Overview of TB treatment regimens and side effects: What DOT workers need to know

Stephanie Leary, M.D.

April 23, 2026

Richmond Henrico Health Districts

DOT workers

- On the front line
- Our eyes and ears to the patient, often the first to see or notice something is off

- Vital part of the treatment team

Importance of completion of therapy – patient and population level

1

Cure the patient → the individual benefits

2

Minimize transmission to other people → the community benefits

3

DOT → associated with treatment success and higher rates of sputum smear conversion during treatment

Objectives

Discuss the standard treatment regimen for active pulmonary TB

Discuss side effects of medications from the standard treatment regimen

Discuss alternative treatment regimens for active TB

- Extrapulmonary TB
- Treatment regimen extension
- **Culture negative TB**
- Resistance/Medication **intolerance**
- **Shortened** regimens – adult and pediatric

LTBI treatment regimens

RIPE: Standard treatment regimen for pulmonary TB

- **R**ifampin (RIF)
- **I**soniazid (INH)
- **P**yrazinamide (PZA)
- **E**thambutol (EMB)

- Standard duration: 6 months

RIPE: 6 months total, 2 phases

- Intensive phase: 2 months of all 4 drugs
- Continuation phase: 4 months of INH and Rifampin
- Why the intensive phase? Due to drug resistance. Each medicaiton has a "role."
- EMB can be taken out of the intensive phase if the patient's strain of M.TB is known to be susceptible to both INH and RIF at the start of treatment or anytime during treatment.

Preferred regimen with the greatest effectiveness

Regimen	Intensive Phase Drugs[1]	Intensive Phase Interval and Doses[2] (minimum duration)	Continuation Phase Drugs	Continuation Phase Interval and Doses[2,3] (minimum duration)	Range of total doses (Intensive and Continuation phases, combined)	Comments[3,4]	Regimen effectiveness
1	**INH** **RIF** **PZA** **EMB**	7 days/week for 56 doses (8 weeks) *or* 5 days/week for 40 doses (8 weeks)	**INH** **RIF**	7 days/week for 126 doses (18 weeks) *or* 5 days/week for 90 doses (18 weeks)	182 to 130	This is the preferred regimen for patients with newly diagnosed pulmonary TB.	**greater** 

- Other regimens use the same medications but have interval dosing during the continuation phase and/or the intensive phase. These regimens are less effective.

RIPE regimen

- All of the drugs can cause a rash that can range in severity.
- All of the drugs can cause anyphylaxis.
- Anyphylaxis: rapid onset of rash, rapid onset of GI sypmtoms, airway swelling, blow blood pressure
- Stop medication if:
  - Patient has a red rash all over their body
  - Fever and/or mucous membrane involvement
- There are rare side effects with each medication that I may not mention in these slides. I will go over the important side effects of each medication. If something seems off, report it to the clinician.
- The clinician can consult a drug database such as LexiComp available through UpToDate or the DailyMed data base which contains labeling submitted to the FDA for each medication.

Photos from top to bottom: urticaria (hives), morbilliform rash (pink/red flat spots and raised bumps), SJS/TEN mucous membrane involvement

Rifampin (RIF)

- Good for killing rapidly diving **and** persistent bacilli
- Many drug-drug interactions

Rifampin: side effects/toxicities

Orange Discoloration of body fluids (Benign)

- Affects urine, sweat, tears, and saliva.
- **Patient Education:** Expected and harmless, but can **permanently stain** soft contact lenses.

Gastrointestinal (GI) Effects (Common)

- Nausea, vomiting, abdominal pain, heartburn, gastritis, cramps, diarrhea

Hepatotoxicity/Drug induced liver injury

- **Monitor for:** Unexplained gastrointestinal symptoms, jaundice – yellowing of the eyes/skin
- Physical exam and LFTs (ALT, AST, Bilirubin, Alk Phos) as needed

Rifampin: side effects/toxicities continued

Skin Reactions

- **Pruritus:** Itching with or without a rash. Generally mild and self limiting.
- **Flushing**. Generally mild and self limiting.
- Report immediately:
- Systemic symptoms (fever) accompanied by a rash. Uncommon.
- **Petechiae** (small purple/red spots) or mucous membrane involvement

Hematologic

- Thrombocytopenia**:** Risk of low platelet counts. Reversible once medication is stopped.
- Leukopenia: low white blood cell count.

Hypersensitivity reactions (Rare)

- Low blood pressure, flu like syndrome, fever, headache, and muscle pain.

