# Strategies for Safe and Effective Tuberculosis Regimens

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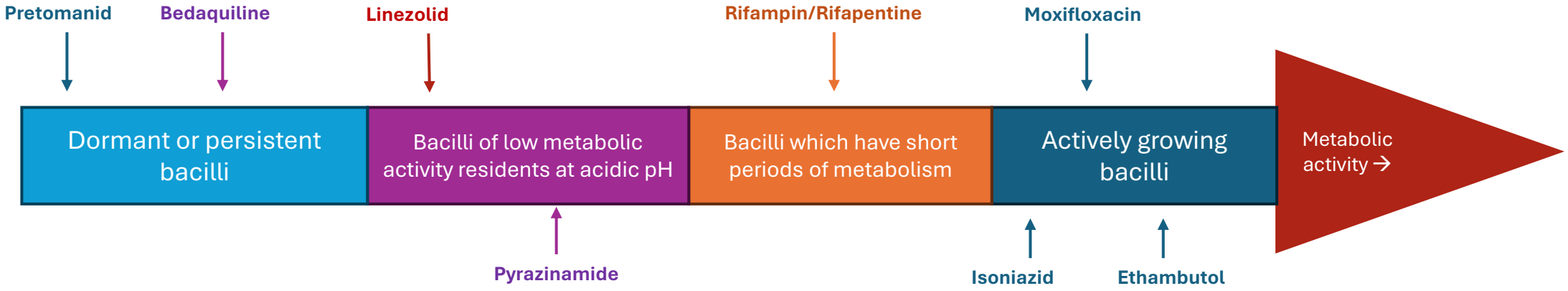
# Learning Objectives

- Review the basic pharmacology and adverse drug effects of pharmacologic regimens for TB
- Discuss strategies to minimize toxicity and optimize outcomes for patients with TB

# Meet the Players



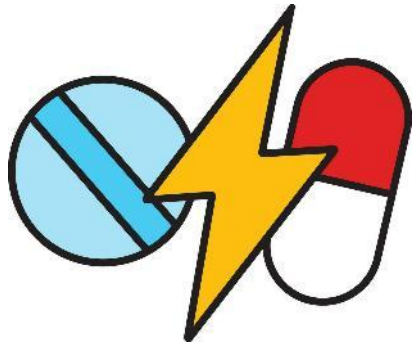

- Early bactericidal activity: isoniazid > rifampin ≈ rifapentine ≈ moxifloxacin > pyrazinamide > linezolid > ethambutol > bedaquiline ≈ pretomanid
- Sterilizing activity: rifampin ≈ rifapentine ≥ bedaquiline ≥ pretomanid ≈ pyrazinamide ≈ moxifloxacin ≈ linezolid > isoniazid > ethambutol
- Resistance prevention: isoniazid > rifampin/rifapentine > ethambutol > pyrazinamide

# Meet the Players - Rifamycins

- Meds: Rifampin, Rifapentine
- Inhibits RNA polymerase (rpoB) blocking transcription
- Take 1 hour prior to of 2 hours after a meal or antacids to increase absorption (rifampin); administer with meals of modest fat (rifapentine)
- Key side effects:

**Red/Orange discoloration of urine, sweat, tears, avoid soft contact lenses**

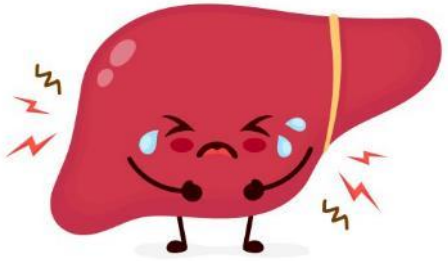
Minor serum AST/ALT increases in 10-20% of patients
Serum bilirubin increases during first few days of therapy



Drug-Drug Interactions!

