Treatment of Tuberculosis

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Disclosures

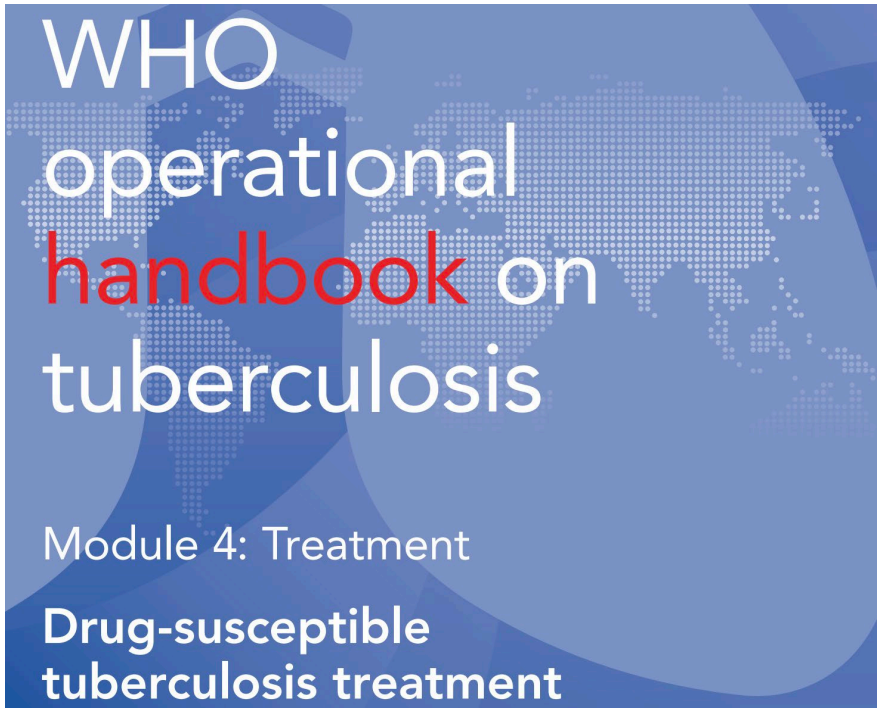
- No conflicts of interest

Objectives

After participating in this lecture, you should be able to describe:

- When empiric TB treatment should be started
- The medication regimens for treating likely or confirmed drug-susceptible TB
- Changes to TB treatment for patients with liver disease, renal disease and other selected scenarios

Care and treatment guidelines may slightly differ depending on practice setting



Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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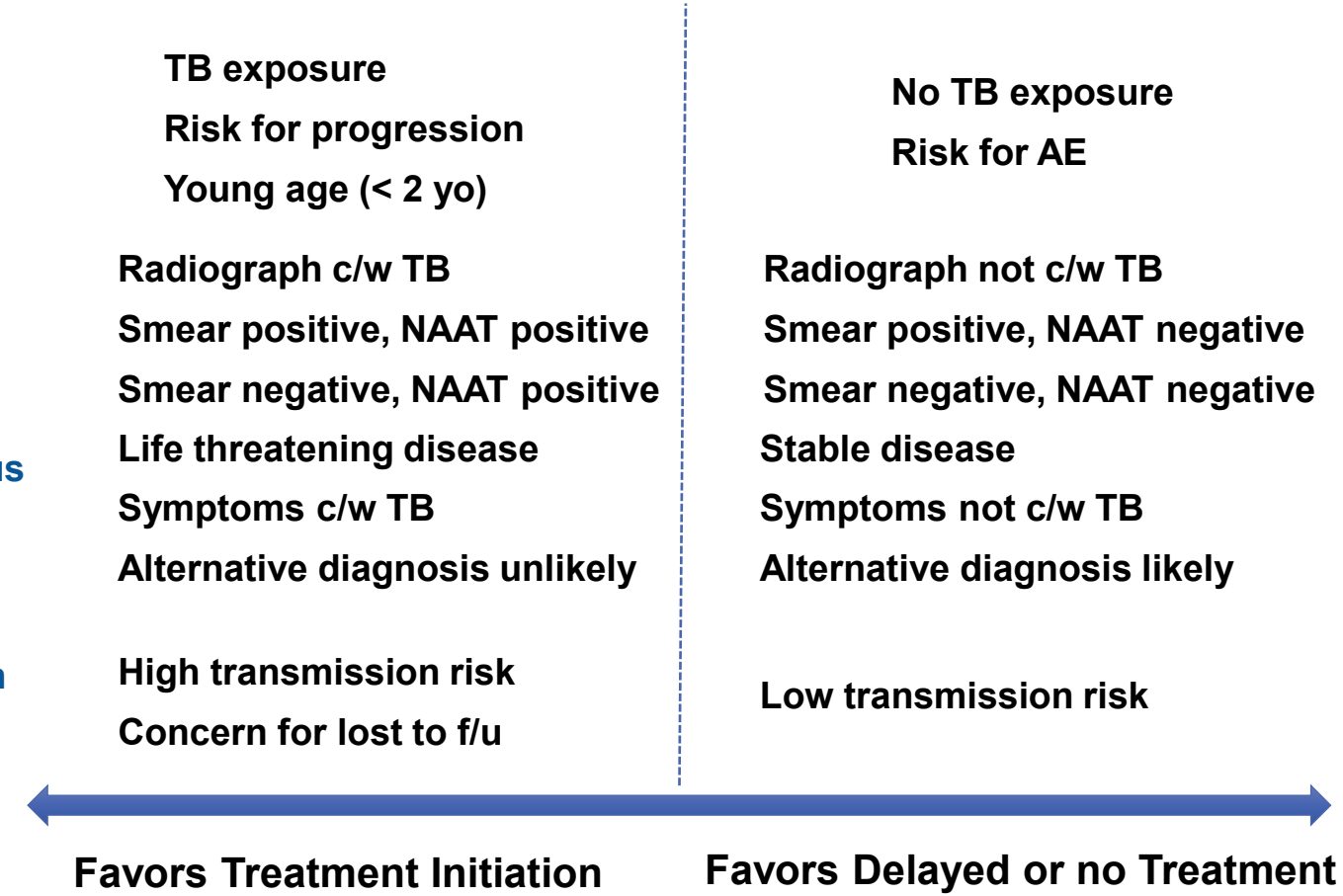
https://www.who.int/publications/i/item/9789240050761

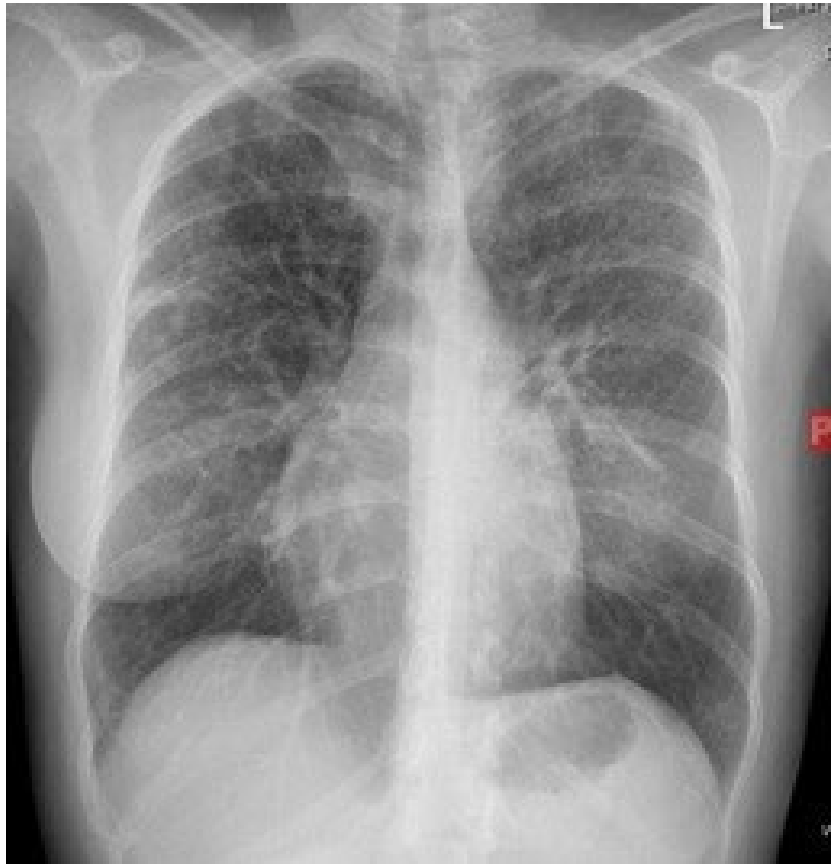
Nahid, CID October 1, 2016; 63(7): e147-195

