# TB TREATMENT

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# Objectives

- Understand the following
  - Rationale and goals for standard TB regimen
  - Standard regimen and potential side effects
  - Review new shorter regimen: HPMZ
  - Monitoring during treatment, treatment failure, treatment completion

# What I'm Not Going To Talk About

- Treatment of latent TB infection
- Treatment of MDR-TB
- Treatment of extrapulmonary TB
- Treatment of TB in special situations: Covered by Dr. Narita's case-based talk later today
- All possible side effects

# 2016 US TB TREATMENT GUIDELINES

*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

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]

Nahid CID 2016

# Nomenclature

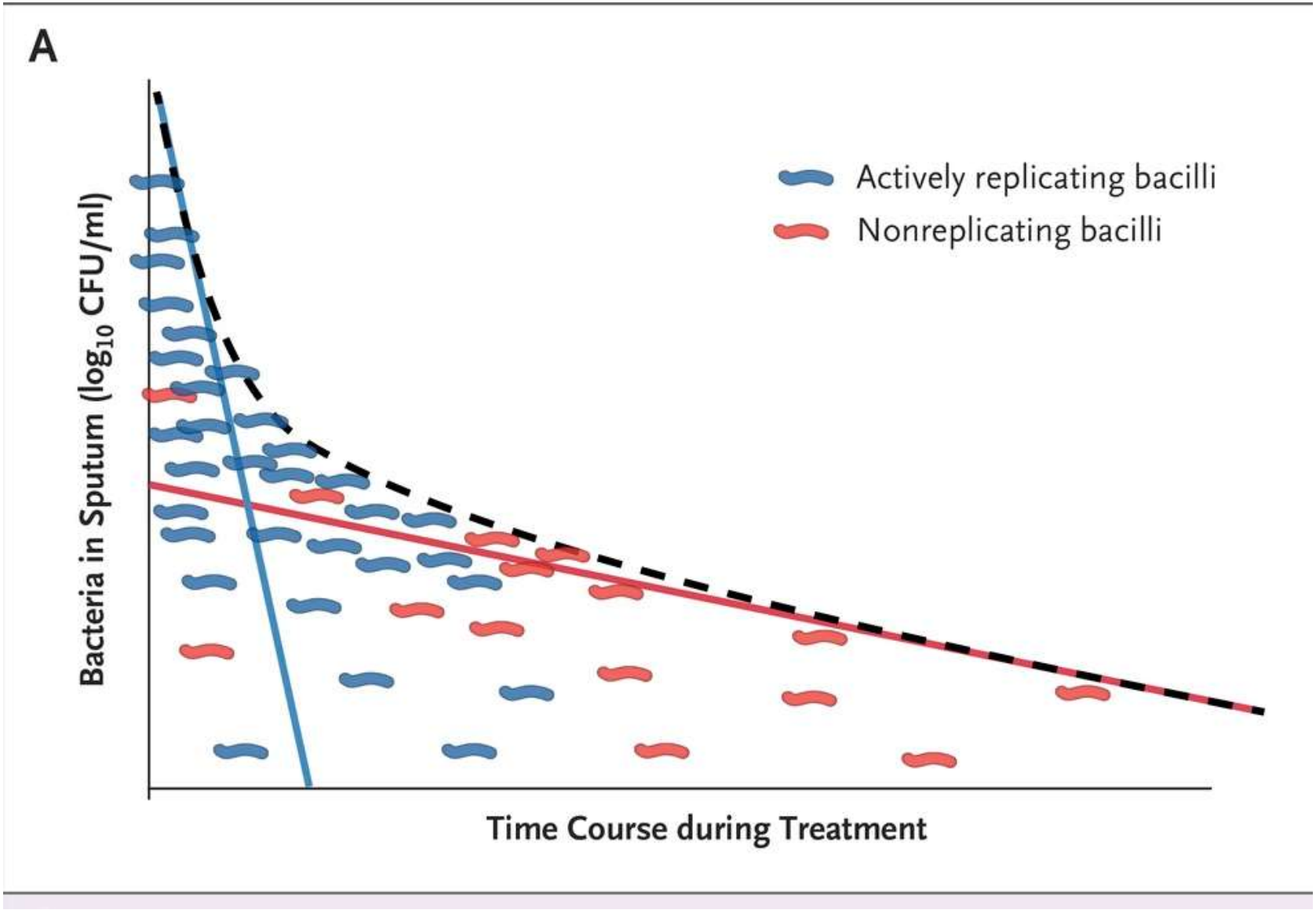
| DRUG | ABBREVIATION | SINGLE LETTER ABREVIATION |
|---|---|---|
| Isoniazid | INH | H (or I) |
| Rifampin | RIF | R |
| Pyrazinamide | PZA | Z (or P) |
| Ethambutol | EMB | E |
| Moxifloxacin | MFX | M |
| Rifapentine | RPT | P |