# Meet the Players - Isoniazid

- Hydrazide
- Prodrug that inhibits InhA blocking mycolic acid synthesis
- Administer apart from antacids
- Key side effects:



- Transient serum AST/ALT elevations in 10-20% of patients
- Elevations >5x upper limit of normal (ULN) in 3-5%
- Fatal acute liver injury 0.05-1%
- Risk factors: older age, women, Black race, pre-existing liver disease, concomitant hepatotoxic meds

- Peripheral neuropathy
- Give with Vitamin B6 (pyridoxine) to prevent

# Meet the Players: Pyrazinamide

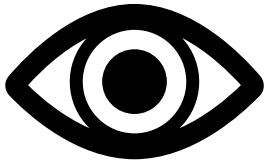
- Nicotinamide analog
- Prodrug that converts to pyrazinoic acid and disrupts membrane energetics
- Requires renal dose adjustment for CrCl < 30 or iHD
- Use adjusted body weight for dosing in BMI ≥30 kg/$m^2$
- Key side effects:

- Transient elevations in serum aminotransferase levels, generally <5x ULN
- Onset generally after 4-8 weeks

- Can cause hyperuricemia
- Caution in patients with chronic gout, contraindicated in acute gout

# Meet the players: Ethambutol

- Arabinosyl transferase inhibitor – inhibits arabinosyl transferases that disrupts cell wall arabinogalactan
- Requires renal dose adjustment for CrCl < 30 or iHD
- Use adjusted body weight for dosing in BMI ≥30 $kg/m^2$
- Key side effects:



Optic Neuritis

- Unilateral or bilateral
- Decreased visual acuity
- Visual disturbances (including color blindness)
- Normally reversible, may take up to a year

# Meet the players - Moxifloxacin

- Fluoroquinolone
- Inhibits DNA gyrase → prevents DNA replication & repair
- Chelate cations – bioavailability decreased when administered with calcium, iron, antacids, milk, multivitamins, magnesium
- Key side effects:

**Rare but serious:**

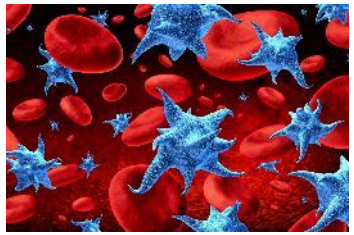
- Achilles tendon rupture
- Aortic aneurysm or aortic dissection
- Lower seizure threshold
- QTc prolongation (moxi greatest risk of all quinolones)

**Common side effects:**

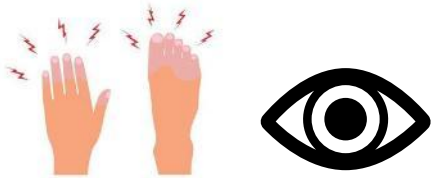
- GI side effects
- Headache
- Photosensitivity
- Hyper or hypoglycemia (particularly hypoglycemia in elderly)
- CNS – dizziness, confusion, hallucinations (especially in elderly)
- Arthralgias

# Meet the players - Linezolid

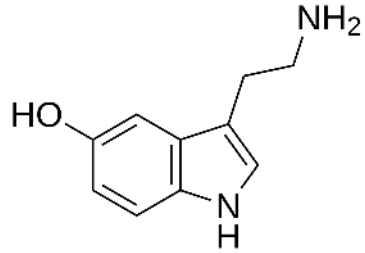
- Oxazolidinone
- Binds 23S rRNA (50S) → blocks 70S initiation complex
- Key side effects



- Myelosuppression, particularly thrombocytopenia
- Patients with renal impairment at higher risk
- Typically occurs ≥14 days from therapy, reversible 1-2 weeks post drug discontinuation



- Peripheral neuropathy and optic neuropathy
- Optic neuropathy generally improves with drug discontinuation, peripheral neuropathy may not recover
- Onset generally >28 days of therapy




- Serotonin syndrome with other serotonergic agents
- Fever, sweating, hallucinations, tachycardia, myoclonus, clonus
- Concurrent use with serotonergic agents (#, dose, duration impact risk)