Caring for someone who could have TB: several factors to consider when initiating testing and treatment

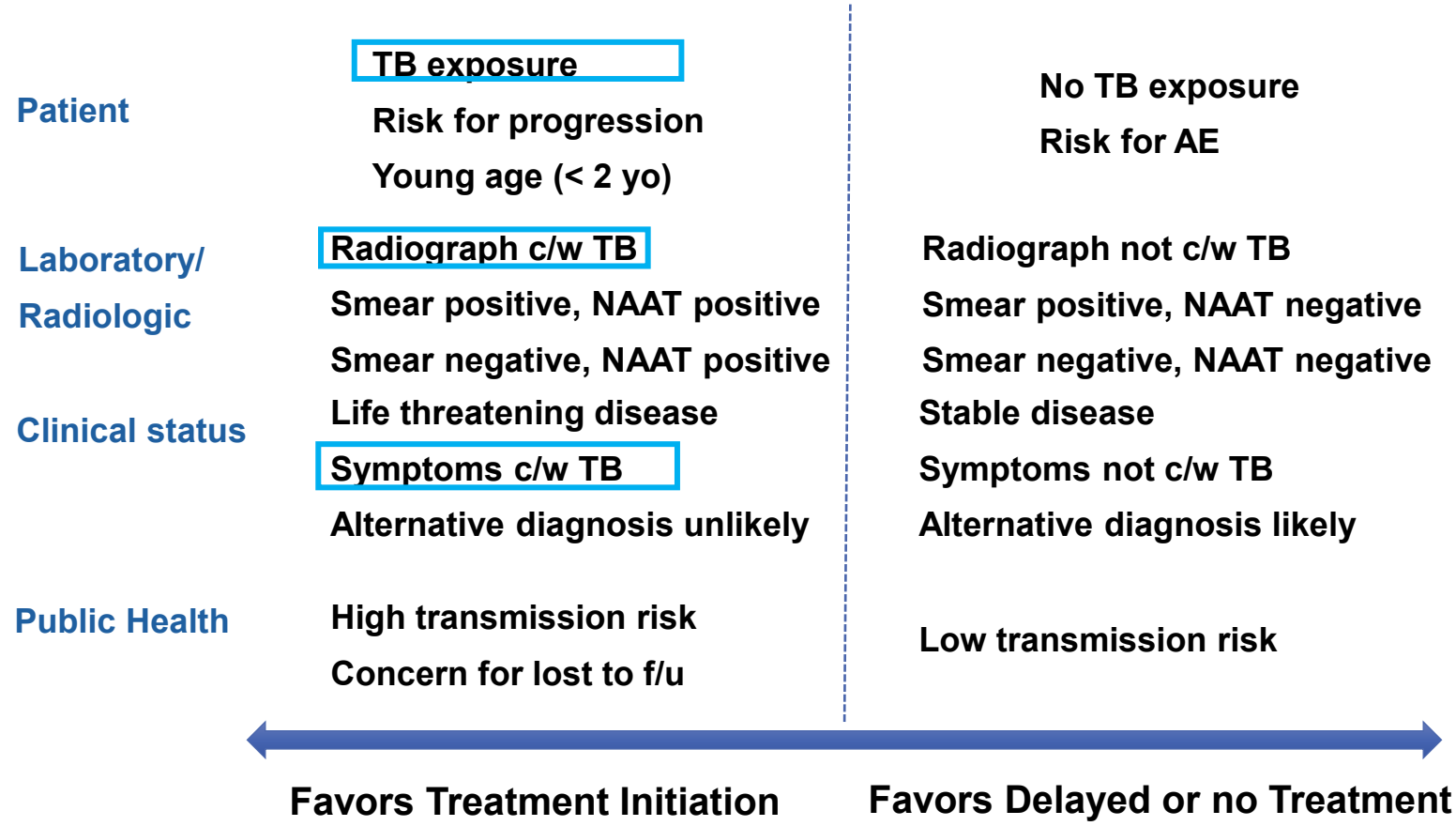


Patient #1

- 26-year-old woman, originally from Honduras, presented to her primary care provider:
  - Cough for 2 months, wheezing noted on exam
  - Inhaler offered, PFTs scheduled
- Urgent care visit 3 days after that visit
  - Continued cough, CXR obtained…

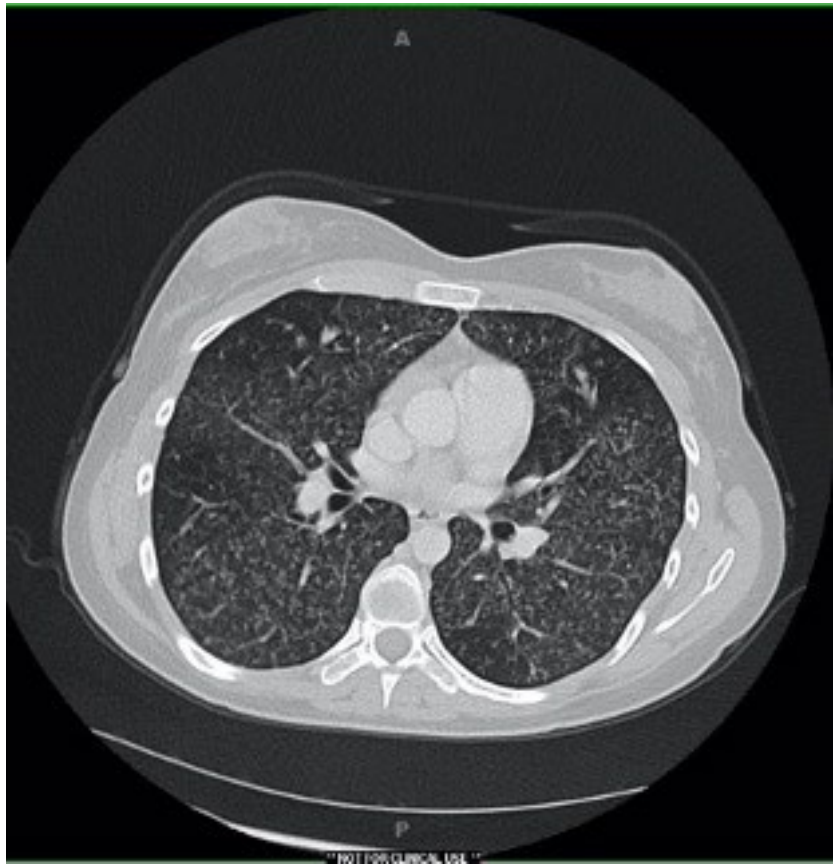


Factors Affecting Decisions to Initiate Testing and Treatment



Patient #1—follow up

- 5 months later: repeat PCP visit for continued cough and now weight loss
- Chest radiograph findings were noted→ referred to pulmonary, CT chest ordered.
- One visit to pulmonary clinic→ ”bronchiolitis”
- Multiple ED visits over the next 7 months
- 8 months into her illness: family took her to another hospital
  - Somnolence, confusion, nausea, vomiting
  - MRI/ brain: diffuse focal flair hyperintensity; diffuse leptomeningeal enhancement compatible with meningitis.
  - **LP: WBC 149, t prot 152, glucose 14**
    - ***M. tuberculosis* PCR positive**



Patient #1--the consequences of delays

- Bronchoalveolar lavage, smear positive for AFB and subsequently was identified to be *Mycobacterium tuberculosis*.
- Additional studies:
  - Quantiferon positive
  - HIV negative
- Hospital course notable for the development of seizures
- Started on TB treatment with isoniazid, rifampin, pyrazinamide and ethambutol and steroids due to meningitis.

