
 - Children: 10-15 mg/kg daily; 20-30 mg/kg twice weekly.
- *Preparations:* Tablets (50 mg, 100 mg, 300 mg); Syrup (50 mg/5 ml); Aqueous solution (100 mg/ml) for intravenous or intramuscular injection.
- *Adverse effects:*
 - Asymptomatic elevation of aminotransferases: Aminotransferase elevations up to 5 times the upper limit of normal occur in 10-20% of persons receiving INH alone for treatment of latent tuberculosis infection [438]. The enzyme concentrations usually do not continue to rise or return to normal even with continued administration of the drug, a phenomenon known as hepatic adaptation.
 - Clinical hepatitis: Hepatitis occurred in 0.1-0.15% of 11,141 persons receiving INH alone as treatment for latent tuberculosis infection in an urban tuberculosis control program [439]. A meta-analysis of 6 studies estimated the rate of clinical hepatitis with INH alone to be 0.6%, with INH administered with other agents *not* including RIF to be 1.6%, and when INH was given with RIF to be 2.7% [187]. For INH alone the risk increases with increasing age; it is uncommon in persons under 20 but is nearly 2% in persons aged 50-64 [440]. The risk increases in persons with underlying liver disease, including viral hepatitis; current heavy alcohol consumption; concomitantly taking hepatotoxic medications, and possibly in postpartum women [441].
 - Fatal hepatitis: Once estimated to be as high as 14 per 100,000 [155], more recent studies suggest the rate of fatal hepatitis is substantially lower, between 1 and 7 per 100,000 [442-444]. Death and liver failure have been associated with continued administration of INH after the onset of symptoms of hepatitis [445].
 - Peripheral neuropathy [357, 446]: This adverse effect is dose-related and is uncommon (<0.2%) at conventional doses in otherwise healthy persons [447, 448]. The risk is increased in persons with nutritional deficiency, diabetes, HIV infection, renal failure, and alcoholism, as well as for pregnant and breastfeeding women and for those on certain chemotherapies [288]. Pyridoxine supplementation (25-50 mg/day) is used to minimize risk of neuropathy [42] and is used by some experts at higher doses (100 mg/day) to treat symptoms of peripheral neuropathy.
 - Central nervous system effects: Effects such as headaches, dysarthria, irritability, seizures, dysphoria, depression, and inability to concentrate have been reported.
 - Lupus-like syndrome [449, 450]: Approximately 20% of patients receiving INH develop antinuclear antibodies. Less than 1% develops clinical lupus erythematosus, necessitating drug discontinuation [451].
 - Hypersensitivity reactions: Reactions, such as fever, rash, Stevens-Johnson syndrome, hemolytic anemia, vasculitis, and neutropenia are rare.
 - Monoamine (histamine/tyramine) poisoning: This rare event produces headaches, flushing, lightheadedness, after consuming foods and drinks (certain cheeses and wine), having high concentrations of monoamines [218, 452-454].
 - Diarrhea: The commercial liquid preparation of INH contains sorbitol and may cause diarrhea.

- *Use in pregnancy:* There are no adequate and well-controlled studies in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of INH are assigned to a Category C risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Based on extensive use, INH is considered safe in pregnancy, even in the setting of HIV-coinfection [455, 456], but the risk of hepatitis has been reported to be increased in the peripartum period [441]. In pregnant patients, pyridoxine supplementation (25-50 mg/day) is used [42].
- *CNS penetration:* Penetration is excellent: cerebrospinal fluid (CSF) concentrations are similar to concentrations achieved in serum [457, 458].
- *Use in renal disease:* INH can be used safely without dose adjustment in patients with renal insufficiency [459] and with end-stage renal disease patients who require chronic hemodialysis (**see Guideline Section on Renal Disease**) [361, 460].
- *Use in hepatic disease:* Drug accumulation may occur in advanced hepatic disease. INH may be considered in patients with stable hepatic disease with frequent laboratory and clinical monitoring (**see Guideline Section on Hepatic Disease**).
- *Monitoring:* Routine monitoring generally is not done. However, in patients with pre-existing liver disease or who develop abnormal liver function that does not require discontinuation, liver function tests and symptoms are closely monitored. Serum concentrations of phenytoin and carbamazepine may be increased in people taking INH without RIF, and monitoring is required.