Isoniazid (INH)

- Very good **early bactericidal activity:** stops multiplication of tuberculosis bacteria. **Acts** very **slowly on persistent bacteria.**
- Kills actively dividing bacteria

Isoniazid side effects

- Asymptomatic elevation of hepatic enzymes occur in 10-20% of patients
- Hepatotoxicity/drug-induced liver injury (less common):
  - Anorexia, nausea, vomiting, abdominal pain, dark urine, jaundice (yellow skin/eyes), fatigue, weakness
  - Usually in the first 3 months of treatment
- Peripheral neuropathy: numbness, tingling and/or pain of the hands/feet

<u>Populations to monitor closely for hepatotoxcitiy</u>

- older adults (>35 years old)
- underlying liver disease
- pregnant or postpartum
- alcohol use
- injection drug use
- use of other hepatotoxic drugs like Tylenol

Isoniazid side effects continued

Gastrointestinal:

- nausea, vomiting, abdominal pain, pancreatitis

CNS (usually mild)

- Dizziness, headache, depression, poor memory/concentration. Can be more severe like psychosis, but rare

Rash – can be mild to severe

When and why do we add Vitamin B6 to the regimen?

- Vitamin B6 = pyridoxine
- Water soluble
- INH prevents Vitamin B6 from working properly in the body to make neurotransmitters
- The result: peripheral neuropathy (numbness and tingling in the extremities), damage to the nerve which can be permanent
- Add B6 for patients at risk of neuropathy while taking INH with the following conditions:
  - Pregnancy
  - Breastfeeding infants
  - HIV infection
  - Malnutrition
  - Advanced age
  - Diabetes
  - Alcoholism
  - Chronic renal failure.

Pyrazinamade (PZA)

- Almost no early bactericidal activity
- Works well in environments where the bacteria is not active. The drug enters the M. tb cell and then is activated by another enzyme in the bacteria
- Kills slow-growing M. tb to prevent it from returning and gone for the long run

Pyrazinamide side effects

- Hepatotoxcity: abdominal pain, fatigue, low appetite, nausea, vomiting, yellow skin/eyes, dark colored urine
- Gastrointestinal upset: vomiting, low appetitie, stomach pain
- Photosensitivity
- Rash
- Gout: increased uric acid levels, joint pain
- Arthralgias

Ethambutol (EMB)

- Prevents antibiotic resistance in case the M.tb bacteria is resistant to INH or RIF
- Stops bacteria from reproducing and growing, does not kill the bacteria
- Used during the intensive phase (first 2 months)
- Once drug sensitivity tests confirm M.tb is susceptible to INH and RIF, the EMB can be stopped

Ethambutol side effects

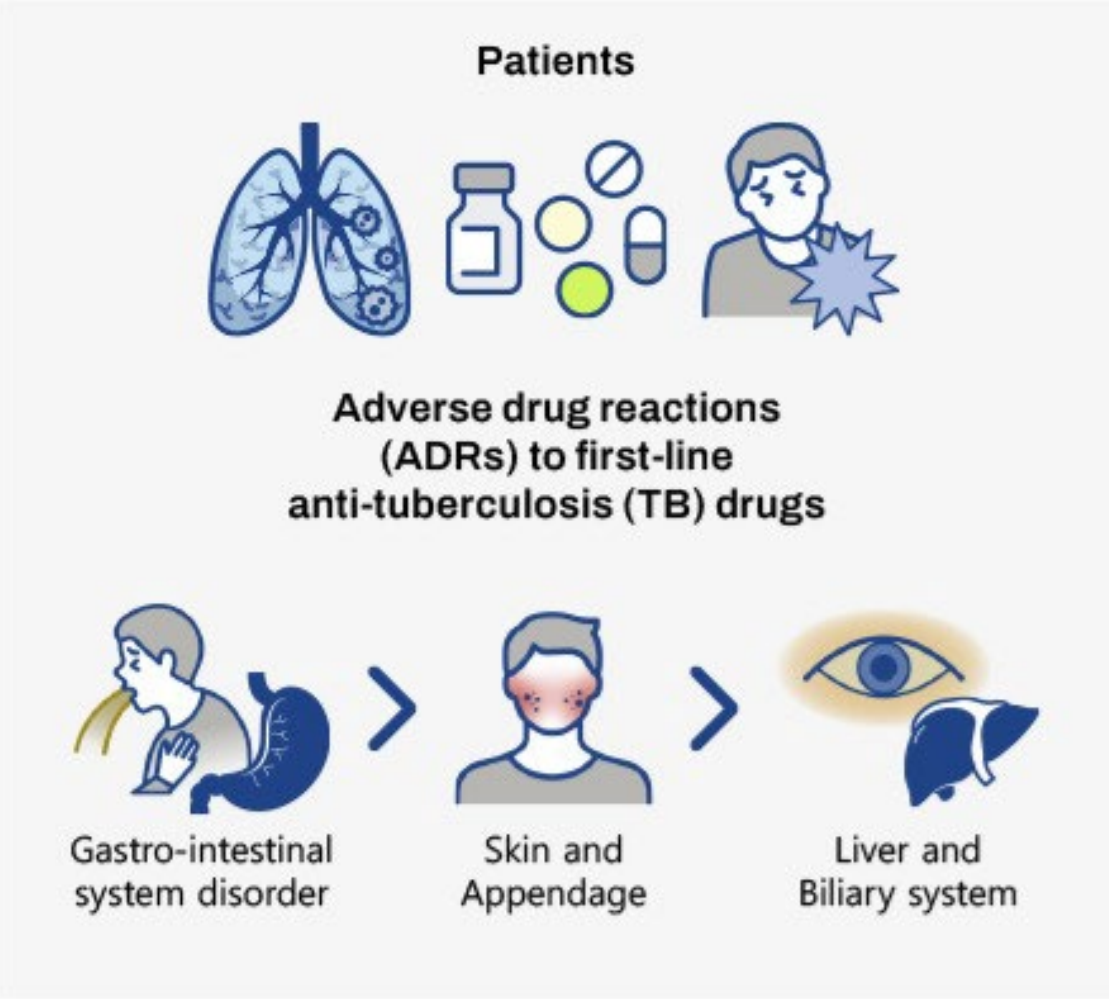
- Major side effect is optic neuritis
- Blurred vision
- Loss of visual acuity
- “Red-green” color blindness
- The longer you use it, the higher the risk
- Administer baseline vison test and color blindness test