- *Profoundly debilitated/confused and unable to care for herself at discharge*

Deciding to start Empiric TB treatment

- **<u>Clinical reasons</u>**
  - at risk for life-threatening TB (e.g. < 50% of TB meningitis is culture positive)

- **<u>Public health reasons</u>**
  - return to work/school while cultures are pending, children at home, staying in a congregate setting

Basics of TB Treatment

- Combination therapy is required to prevent failure and resistance
- Standard medications for drug sensitive TB
  - **Isoniazid (INH, H, I)**
  - **Rifampin (RIF, R)**
  - **Pyrazinamide (PZA, Z) NOTE:** some abbreviate with P but that usually refers to rifapentine
  - **Ethambutol (EMB, E)**

Role of each drug in the TB regimen

Rapid killing of multiplying bacilli (bactericidal effect)	INH
Achievement of relapse-free cure (sterilizing effect)	RIF, PZA
Protection against acquisition of drug resistance	INH, RIF, EMB

Never treat active TB with a single drug

Treatment of Tuberculosis
Standard Regimen

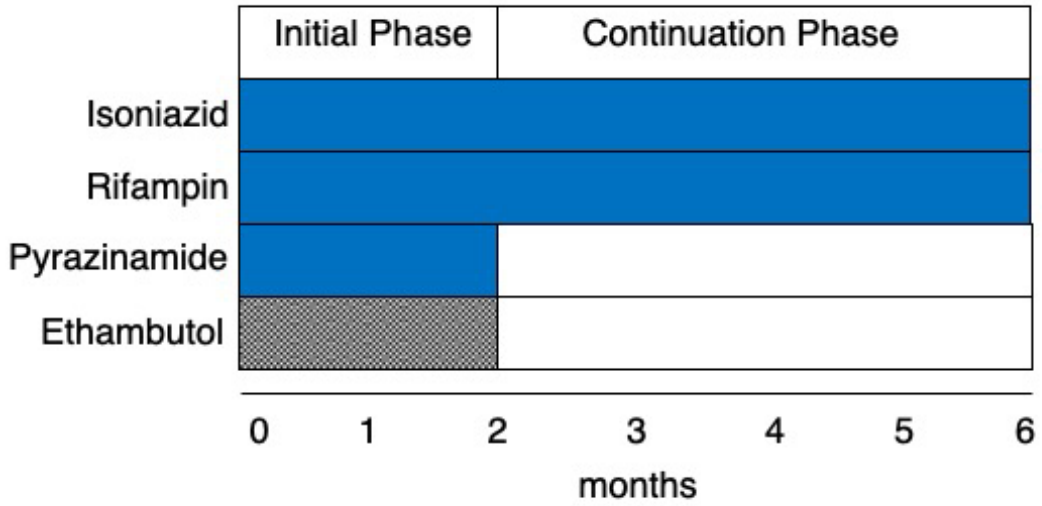


Table 3. Doses[a] of Antituberculosis Drugs for Adults and Children[b]

Drug	Preparation	Population	Daily	Once-Weekly	Twice-Weekly	Thrice-Weekly
First-line drugs						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for intravenous or intramuscular injection. Note: Pyridoxine (vitamin B6), 25–50 mg/day, is given with INH to all persons at risk of neuropathy (eg, pregnant women; breastfeeding infants; persons with HIV; patients with diabetes, alcoholism, malnutrition, or chronic renal failure; or patients with advanced age). For patients with peripheral neuropathy, experts recommend increasing pyridoxine dose to 100 mg/d.	Adults	5 mg/kg (typically 300 mg)	15 mg/kg (typically 900 mg)	15 mg/kg (typically 900 mg)	15 mg/kg (typically 900 mg)
		Children	10–15 mg/kg	. . .	20–30 mg/kg	. . .[b]
Rifampin	Capsule (150 mg, 300 mg). Powder may be suspended for oral administration. Aqueous solution for intravenous injection.	Adults[c]	10 mg/kg (typically 600 mg)	. . .	10 mg/kg (typically 600 mg)	10 mg/kg (typically 600 mg)
		Children	10–20 mg/kg	. . .	10–20 mg/kg	. . .[b]
Rifabutin	Capsule (150 mg)	Adults[d]	5 mg/kg (typically 300 mg)	. . .	Not recommended	Not recommended
		Children	Appropriate dosing for children is unknown. Estimated at 5 mg/kg.			
Rifapentine	Tablet (150 mg film coated)	Adults	10–20 mg/kg[e]		. . .	. . .
		Children	Active tuberculosis: for children ≥12 y of age, same dosing as for adults, administered once weekly. Rifapentine is not FDA-approved for treatment of active tuberculosis in children <12 y of age.			
Pyrazinamide	Tablet (500 mg scored)	Adults	See Table 10	. . .	See Table 10	See Table 10
		Children	35 (30–40) mg/kg	. . .	50 mg/kg	. . .[b]
Ethambutol	Tablet (100 mg; 400 mg)	Adults	See Table 11	. . .	See Table 11	See Table 11
		Children[f]	20 (15–25) mg/kg	. . .	50 mg/kg	. . .[b]

Preferred Regimen is daily dosing

Effectiveness

Initial			Continuation	
Reg	Drugs	Interval/Dose	Drugs	Interval/Dose
1	INH RIF EMB PZA	7 days/wk (56) or 5 days/wk (40)	INH/RIF	7 days/wk (126) or 5 days/wk (90)
2	INH RIF EMB PZA	7 days/wk (56) or 5 days/wk (40)	INH/RIF	3 days/wk (54)

Nahid, CID October 1, 2016; 63(7): e147-195

Organization and Supervision of Therapy

2. Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of TB?

We suggest **using DOT rather than SAT**

(conditional recommendation, low quality of evidence)

	Studies	DOT	SAT	Relative Risk
Treatment Success	5	74.6%	73.0%	0.94 (0.89-0.98)

No difference in mortality, treatment completion or relapse

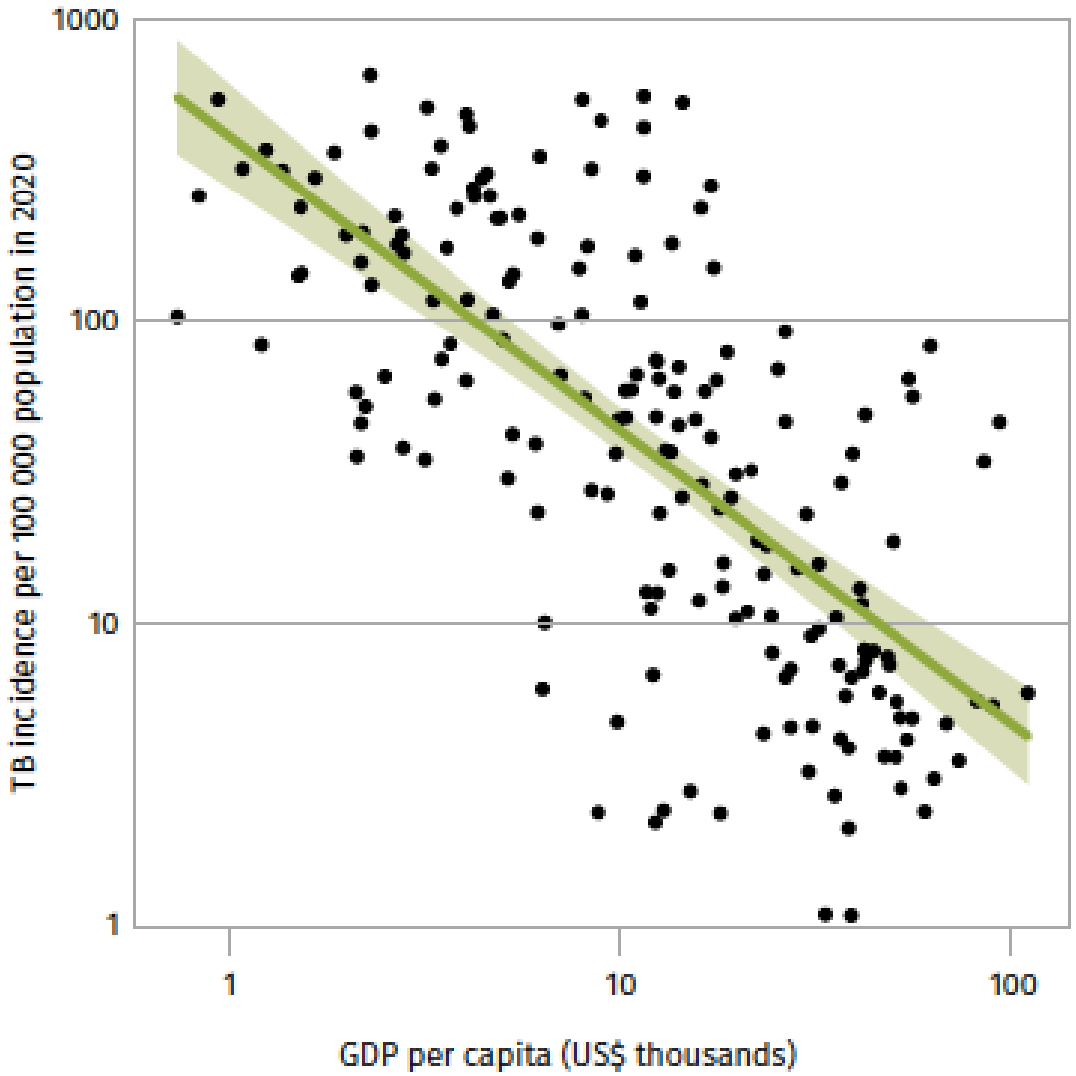
Patient-Centered Care

- **Trust must be earned**
  - Trauma-informed care
  - Address needs of the entire household
  - Always provide interpretation services when needed
  - The patient's priorities are your priorities
    - TB treatment is not always #1
- **Addressing social needs is critical**
  - Meet people where they are and connect to other healthcare providers who may have shared lived experiences
- **Coordination of care for other health issues**
- **Flexibility with directly observed therapy**
  - Clinic, field and/or home visits
  - Use of video technology

