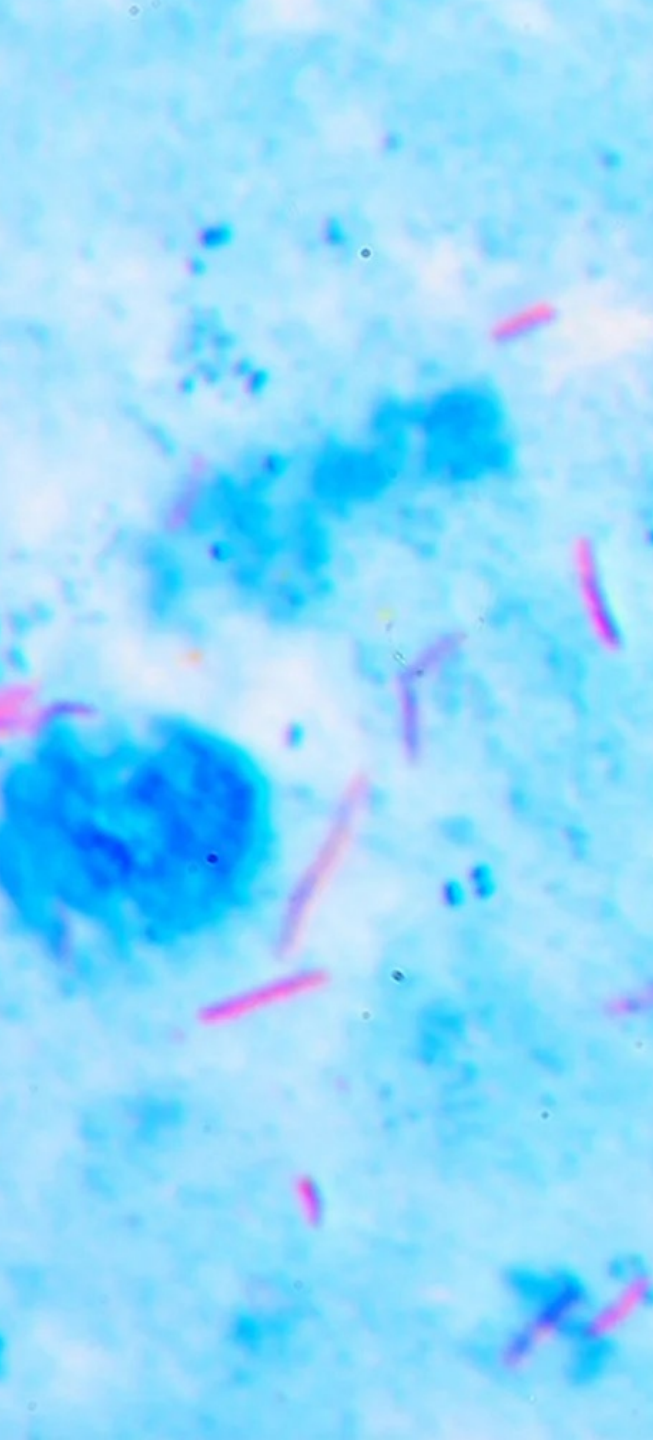


# Treatment of rifampin-susceptible TB

John Szumowski MD, MPH

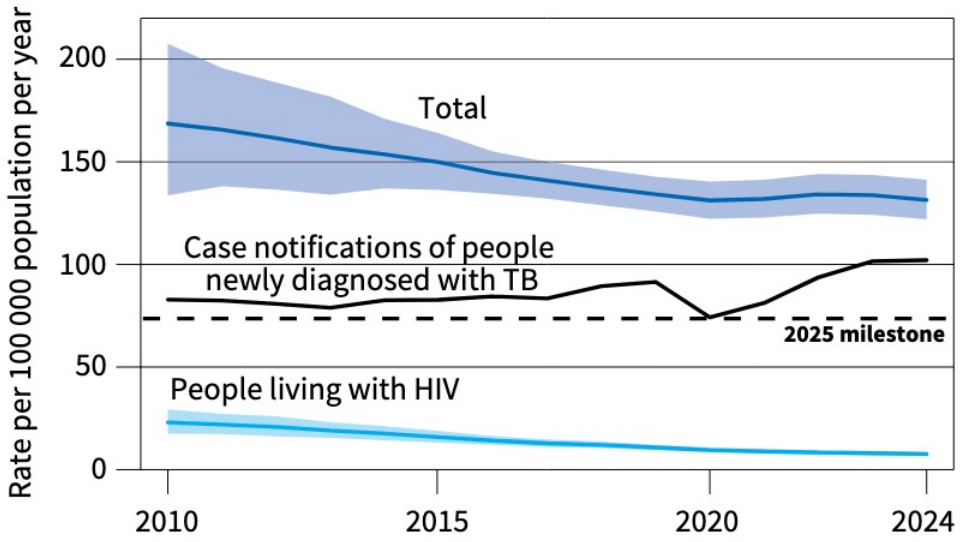
Curry Center / UCSF

1-2026

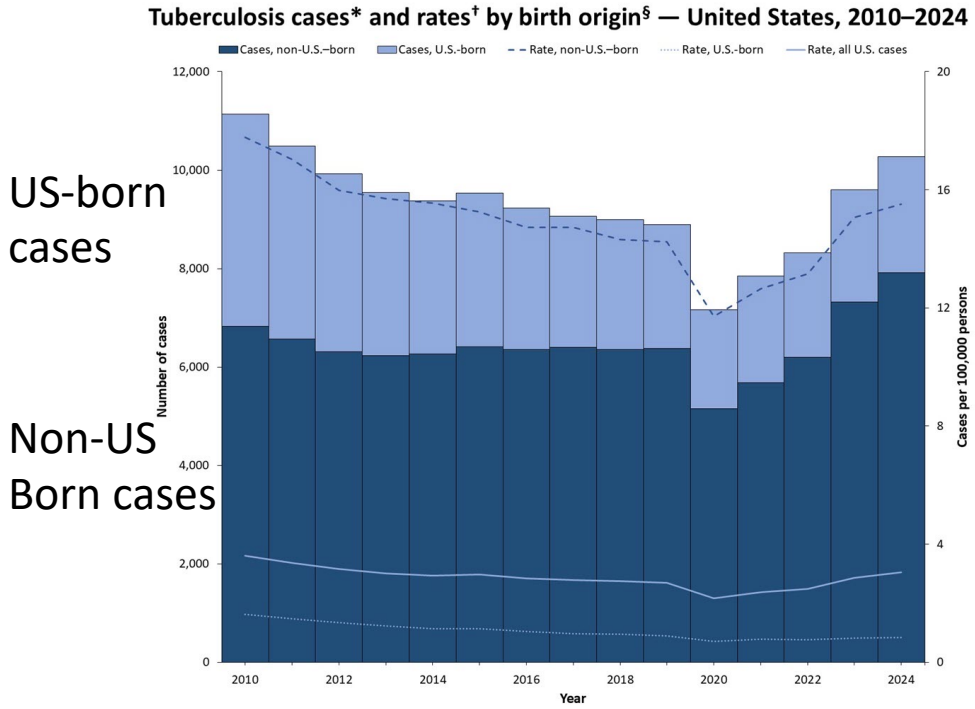
# Disclosures

- I am a federal employee (VA). However, I am presenting today in an individual capacity.

# TB remains the top infectious cause of death globally and progress has stalled




Global TB incidence rates




US-born cases

Non-US Born cases

Rate, non-US born

Rate, all US

Rate, US-born

WHO Global Tuberculosis Report 2025, CDC

# Pulmonary TB symptoms

| | |
|---|---|
| Cough (dry/productive sputum) | 75-80% |
| Weight loss | 45-75% |
| Fatigue | 60-70% |
| Fever | 50-60% |
| Night sweats | 50-55% |
| Hemoptysis | 25-35% |
| No symptoms | 10-20% |

BUT: Elderly, immunocompromised, and persons with low TB burden **may have minimal/nonspecific symptoms**!

# Respiratory sampling

- **Expectorated vs induced** specimens
  - Induced specimens may resemble saliva (label appropriately for lab)
- Collect samples 8-24h apart
- Ideally at least 3-5 mL sample volume

# Respiratory sampling

- Traditionally 3 sputa samples are collected in US
- Smear performance, among culture-positive cases
  - First sputum: 54% sensitivity
  - Second sputum: incremental 11% sensitivity
  - Third sputum: incremental 3% sensitivity

- Increased yield (~12%) with **first AM specimen** vs spot sample

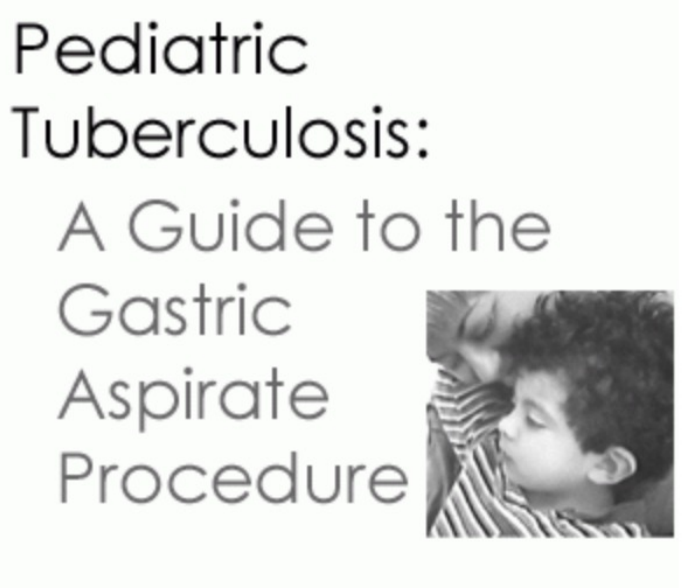
Mase et al. Int J Tuberc Lung Dis 2007

# Respiratory sampling

**Bronchoscopy**

- Induced sputa have similar (or better) sensitivity than BAL but sometimes cannot be obtained
- Can obtain biopsy along with BAL
- **Post bronchoscopy sputa** testing increases diagnostic yield

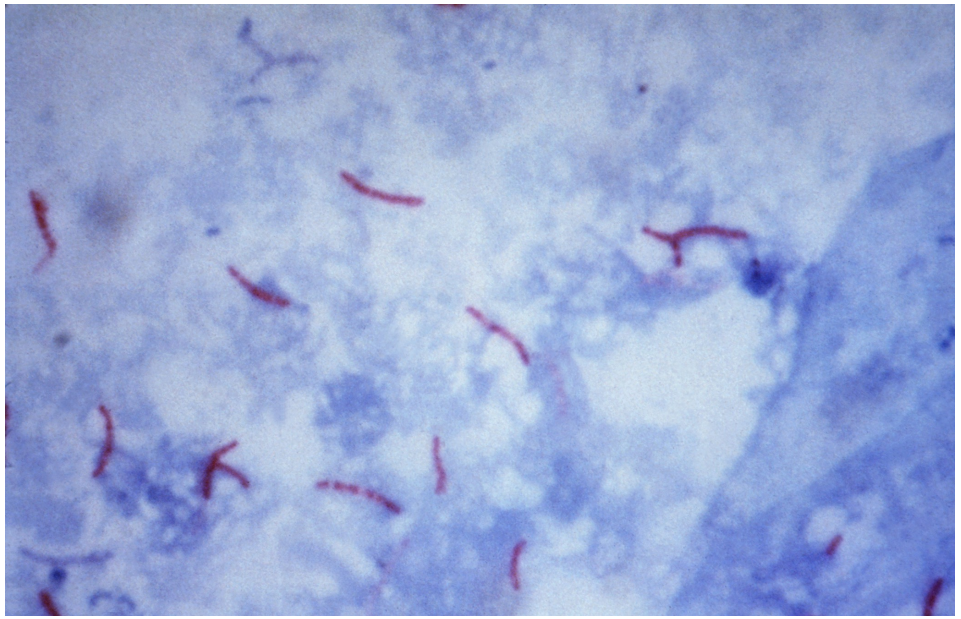
**Gastric aspirate** less often used in adults, but may be needed in pediatric cases