RIPE regimen side effects summary

Drug	Adverse Reaction	Signs & Symptoms
Any of the drugs	• Rash	• Itching, morbilliform rash, hives
Rifampin	• **Orange** discoloration of body fluids • Hepatitis/ GI upset  • Flu-like syndrome	• Orange tinge to body fluids • Nausea, vomiting, abdominal pain • Fever, chills, muscle pain
Isoniazid	• Hepatitis/GI upset  • Neuropathy 	• Jaundice (yellow skin/eyes), dark urine, GI sypmtoms • Tingling/numbness in hands or feet
Pyrazinamide	• Hepatitis/GI upset  • Gout/Arthralgia	• Jaundice (yellow skin/eyes), dark urine, GI sypmtoms • Joint pain/swelling
Ethambutol	• Optic Neuritis 	• Blurred vision, red-green color blindness

Data adapted from CDC (2025).

Study using data from Korea Adverse Event Reporting System from 2009-2018



- 1.5+ million adverse drug reactions reported

Chung SJ, Byeon SJ, Choi JH. Analysis of Adverse Drug Reactions to First-Line Anti-Tuberculosis Drugs Using the Korea Adverse Event Reporting System. J Korean Med Sci. 2022 Apr;37(16):e128. https://doi.org/10.3346/jkms.2022.37.e128