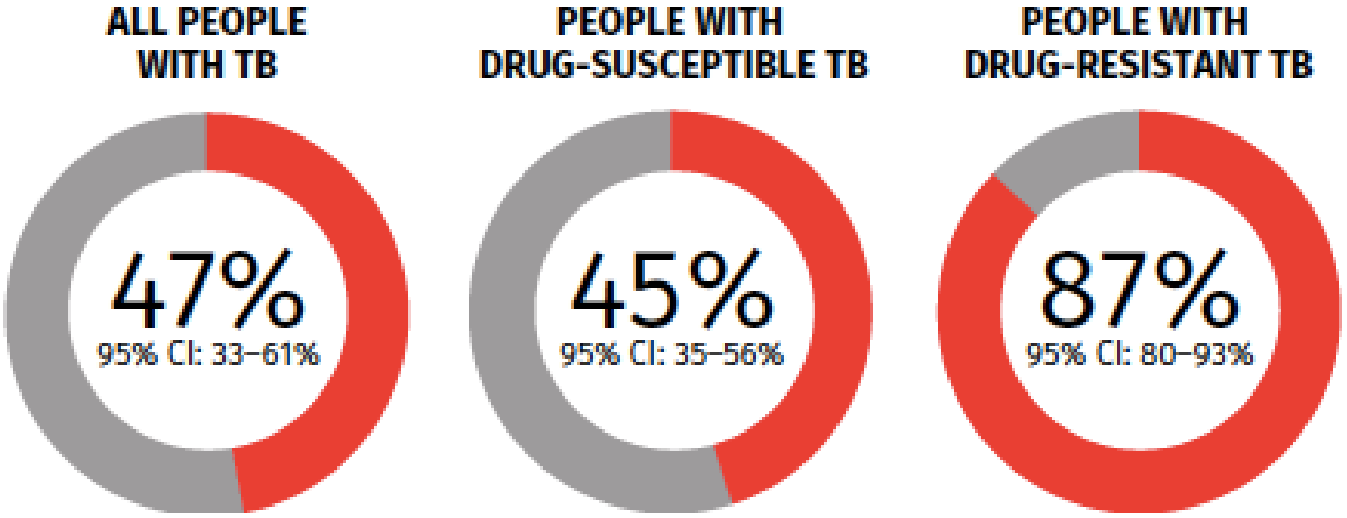
What happens after you have started TB treatment?

- **Address social, financial, mental health needs before, during and after, initiating treatment**
- Outpatient linkage to care: connect to public health within one business day
- Hospital discharge planning:
  - Contact public health, coordinate warm hand-off with TB clinic attending or nurse
- Provide support for FMLA if this is an option
  - Indirect costs from TB (lost wages, transportation costs) can be devastating

Relationship between wealth and TB: higher GDP, lower TB incidence but TB associated with catastrophic costs



Average percentage of people with TB and their households facing catastrophic costs in 23 national surveys completed since 2015



Global TB Report, 2021

Monitoring for Treatment Response and Adverse Reactions

Activity	Baseline	Month of Treatment Completed 1	2	3	4	5	6	7	8	End of Treatment Visit
MICROBIOLOGY										
Sputum smears and culture[1]	☐	☐	☐	☐	☐					☐
Drug susceptibility testing[2]	☐			☐						
IMAGING										
Chest radiograph or other imaging[3]	☐		☐							☐
CLINICAL ASSESSMENT										
Weight[4]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Symptom and adherence review[5]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Vision assessment[6]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
LABORATORY TESTING										
AST, ALT, bilirubin, alkaline phosphate[7]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Platelet count[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Creatinine[8]	☐	☐	☐	☐	☐	☐	☐	☐	☐	
HIV[9]	☐									
Hepatitis B and C screen[10]	☐									
Diabetes Screen[11]	☐									

Shaded - optional

Nahid, CID October 1, 2016; 63(7): e147-195

Intermittent dosing-less effective, should be used selectively

Effectiveness

Initial			Continuation	
Reg	Drugs	Interval/Dose	Drugs	Interval/Dose
3*	INH RIF EMB PZA	3X wkly (24)	INH/RIF	3X wkly (54)
4**	INH RIF EMB PZA	7 days/wk (14) then twice wkly (12)	INH/RIF	2X wkly (36)

*Use with caution in patients with cavitary disease

**Do not use in patients with HIV or smear positive and/or cavitary disease

Nahid, CID October 1, 2016; 63(7): e147-195

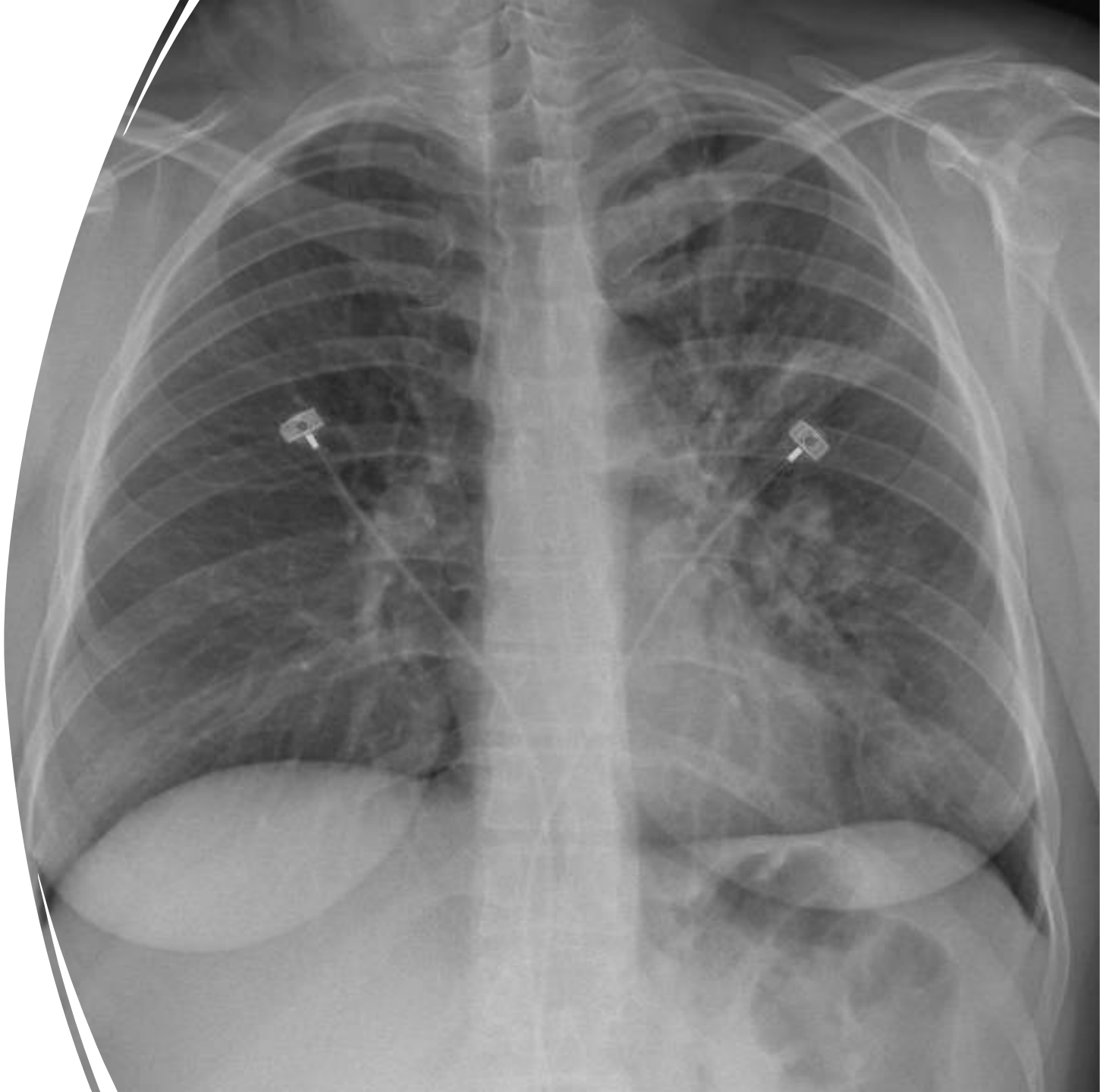
Other guideline recommended alternatives for drug-susceptible TB:

"In situations in which several of the first-line agents cannot be used because of intolerance, regimens based on the principles described for treating drug-resistant tuberculosis are used"

CID 2016;63(7):e147–95

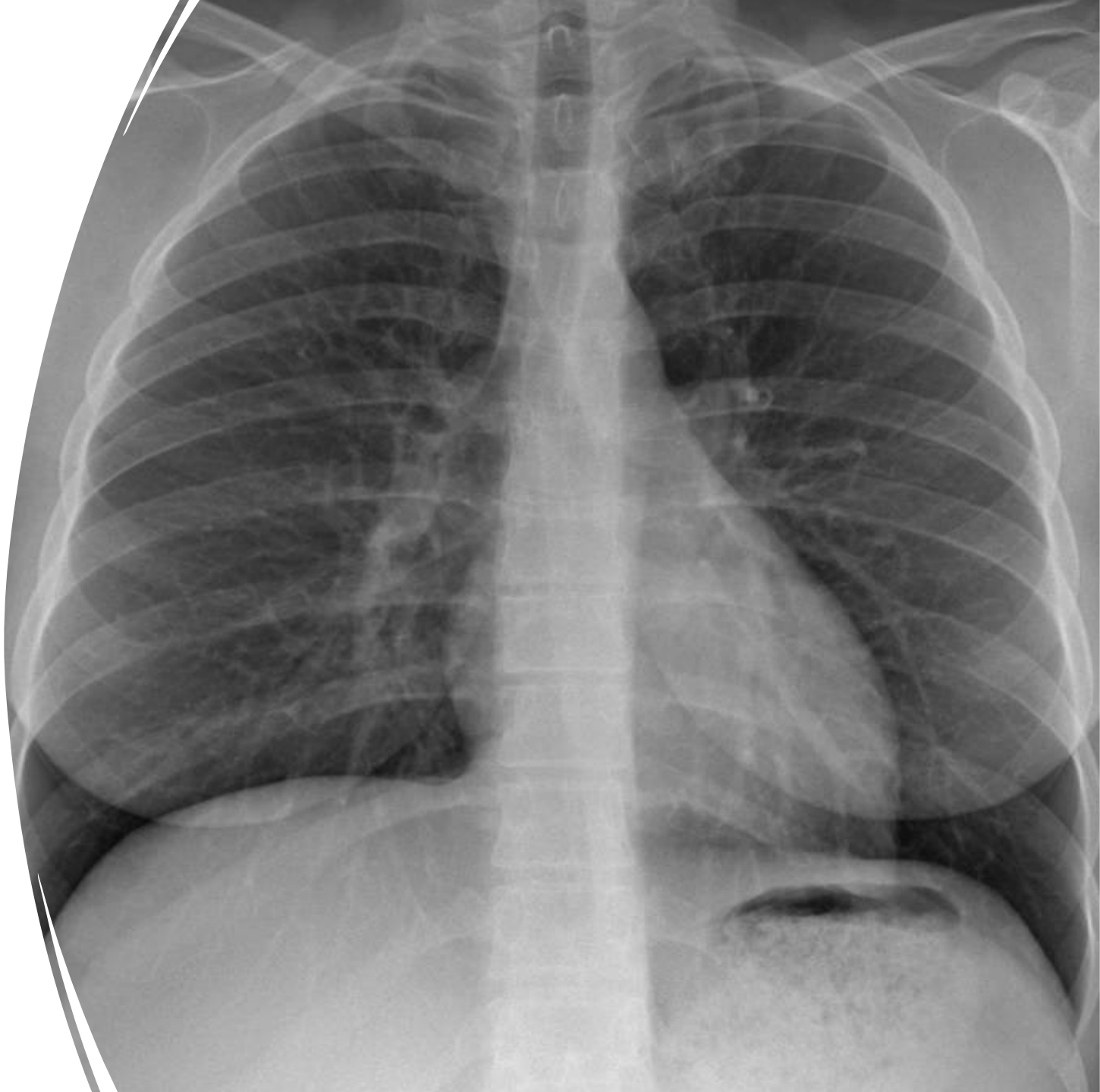
Patient #2

- 37-year-old woman with uncontrolled diabetes, recently moved from Central America
  - DOT isn't feasible due to work, not adherent with videos
    - Consistently doing 3-4 days of daily treatment by week 18
  - After 20 weeks, she's expresses that she's done with treatment



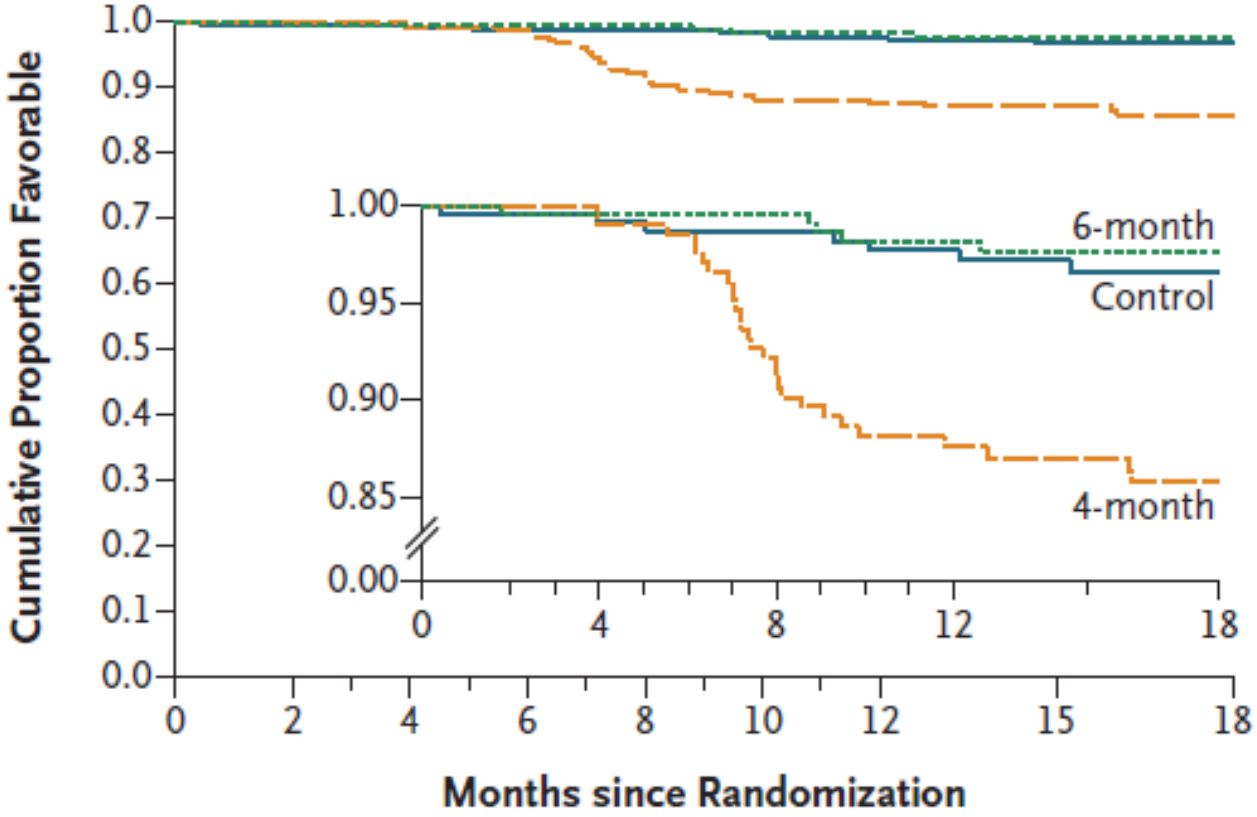
Patient #2: Role for intermittent regimens: when daily isn't feasible

- Agrees to treatment once per week
  - Started Moxifloxacin+ rifapentine once weekly
  - Weekly, in person DOT, provided grocery card to reimburse for time
  - Completed 36 weeks/39 weeks of planned treatment



The forgotten arm of RIFAQUIN

- 6-month arm
- N=212
- 63% with cavitary disease
- Moxifloxacin+ EMB, RIF, PZA x daily 2 months followed by:
  - Moxifloxacin 400mg + rifapentine 1200 mg weekly



No. at Risk

Control	240	232	227	213	210	203	195	175	142
4-month	239	223	211	202	185	172	169	147	127
6-month	251	234	224	217	212	207	205	180	153

N Engl J Med 2014;371:1599-608.