Rifampin (RIF)

- *Role in treatment regimen:* RIF is a first-line agent for treatment of all forms of RIF-susceptible tuberculosis. It has substantial sterilizing activity [461]. RIF is an essential component of all short-course regimens.
- *Dose:* (See **Table 2**)
 - Adults: typically 600 mg once daily, or with careful patient selection, twice weekly, or three times weekly. Higher daily doses are being studied.
 - Children: 10-20 mg/kg once daily or twice weekly
- *Preparations:* Capsules (150 mg, 300 mg) contents of capsule may also be mixed into an oral suspension; aqueous solution for parenteral administration.
- *Adverse effects* [462, 463]:[464]
 - Cutaneous reactions [465]: Pruritis with or without rash (6% of patients) is generally self-limited [466]. Continued treatment may be possible. More severe, true hypersensitivity reactions occur in 0.07-0.3% of patients [447, 467, 468].
 - Gastrointestinal reactions (nausea, anorexia, abdominal pain): Incidence is variable but rarely severe enough to require discontinuation [463, 465, 466].
 - Flu-like syndrome: Historically seen with intermittent high dose administration (900mg or higher administered intermittently) [465, 469, 470]. This reaction is uncommon with daily dosing [6, 467, 468].
 - Hepatotoxicity Transient asymptomatic hyperbilirubinemia may occur [56]. Clinical hepatitis with a cholestatic pattern also may occur [187, 471]. Hepatitis is more common when combined with INH (2.7%) [187].
 - Severe immunologic reactions: In addition to cutaneous reactions and flu-like syndrome, other reactions thought to be immune mediated include the following: thrombocytopenia, hemolytic anemia, acute renal failure, and thrombotic thrombocytopenic purpura [472-474]. These reactions are rare, each occurring in <0.1% of patients [467, 468]. RIF must be permanently discontinued in the setting of severe immunologic reactions.
 - Orange discoloration of bodily fluids (sputum, urine, sweat, tears): Patients should be warned of this effect. Soft contact lenses and clothing may be permanently stained.

- Drug interactions due to induction of hepatic microsomal enzymes: RIF is a major cause of drug interactions (**see Section on Drug-Drug Interactions**) with potentially serious consequences. Affected drugs include oral contraceptives, methadone, and warfarin. Readers are advised to consult the CDC website <http://www.cdc.gov/tb/default.htm> to obtain the most up-to-date information.
- False-positive opiate results: RIF can cause false-positive immunoassay results for urine opiates [475].
- *Use in pregnancy:* There are no adequate and well-controlled studies in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of RIF are assigned to a Category C risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Based on extensive use, RIF is considered safe in pregnancy [476].
- *CNS penetration:* Concentrations in the CSF may be only 10-20% of serum concentrations. Higher doses of RIF may be more effective [77, 477, 478].
- *Use in renal disease:* RIF can be used safely without dose adjustment in patients with renal insufficiency and end-stage renal disease (**see Guideline Section on Renal Disease**) [361, 478].
- *Use in hepatic disease:* Reduced RIF clearance may occur with advanced liver disease [478]. Other than in settings of advanced liver disease, RIF generally can be used safely, with increased frequency of clinical and laboratory monitoring (**see Guideline Section on Hepatic Disease**).
- *Monitoring:* No routine monitoring tests are required. Drug interactions may necessitate therapeutic concentration monitoring of other drugs.

Rifabutin (RFB)

- *Role in treatment regimen:* RFB generally is reserved for patients who are receiving any medication having unacceptable interactions with RIF (e.g., select antiretroviral therapies) or have experienced intolerance to RIF. The replacement of rifampicin by rifabutin for first-line treatment of tuberculosis is otherwise not supported by current evidence [432].
- *Dose:* (See **Table 2**)
 - Adults: typically 300 mg daily. With concomitant use of boosted protease inhibitors (i.e. with ritonavir or cobicistat), a starting dose of 150 mg daily. With efavirenz, RFB is increased to 450-600 mg daily. See http://www.cdc.gov/tb/publications/guidelines/HIV_AIDS.htm to obtain the most up-to-date information.
 - Children: Pediatric doses are not established. Serum concentrations can direct dosing. 5 mg per kg may be a reasonable starting dose.
- *Preparations:* Capsules (150 mg) for oral administration.
- *Adverse effects:*
 - Hematologic toxicity: Neutropenia and thrombocytopenia may occur in patients receiving RFB [479-481].
 - Uveitis: This is rare (<0.01%) in the absence of drug-interactions. Rates are higher when RFB is combined with inhibitors of CYP3A4 (macrolides, azoles, ritonavir or cobicistat) that reduce clearance of RFB and its 25-desacetyl metabolite [195, 480, 482, 483].
 - Gastrointestinal symptoms: GI symptoms may occur, as with RIF.
 - Polyarthralgias: This symptom may occur [484].
 - Hepatotoxicity: At the usual doses (150–300 mg/day), hepatotoxicity is uncommon [56]. Asymptomatic elevation of liver enzymes has been reported with high-dose rifabutin treatment in combination with macrolides [195].
 - Pseudo-jaundice (skin discoloration with normal bilirubin): This is usually self-limited and resolves with discontinuation of the drug [482].