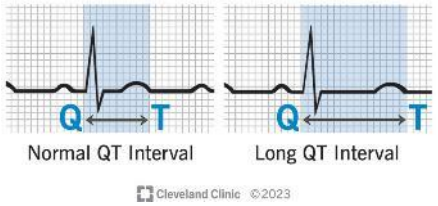
# NIX-TB and Ze-NIX Trials

- NIX-TB – open label stud in South Africa using 1200 mg daily linezolid with bedaquiline and pretomanid
  - 81% had peripheral neuropathy and 48% myelosuppression
- Ze-NIX – bedaquiline, pretomanid and linezolid
  - Linezolid 1200 mg arm for 26 weeks had 38% neuropathy, 22% myelosuppression, and 51% required a linezolid dose modification
  - Linezolid 600 mg arm for 26 weeks had 24% neuropathy, 15% myelosuppression, and 30% required a linezolid dose modification

Conradie F et al. NEJM 2020;382:893-902.
Conradie F et al. NEJM 2022;387:810-823.

# Meet the players: Bedaquiline

- Diarylquinoline
- Inhibits ATP synthase → depletes bacterial ATP
- Administer with food
- CYP3A4 substrate, avoid co-administration with rifampin
- Key side effects:




QTc prolongation
Monitor ECGs, discontinue if QTc interval >500 msec develops

Hepatotoxicity
Mild to moderate LFT abnormalities in 8-12% of patients, self limited

# Meet the players: Pretomanid

- Nitroimidazooxazine
- Prodrug that inhibits cell wall and anaerobic killing
- Must be administered with a substantial meal
- Key side effects:

Peripheral neuropathy
Occurs in 80% of patients, severe in ~20%

Acne (~40% of patients)

QTc, hepatotoxicity – since used in combination with bedaquiline and linezolid, hard to disentangle if causative agent, likely additive risk

# Shorter 4-month regimen for DS-TB: HPMZ

- Similar incidence of grade 3 or higher AEs in the trials
- Low real-world uptake due to tolerability/high discontinuation rates
  - San Francisco cohort of 22 patients treated with the HPMZ regimen
    - 82% experience any adverse event to the drug
      - Moderate GI upset, LFTs >3x ULN, rash, myalgias
    - 50% discontinued the treatment due to adverse events a median of 10.5 days into treatment
  - NYC cohort of 36 patients treated with HPMZ
    - 64% discontinued early, 42% due to adverse drug effects
- Challenge with extrapolating findings from TB clinical trials commonly conduced in high-incidence, non-US settings

Louie JK et al. Open Forum Infect Dis 2024;ofae178.
Galvis ME, et al. IJTLD 2025; 29(7):318-24.

# Barriers to Drug-Resistant TB treatment success

# Monitoring for ADRs during treatment

**Targeted Clinical Assessment**

**Tests**

Before Treatment
Identify risk factors for ADRs
Pregnancy/breastfeeding status

Color vision/visual acuity
Mental health/neuropsychiatric assessment
HIV, LFTs, SCr, CBC, HBV, HCV serologies, HbA1c

During Treatment
GI upset
Hepatotoxicity (e.g., anorexia, nausea, fatigue, pruritic, jaundice, easy bruising, ab pain)
Joint pain/arthritis
Neuropathy
Blurred/altered vision
Rash
Neuropsychiatric disorders
Anemia

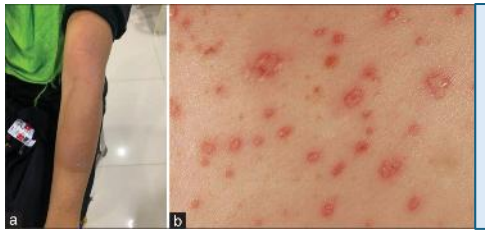
Symptoms should prompt specific lab assessment
Lab tests without symptoms or baseline abnormalities not needed
Consider tests for other causes (e.g., LFT derangement, test for HAV)
Rash, if severe, assess for organ dysfunction; LFTs/creatinine, eosinophils (DRESS)