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

Inclusion

- Positive AFB sputum smear or positive *Xpert MTB* (medium/high, no RIF-R)
- Age ≥12 y.o.
- If HIV-positive, CD4 T cell count ≥100 cells/mm^3, EFV-based ART

Exclusion

- Pregnant and breastfeeding women
- Known history of prolonged QT syndrome
- Extrapulmonary TB (CNS, bones or joints, miliary, pericardial)
- Weight <40 kg
- Known drug resistance

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

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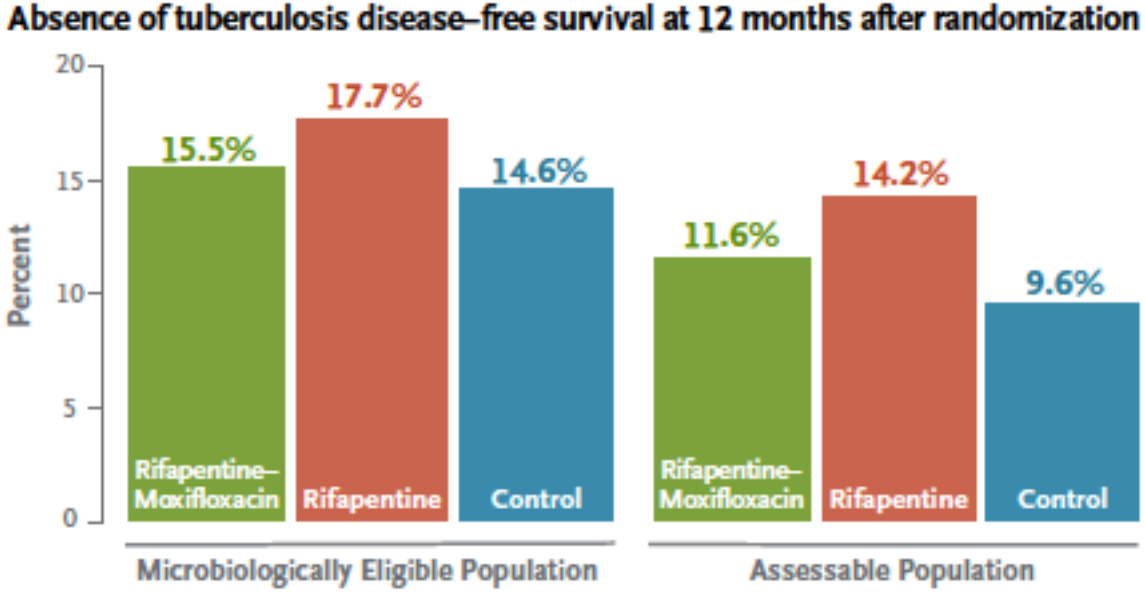
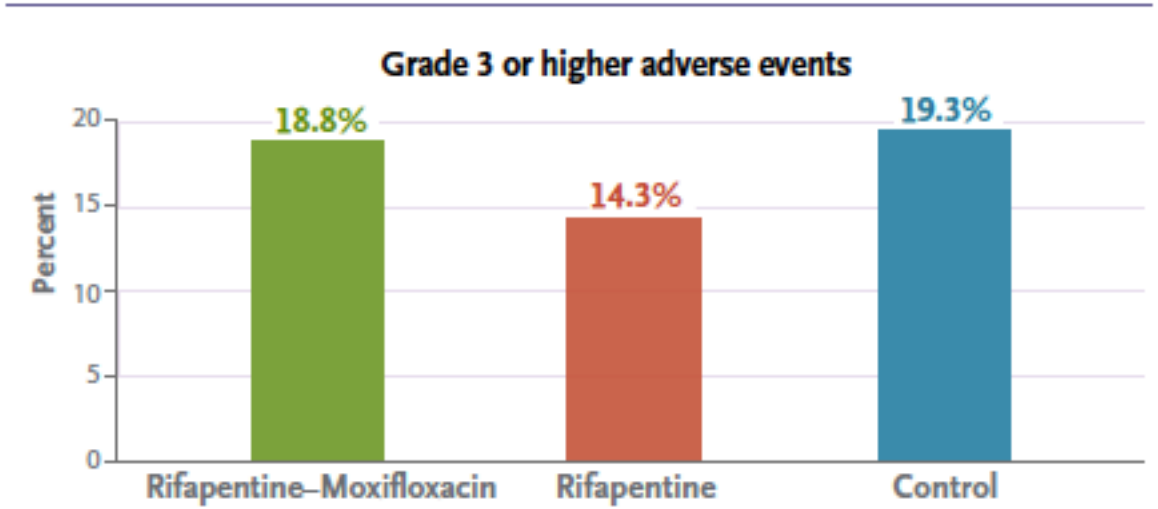




N= 2516, newly diagnosed TB

RCT: control, 4-month regimen with rifampin replaced by rifapentine (rifapentine Group or IPEZ/IP), or 4-month regimen with rifampin replaced by rifapentine, ethambutol by moxifloxacin (rifapentine–moxifloxacin group or IPMZ/IPM).

Primary outcome: TB-free survival at 12 months.

Results: 4 months Moxi-rifapentine was not inferior to control arm

MMWR Morb Mortal Wkly Rep 2022;71:285–289.

50% of patient discontinue 4-month rifapentine/moxifloxacin under operational conditions

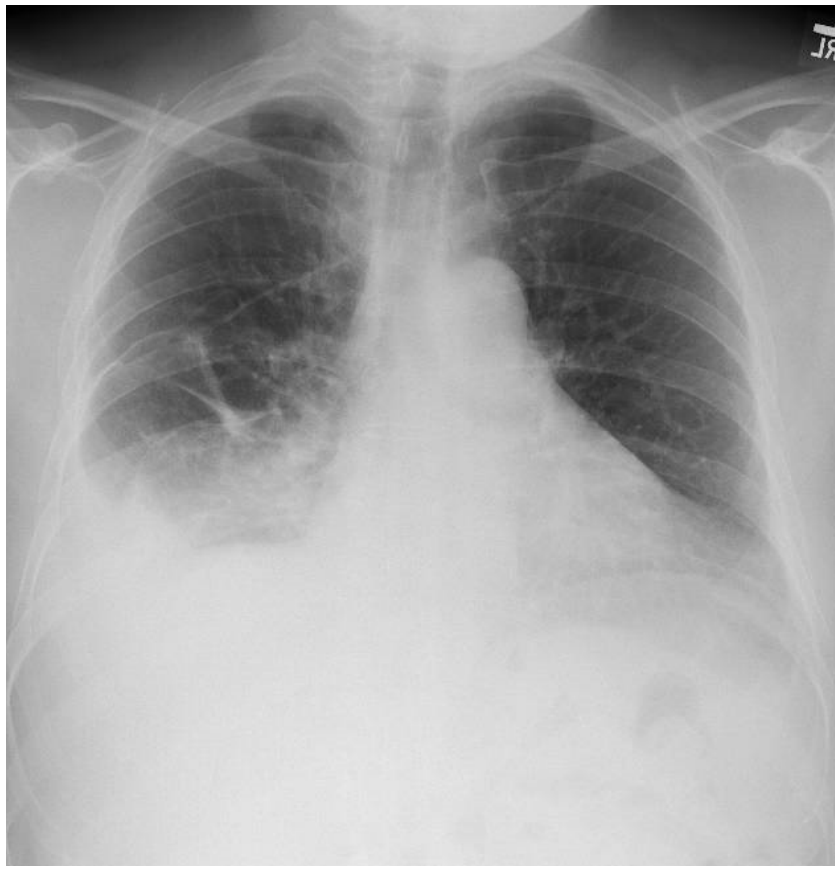
- August 2021 to December 2023, 30 (18.8%) of 160 patients diagnosed with active TB met HPMZ inclusion criteria;
  - 22 (13.8%) started HPMZ.
  - median age (range) was 32.5 (14–86) years, 17 (77.3%) were otherwise healthy, and 19 (86.4%) had pulmonary TB, including 7 (36.8%) with cavitary disease.
  - Eighteen (81.8%) patients had an adverse event,
  - 11 (50%) prematurely discontinuing HPMZ;
    - the most common adverse events were vomiting, elevated transaminases, and rash.
  - 9 (40.9%) have completed treatment, with most achieving criteria for cure.
    - One patient was diagnosed with possible TB recurrence and restarted standard TB treatment.