Study using data from Korea Adverse Event Reporting System from 2009-2018

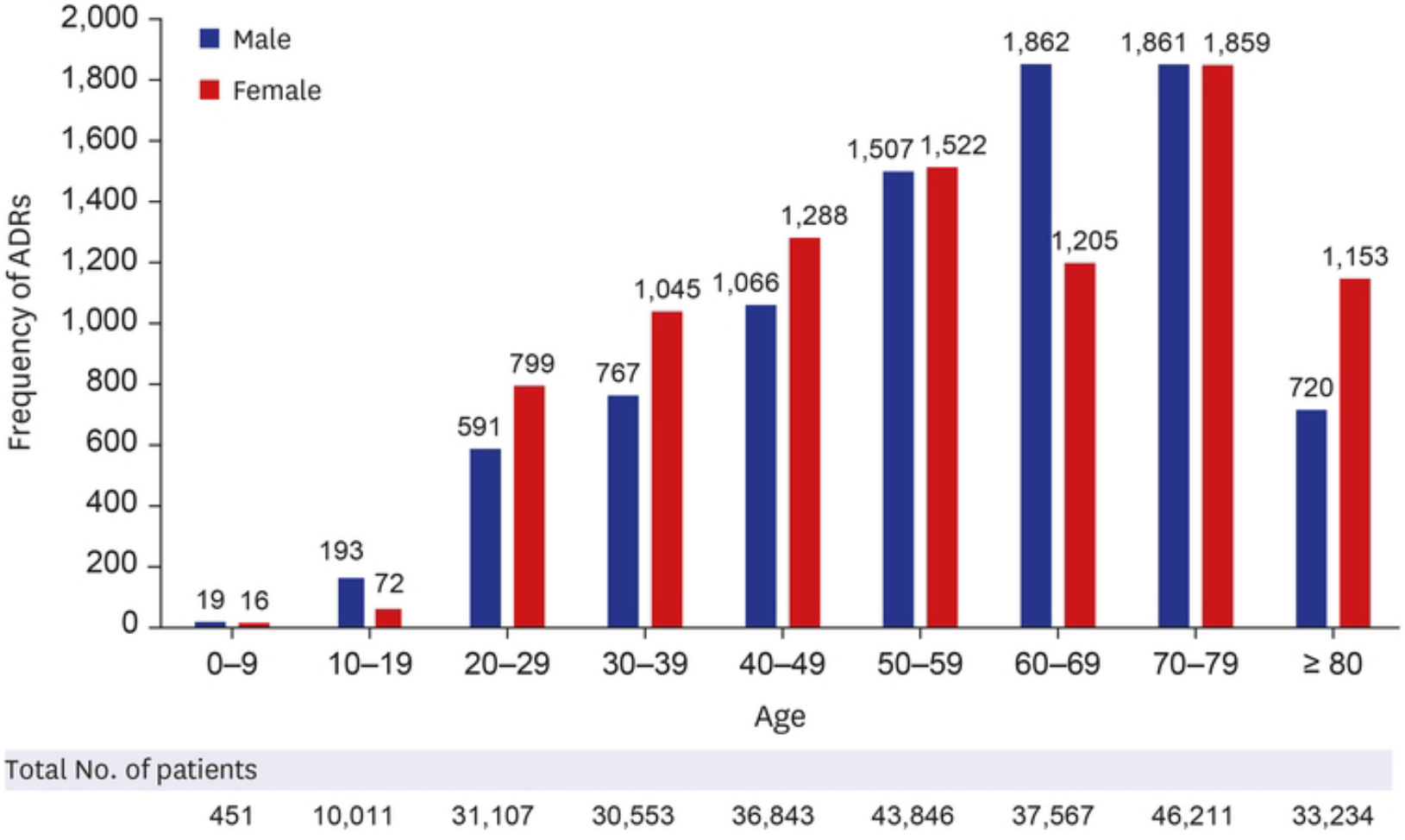


Fig. 2. Frequencies of ADRs of first-line anti-tuberculosis drugs according to age and sex.

Chung SJ, Byeon SJ, Choi JH. Analysis of Adverse Drug Reactions to First-Line Anti-Tuberculosis Drugs Using the Korea Adverse Event Reporting System. J Korean Med Sci. 2022 Apr;37(16):e128. https://doi.org/10.3346/jkms.2022.37.e128

Additional treatment regimens

- Other primary sites of TB infection
- When to extend the treatment regimen
- Culture negative TB
- Shortened 4 month adult treatment regimen & side effects
- Shortened 4 month pediatric treatment regimen
- Resistance
- Medication intolerance

Treatment of extrapulmonary TB infection: 3 main sites

Lymph node TB

- Monitor for lumps/bumps, swelling in the neck
- 6 month treatmemt

Pleural TB

- Lining of the lungs
- Shortness of breath

Bone and joint TB:

- 3rd most common site
- CDC recommends 6-9 months
- Spinal TB or Pott's disease: usually extended to 9-12 months as it is harder for the drugs to get into the vertebrae
- Joint disease in children: 12 months

Treatment of extrapulmonary TB infection, less common sites

TB meningitis:

- Intensive phase x 2 months. PZA penetrates the CSF well.
- INH and RIF continue for 7-10 months for a total of 9-12 months of treatment
- In children: intensive phase with INH, RIF, PZA and ethionamide/fluoroquinolone followed by 7-10 months of RIF and INH
- Steroids, reduce inflammation