# Managing ADEs - Gastrointestinal

- Intermittent dosing (< daily) – not shown to decrease adverse events other than potentially hepatotoxicity
- Divide dosing into twice daily (2 meds in the am, other 2 in the pm) – decreases gastrointestinal adverse events
- Split dosing (daily treatment with 2 medications every other day, alternating with the other 2 medications) – decreases gastrointestinal adverse events and all adverse events
- No studies have evaluating dosing at bedtime or dosing with food
- Some very small studies have evaluated ginger and a lactobacillus based probiotic to decrease GI upset

Indian J Gastroenterol. 2025;44(1):35–46
J Med Assoc Thai. 2012;95(Suppl 8):S1-5.
Trop Med Int Health. 2004;9(5):551–8.
Phytother Res. 2016;30(6):1003–9
Food Funct. 2020;11(1):370–7.

# Rashes!



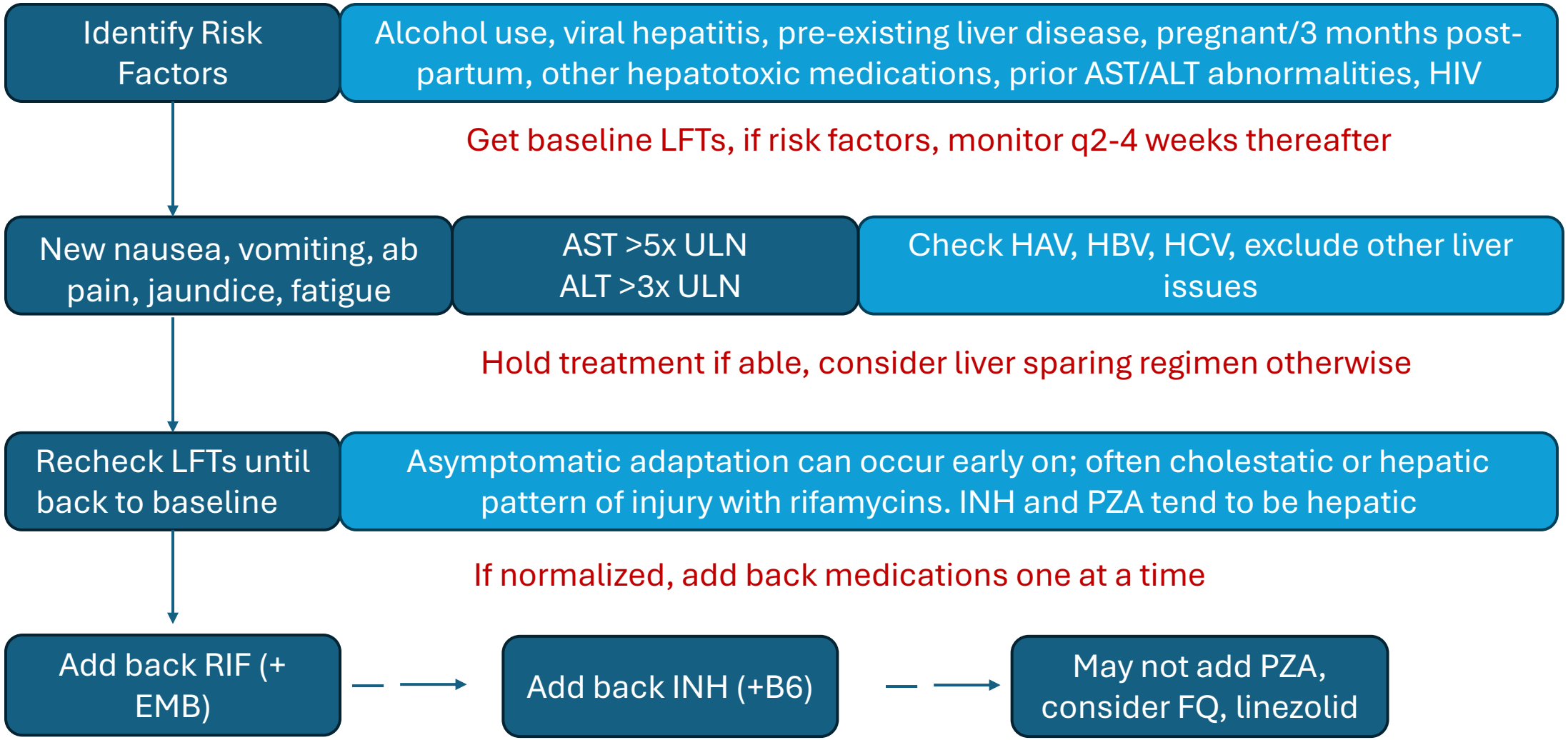
Maculopapular rash – most common with RIF & PZA, treat with antihistamines, withdraw suspected culprit agent