# Question

How long is a “standard” course of treatment for fully sensitive, non-cavitary, pulmonary TB assuming sputum culture conversion occurs prior to 8 weeks into treatment?

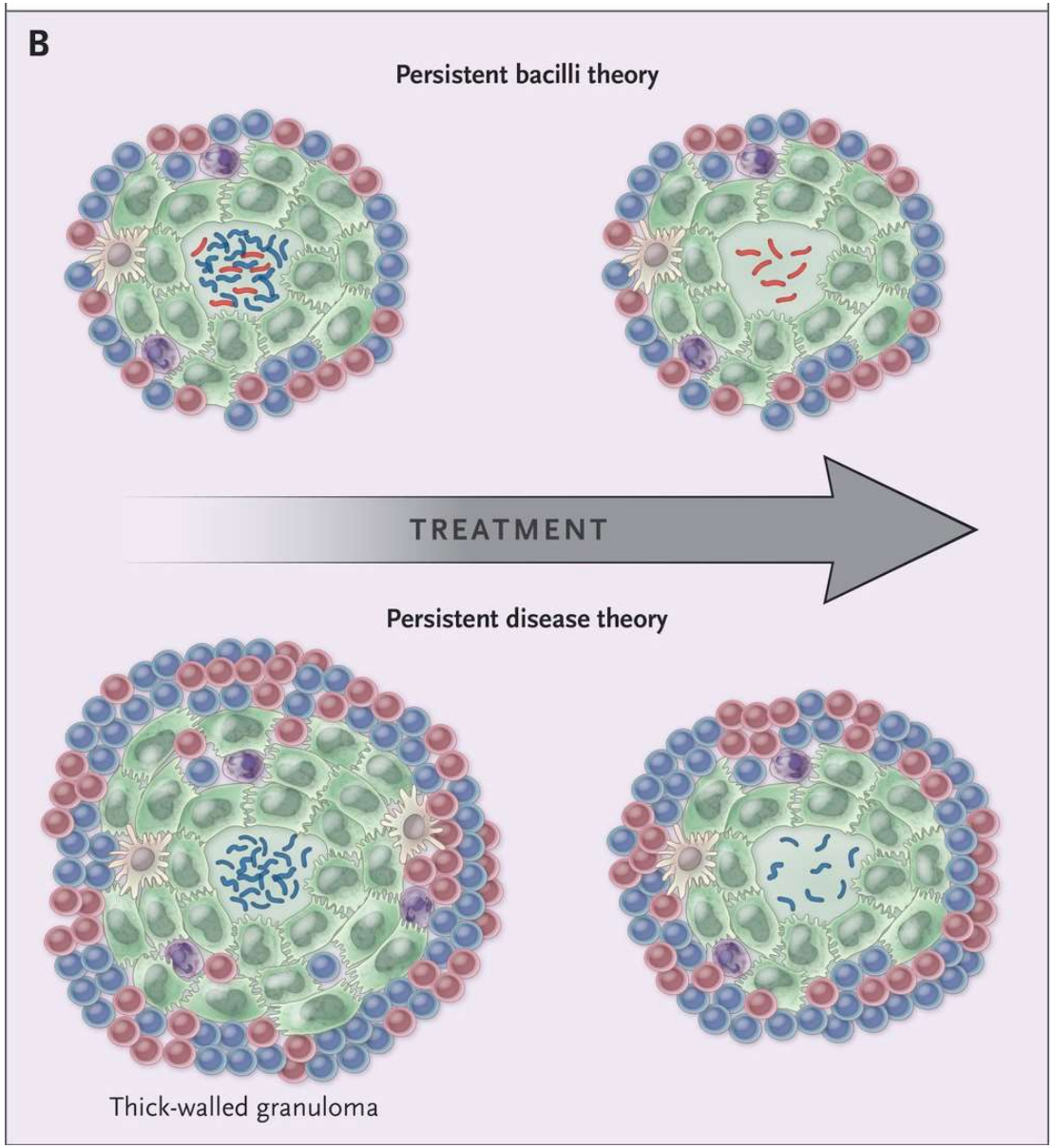
A. 18 months
B. 9 months
C. 6 months
D. 4 months