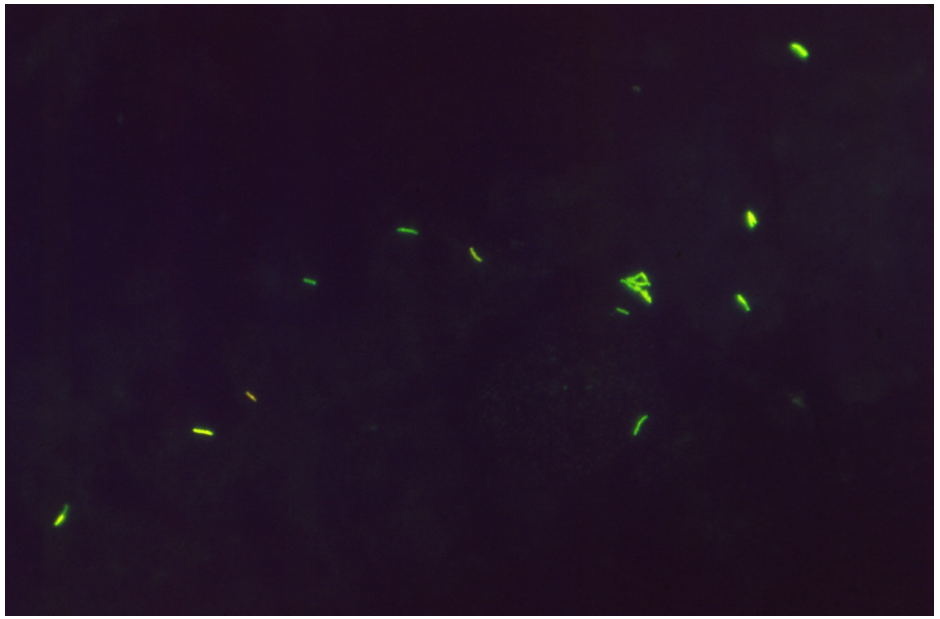

https://www.currytbcenter.ucsf.edu/product/guide/pediatric-tuberculosis-a-guide-to-the-gastric-aspirate-procedure

CDC

# Traditional diagnostics – AFB smear



Ziehl-Neelsen stain



Fluorochrome staining

CDC

# AFB smear

- Provides rough estimate of bacterial burden
  - **Correlates with transmission risk**
  - Follow serially on PTB treatment*

- Positive smear requires approx. $10^4$ bacilli/mL
  - **A negative smear does not "rule out" TB!**
    - **Continue isolation in hospital if high clinical suspicion**
- Approximately 50% of US cases were smear-negative in 2021

Lohmann Int J Tuberc Lung Dis 2012
Filardo et al. MMWR 2022

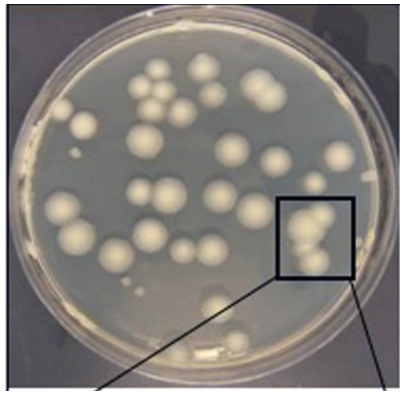
# AFB smear - additional limitations

- **Not all AFB are Mtb!**
  - Nontuberculous mycobacteria (NTM), e.g. MAC
  - Weakly acid fast organisms, e.g. *Nocardia*

- **Does not discriminate viable vs. nonviable** bacilli
  - Can cause confusion during follow up

# Traditional diagnostics – AFB culture

- Culture needed for phenotypic susceptibility data
- Use solid and liquid media (MGIT)
  - May take up to 8 weeks to detect growth
  - Average time to growth on MGIT 10-14 days versus 3-4 weeks on solid media
  - Sensitivity is approximately 10% greater with liquid media



Images:
Caulfield et al. 2016
Campodónico et al. 2018

# Molecular Testing

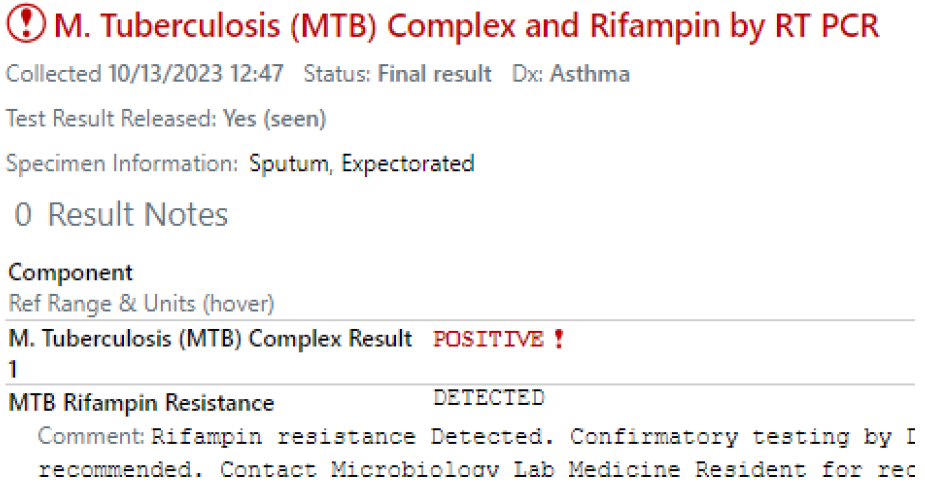
Quicker turnaround time (compared to phenotypic methods)

- Earlier initiation of effective treatment, decreasing period of infectiousness
- Earlier involvement of drug resistant TB expert
- Earlier request for additional susceptibility testing

**NAAT (nucleic acid amplification test) – e.g. Xpert MTB/RIF - recommended to be done routinely as part of evaluation of possible PTB.**

# Xpert MTB/RIF

- Widely used due to simple, relatively quick assay. Detects:
  1) presence of *Mtb*
  2) mutations in *rpoB* (responsible for most RIF-R) – ***use as proxy for MDR TB***
- In principle can be done on many sample types



# Xpert MTB/RIF test performance

| | Sensitivity | Specificity |
|---|---|---|
| Smear positive PTB | 98.9% | ~99% |
| Smear negative PTB | 41-77% | 78-100% |
| Rifampin resistance | 93-100% | 95-100% |

Boehme et al NEJM 2010
Zifodya et al. Cochrane Rev 2021

# Xpert MTB/RIF Report- under the hood

Test Result: MTB DETECTED; Rif Resistance DETECTED

Analyte Result

| Analyte Name | Ct | EndPt | Analyte Result | Probe Check Result |
|---|---|---|---|---|
| Probe D | 13.3 | 249 | POS | PASS |
| Probe C | 12.4 | 260 | POS | PASS |
| Probe E | 0.0 | -11 | NEG | PASS |
| Probe B | 13.2 | 129 | POS | PASS |
| SPC | 28.0 | 214 | NA | PASS |
| Probe A | 11.7 | 147 | POS | PASS |
| QC-1 | 0.0 | 0 | NEG | PASS |
| QC-2 | 0.0 | 0 | NEG | PASS |

$C_T$ (cycle threshold)
The higher the $C_T$, the lower the amount of *Mtb* DNA present

5 molecular beacon probes span *rpoB*
Probe E contains the most common resistance mutation (531 TTG)
Probe B contains the most common silent mutation (514 TTT)

# Rapid molecular testing utility

- The utility of NAAT depends on the AFB smear results and clinical suspicion (i.e., pre-test probability).
  - High clinical TB suspicion → positive NAAT confirms TB.
  - Smear positive, low clinical TB suspicion → negative NAAT supports NTM diagnosis.

# TB Treatment - Overview

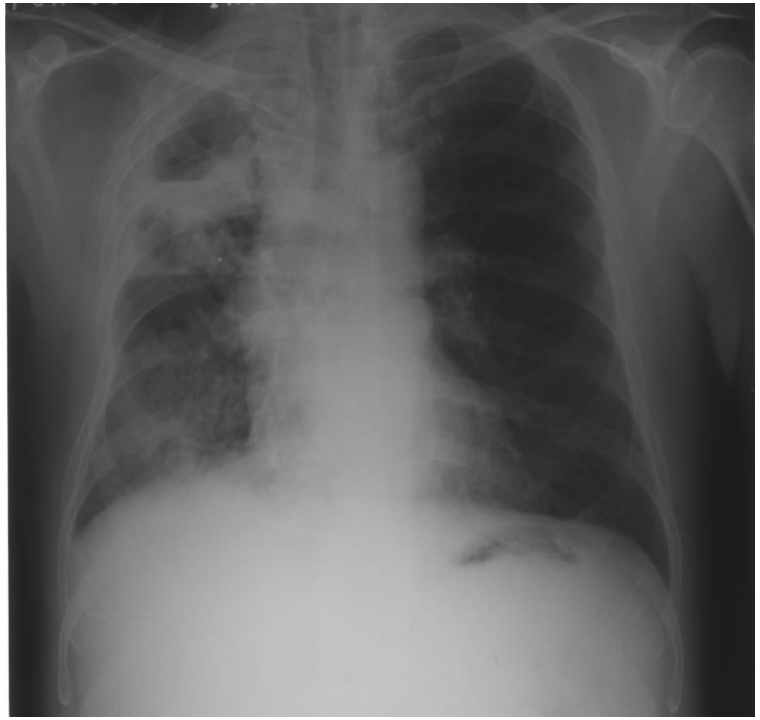
- Principles and goals of treatment
- Current drugs, recommended regimens, and duration of treatment for drug-sensitive (DS)-TB
- Adverse drug reactions and monitoring
- Management of treatment failure
- End of treatment

# Case 1

50 year-old Filipino man recently diagnosed with cough and night sweats x3 weeks

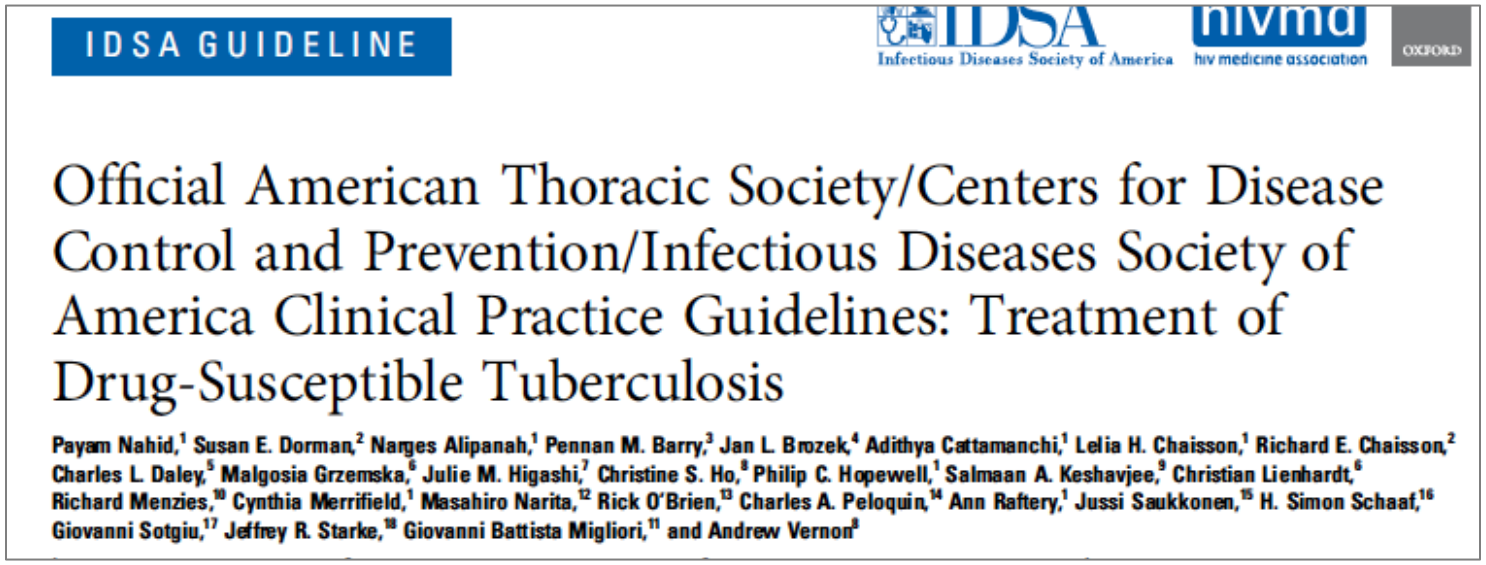
- No prior TB rx, no known contact with active case
- AFB smear+ *(other tests?)*

What drugs will you start?