Petechial rash – rule out thrombocytopenia secondary to rifamycins

Severe rash with fever, hepatitis → stop possible offending agent, rule out DRESS (most commonly RIF, PZA)

Images: Wiki Commons
Kaswala D et al. J Fam Med Prim Care 2013;2:83-85.

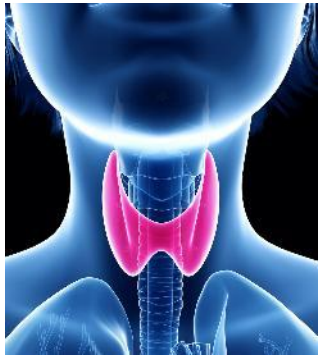
# Approach to Drug-Induced Hepatotoxicity



# Monitoring for 2nd Line Drugs

QT prolonging agents (fluoroquinolones, bedaqueline, clofazimine, delamanid)
Measure electrolytes, ECG at 2w, 12w, 24w or in case of symptoms)

Linezolid:
Monthly CBC
s/sx of peripheral neuropathy
Optic neuritis



Thyroid studies every 2 months
Ethionamide, para-aminosalicyclic acid

Clofazimine:
skin discoloration, icthyosis

Images: wiki commons, Bishnoi et al. Brit J Derm 2019

# Managing Drug-Drug Interactions

# Cytochrome P450 Interactions

**Fast onset, fast offset, more predictable**

**Slow onset, slow offset, harder to predict**

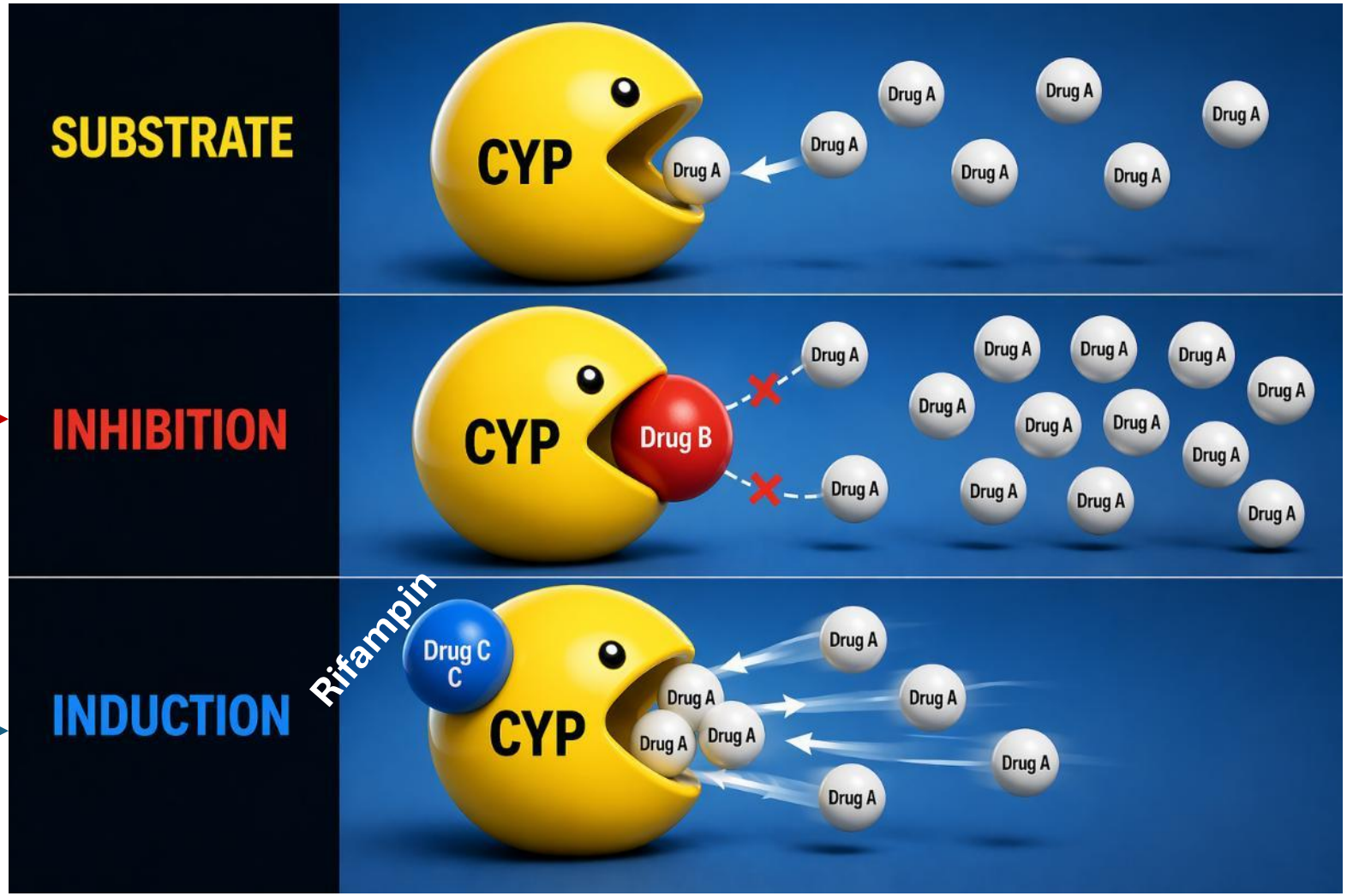



Illustration created by author using AI tools

# Major Challenges with Rifampin/Rifapentine*

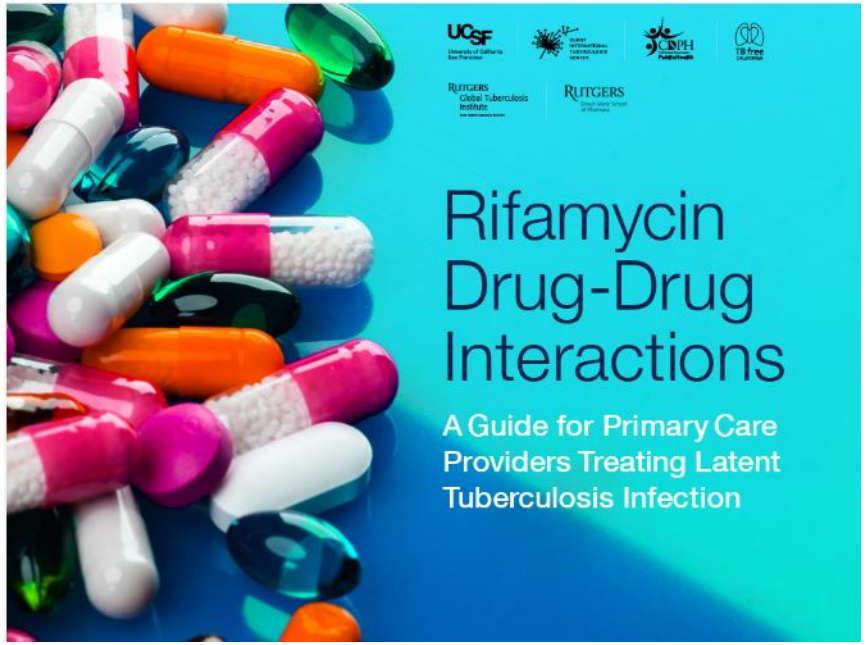
- Antiretrovirals – decreased levels of most ARVs, can lead to virologic failure
- Oral contraception – increased metabolism of OCPs can lead to contraception failure
- Warfarin (via CYP2C9 induction) – decreased INR
- DOACs – decreased levels, increased risk of VTE
- Azole antifungals – decreased azole levels