# Why Is TB Therapy So Long?




Horsburgh NEJM 2015

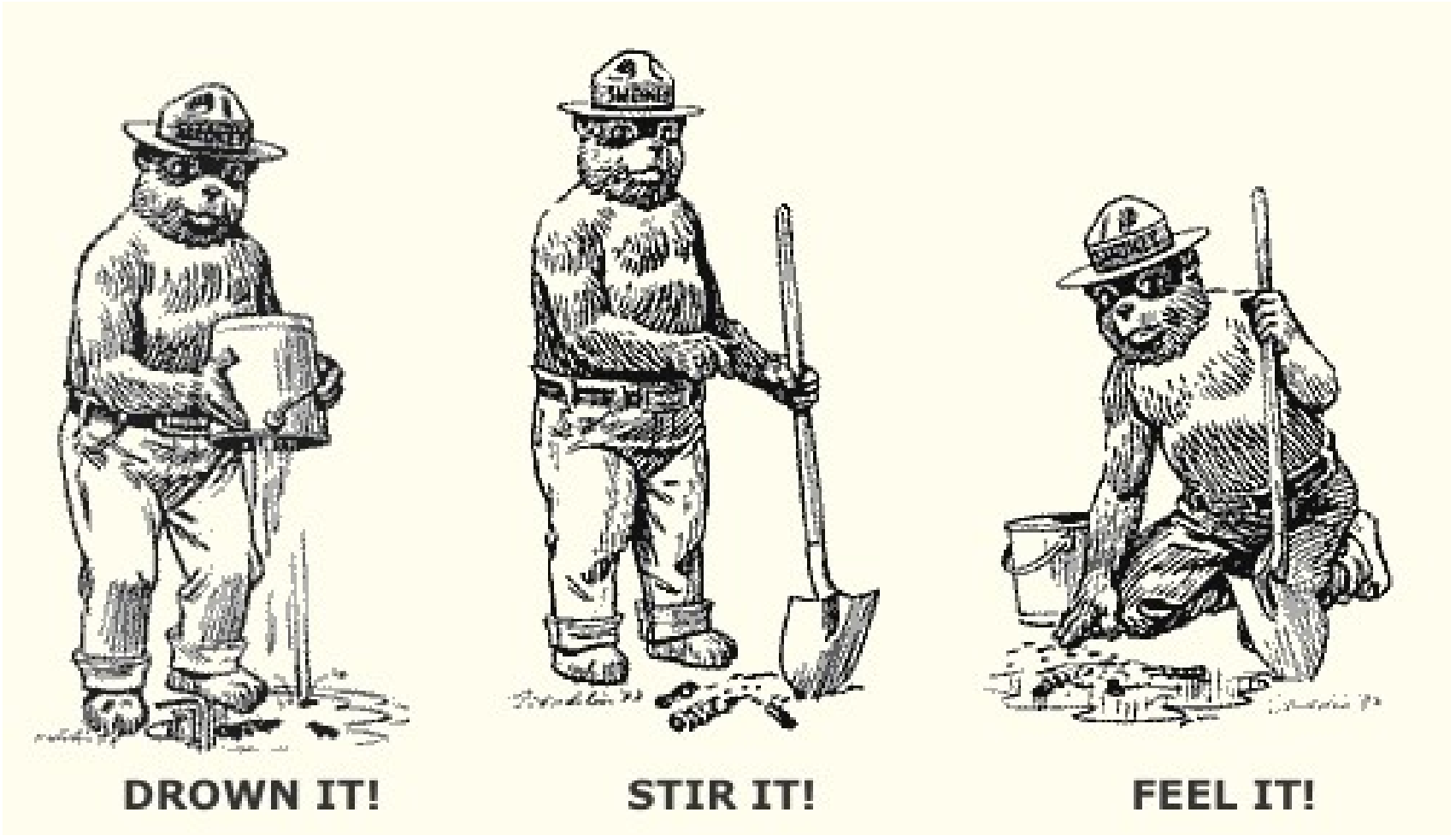
# Why Is TB Therapy So Long?