# ATS/CDC/IDSA Treatment Guidelines Drug-susceptible TB (DS-TB)

*Nahid et al, CID 2016**



IDSA GUIDELINE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

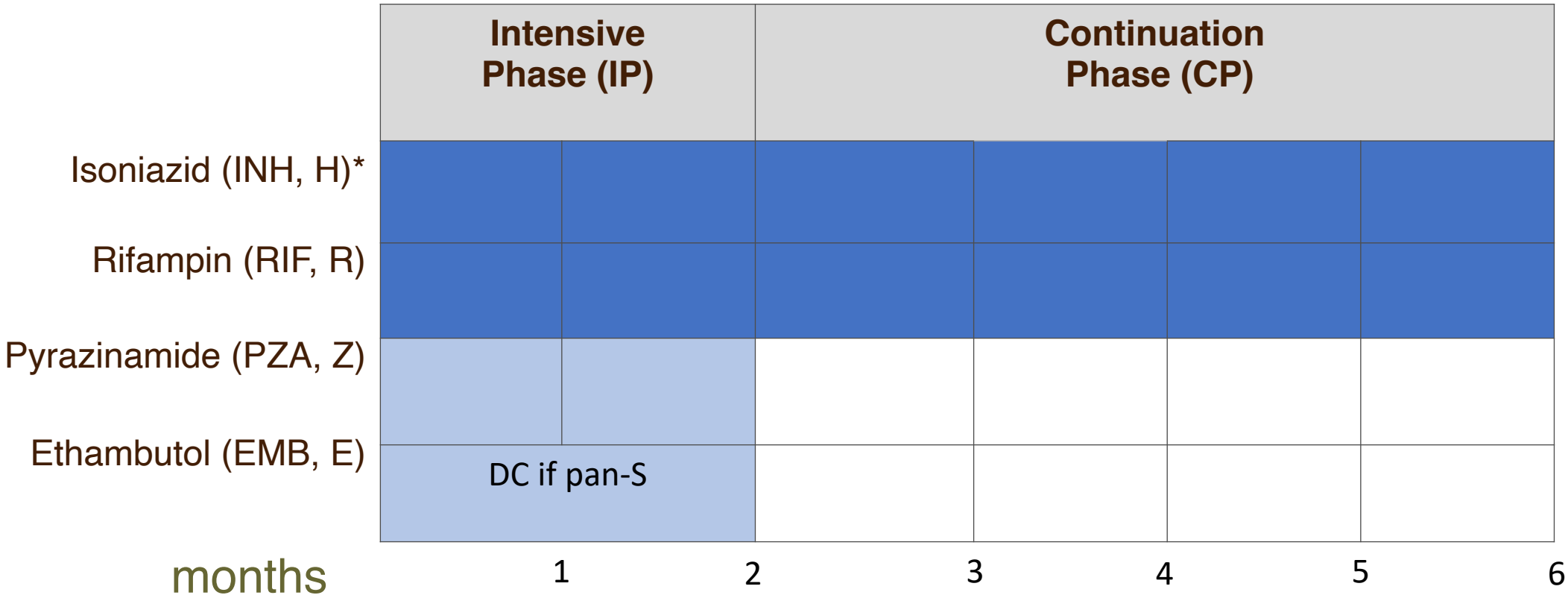
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

* *Note: Limited DS+DR-TB for peds, 4m regimen, BPaL/M update; Saukkonen 10/2024*

# Standard Pulmonary TB Treatment: 6-month “short course”

[RIPE = HRZE]

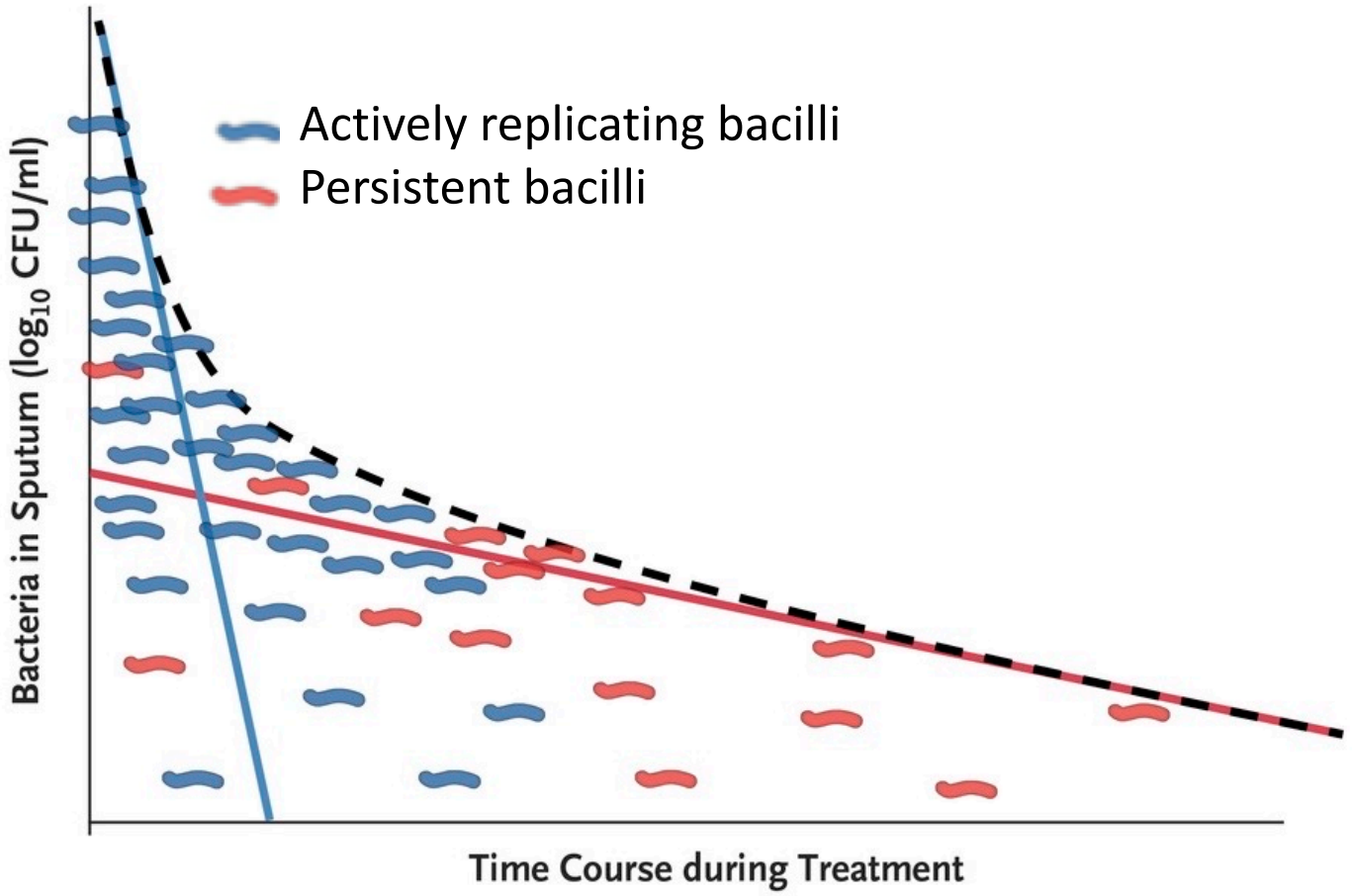



* With Pyridoxine (Vit B6) 25-50mg if neuropathy risks

# Microbiological goals of TB treatment

1. Kill multiplying Mtb rapidly (bactericidal effect)
2. Eliminate persistent bacilli to achieve durable cure, i.e., prevent relapse (sterilizing effect)
3. Prevent the emergence of drug resistance

# Action of Anti-TB drugs & Clinical correlation




- **Bactericidal effect:**
  (**INH**/FQ >>RIF/SM >E)
  Rapid early reduction #'s & stop transmission
- **Sterilizing effect:**
  **(RIF/PZA**)
  Target persistent Mtb and prevent relapse

Horsburgh NEJM 2015

# What does RIF contribute to TB therapy?

- Incorporation of rifampin into TB therapy allowed regimens to be shortened from the traditional 18-24 month durations
  - When RIF cannot be used, TB therapy is greatly extended (unless newer regimens such as BPaL/M are used)
- Along with PZA, targets persistent bacterial populations

# What does PZA contribute to TB therapy?

- Sterilizing ability permitted treatment shortening from 9 months to 6 months when used with RIF
  - *M bovis* is naturally PZA-R so requires 9 month therapy

- PZA has limited ability as a companion drug to protect against development of resistance (avoid use if only two-drug combo)

# What does EMB contribute to TB therapy?

## Prevention of drug resistance development while awaiting DST:

Use HRZ+E until susceptibility test results reported

- Remember: INH mono-resistance 8-10% in US
- Do not need EMB if already known pan-sensitive
- Should be on at least HR (and known HR sensitive) before stopping

# Case 2

66 year old woman from Vietnam; IGRA+

CXR report: Left apical nodular densities “consistent w/ prior granulomatous disease”, pleural thickening

- No symptoms, otherwise healthy
- PMD treats with INH for LTBI x9 months

She returns 1 year later with 2 months of cough, weight loss, and CXR reveals LUL infiltrate with small cavitary lesion