- Rash: Only rarely associated with RFB. Acute generalized exanthematous pustulosis (AGEP) has been reported with RFB [485].
- Flu-like syndrome: Flu-like syndrome is rare in patients taking RFB.
- Orange discoloration of bodily fluids (sputum, urine, sweat, tears): Patients should be warned of this effect. Soft contact lenses and clothing may be permanently stained.
- *Use in pregnancy*: There are no adequate and well-controlled studies in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of RFB are assigned to a Category B risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks). In rats and rabbits, RFB used at 6 to 13 times the recommended human daily dose based on body surface area comparisons, no teratogenicity was observed [486].
- *CNS Penetration*: The drug has variable penetration of inflamed meninges, based largely on animal model and very limited clinical data [487-489].
- *Use in renal disease*: RFB may be used without dosage adjustment in patients with renal insufficiency and end-stage renal disease (**see Guideline Section on Renal Disease**) [490, 491].
- *Use in hepatic disease*: Reduced RFB clearance may occur with advanced liver disease [490][427][408]. Increase the frequency of clinical and laboratory monitoring when using RFB (or other rifamycin) in the setting of hepatic disease (**see Guideline Section on Hepatic Disease**).
- *Monitoring*: No routine monitoring tests are required. Two-way drug interactions may necessitate therapeutic concentration monitoring of RFB and the other drugs.

Rifapentine (RPT)

- *Role in treatment*: Previously, RPT was approved for use once-weekly, with INH, in the continuation phase of treatment for HIV-seronegative patients with noncavitary, drug-susceptible pulmonary tuberculosis who have negative sputum smears at completion of the intensive phase of treatment [9]. A 6-month regimen in which in the two-month intensive phase, INH is replaced by daily moxifloxacin 400mg followed by one weekly dose of both moxifloxacin 400mg and 1200 mg of RPT for 4 months in the continuation phase, has also been investigated in one clinical trial for pulmonary tuberculosis [163].
- *Dose*: (See **Table 2**)
 - Adults: Previously 10 mg/kg (typically 600 mg) once weekly during the continuation phase of treatment. Currently, 900 mg RPT once weekly (with INH 900 mg) has been approved for latent tuberculosis infection. Additionally, daily doses of 1200mg of RPT daily are being evaluated for active tuberculosis disease (ClinicalTrials.gov Identifier: NCT02410772).
 - Children: The drug is being studied in children. Proportionally higher doses (up to 2 times the adult mg per kg dose) may be needed.
- *Preparation*: Tablet (150 mg film coated).
- *Adverse effects*: The adverse effects of RPT are similar to those associated with RIF. Like RIF, RPT is a strong inducer of multiple hepatic enzymes and may cause drug-interactions. (**see Section on Drug-Drug Interactions**).
- *Use in pregnancy*: There are no adequate and well-controlled trials of RPT in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of RPT are assigned to a Category C risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks).
- *CNS penetration*: Insufficient information.
- *Use in renal disease*: Like RIF, RPT shows minimal renal clearance and thus likely can be used safely without dose adjustment in patients with renal insufficiency and end-stage renal disease (**see Guideline Section on Renal Disease**).

- *Use in hepatic disease:* Reduced RPT clearance may occur with advanced liver disease. Increase the frequency of clinical and laboratory monitoring when using RFB (or other rifamycin) in the setting of hepatic disease (**see Guideline Section on Hepatic Disease**).
- *Monitoring:* Monitoring is similar to that for RIF. Drug interactions involving RPT are comparable to those of RIF.