Louie JK, et al. OFID 2024

Managing hepatotoxicity

- 67-year-old man with +IGRA referred for treatment for probable Pleural TB, no pulmonary TB:
  - pleural fluid neg AFB; Pleural biopsy: necrotizing granulomas
  - Started IRE, then added PZA→ hepatotoxicity
  - Treatment changed to Levo/EMB x one week, then rifampin added
  - Pleural tissue grew at 3 weeks, confirmed TB

  - 2 weeks later—INH resistance, request for testing for fluoroquinolone resistance (several days of calls)
  - Tendonitis on Levofloxacin, switched to Moxifloxacin + EMB + rifampin
    - Symptoms improved



TB Treatment in Liver Disease

Mild

- No pyrazinamide; continue isoniazid, rifampin, and ethambutol

Moderate

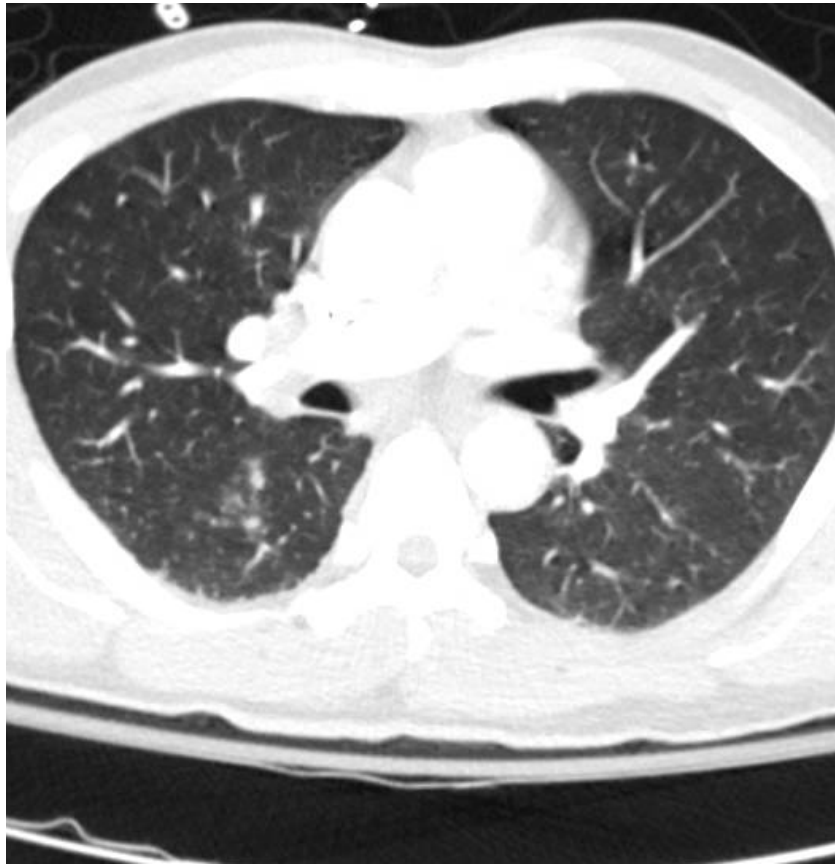
- No Isoniazid or pyrazinamide
- Continue rifampin, ethambutol, substitute in a fluoroquinolone (Levofloxacin)

Severe / Unstable

- Fluoroquinolone (Levofloxacin), ethambutol, linezolid, carbapenem (meropenem), amikacin, Cycloserine

TB and renal disease

- 36 year old man, originally from Thailand*, PMH of hypertension who presents in renal failure and is diagnosed with disseminated TB:
- MTB sputa + X 2
- QFT indeterminate
- HIV negative 1/29/2023
- Etiology of renal failure uncertain
- Also has involvement of mediastinal, hilar nodes, peritoneum, and pleura



*some information changed to protect the patient's privacy

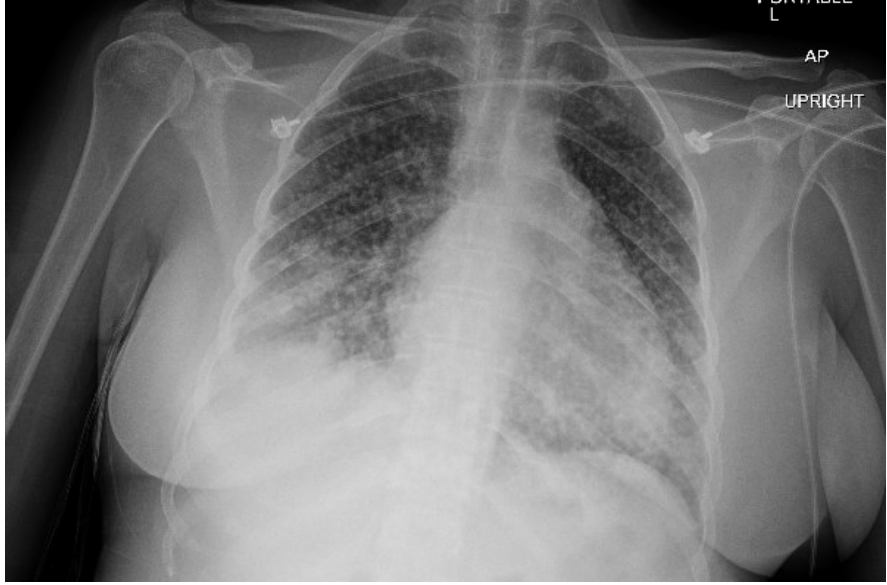
Renal Dosing for Standard TB Treatment

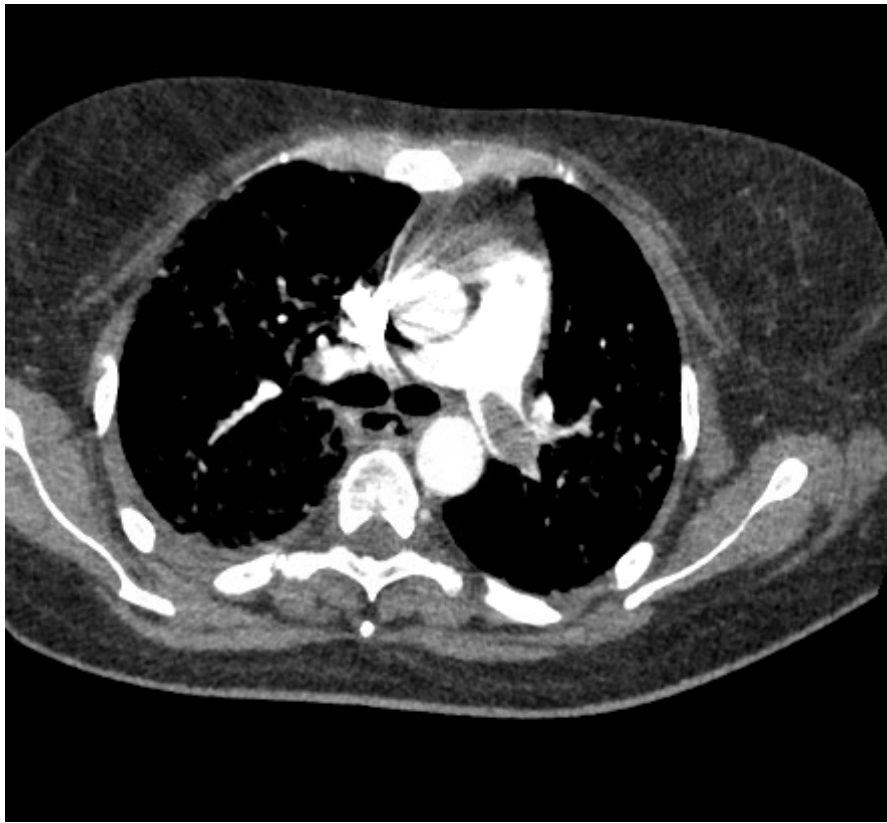
Drug	Change in Frequency?	Recommended Dose and Frequency for Patients With Creatinine Clearance <30 mL/min, or Patients Receiving Hemodialysis
Isoniazid	No	300 mg once daily, or 900 mg 3 times/wk
Rifampin	No	600 mg once daily, or 600 mg 3 times/wk
Pyrazinamide	Yes	25–35 mg/kg/dose 3 times/wk (not daily)
Ethambutol	Yes	20–25 mg/kg/dose 3 times/wk (not daily)
Levofloxacin	Yes	750–1000 mg/dose 3 times/wk (not daily)
Moxifloxacin	No	400 mg once daily

Nahid, CID October 1, 2016; 63(7): e147-195

What if you can't offer RIPE?