# Case 2: Poll

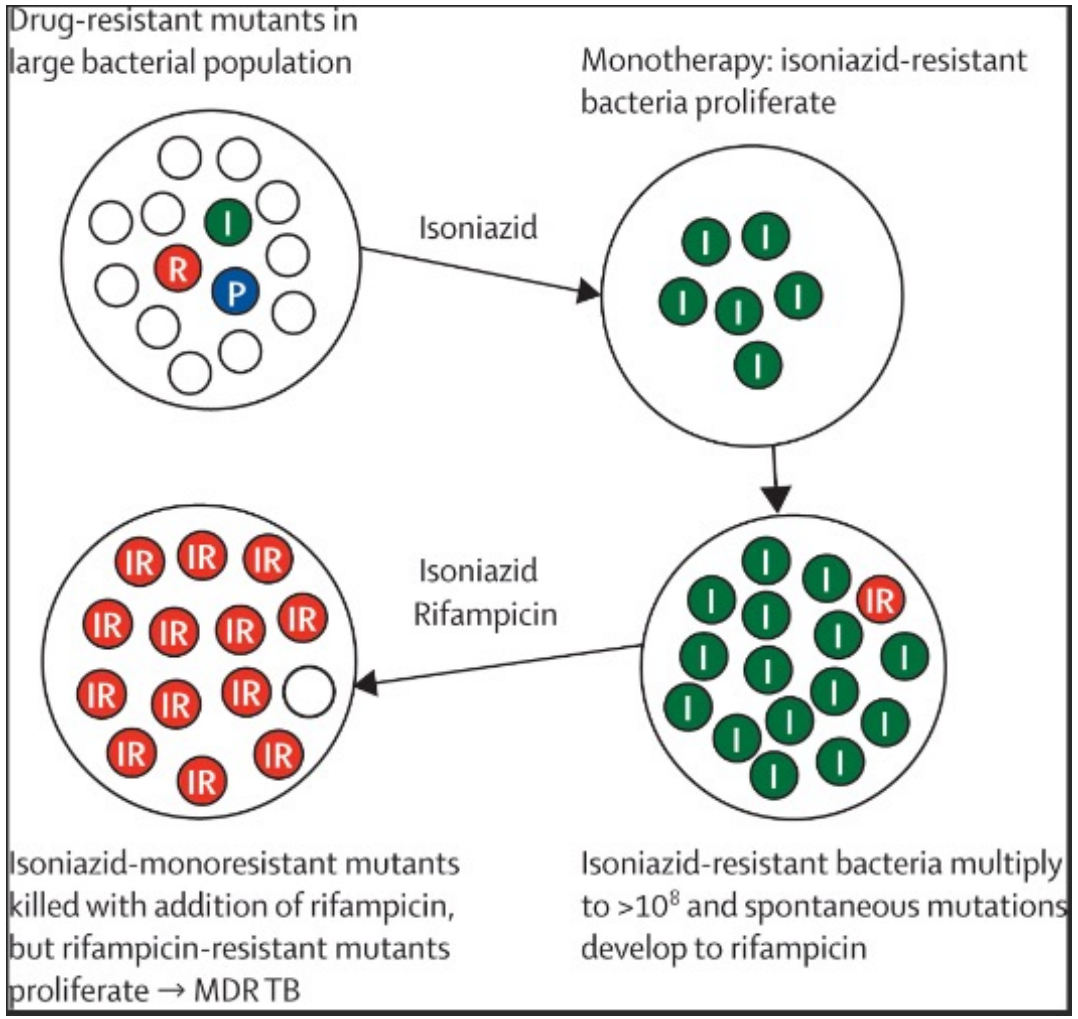
## Which of the following is incorrect?

A. With initial abnormal CXR and IGRA+ she should have been treated with HREZ

B. Even if asymptomatic, sputum for AFB should have been checked before starting LTBI rx

C. Monotherapy with INH puts her at risk for INH-resistant TB

# Drug resistant bacteria are selected by inadequate therapy




Frequency of naturally occurring mutations in Mtb

**INH** = 1 in $10^6$

**RIF** = 1 in $10^8$

**INH + RIF** = 1 in $10^{14}$

Gandhi NR, et al. Lancet 2010.

# Drug Resistant Mutants Selected by:

- Inadequate drug exposure
  - Not taking/missing doses
  - Malabsorption
  - Drug-drug interactions
- Weak drug regimen

*Remember: The higher the burden of disease, the greater the number of wild/resistant mutants* (“more bugs, more drugs”)

# Supporting ongoing TB therapy through patient-centered DOT

**Elements of a successful DOT program**

- **In clinic:** supportive, welcoming atmosphere; incentives/enablers to overcome barriers
- **In the field:** dedicated outreach workers who are comfortable in variety of community settings
- Growing reliance on Video DOT (VDOT)

# When to suspect drug resistance in new cases

- MDR (multi-drug resistant TB) Mtb has resistance to INH and RIF
  - Standard TB treatment ineffective, historically poor outcomes
- Higher rates among previously-treated persons vs. patients without TB history (16% vs. 3.2% globally, WHO 2025 report)
- Largest number of cases reported from India, China, Philippines, former Soviet Union.
- Close contacts, esp in children
- **Recommend expert input in these cases**

**To obtain an MDR TB Consultation, contact:**
Reiko Okada (Reiko.Okada@cdph.ca.gov), MDR Service Coordinator,
or Rebecca Wang (Rebecca.Wang@cdph.ca.gov), MDR Service Project Specialist

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/MDR-Service-Fact-Sheet.pdf

# Recommended Regimens for DS Pulmonary TB

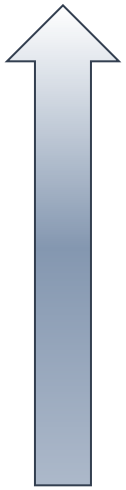
| Intensive Phase | | | Continuation Phase | |
|---|---|---|---|---|
| Reg | Drugs | Interval/Dose | Drugs | Interval/Dose |
| 1 | HRZE | 7 days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk) | HR | 7 days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)<br>Total range of doses 182-130 |
| Preferred regimen for patients with newly diagnosed pulmonary TB | | | | |

## 5 vs. 7 daily doses:

- When DOT is used, drugs may be given 5 d/wk and the necessary number of doses adjusted accordingly
- Although no studies compare 5 with 7 daily doses, program experience & guidelines consider acceptable practice

# Recommended Regimens for DS Pulmonary TB

## INTERMITTENT DOSING

| Intensive Phase | | | Continuation Phase | | Effective-ness |
|---|---|---|---|---|---|
| | Drugs | Interval/Dose | Drugs | Interval/Dose | |
| 2 | HRZE | 7d/wk x8wk<br>or 5d/wk x8wk | HR | 3x /wk for 54 doses (18 wk) |  |
| 3 | HRZE | 3x /wk x8wk | HR | 3x /wk for 54 doses (18 wk) | |
| 4 | HRZE | 7d/wk x14 doses then<br>2x /wk x12doses | HR | 2x /wk for 36 doses (18wk) | |

- DOT should be used when drugs are administered <7 days per wk.
- Relapse risk increases with ↑ intermittent dosing (once per wk no longer recommended; 7-fold increase) *[Systematic review Chang ARCCM 2006]*

# Intermittent dosing

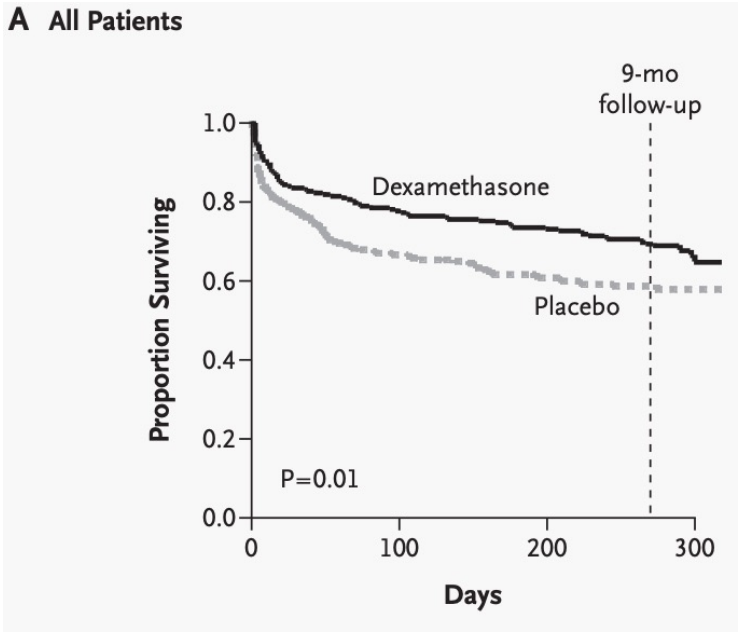
Preferred to treat once daily for intensive and continuation phases *(Strong recommendation; moderate certainty in the evidence)*

- Alternate regimens acceptable in certain program/public health situations (require DOT)
  - Non-HIV, non-cavitary, low-risk for relapse: can consider 3x wk dosing
  - Some public health programs successfully use 2x wk dosing – *new guidelines suggest caution* – one missed dose is equivalent to 1 per wk dosing (shown inferior)

# Adjunctive therapies

- Adjunctive steroids are routinely used in cases of TB meningitis and considered in certain cases of TB pericarditis
- An area of ongoing research

TBM +dexamethasone vs placebo



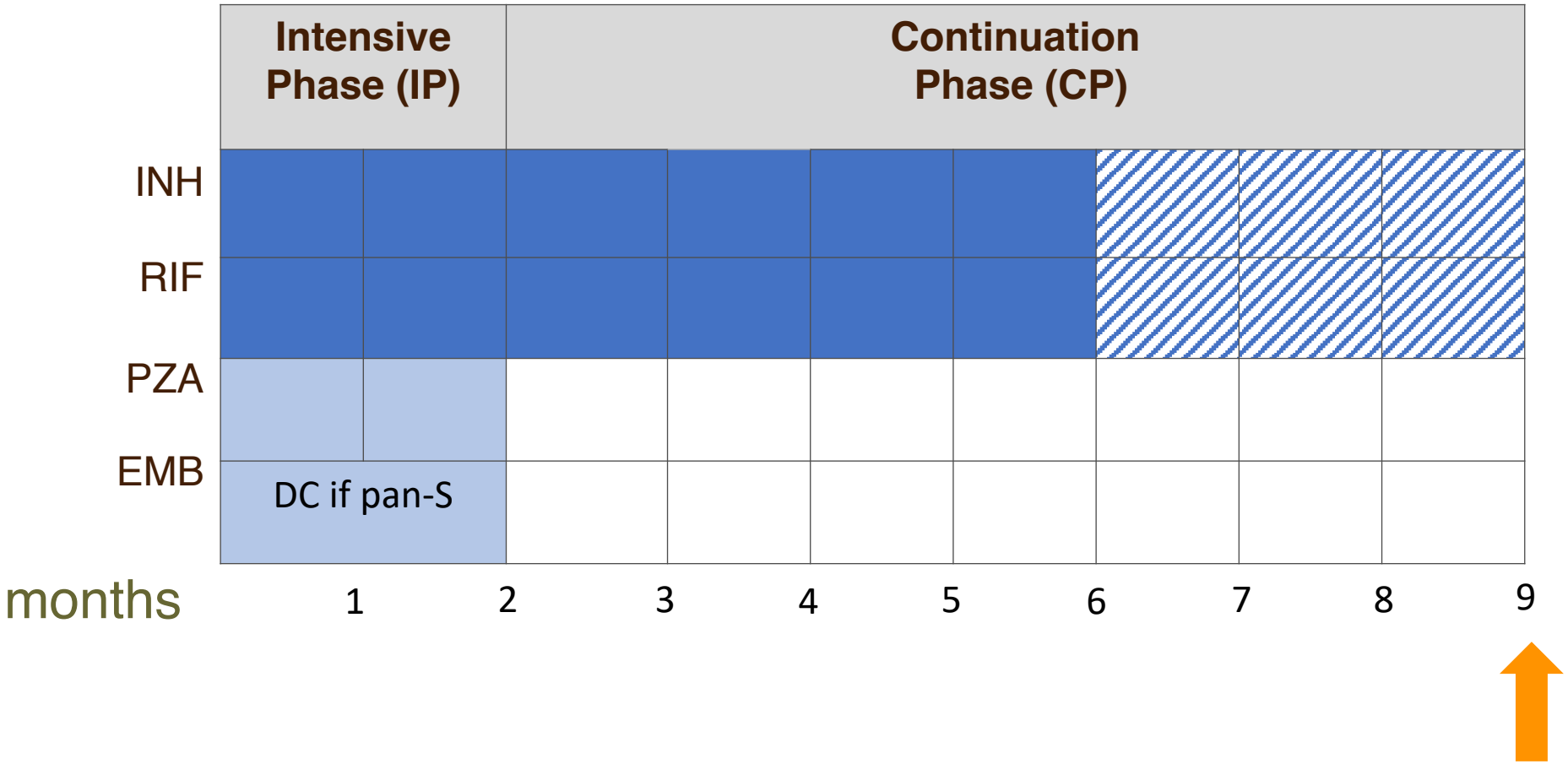

Thwaites et al. NEJM 2004

# Identifying patients at increased risk of relapse

- **2-month culture positive status**
  - 7 BMRC trials
  - USPHS trial in Poland
  - TBTC Study 22 (2002)
- **Cavitary disease**
  - TBTC Study 22 (2002)
  - Hong Kong (2004)