Pyrazinamide (PZA)

- *Role in treatment regimen:* PZA is a first-line agent for all PZA-susceptible isolates of tuberculosis. The drug is believed to exert greatest activity against dormant or semi-dormant organisms in an acidic environment [98, 492].
- *Dose:* (see **Tables 2, 9**)
 - Adults: typically 25 mg/kg daily (20-30 mg/kg); 35 mg/kg thrice weekly (30-40 mg/kg); 50 mg/kg twice weekly. The BMRC original short-course regimen clinical trials used PZA at 36 mg/kg/day [433-436].
 - Children: 30-40 mg/kg daily; 50 mg/kg twice weekly.
- *Preparations:* 500 mg (scored) tablets.
- *Adverse effects:*
 - Hepatotoxicity: PZA has been identified as the most hepatotoxic of the first line drugs [378]. Early studies using doses of 50-70 mg/kg/day reported high rates of hepatotoxicity [493, 494]. However, liver toxicity was less common at doses of 30-40 mg/kg/day in the BMRC short-course clinical trials. Both dose related and idiosyncratic hepatotoxicity may occur [56, 495].
 - Gastrointestinal symptoms (nausea, vomiting): Mild anorexia and nausea are common, severe nausea and vomiting are uncommon [496].
 - Non-gouty polyarthralgia: Polyarthralgias may occur in up to 40% of patients receiving PZA, not requiring discontinuation [497]. Pain usually responds to non-steroidal anti-inflammatory agents.
 - Asymptomatic hyperuricemia: This is expected [6, 498, 499], and even can assist in monitoring patient adherence.
 - Acute gouty arthritis: Acute gout is rare [499, 500], except in patients with pre-existing gout [501]; in patients with severe gout, the decision to use PZA is made in consultation with tuberculosis experts.
 - Transient morbiliform rash: This usually is self-limited, with continuation of the drug.
 - Dermatitis: PZA may cause cutaneous adverse drug reactions as well as photosensitive dermatitis [496, 502-505].
- *Use in pregnancy:* There are no adequate and well-controlled studies in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of PZA are assigned to a Category C risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks). The World Health Organization has included PZA in the regimen for pregnant women in their tuberculosis treatment guidelines since the first edition in 1993 [97].
- *CNS penetration:* The drug passes freely into the CSF [506]. In seven studies recording CSF concentrations of PZA, concentrations appear satisfactory and comparable to those in blood [458].
- *Use in renal disease:* PZA is cleared primarily by the liver, but its metabolites are excreted in the urine and may accumulate in patients with renal insufficiency [507]. The daily dose may be given three times a week following dialysis in patients with end stage renal disease (**Table 11**) (**see Guideline Section on Renal Disease**) [361].
- *Use in hepatic disease:* PZA can cause liver injury that may be severe and prolonged. If PZA is used in patients with liver disease, laboratory and clinical monitoring is increased and expert consultation sought (**see Guideline Section on Hepatic Disease**).

- *Monitoring:* Routine serum uric acid measurements are not necessary but may serve as a marker for adherence. Liver chemistry monitoring is performed when the drug is used in patients at risk for, or with pre-existing, liver disease.

Ethambutol (EMB)