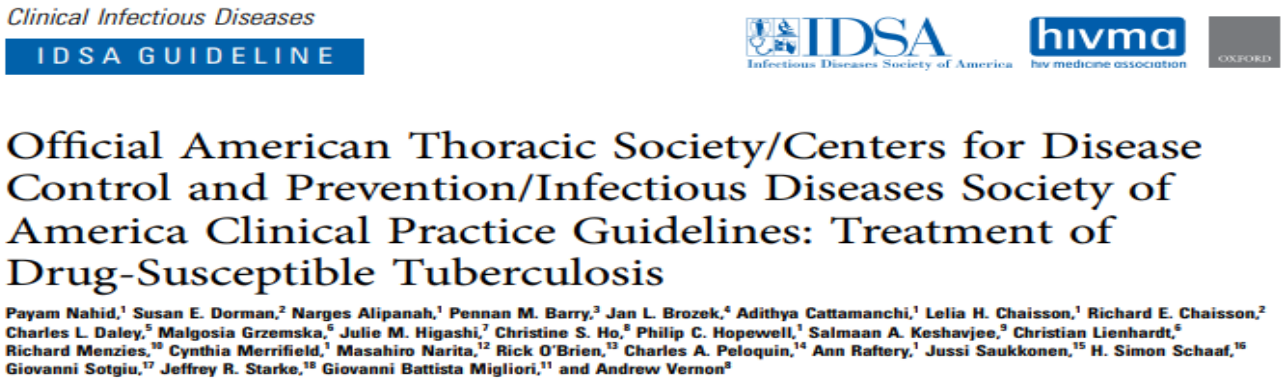
Genitourinary TB

- 6 month treatment, same regimen as for pulmonary TB

Abdominal TB

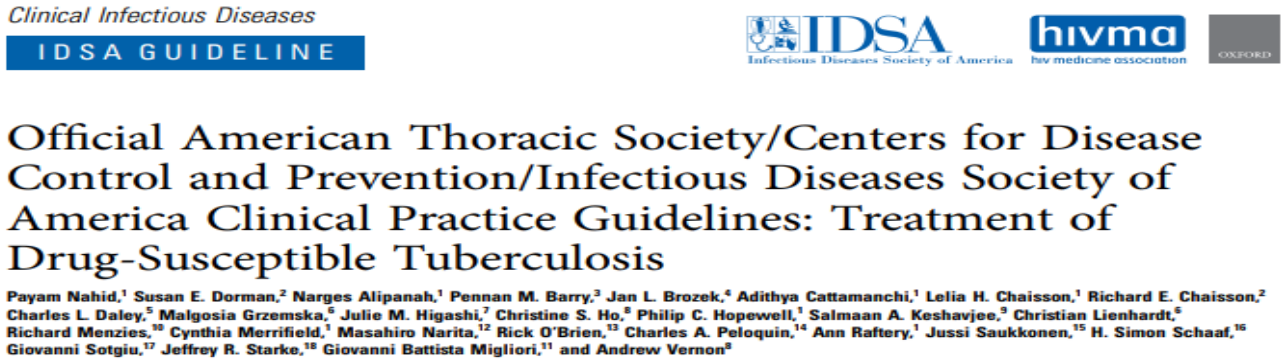
- 6 month treatment, same regimen as for pulmonary TB

9-month treatment regimen: initial cavitation on chest film and culture positivity at 2 months



- 2016 IDSA guidelines
- Patient with BOTH a **cavitation** on initial chest radiograph AND **positive cultures after 2 months** of therapy are associated with having **relapse rates** of approximately **20%** compared to 2% with neither risk factors
- Expert opinion → **extend** the continuation phase for **3 months** for a total of 9 months of treatment

Culture negative, smear negative pulmonary TB



- 2016 IDSA guidelines
- These patients have been started on treatment due to clinical and radiographic evaluation
- Clinical and radiographic improvement after 2-2 months of the intensive phase
- Optimal treatment duration not established
- Based on a systematic review, guidelines suggest a 4-month treatment regimen for **smear-negative, culture-negative pulmonary tuberculosis**
- The intensive phase of 2 months remains the same
- The continuation phase is **shortened** to **2 months**.

AMERICAN THORACIC SOCIETY DOCUMENTS

Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Jussi J. Saukkonen*, Raquel Duarte*, Sonal S. Munsiff*, Carla A. Winston*, Manoj J. Mammen, Ibrahim Abubakar, Carlos Acuña-Villaorduña, Pennan M. Barry, Mayara L. Bastos, Wendy Carr, Hassan Chami, Lisa L. Chen, Terence Chorba, Charles L. Daley, Anthony J. Garcia-Prats, Kelly Holland, Ioannis Konstantinidis, Marc Lipman, Giovanni Battista Migliori, Farah M. Parvez, Adrienne E. Shapiro, Giovanni Sotgiu, Jeffrey R. Starke, Angela M. Starks, Sanket Thakore, Shu-Hua Wang, Jonathan M. Wortham, and Payam Nahid; on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

- Published December 30, 2024
- Novel **4 month adult regime**n for pulmonary TB
- Shortened **4 month regimen** for children with non severe TB
- **Drug resistant** TB recommendation updates