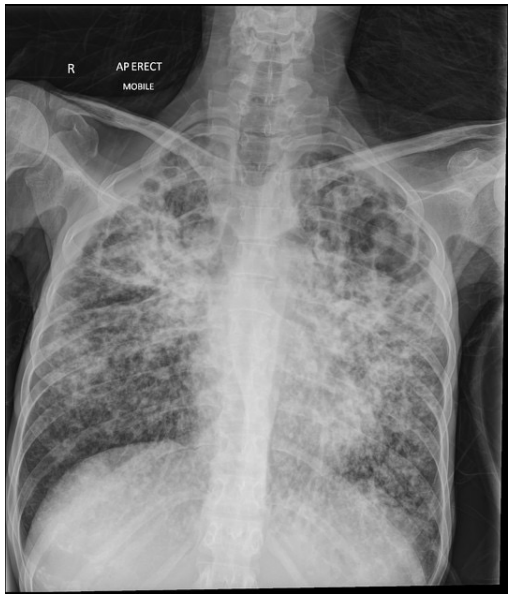
*TBTC. Lancet 2002;360:528*

# Extend treatment to 9 months if cavitary disease and 2 month culture positive



# Other scenarios that may prompt extending TB therapy

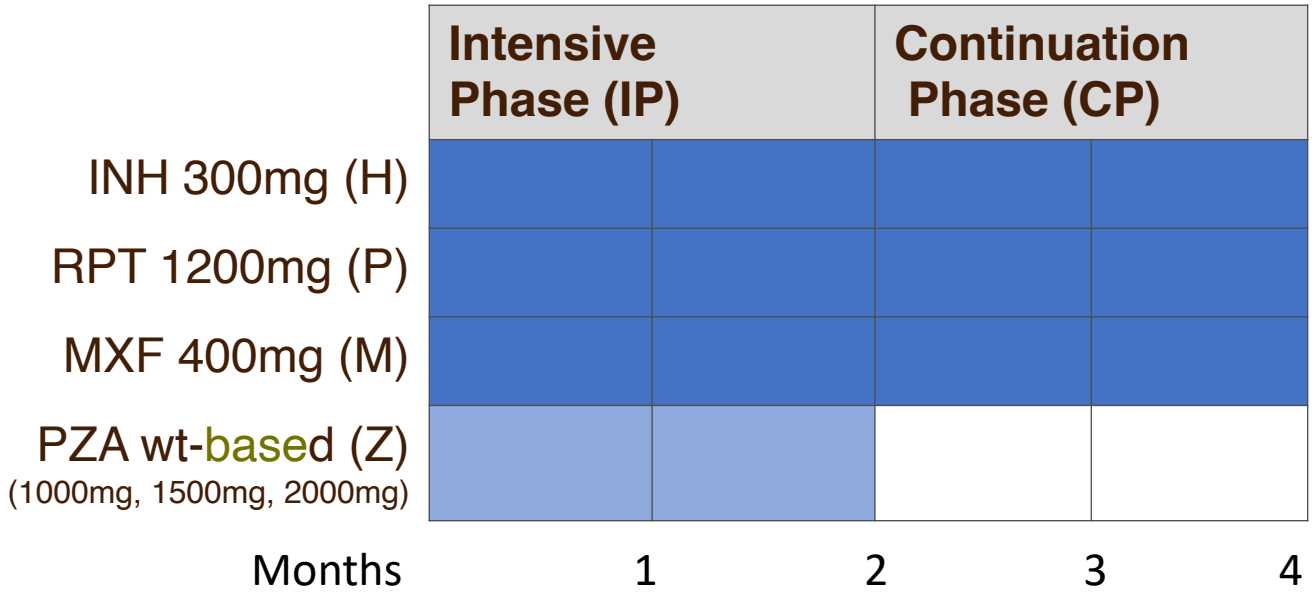
- Some experts consider extending the continuation phase with either <u>cavitation or delayed culture conversion</u> **plus**:
  - HIV infection, particularly if advanced
  - Other form of immunosuppression, diabetes, or significant tobacco hx
  - Underweight (< 90% of IBW)
  - High burden: extensive radiographic disease




Radiopaedia.org

# A 4 month option for DS-TB treatment: HPMZ

- Criteria: ≥12yo, ≥40kg
- If HIV-positive: CD4≥100 and EFV-based rx
- Not studied in pregnancy/lactation, extra-pulmonary*, or ↑QT




- Daily 7/7 dosing (DOT 5/7) w/ food
- Total doses 119; (complete within 5mo)
- Can consider treatment extension with more severe disease

# HPMZ 4mo. regimen for DS-TB

TBTC Study 31: Randomized, open-label, controlled Phase 3; noninferiority design. Primary outcome 12 mo TB free survival.

N = 2516, >12yo; 7d/wk (at least 5d DOT)

- 4m RPT arm: 2HPZE/2HP
- 4m RPT+MXF arm: 2HPZM/2HPM
- vs. 6m HRZE

- Study population
  - 71% male, median age 31 (13.7-81.4)
  - 8.2% HIV+, median BMI 18.9 (17.4-20.8)
  - 72.6% cavitary CXR

- **4m HPMZ arm noninferior to standard rx**
- No significant differences in AE
  - Gr 3-5 AE across all arms: 6% blood/lymph AE (mostly neutropenia), 3.6% hepatic AEs
  - Exception: > hyperbili in both RPT arms

Dorman et al, NEJM 2021

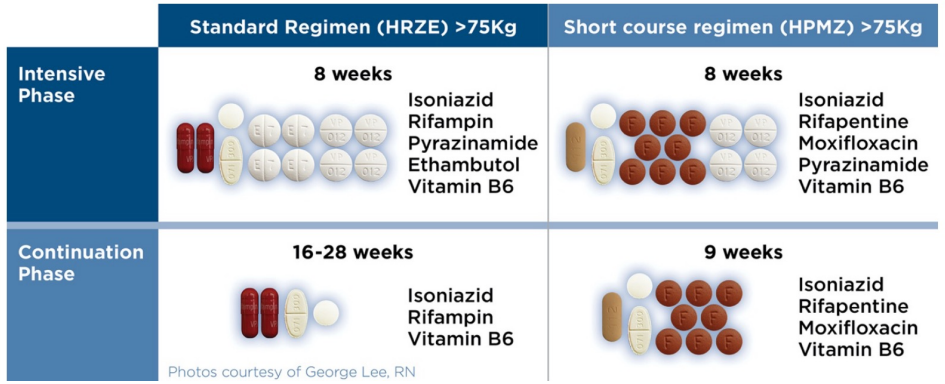
# 4-mo HPMZ regimen: Real-world considerations

8/2021-12/2023 -> 22 rx with HPMZ

- 8 declined (rx too untested, high #pills)
- Exclusions: severity, comorbidities, extrapulmonary
- Median age 32.5 (14-86 range)

AE in 18 (82%); 11/18 (61%) stopped HPMZ

- AE median onset 4.3d (1-63)
- AE: 10 moderate N/V, ↑LFTs, rash, dizziness, anxiety; 1 severe syncope/↓$K^+$




Note: Pt. population & feasibility considerations

- Higher AE c/w study
- Rifapentine supply shortages

Louie et al, OFID 2024

# Monitoring: Adverse Reactions

| Adverse Reaction | Drugs |
|---|---|
| Rash | PZA, INH, RIF, EMB |
| GI intolerance (N/V) | PZA, RIF |
| Liver toxicity | PZA>INH>>RIF (↑ if combo) |
| Peripheral neuropathy | INH>>EMB |
| Cytopenias | RIF>INH>EMB |
| Optic neuritis | EMB>>INH (rare) |
| Arthralgia | PZA>FQN>RIF, INH |
| Gout | PZA |

Adapted from: C. Spitters and ISTC TB Training Modules 2009

# Routine Monitoring and Frequency

| | **Monitoring Frequency** |
|---|---|
| Sputum conversion | Baseline, monthly till negative; end of treatment |
| Weight | Monthly |
| LFTs | Baseline, 1mo. then prn* |
| Side effects | Ask routinely with DOT: GI complaints, joints/arthralgias, rash, neuropathy<br>Monthly: visual acuity, red/green discrimination (EMB) |
| Chest imaging | Baseline, month 2, and EOT |
| Adherence and psychosocial issues affecting treatment | Weekly for DOT patients |
| MD evaluations | Minimum: baseline, 3mo., and EOT |

# ATS/CDC/IDSA Treatment Guidelines

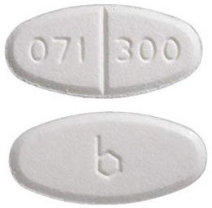
## Example monitoring flow sheet

https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

| 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] | ☐ | | | | | | | | | |

Shading indicates activities that are optional or contingent on other information

# INH Adverse Effects




- Asymptomatic transaminitis (10-20%)
- Clinical hepatitis (0.1% INH alone)
  - Increases with age (up to 2% in 50-65 yo) or with underlying liver disease/ETOH
  - Increases in combination w/ RIF (2.7% )
- Peripheral neuropathy (INH causes ↓ pyridoxine/B6)
  - <0.2% unless predisposing factors
- Mild central nervous system effects
  - Cognitive issue not well quantified; (rare: seizure, psychosis)
- Rash
- Lupus-like reaction (rare <1%; but +ANA in 20%)

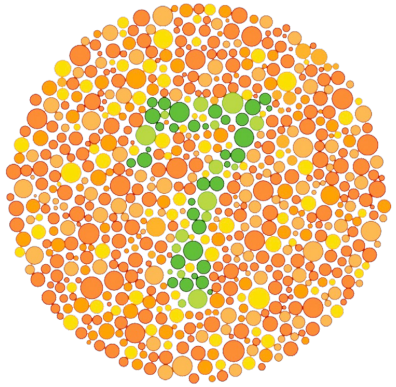
# RIF Adverse Effects

- Cutaneous reactions (in up to 6%)
  - Pruritus with or without rash
- GI (nausea, anorexia, abdominal pain)
  - Variable incidence but usually mild
- Hypersensitivity/flu-like sx (↑ with intermittent dosing)
  - Occurs in 0.4-0.7% receiving 600 mg twice weekly
- Hepatotoxicity
  - Transient asymptomatic hyperbilirubinemia (0.6%)
  - Clinical hepatitis uncommon (↑combo rx), often cholestatic
- Immunological reactions (<0.1% )
  - ↓plts, TTP (rare), anemia, interstitial nephritis