Blue bugs: Active
Red bugs: Dormant

Horsburgh NEJM 2015

# Why Is TB Therapy So Long?

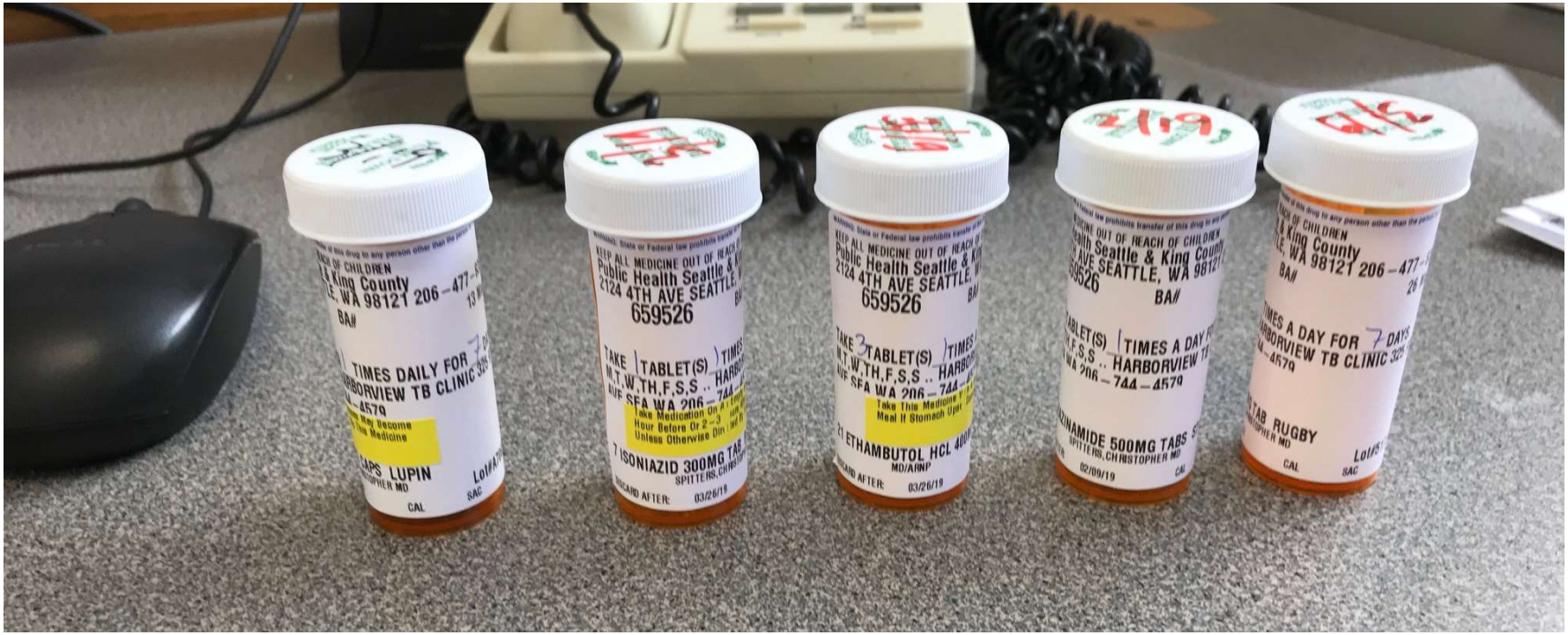



**INTENSIVE PHASE:**
**2 MONTHS HRZE**

**CONTINUATION PHASE:**
**4 MONTHS HR**

**ASSESSING RESPONSE:**
**CLINICAL, SPUTUM**

# Why So Many Drugs?



# Why So Many Drugs?

- In a population of TB bugs, there is a constant "natural" low level mutation rate resulting in drug resistance
  - Single drug therapy causes selective pressure favoring resistant bugs
- In patients with high burden disease, the likelihood of naturally occurring mutations to…
  - Single drug is likely
  - Two drugs is possible
  - Three drugs is highly unlikely