- *Role in treatment regimen:* EMB is a first line drug used to treat all forms of tuberculosis and prevent emergence of RIF resistance when primary resistance to INH may be present.
- *Dose:* (see **Tables 2, 10**)
 - Adults: Recent guidelines have recommended 15-20 mg/kg/day. However, the BMRC original short-course regimen clinical trials used 25 mg per kg daily [436, 508]. Doses of 20-25 mg/kg may be appropriate (refs). **Table 10** lists recommended dosages for adults, using whole tablets.
 - Children: (**Table 2**): 20 mg/kg/day (15-25 mg/kg); 50 mg/kg twice weekly. The drug can be used safely in children, including pre-verbal children, with appropriate caution (**see Adverse effects below**).
- *Preparations:* Tablets (100 mg; 400 mg) for oral administration
- *Adverse effects:*
 - Optic (retrobulbar) neuritis: Rarely, decreased visual acuity or decreased red/green color discrimination that may affect one or both eyes can occur [509]. The risk is higher with higher daily doses (>27.5 mg/kg/day) [189], prolonged duration of therapy (range 2-9 months) [189-191], and in patients with renal insufficiency who accumulate EMB [510]. Higher doses can be given safely two or three times weekly. Risk factors include age, hypertension, renal failure and HIV [191, 511, 512]. With appropriate caution, experts believe that EMB can be used safely in children, including pre-verbal children whose visual acuity cannot be monitored.
 - Peripheral neuritis: This is rare [513].
 - Cutaneous reactions: Skin reactions requiring discontinuation of the drug occur in 0.2-0.7% of patients [514].
- *Use in pregnancy:* There are no adequate and well-controlled studies in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of EMB are assigned to a Category C risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Based on extensive use, EMB is considered safe for use in pregnancy [342, 515, 516].
- *CNS penetration:* The agent penetrates meninges variably in the presence of inflammation but does not have demonstrated efficacy in tuberculous meningitis [458, 517].
- *Use in renal disease:* EMB is cleared primarily by the kidneys. The dosing interval may be increased when creatinine clearance decreases (especially less than 30 ml/min), although a single ml/min clearance cut-off may not be appropriate for all patients [510, 518]. Therapeutic drug monitoring can be considered in such patients in order to avoid under- or overdosing [241]. EMB is administered at a dose of 20-25 mg/kg 3 times a week by DOT after dialysis in patients with end-stage renal disease (**Table 11**) (see **Guideline Section on Renal Disease**) [361].
- *Use in hepatic disease:* EMB can be used safely in patients with hepatic disease (**see Guideline Section on Hepatic Disease**).
- *Monitoring:* While receiving EMB, patients have baseline visual acuity testing (Snellen chart) and testing of color discrimination (Ishihara Color Test). At each monthly visit patients should be questioned regarding possible visual disturbances including blurred vision or scotomata. Monthly testing of visual acuity (Snellen chart) and color discrimination (Ishihara plates) in the clinic is simple to do and is advisable; such monitoring is essential for any patient with renal insufficiency. Patients should be instructed to contact their physician or public health clinic immediately if they experience a change in vision. EMB should be discontinued immediately and permanently if there are any signs of visual toxicity.

Fixed-dose combination (FDC) preparations

- *Role in treatment regimen:* Two combined preparations, INH and RIF (Rifamate®) and INH, RIF and PZA (Rifater®), are available in the U.S. These formulations are a means of minimizing inadvertent monotherapy (which increases risk for acquired drug resistance), particularly when DOT is not possible [174, 175, 177, 519]. The use of FDC formulations also reduces the number of tablets or capsules that must be taken daily. Constituent drugs are combined in proportions compatible with daily treatment regimens. Formulations for intermittent administration are not available in the U.S.
 - *Preparations and Dose:* Rifamate®: As sold in North America, each capsule contains RIF 300 mg and INH 150 mg, thus, the daily dose is 2 capsules (600 mg RIF and 300 mg INH). Two capsules of Rifamate plus two 300 mg tablets of INH are used by some programs for intermittent therapy given twice weekly as DOT. Rifater®: Each tablet contains RIF, 120 mg, INH, 50 mg, and PZA, 300 mg. The daily dose is based on weight as follows: ≤ 44 kg - 4 tablets; 45-54 kg - 5 tablets; ≥ 55 kg - 6 tablets. To obtain an adequate dose of PZA in people weighing more than 90 kg additional PZA tablets must be given.
- *Adverse effects:* Information provided under individual drugs above.