# EMB Adverse Effects




- Retrobulbar neuritis – dose-related
  - Less than 1% with dose of 15 mg/kg
  - 18% with more than 30 mg/kg/day
  - Ishihara & visual acuity screening should be done while on EMB
- Peripheral neuritis
  - Rare
- Cutaneous reactions
  - Approximately 0.2-0.7% require discontinuation of drug



# PZA Adverse Effects


- Hepatotoxicity
  - About 1% develop clinical hepatitis, can be severe
- Gastrointestinal symptoms
  - Mild anorexia and nausea are common
- Non-gouty polyarthralgia (usually mild)
- Hyperuricemia
  - Asymptomatic - expected effect
  - Acute gouty arthritis - rare except if pre-existing gout
- Cutaneous reactions
  - Transient morbilliform rash, self-limited
  - Photosensitive dermatitis

# INH & RIF: Drug Interactions

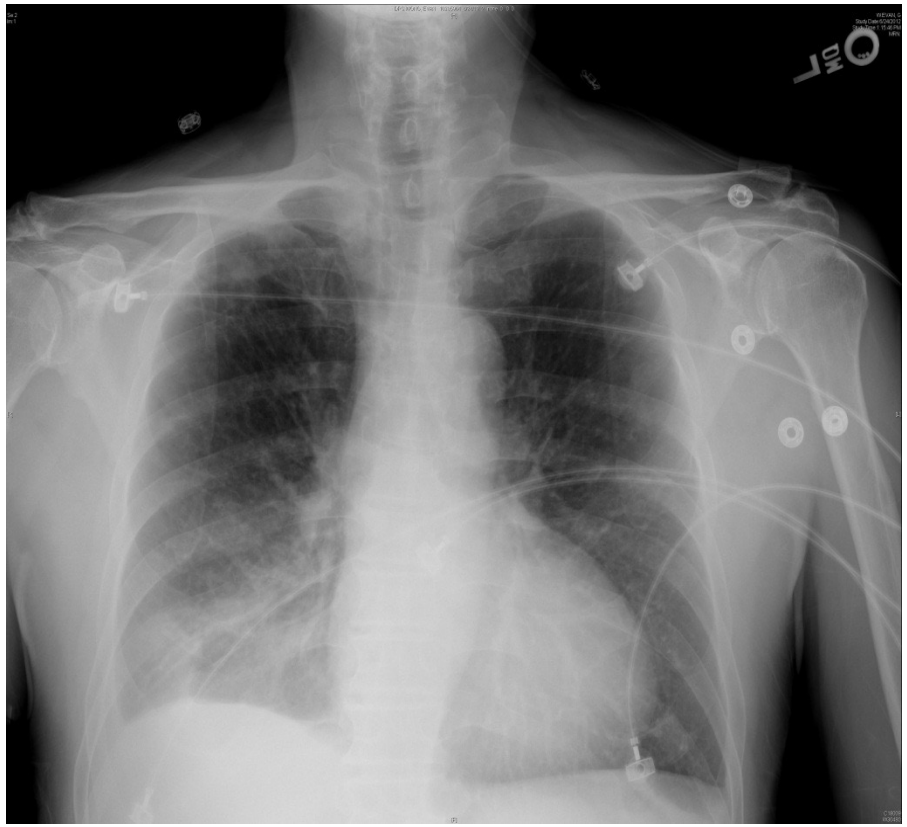
- Ask patients to bring in all concurrent medications ⟶ *use interaction checker (Lexicomp etc)!*
- ***Communicate*** with the primary care provider

- INH - Relatively potent inhibitor of several cytochrome P450 isozymes
  - Inhibitory activity of INH can ↑ serum concentrations of phenytoin (Dilantin ®), carbamazepine (Tegretol ®), and warfarin
  - Can ↑ hepatotoxic adverse effects in combination (ex. acetaminophen, rifampin, etc.)
- RIF has opposite effect and outweighs inhibitory effect of INH if combined

# Watch out with rifamycin drug interactions!

- Rifamycins induce multiple enzymes and transporters (eg CYP3A4, P-glycoprotein) resulting in ↓ in serum levels of many drugs
  - Enzyme induction: rifampin > rifapentine > rifabutin*
  - *Monitor and may need to dose adjust or switch therapies*
  - DOACs, steroids, oral contraceptives, antiretroviral agents, methadone, immunosuppressants, etc.

# Case 3

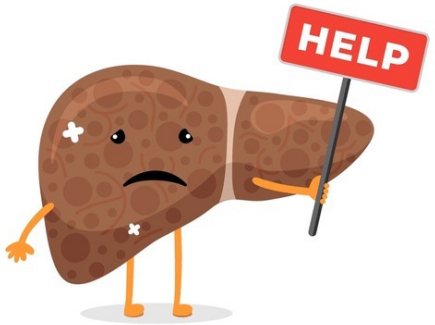


58 yo man from India, diabetic, IGRA neg.

He lives with his son, daughter-in-law who is pregnant, and 2 yo grandson

- He drinks heavily and has hepatitis C infection
- Cough x 6 wks, seen by PMD (failed trial of azithromycin)
- *What are you thinking?*
- *Potential AE concern?*

# Liver toxicity




Most feared adverse reaction: PZA>INH>>RIF

- Hepatocellular (INH & PZA);  cholestatic (RIF)
  - Educate pts. to seek immediate attention if anorexia, nausea, emesis, abdominal discomfort, fatigue, (or if jaundice develops → but this is late!)
  - Increased risk with chronic hepatitis B or C
- **Prevention:** avoidance of alcohol; monitor LFTs; hepatitis treatment
- Mild GI intolerance is common (N/V)
  - Discern transient vs persistent? Is it pill burden? Dyspepsia (proton-pump inhibitor)? N/V (anti-emetic)?

Shutterstock.com

# Liver toxicity management

- HOLD TB medications pending urgent LFT check if there is any concern regarding potential hepatotoxicity!
- Severely ill patients unable to pause TB therapy (respiratory distress, TBM) will require an alternative “liver-sparing” regimen- **seek expert input in these cases**
- Conventional hold parameters:
  - Asymptomatic: hold for AST, ALT >5x ULN.  Or with Bilirubin >3 mg/dL*
  - Symptomatic: hold for AST, ALT >3x ULN
- Consider non-medication causes (viral hepatitis, EtoH, meds etc)

# Liver toxicity management

- Once LFTs have improved (~normal) then sequential drug rechallenge can be undertaken.
- Recovery might take weeks in some cases
- **With severe hepatotoxicity, PZA is usually not reintroduced**

# TB Treatment Interruptions

(ATS/CDC/IDSA 2016 Guidelines)

| **Intensive Phase** | |
|---|---|
| Lapse <14d<br>Lapse >14d | Continue: (finish IP doses within 3m)<br>Restart IP from beginning |
| **Continuation Phase** | |
| ≥80% doses & initial sm- | Further tx may not be necessary |
| ≥80% doses & initial sm+ | Continue until all doses completed |
| <80% doses & cumulative lapse <3m | Continue until all doses completed unless consecutive lapse is >2m |
| <80% doses & lapse ≥3m | Restart from beginning (IP & CP) |

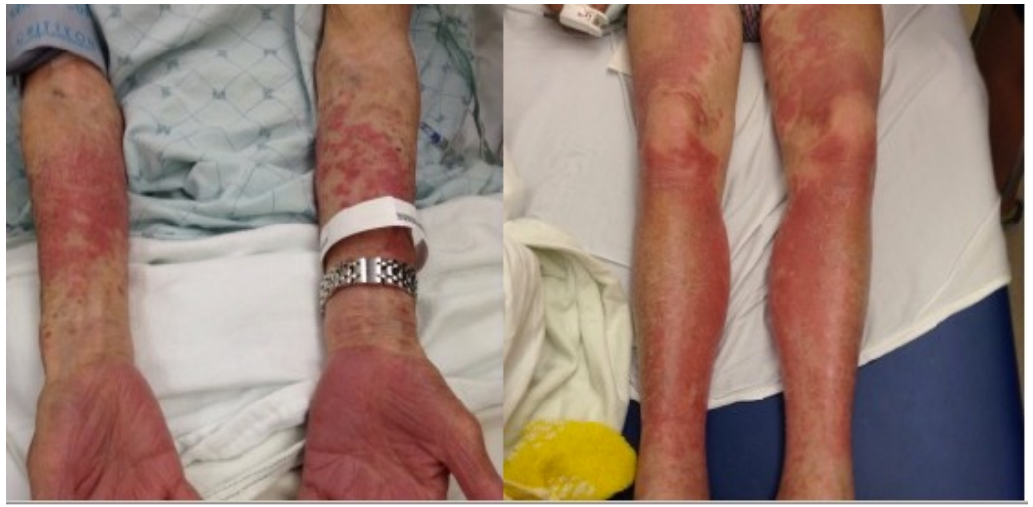
# Peripheral Neurotoxicity

- Drugs: INH, (EMB)
  More common in patients with:
  - Diabetes
  - Alcoholism
  - HIV infection
  - Pregnancy
- Usually symmetrical - tingling, prickling, burning
- Pyridoxine (B6) to prevent: 25-50 mg daily
  - Higher dose (up to 100mg/d) can be used to treat mild symptoms → but caution as B6 alone can cause neuropathy with higher doses

Image credit: https://www.health.harvard.edu/diseases-and-conditions/the-big-pain-of-small-fiber-neuropathy

# Drug rash

- Fixed drug eruption
- Rash, itching (1-5%, RIF)
- Pemphigoid reaction
- DRESS (drug rxn with eosinophila and systemic symptoms)/DIHS (drug-induced hypersensitivity syndrome)
- Anaphylaxis, urticaria



Management varies by severity:

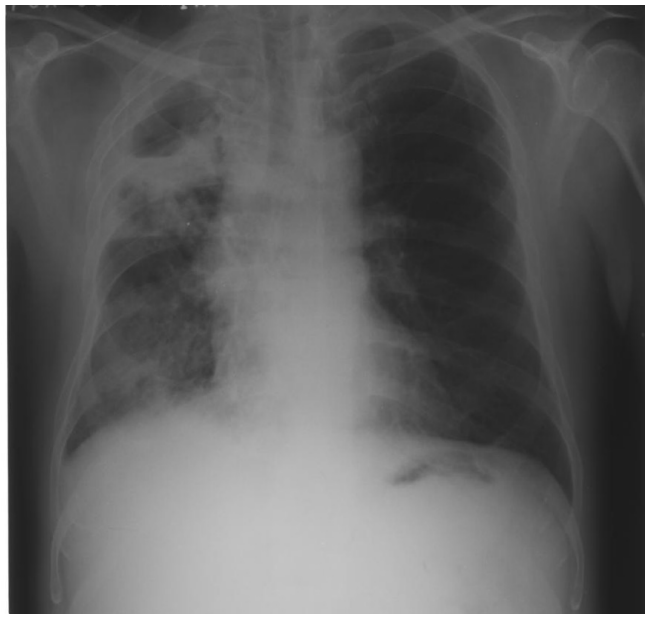
- Mild: anti-histamine, topical steroids, f/u visit.
- Mild-moderate: hold meds, **sequential drug re-challenge once resolves.**
- Mod-severe: hold meds, emergency care / derm consult. Consider alternate therapy once resolves.