# Shorter TB regimens over time

- First curative TB treatment: INH, SM, aminosalicylic acid for up to 2 years
- Series of clinical trials (late 1940s to mid 1980s)
  - RIF plus INH allowed shortening duration from 18 to 9 months
  - Adding PZA to the first 2 months allowed shortening from 9 to 6 months
- EMB added to regimen to prevent resistance
- 2022: CDC approves HPMZ for 4 months

Horsburgh NEJM 2015

# 3 Goals of TB Treatment

- Rapid killing of multiplying bacteria
  - Individual impact: Decrease severity of disease and prevent death
  - Population impact: Decrease transmission
- Eradicate remaining bacteria (“persisters”) to achieve durable cure (“sterilization”)
- Prevent acquisition of drug resistance during therapy

# First Line TB Drug Activity

| *Drug* | *Early bactericidal activity* | *Preventing drug resistance* | *Sterilizing activity* |
|---|---|---|---|
| Isoniazid | ++++ | +++ | ++ |
| Rifampin | ++ | +++ | ++++ |
| Pyrazinamide | + | + | +++ |
| Ethambutol | +/++ | ++ | + |

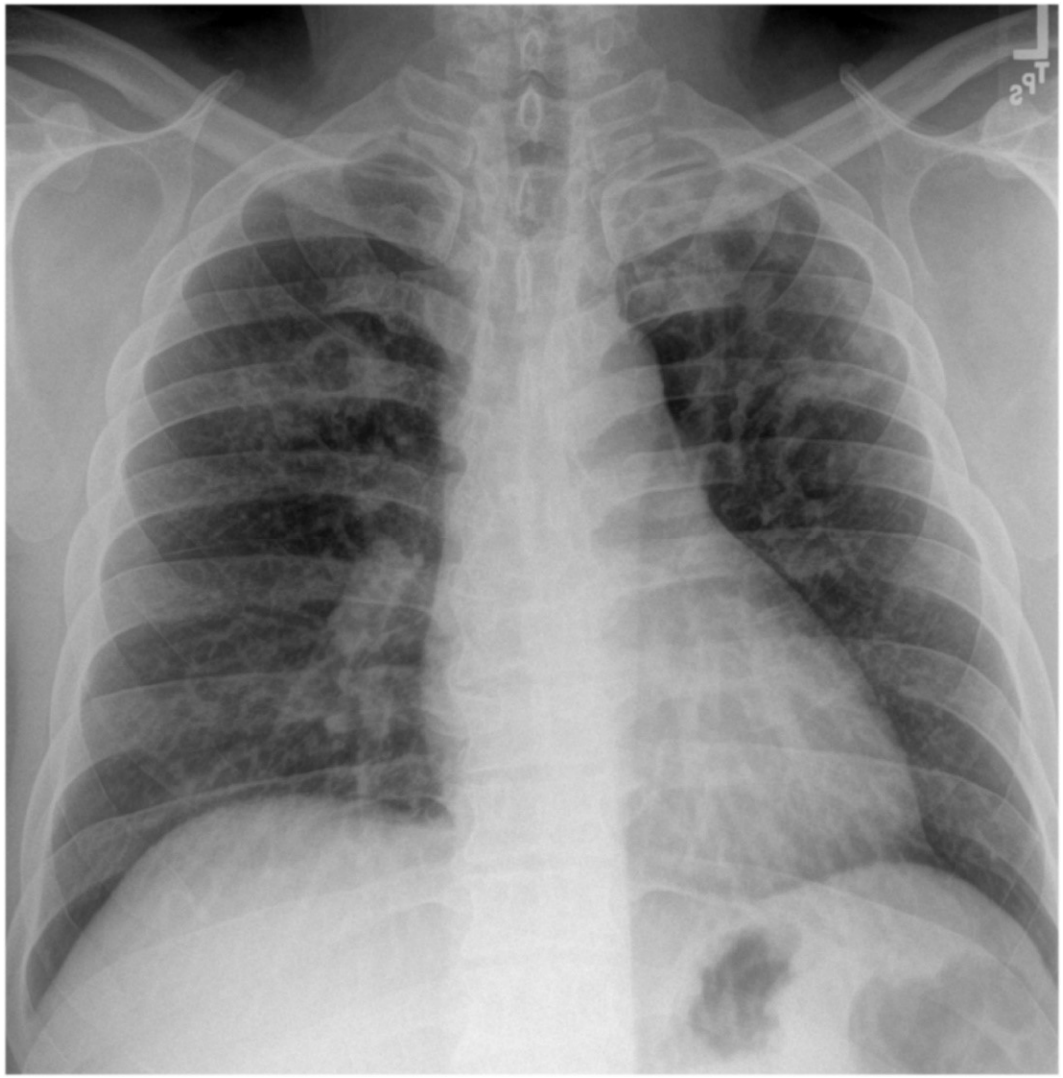
Highest ++++, High +++, Intermediate ++, Low +