*Not a comprehensive list

# Major Challenges with other meds

| Isoniazid | Bedaquiline | Linezolid |
|---|---|---|
| • Phenytoin (increased levels, toxicity)<br>• Antacids (chelation, decreased GI absorption) | • Other QTc prolonging medications (e.g., macrolides, certain antipsychotic medications)<br>• Strong CYP3A4 inhibitors (e.g., ritonavir) decrease bedaquiline first pass metabolism and increase AUC – higher risk of QTc prolongation | • Caution with serotonergic agents: SSRIs, SNRIs, MAOIs, tramadol, fentanyl, methadone<br>• Caution with sympathomimetics (e.g., pseudoephedrine, dopamine) |

# Help!




https://www.currytbcenter.ucsf.edu/products/rifamycin-drugdrug-interactions-a-guide-for-primary-care-providers-treating-latent-tuberculosis

University of Liverpool HIV Drug Interactions Checker: Highly useful for checking complex overlaps between TB therapies and antiretroviral drugs

Tertiary drug information resources:
Lexi-Comp®
Micromedex®

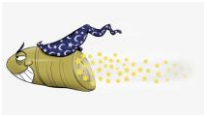
University of Maryland School of Pharmacy Infectious Diseases Pharmacotherapy Faculty:

- Me!
- Mandee Booth
- Neha Pandit

# Therapeutic Drug Monitoring (TDM)

# Therapeutic Drug Monitoring: WHY

- Standard dosing is not designed to account for patient specific factors outside of renal function
- Meet efficacy targets (limited data)
  - Adequate RIF & INH levels correlated with faster negative sputum culture conversion
- Minimize toxicities
- Compliance measure
- Confirm absorption
- Assess for drug-drug interactions



Not a magic bullet, but one factor in contributing to patient outcomes

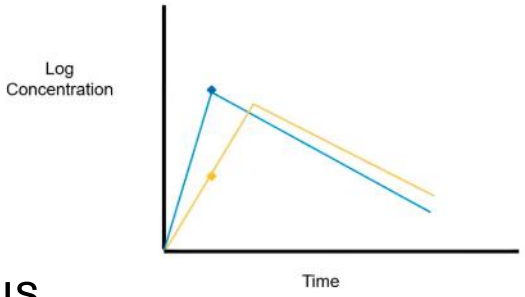
# Therapeutic Drug Monitoring: WHO

Who to consider TDM:

- Poor response to treatment despite adherence and fully drug-susceptible Mycobacterium tuberculosis strain
- Severe GI abnormalities (e.g., gastroparesis, chronic diarrhea with malabsorption, history of GI surgery)
- Pregnancy
- Drug-drug interactions
- Impaired renal clearance (including hemodialysis, peritoneal dialysis)
- Concomitant HIV infection
- Diabetes
- Treatment using second line drugs → particularly linezolid!
- CNS tuberculosis
- Extremes in weight