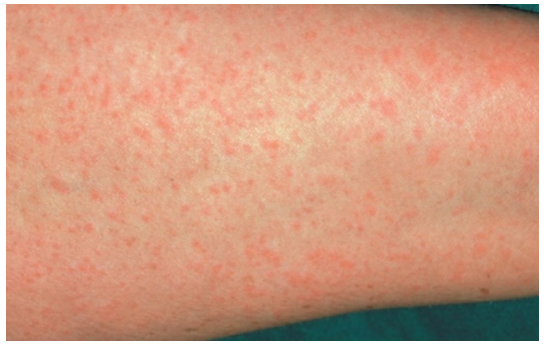
# Case 1 continued

50 yo male from the Philippines recently diagnosed with smear+ TB

- Rash after 10 days INH/RIF/PZA/EMB
- Serial restart (q2-3 days) points to INH as source of rash

➡ *What would you treat with?*

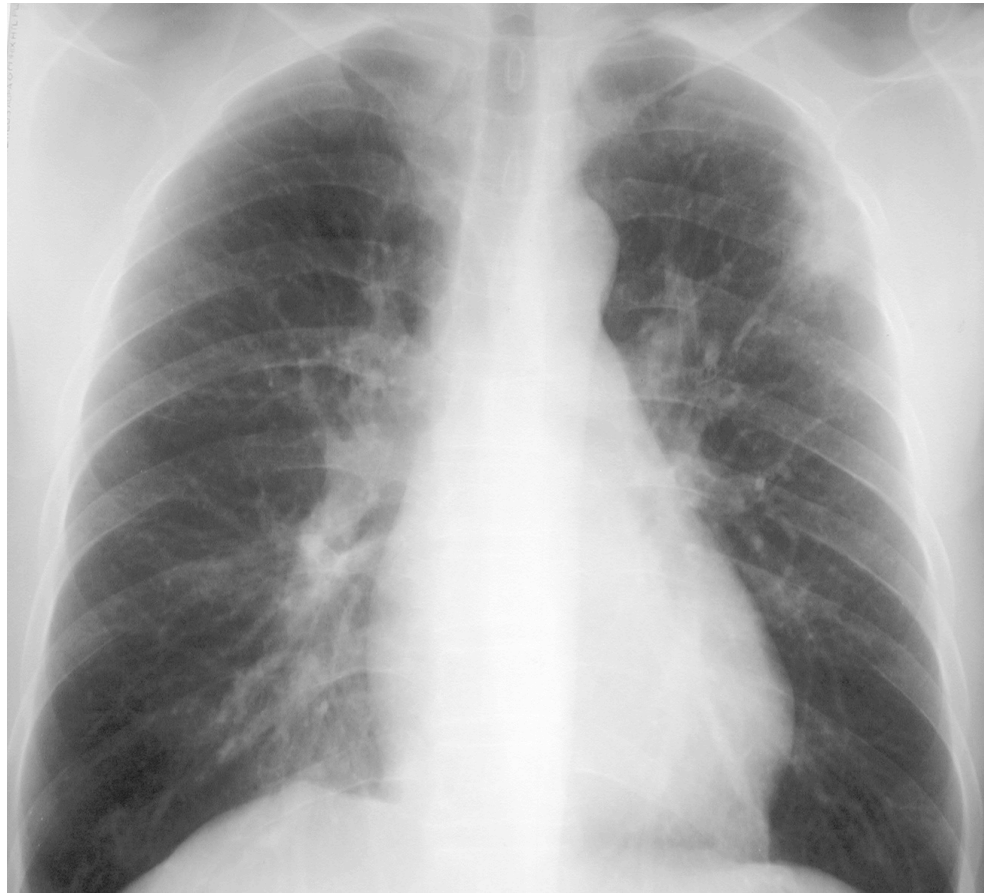




# Alternate Regimens
# Drug Resistance (or intolerance)

- **Without INH**
  - 6m FQ/RIF/EMB/PZA (DR-TB guidelines 2019); *(change!)*
  - 2m PZA okay if toxicity concerns or lower burden
- **Without RIF** -> consider 6m MDR regimen or
  older options for RIF-mono (consult expert)
- **Without PZA** (ex. *M. bovis*)
  - 9m of INH/RIF (initial use of EMB while await DST)

# Case 4

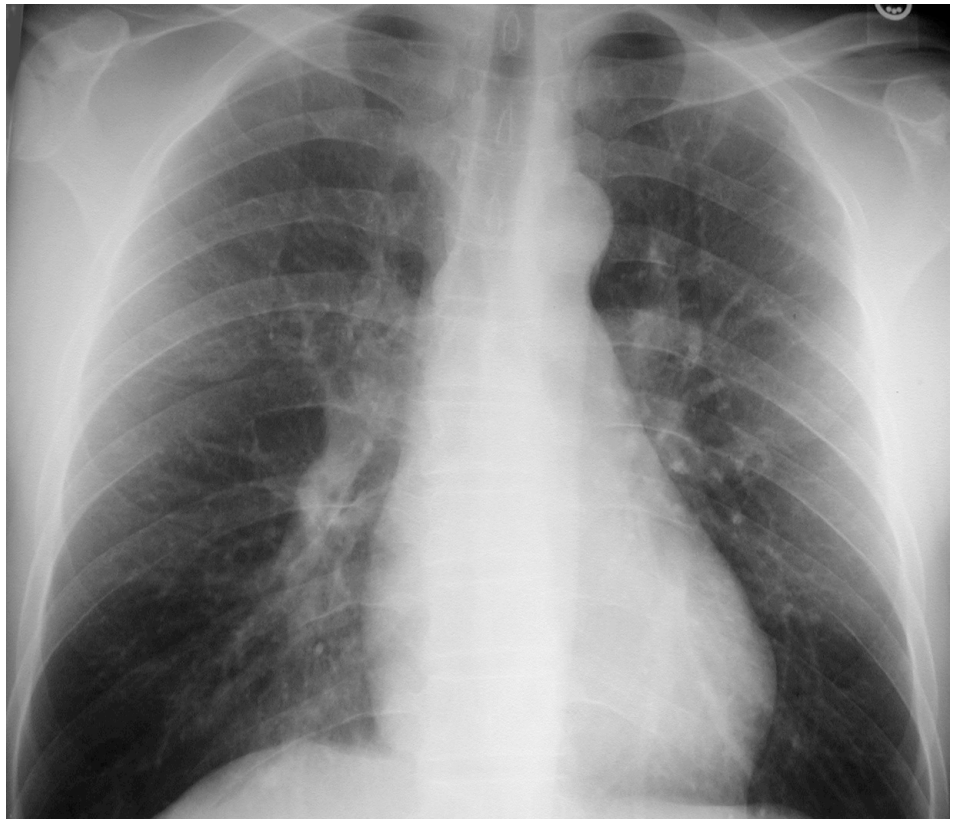


30 yo woman moved to US from India 4 yrs ago

- Needs clearance to work in school
- TST 12 mm
- Mild cough x 2wks,  5 lbs weight loss

*Smear/NAAT neg → now what?*

# Case 4



Started on HREZ,

Cough resolves, wt.↑

All cultures negative at 2mo.

# Culture Negative TB

## CDC clinical diagnosis criteria (all required for reporting) 2009

- Clinical presentation consistent with TB
- Completed an evaluation, and clinical or radiographic response to anti-TB therapy (at least 2 drugs) in the absence of another diagnosis
- Positive TB skin test or IGRA

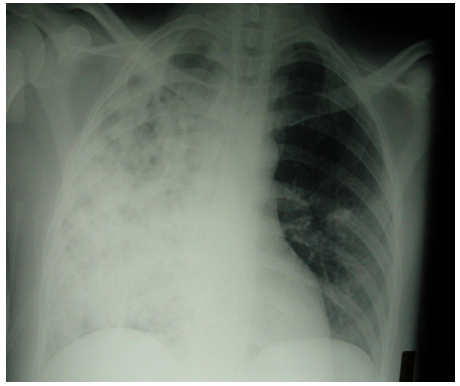
*Approx. 15-20% of cases in U.S. are culture negative*

** **Clinical acumen** and **index of suspicion** remain key*

- ATS/CDC/IDSA 2016 guidelines – can rx culture negative <u>pulmonary</u> TB 4 mo (2HREZ/2HR)

# TB Treatment Failure

- 90-95% of patients treated for pulmonary TB will have negative sputum cultures by 3 months
- If still culture positive after 3 months of therapy:
  - Re-check drug susceptibility tests
  - Assess adherence
  - Consider malabsorption of drugs;
    - Check therapeutic drug levels



# Management of TB Treatment Failure

**Treatment failure:** Culture positive after 4mo. of rx

- Obtain rapid molecular & phenotypic DST (often earlier on month 3 samples)
  - If the patient is seriously ill or sputum AFB smear +, an empiric expanded regimen should be started with at least two new drugs
  - If the patient is not seriously ill, consider waiting for the results of molecular DST
  - If malabsorption suspected, check therapeutic drug levels and consider IV therapy (LNZ, rifampin, FQ)

# End of Therapy

- Determined by number of doses completed and not number of months
- Duration of treatment is **a clinical decision** based on the following factors:
  - Extent and site(s) of disease
  - Time to sputum culture conversion and clinical response
  - Presence of drug resistance
  - Drugs used in regimen
  - Comorbidities
- End of treatment evaluation:

  - Chest x-ray and sputum

# Key learning points (1)

- Maintain a high clinical suspicion for PTB and incorporate molecular testing in diagnostics
- Consider risk factors for drug resistance up front and repeat testing if slow response
- Supporting patient adherence remains critical

# Key learning points (2)

- **Always treat with a multiple-drug regimen**
- **Never add a single drug to a failing regimen**
- Drug toxicity remains a challenge with current TB therapy and requires careful monitoring during therapy.
- Be very cautious with drug-drug interactions when starting or stopping rifampin!

# Resources

Nahid et al. ATS/IDSA/CDC guidelines for treatment of drug-susceptible TB.
https://www.cdc.gov/tb/publications/guidelines/pdf/clin-infect-dis.-2016-nahid-cid_ciw376.pdf

Saukkonen et al. Update on treatment of drug-susceptible and drug-resistant TB.
doi: 10.1164/rccm.202410-2096ST