Slide c/o Masa Narita

# First Line Drug Take Home Points

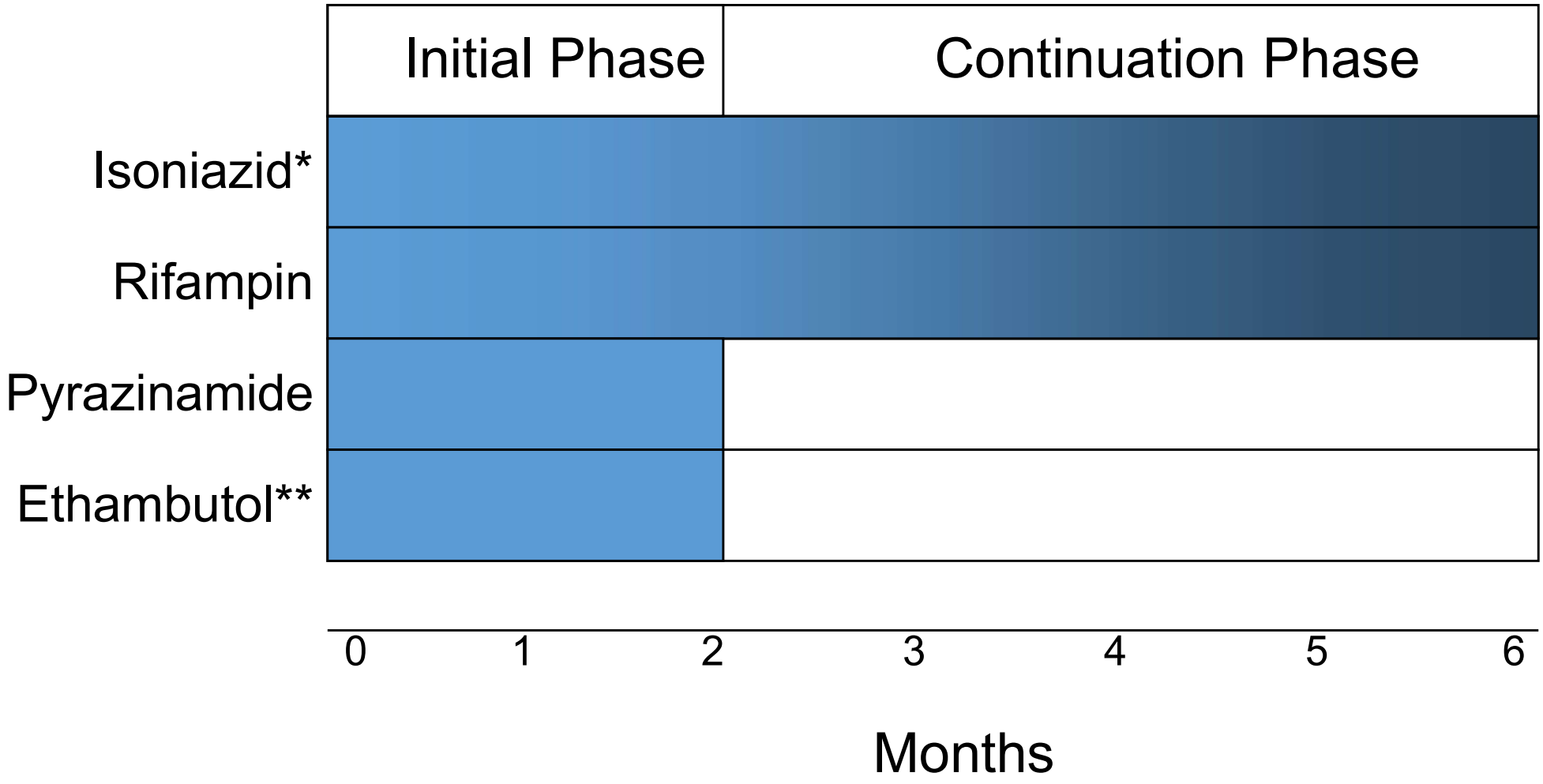
- Rapid killing of multiplying bacteria → INH>RIF
- "Sterilizing Effect" preventing relapse → PZA, RIF
- Prevent drug resistance → INH, RIF, EMB
  - Not PZA (limited effectiveness against rapidly growing bacteria, and works in acidic microenvironments)
    - You won't see a regimen of PZA and only 1 other drug