Conditional recommendation of 4-month rifapentine-moxifloxacin regimen

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- > 12 years old
- Drug susceptible pulmonary TB
- Use of 4 months of INH, rifapentine, moxifloxacin and PZA

Q1: Treatment of Isoniazid-Susceptible, Rifampin-Susceptible TB in Adults

Recommended 4-mo Rifapentine-Moxifloxacin–Containing Regimen*

Isoniazid†	300 mg daily for 17 wk
Rifapentine	1,200 mg daily for 17 wk
Pyrazinamide	Weight-based dosing daily for 8 wk: 40 to <55 kg: 1,000 mg; ≥55–75 kg: 1,500 mg >75 kg: 2,000 mg
Moxifloxacin	400 mg daily for 17 wk

VDH/CDC guidelines

- VDH: Four-Month-Treatment-Regimen-Guidance_112023.pdf (Updated 11/27/2023)
- VDH TB program recommends this regimen in limited instances
- Consultation with VDH TB Program nurses required
- Inclusion criteria:
  - Pulmonary TB without resistance to INH, RPT (or rifampin as surrogate), PZA, or fluoroquinolones
  - >12 years of age
  - Body weight >40kg
  - Not pregnant or breasfeeding
  - No history of prolonged QT interval or current use of QT prolonging medications
  - No drug interactions
  - If patient is already on standard RIPE treatment, the patient has been on treatment for < 30 days.

Rifapentine (RPT)

- In the same family of antibiotics as Rifampin: rifamycins
- Rifapentine has a longer half life than rifampin
- More potent against TB bacteria
- Binds to protein which keeps it in the blood longer

Rifapentine side effects similar to Rifampin

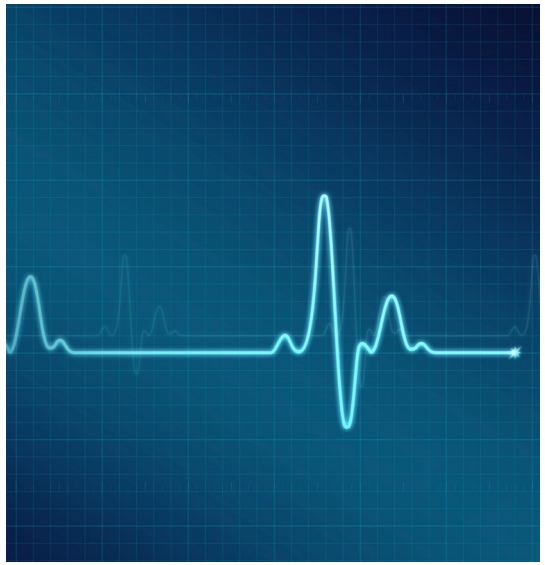
- Hepatotoxicity
- GI symptoms
- Discoloration of body fluids
- Hematologic: low platelet counts. Monitor for easy bruising/nose bleeds
- Cutaneous reactions
- Hypersensitivity reactions
- More likely to cause flu-like reaction especially with intermittent dosing

Moxifloxacin

- Fluoroquinolone
- Now a first line drug for multi-drug resistance TB (will discuss later)
- Really good at killing M. tb bacteria

Moxifloxacin side effects

- GI disturbance: nausea, diarrhea, vomiting
- Peripheral neuropathy (cumulative) - burning/numbless/change of sensation in hands/feet
- Muskoluskeletal: Athralgia/arthritis - pain and tenderness of muscles and joints, inflammation of the tendons/tendon rupture
- CNS effects: hallucinations, anxiety, depression, insomnia, severe headaches, and confusion
- Cardiac: QT interval prolongation. Monitor for change in heartbeat, palpitations, feeling dizzy or faint
- Photosensitivity
- Rash
- Hypersensitivty/anaphylaxis



Shortened regimen in children

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Q2: Treatment of Nonsevere, Presumed Isoniazid-Susceptible, Rifampin-Susceptible TB in Children

Recommended Regimen	Intensive Phase (*8 wk*)‡	Continuation Phase (*8 wk*)
Isoniazid†	10–15 mg/kg	10–15 mg/kg
Rifampin	10–20 mg/kg	10–20 mg/kg
Pyrazinamide	35 (30–40) mg/kg	None
Ethambutol§	20 (15–25) mg/kg (included/excluded based on local guidelines)	None

- Children 3 months – 16 year old age with non-severe TB
- SHINE trial conclusion: 4 months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, non-severe, smear –negative tuberculosis