Fluoroquinolones

- *Role in treatment regimen:* Of the available fluoroquinolones, levofloxacin and moxifloxacin have the most activity against *M. tuberculosis*. Cross-resistance has been demonstrated among ciprofloxacin, ofloxacin, and levofloxacin and presumably is a class effect. Fluoroquinolones are not considered first-line agents for the treatment of *drug-susceptible* tuberculosis, except in patients who are intolerant of first-line drugs.
- *Dose:* (**Table 2**).
 - Adults: Levofloxacin 750-1000 mg daily; moxifloxacin 400 mg daily. Higher doses of levofloxacin are being studied (ClinicalTrials.gov Identifier: NCT01918397).
 - Children: Most experts agree that fluoroquinolones can be considered for children with MDR tuberculosis. Limited data suggest that levofloxacin doses of 15 mg per kg may be appropriate. Pediatric doses of moxifloxacin have not been established.
- *Preparations:* Levofloxacin - tablets (250 mg, 500 mg, 750 mg); aqueous solution (500 mg) for intravenous administration. Moxifloxacin - tablets 400 mg; aqueous solution (400 mg) for intravenous administration
- *Adverse effects:* In general, a similar pattern of adverse effects is seen with levofloxacin and moxifloxacin. Moxifloxacin carries the greatest risk of QT prolongation as compared to other available fluoroquinolones in clinical practice [520]. By itself, moxifloxacin rarely is associated with cardiac dysrhythmias. However, in combination with other drugs that prolong QTc interval (bedaquiline, delamanid, and clofazimine are some examples) this may be of greater concern, and may require monitoring.
 - Gastrointestinal disturbance: Nausea, anorexia, vomiting, abdominal pain, diarrhea, and taste disturbance have been reported [521].
 - Neurologic effects: Dizziness, insomnia, tremulousness, and headache occur in 1-2% of patients [521].
 - Cutaneous reactions: Rash, pruritis, and photosensitivity have been reported. Levofloxacin and moxifloxacin have lower potential for phototoxicity than other available fluoroquinolones [521].
 - Arthropathy and tendinopathy: Arthropathy, fluoroquinolone-associated tendinitis and tendon rupture are uncommon, reported at 0.5 and 0.6 cases/100,000 antibiotic treatments in levofloxacin and moxifloxacin, respectively [521, 522]. Tuberculosis trials evaluating moxifloxacin have not reported any episodes of tendinopathy or arthropathy [5, 163]. Although there is a paucity of data, observational studies of children treated with fluoroquinolones for up

to 12 months do not demonstrate any serious arthropathy or other severe musculoskeletal adverse events in the pediatric population [523-525].

- *Use in pregnancy:* There are no adequate and well-controlled studies in pregnant women. According to previous FDA classification systems (currently under revision [350]) and drug package inserts, the potential teratogenic effects of levofloxacin and moxifloxacin are assigned to a Category C risk (Risk not ruled out, but potential benefits may warrant use of the drug in pregnant women despite potential risks). Registry data do not reveal any clear adverse reactions (fetal and neonatal toxicity, including birth defects) due to in-utero exposure to fluoroquinolones [526].
- *CNS penetration:* The concentration in the CSF after administration of a standard dose of levofloxacin is lower than that in serum [178]. Cerebrospinal fluid penetration, measured by the ratio of the plasma area under the concentration-time curve from 0 to 24 h (AUC_{0–24}) to the cerebrospinal fluid AUC_{0–24}, is greater for levofloxacin (median, 0.74; range, 0.58 to 1.03) than for gatifloxacin (median, 0.48; range, 0.47 to 0.50) or ciprofloxacin (median, 0.26; range, 0.11 to 0.77) [291, 458].
- *Interference with absorption:* Antacids and other medications containing divalent cations markedly decrease the absorption of the fluoroquinolones. Fluoroquinolones should be administered first and a minimum of 2-3 hours interval (ideally longer) should be provided before use of products containing divalent cations. Examples of products that decrease absorption of the fluoroquinolones include any medications containing aluminum, magnesium, calcium, zinc, iron; selected dietary supplements (e.g. Sustacal, Ensure); and vitamins that also contain minerals.
- *Use in renal disease:* Levofloxacin is cleared primarily (>85%) by the kidney [178]. Dosage adjustment (750-1000mg 3 times a week) is recommended if creatinine clearance is <30 ml/min (**Table 11**). Based on studies in conditions other than tuberculosis, levofloxacin is removed by intermittent hemodialysis, however, at a lower total clearance compared with healthy subjects [527, 528]. Moxifloxacin is cleared both hepatically and renally. Typically, dose adjustment of moxifloxacin is not needed in renal dysfunction (**see Guideline Section on Renal Disease**).
- *Use in hepatic disease:* Levofloxacin and moxifloxacin plasma concentrations are not affected by hepatic disease [529]. Levofloxacin and moxifloxacin have been used in the setting of liver disease, including when hepatotoxicity is attributed to antituberculosis drugs [530], however, when used, routine monitoring of liver enzymes is recommended (**see Guideline Section on Hepatic Disease**).
- *Monitoring:* No specific monitoring is recommended.

References:

Please see Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis document for full references for citations listed in Appendix C.