- 24-year-old woman who presents with bilateral LE swelling and shortness of breath, fevers
  - Recent travel back from India after visiting family
  - 77% on RA upon arrival, titrated up to 6L NC
  - Develops shock, is intubated
- AFB smear negative, MTB PCR+
- CT scan with submassive PE
- Esophageal perforation
- Worsening shock, likely mixed picture
- TTE with clear evidence of RV strain
- Team wants to give lytics, now NPO after esophageal stent placement





Most of the medications in RIPE cannot be given parenterally

- INH
  - Challenging to offer IV; often not available
- Rifampin
  - Available IV
- Pyrazinamide
  - Only available orally
- Ethambutol
  - Only available orally

Our patient

- Linezolid
- Moxifloxacin
- Meropenem*
- Amikacin
- IV rifampin
- When tolerating orals:
  - Gradual switch to INH, pyrazinamide, ethambutol, rifabutin

*Added amox-clav when able to tolerate orals but still intubated

Optimizing TB treatment in older adults: an unmet need

- Proportion of individuals aged 65 and older with TB is increasing in the US
- Active TB treatment toxicity increases with age
  - Clearly associated with use of INH; PZA probable but less clear
  - Age at which risk increases is poorly defined
    - Some studies <40
- Optimal regimen is uncertain
  - Most clinical trials have <10% of participants in the 65 and older group
- Guidelines:
  - Some experts hold PZA in patients aged 75 and older

Fluoroquinolones + ethambutol, + rifampin

Observational study of patients with INH-R TB in Atlanta: used after 2 months of PZA (N=13)

Individual patient meta-analysis, INH-resistant TB

- N=118 patients received fluoroquinolone + EMB + rifampin; all also received 1-3 months of PZA

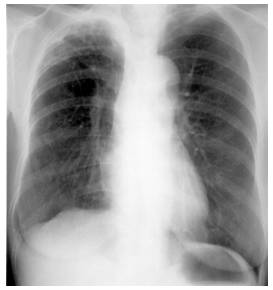
Increasingly used, limited data

Schecter, M. Clinical Infectious Diseases® 2017;65(11):1862–71
Lancet Respir Med. 2018 April ; 6(4): 265–275.

Extending the Duration of Therapy

- Extension to 9 months:
  - Either cavitation or positive sputum culture at 2 months of therapy
    - Many experts would extend for either
  - Involvement of bone/joint without hardware
  - Meningitis (see below)
  - Other considerations
    - >10 % below ideal body weight
    - People who use tobacco
    - Diabetes mellitus
    - Other immunosuppressive conditions
    - Extensive disease on chest radiograph
- Extension to 12 months
  - Meningitis or other CNS disease
  - Bone/joint disease with hardware in place

Shorter treatment for pauci-bacillary disease



On anti-TB Rx

2 mos

4 mos

Initial culture negative?

Yes

Clinical or x-ray improved

Yes

Give continuation-phase treatment for 2 months

No

Stop treatment

Interruptions in Treatment

Time point of interruption	Details of interruption	Approach
Intensive Phase	Lapse is < 14 days	Continue treatment
	Lapse is ≥ 14 days	Restart treatment
Continuation Phase	Received ≥ 80% of doses and was sm (-) at diagnosis	Further treatment may not be necessary
	Received ≥ 80% of doses and was sm (+) at diagnosis	Continue treatment unless 2 consecutive mos missed then restart
	Received < 80% of doses and lapse < 3 mos	Continue treatment
	Received < 80% of doses and lapse ≥ 3 mos	Restart treatment

- Nahid, CID October 1, 2016; 63(7): e147-195

Management of Treatment Failure

90-95% of patients treated for pulmonary TB with regimens containing INH and RIF will have negative sputum cultures by 3 mos

Treatment failure is defined as continuously or recurrently positive cultures after 4 mos

If still culture positive after 3 months of therapy:

- Recheck drug susceptibility tests
- Assess adherence
- Consider malabsorption of drugs

Management of Treatment Failure

- Treatment failure - Culture positive after 4 months of therapy:
  - If the patient is seriously ill or sputum AFB smear +, an empirical regimen should be started with at least 2-3 new drugs
  - If the patient is not seriously ill consider waiting for the results of drug susceptibility testing

Completion of TB Therapy

Completion of therapy is **defined as the number of doses** taken

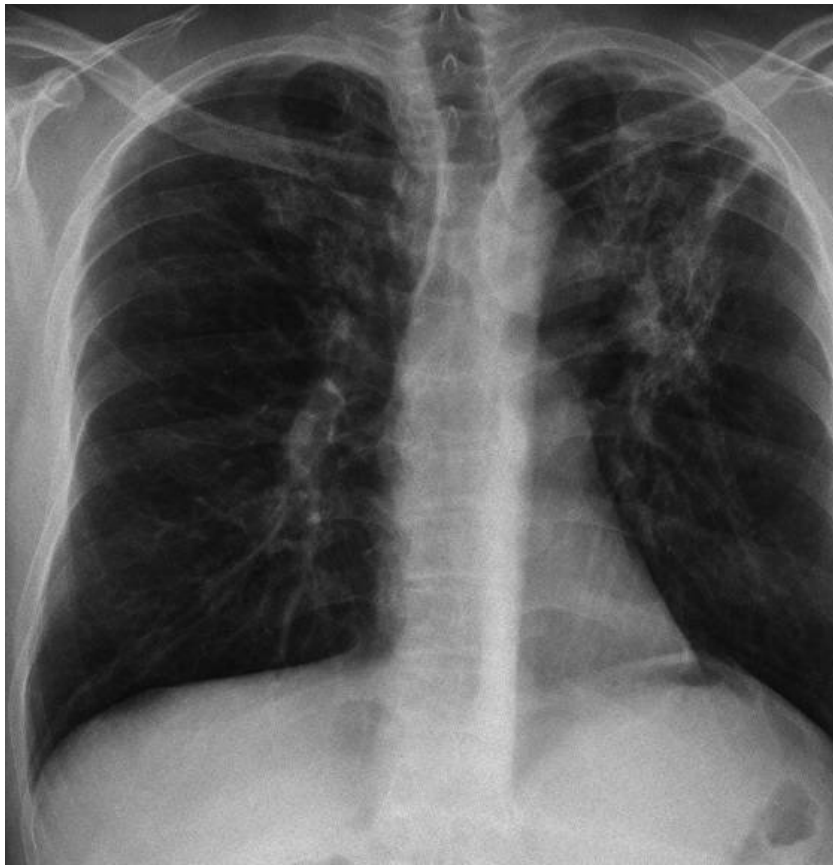
Initial phase - All doses should be taken within **3 months**

Continuation phase - All doses should be taken within **6 months**

Thus, a 6-month regimen should be completed within 9 months

Follow-up after treatment—also an unmet need for guidance

- Not addressed in the guidelines
- No consensus for optimal approach
- Lasting mental health and social needs
- Risk of death 2.91 higher than those who never had TB
- Lingering respiratory symptoms in up to 31% 12 months after treatment
- Risk of relapse likely highest in the first 2 years after treatment
- Denver's approach
  - Stratify by drug-resistance, risk of relapse by baseline burden of disease and residual disease
  - Encourage patients to return to care if they have worrisome symptoms



Ingrid Schoeman, Zolelwa Sifumba. Lancet Infect Dis 2021
Romanowski K, et al.. Lancet Infect Dis 2019; 19: 1129–37.

Summary

- Important to consider both the social, public health, and individual patient factors in starting and continuing TB treatment
- Clear role for empiric treatment pending culture results for many clinical scenarios
- Both individualization and a public health approach are important
  - Patients with underlying medical comorbidities that impact treatment
  - Starting treatment to limit disruptions in life circumstances also important

Summary

- TB treatment is lengthy and difficult
  - Establish and maintain trust with your patients, their household, and community
- Know the resources and guidelines for your practice setting
  - Vast majority of patients can complete treatment in 6 months with:
    - Isoniazid, Pyrazinamide, Ethambutol, rifampin x 2 months followed by:
      - Isoniazid and rifampin x 4 months

Additional Discussion and Questions?