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

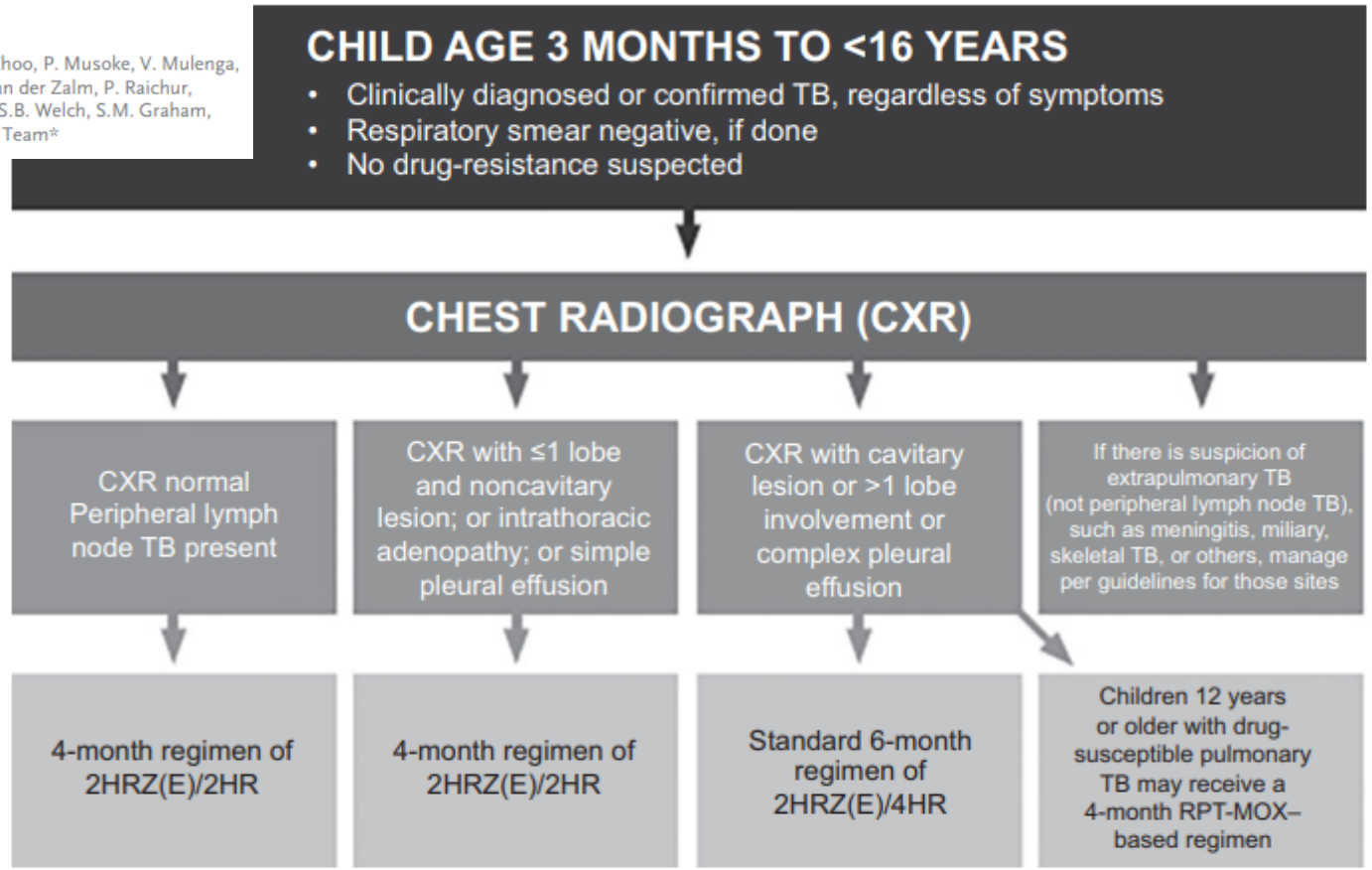

Figure 1. Identifying children eligible for 4-month regimens. Figure developed by the Joint Panel on the basis of data in the SHINE trial and Study 31/A5349 to address eligibility of some children for either the RPT/MOX regimen or the 4-month standard drug regimen. CXR = chest x-ray; HRZE = isoniazid, rifampin, pyrazinamide, ethambutol; RPT-MOX = rifapentine-moxifloxacin.