# Therapeutic Drug Monitoring: HOW

- Patients should be at steady state (generally 1-2 weeks post drug initiation)
- Ideally measure levels at 2 hours and 6 hours post dose
  - 2-hour level approximates “peak” in most oral TB drugs, gives info on absorption
  - 6-hour level tells rate and extent of absorption




  - Having both levels can differentiate between delayed absorption versus malabsorption → if delayed absorption can take on an empty stomach
  - Accuracy at 2 hours highest for INH, lowest for PZA, adding a 6-hour sample can lead to better accuracy with RIF
- Some exceptions: Bedaquiline, pretomanid, rifapentine, first level at 5 hours and second level at 24 hours
- Generally, 5 mL in plain red-top tube for each test

# Labs that Offer TB Med TDM

University of Florida
Website: idpl.pharmacy.ufl.edu Email: peloquinlab@cop.ufl.edu Phone number: 352-273-6710

National Jewish Health Website: https://www.nationaljewish.org/for-professionals/diagnostic-testing/advanced-diagnostic-laboratories/our-laboratories/therapeutic-drug-monitoring
Email: clinreflabs@njhealth.org
Phone number: 800-550-6227

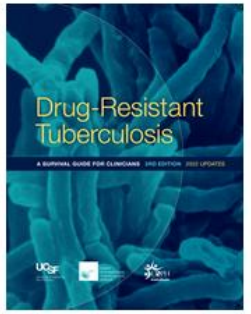
# Adjusting Medications Based on TDM

**Table 1** Pharmacokinetic parameters of the anti-tuberculosis drugs

| Drug | Normal adult dose | Normal $C_{max}$ (μg/mL) | Normal $T_{max}$ (h) | Normal $t_{½}$ (h) |
|---|---|---|---|---|
| Isoniazid | 300 mg daily | 3–6 | 0.75–2 | Polymorphic: |
| | 900 mg biw | 9–15 | | fast: 1.5; slow: 4 |
| Rifampin | 600 mg daily | 8–24 | 2 | 2–3 |
| Rifabutin | 300 mg daily | 0.45–0.90[a] | 3–4 | 25–36 |
| Rifapentine | 600 mg daily[b] | 8–30 | 5 | 15 |
| Pyrazinamide | 25–35 mg/kg daily | 20–60 | 1–2 | 9 |
| | 50 mg/kg biw | 60–90 | | |
| Ethambutol | 25 mg/kg daily | 2–6 | 2–3 | Biphasic: |
| | 50 mg/kg biw | 4–12 | | 2–4, then 12–14 |
| Cycloserine | 250–500 mg daily or biw | 20–35 | 2 | 7 |
| Ethionamide | 250–500 mg daily or biw | 2–5 | 2 | 2 |
| Streptomycin/ kanamycin/ amikacin | 15 mg/kg daily<br>25 mg/kg biw | 35–45[c]<br>65–80[c] | 0.5–1.5 h IM dose or calculated to the end of IV infusion | 3 |
| PAS granules | 4,000 mg bid | 20–60 | 4–8 | 1 |
| Levofloxacin | 500–1,000 mg daily | 8–13 | 1–2 | 9 |
| Moxifloxacin | 400 mg daily | 3–5 | 1–2 | 7 |
| Linezolid | 600–300 mg | 12–26 | 1.5 | 5–6 |
| | 1–2 times daily | | | |
| Clofazimine | 100 mg daily | 0.5–2.0 | 2–7 | Biphasic: several days, then many weeks |

Alsultan, Peloquin. Drugs 2014;839-54.

# Conclusions

- Adverse drug events with TB meds are very common
- The field would benefit from more research and protocolization surrounding ADR management
- TDM can help move towards more personalized medicine to help with ADR management

- **Further reading/helpful resource**:
- https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
- Includes a full chapter outlining ADR management