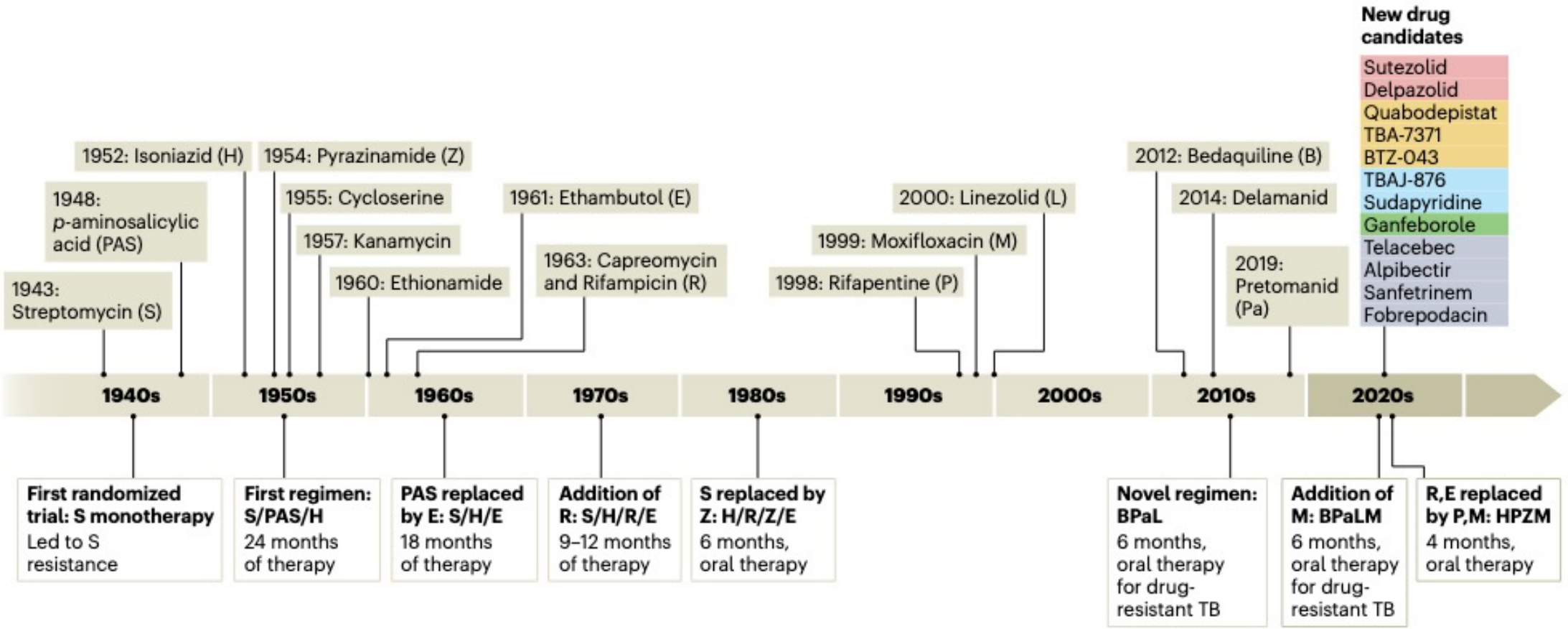
NSTC/NTNC HPMZ Fact Sheet & FAQ 5/2022; https://www.tbcontrollers.org/docs/resources/4-Month-HPMZ-TB-Regimen_NTCA-FAQ.pdf

Rifamycin drug-drug interaction guide https://www.currytbcenter.ucsf.edu/sites/default/files/2022-12/Rifamycin_2022.pdf

DHHS HIV-info (HIV specific)
https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-overview?view=full

# Additional slides

# New TB drugs in the pipeline… at last




Nuermberger and Chaisson Nat Med 2025

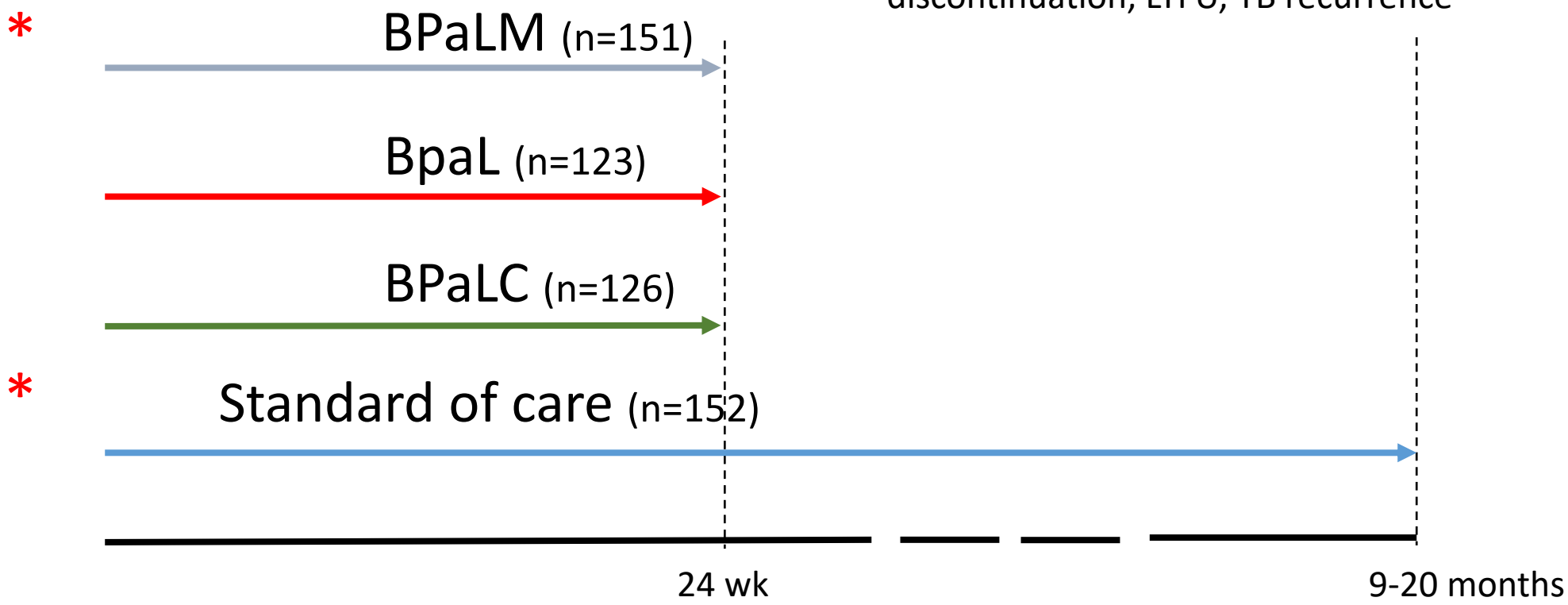
# A changing landscape in RIF-resistant TB

- The NiX-TB trial enrolled persons with XDR along with MDR cases intolerant/responding poorly to standard therapies
  - Single arm, open-label study in S Africa, age 14+
  - 26 week treatment with bedaquiline, pretomanid, and linezolid lead to **90% achieving a favorable outcome**
  - High doses of linezolid used (1200mg/d)
  - Neuropathy (81%) and myelosuppression (48%) were noted commonly

Conradie et al. NEJM 2020

# TB PRACTECAL

**Primary outcome:**
**Unfavorable status at 72 weeks**
- Death, treatment failure or discontinuation, LTFU, TB recurrence




B: bedaquiline; Pa: pretomanid; L: linezolid (600mg/d x16 wk-> 300mg/d after);
M: moxifloxacin; C: clofazimine

Nyang'wa et al. NEJM 2022 & Lancet Resp Med 2025

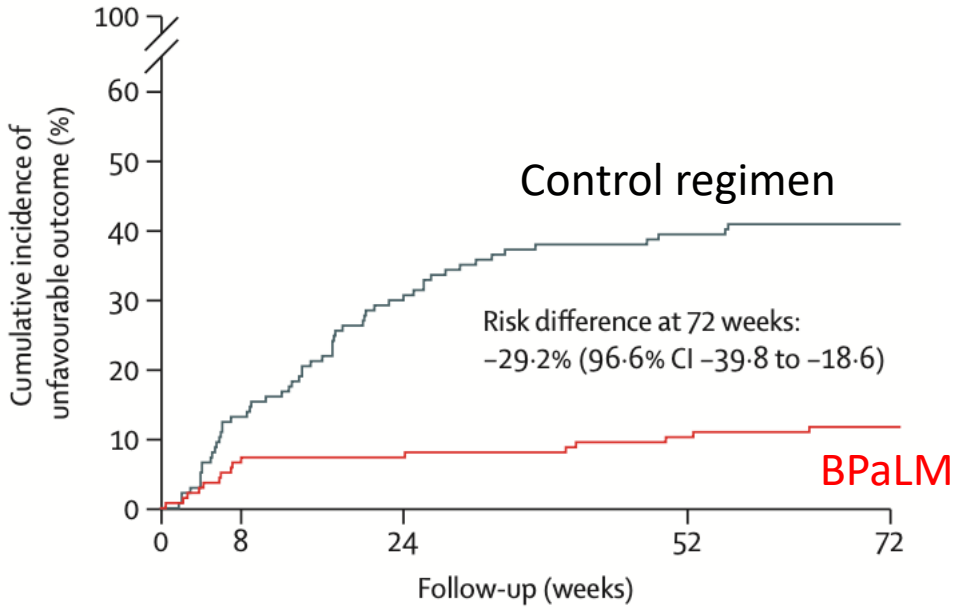
# TB PRACTECAL- Participants

| Characteristic | Standard-Care Group | BPaLM Group | BPaLC Group | BPaL Group |
|---|---|---|---|---|
| **Intention-to-treat population** | | | | |
| No. of patients | 152 | 151 | 126 | 123 |
| Geographic distribution — no. (%) | | | | |
| Belarus | 29 (19.1) | 28 (18.5) | 21 (16.7) | 21 (17.1) |
| South Africa | 54 (35.5) | 56 (37.1) | 48 (38.1) | 47 (38.2) |
| Uzbekistan | 69 (45.4) | 67 (44.4) | 57 (45.2) | 55 (44.7) |
| Median age (range) — yr | 37 (18–71) | 35 (17–71) | 32 (15–67) | 35 (15–72) |
| Female sex — no. (%) | 56 (36.8) | 66 (43.7) | 42 (33.3) | 58 (47.2) |
| Median BMI (IQR)† | 19.9 (17.3–22.8) | 19.8 (17.7–22.7) | 19.5 (17.7–22.2) | 20.0 (18.1–22.4) |
| * HIV-positive status — no. (%) | 41 (27.0) | 38 (25.2) | 33 (26.2) | 41 (33.3) |
| Median CD4 cell count (IQR) in HIV-infected patients — cells/mm³‡ | 250 (132–460) | 330 (209–547) | 297 (114–481) | 326 (153–550) |
| * Smear positivity — no. (%) | 98 (64.5) | 91 (60.3) | 84 (66.7) | 77 (63) |
| Cavitation on chest radiography present — no. (%) | 95 (62.5) | 80 (53.0) | 79 (62.7) | 74 (60.2) |
| * Fluoroquinolone-resistant tuberculosis — no./total no. (%) | 32/131 (24.4) | 32/134 (23.9) | 22/118 (18.6) | 25/104 (24.0) |
| QTcF interval — msec§ | 401±19 | 398±19 | 395±19 | 398±19 |
| Median ALT level (IQR) — IU/liter¶ | 20 (15–28) | 19 (14–28) | 17 (14–26) | 20 (14–31) |

Nyang'wa et al. NEJM 2022

# TB PRACTECAL- Efficacy and Safety

- Study stopped early due to efficacy.
- BPaLM arm showed:
  - More favorable outcomes vs SOC (88% vs 59%).
  - More early treatment discontinuation due to AE were noted in SOC group.
  - Fewer grade 3 AE or SAE (23% vs 48%)
  - Fewer cases of QTc prolongation




Nyang'wa et al. NEJM 2022 & Lancet Resp Med 2025

# RIF-R TB: Where do we go from here?

## BPaL and BPaLM 6-month regimens

### Expert consensus dosing recommendations (combining WHO and CDC):

For age 14+ years:

**BPaL***

- **Bedaquiline** 400 mg once daily x 2 weeks (load), then 200 mg 3x/week x 24 weeks
- **Pretomanid** 200 mg once daily x 26 weeks
- **Linezolid** 600 mg once daily x 26 weeks

**BPaLM*** — same as above and add:

- **Moxifloxacin** 400 mg once daily x 26 weeks

Extend either regimen to 9 months (39 weeks) if evidence for delayed response to treatment (> 8 weeks per CDC criteria below).

Drug-resistant TB: A Survival Guide for Clinicians (Curry Center)

# RIF-R TB: Where do we go from here?

- How durable will BPaL/M be in the coming years?
  - Bedaquiline resistance is a concern, though remains uncommon
  - Critical need for timely access to DST
- Practical challenges with BPaL/M persist
  - Prior approval paperwork burden
  - Cost
  - EKG monitoring
- More attention needed for populations not included in BPaL trials