BPaLM regimen for Rifampin resistance or Rifampin intolerance

Q4: Treatment of Rifampin-Resistant, Fluoroquinolone-Susceptible TB	
Recommended BPaLM Regimen[¶]	
Bedaquiline	400 mg daily for 2 wk, then 200 mg three times/wk for subsequent 24 wk
Pretomanid	200 mg daily for 26 wk
Linezolid	600 mg daily for 26 wk
Moxifloxacin	400 mg daily for 26 wk

- 14 years and older
- Consult with TB experts
- Previously would have been on a 15 month or longer regimen

BPaLM: intensive monitoring

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Table 8. Monitoring Plan for Patients Treated with BPaL or BPaLM*

	Month of Treatment												Post-Treatment†				
Activity	0 (Baseline)	1‡			2		3	4	5	6	7	8	9	3	6	12	18	24
Sputum smear and culture§	●	●	●	●	●		●	●	●	●	○	○	○	●	●	●	●	●
Imaging (CXR, CT, other)‖	●						●			●			○	○	○	○	○	○
Weight¶	●		●		●		●	●	●	●	○	○	○	●	●	●	●	●
Symptom review**	●		●		●		●	●	●	●	○	○	○	●	●	●	●	●
DST††	●						○											
CBC‡‡	●	●	●	●	●	●	●	●	●	●	○	○	○					
Creatinine§§	●		●		●		●	●	●	●	○	○	○					
ALT/AST, alkaline phosphatase, bilirubin‖‖	●		●		●		●	●	●	●	○	○	○					
K^+, Ca^{2+}, Mg^{2+}, bicarbonate¶¶	●		●		●		●	●	●	●	○	○	○					
Serum drug concentration***			○															
HIV†††	●																	
Pregnancy‡‡‡	○		○		○		○	○	○	○	○	○	○					
EKG§§§	●	●		○	○		●	○	○	●	○	○	○					
Vision exam‖‖‖	●		●		●		●	●	●	●	○	○	○					
Peripheral neuropathy¶¶¶	●		●		●		●	●	●	●	○	○	○					
Arthralgias****	●		○		○		○	○	○	○	○	○	○					
Amylase, lipase, TSH††††	○																	

INH resistance or intolerance

Treatment for Drug-Resistant Tuberculosis Disease

For Health Care Providers
APRIL 17, 2025

Treating patients with isonaizid-resistant TB disease

Patients with TB disease that is resistant to isonaizid only (sometimes referred to as isonaizid monoresistance) should be treated with a 6-month daily regimen of:

- Rifampin,
- Ethambutol,
- Pyrazinamide, and
- A later-generation fluoroquinolone.

In certain situations, the duration of pyrazinamide can be shortened to two months.

https://www.cdc.gov/tb/hcp/treatment/drug-resistant-tuberculosis-disease.html

PZA resistance or intolerance

- Treat with INH and Rifampin for 9 months
- EMB in the early months
- Cannot shorten regimen to 9 months
- PZA is good at killing dormant or sleeping bacteria
- Think about M. bovis (from infected animals, unpasteurized dairy products) which is clinically the same as M.Tb

LTBI treatment regimens

- Household contact of active cases will often be on LTBI treatment
- Children under 5 years old that are contacts will be on window prophylaxis which is the same as LTBI treatment regimens
- Option for one of the LTBI treatment regimens to be administered via DOT (3HP)

LTBI regimens

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

Timothy R. Sterling, MD[1]; Gibril Njie, MPH[2]; Dominik Zenner, MD[3]; David L. Cohn, MD[4]; Randall Reves, MD[4]; Amina Ahmed, MD[5]; Dick Menzies, MD[6]; C. Robert Horsburgh, Jr., MD[7]; Charles M. Crane, MD[8]; Marcos Burgos, MD[8,9]; Philip LoBue, MD[2]; Carla A. Winston, PhD[2]; Robert Belknap, MD[4,8]

TABLE 3. Recommendations for regimens to treat latent tuberculosis infection

Return

Priority rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 mos isoniazid plus rifapentine given once weekly	Strong	Moderate
Preferred	4 mos rifampin given daily	Strong	Moderate (HIV negative)†
Preferred	3 mos isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
		Conditional	Low (HIV positive)
Alternative	6 mos isoniazid given daily	Strong§	Moderate (HIV negative)
		Conditional	Moderate (HIV positive)
Alternative	9 mos isoniazid given daily	Conditional	Moderate

Abbreviation: HIV = human immunodeficiency virus.

* *Preferred:* excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens and therefore higher effectiveness; *alternative:* excellent efficacy but concerns regarding longer treatment duration, lower completion rates, and therefore lower effectiveness.

† No evidence reported in HIV-positive persons.

§ Strong recommendation for those persons unable to take a preferred regimen (e.g., due to drug intolerability or drug-drug interactions).

Questions?

Summary

- Many different regimens
- Common things being common --> we use RIPE the most
- Move towards shorter regimens for treatment of TB without sacrificing cure
- TB outreach workers are a vital part of the team! ***THANK YOU!***