# Case: 21 yo M From India



- 2 months of fever, cough, weight loss, sweats, hemoptysis
- Sputum: AFB smear positive, MTB PCR positive (rpoB mutation negative)
- What treatment to start? Other initial considerations?

# The Standard Regimen




*Administer B6 with INH to those at risk of peripheral neuropathy

**EMB can be stopped if TB is sensitive to INH and RIF

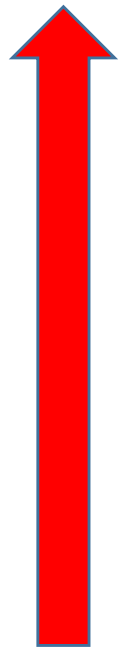
# Treatment Initiation Considerations:

- Risk for drug resistance? Obtain molecular DST
  - Previous treatment, non-DOT
  - From country with high rate of drug resistance
  - Known contact to drug resistant case
- Comorbidities: HIV, liver disease, renal disease, advanced age
- Drug interactions
  - Few medications impact TB drugs
  - INH impacts a few drugs
  - RIF impacts MANY drugs
- Assess barriers to adherence

# Dosing Frequency

STRONGER

| | Intensive Phase | | Continuation Phase | |
|---|---|---|---|---|
| Regimen | Drugs | Frequency | Drugs | Frequency |
| 1 | HRZE | -7 days/wk X 8 wks<br>-5 days/wk X 8 wks | HR | -7 days/wk X 18 wks<br>-5 days/wk X 18 wks |
| 2 | HRZE | -7 days/wk X 8 wks<br>-5 days/wk X 8 wks | HR | -TIW X 18 wks |
| 3 | HRZE | -TIW X 8 wks | HR | -TIW X 8 wks |



WEAKER

- DOT strongly recommended
- Daily dosing is preferred
- TIW during continuation phase an acceptable alternative
- Use Regimen 3 with caution if: HIV, smear positive, or cavitary disease. Missed doses can lead to risk of treatment failure, relapse, drug resistance
- BIW dosing not recommended. Dose missed?→ weekly dosing (inferior)

Nahid CID 2016

# Dosing Frequency and Relapse Risk

| | Cavitary | | Non-cavitary | |
|---|---|---|---|---|
| **6 month regimens** | **2 month culture +** | **2 month culture -** | **2 month culture +** | **2 month culture -** |
| **Daily throughout** | 6.0% | 2.2% | 1.8% | 0.6% |
| **Daily intensive phase THEN TIW continuation phase** | 6.1% | 3.3% | 2.2% | 1.2% |
| **Daily intensive phase THEN BIW continuation phase** | 15.6% | 5.7% | 5.4% | 1.9% |
| **TIW throughout** | 14.5% | 5.3% | 4.6% | 1.7% |

Chang AJRCCM 2006

# Question

- A 33 yo M has fully sensitive, smear positive, cavitary pulmonary TB. After treatment initiation, when is the most important time to repeat sputum evaluation?

A. 2 weeks into treatment

B. 1 month into treatment

C. 2 months into treatment

D. At the end of treatment

# Risk Factors For Relapse

| | Cavitary | | Non-cavitary | |
|---|---|---|---|---|
| 6 month regimens | 2 month culture + | 2 month culture - | 2 month culture + | 2 month culture - |
| Daily throughout | 6.0% | 2.2% | 1.8% | 0.6% |
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| TIW throughout | 14.5% | 5.3% | 4.6% | 1.7% |

Chang AJRCCM 2006

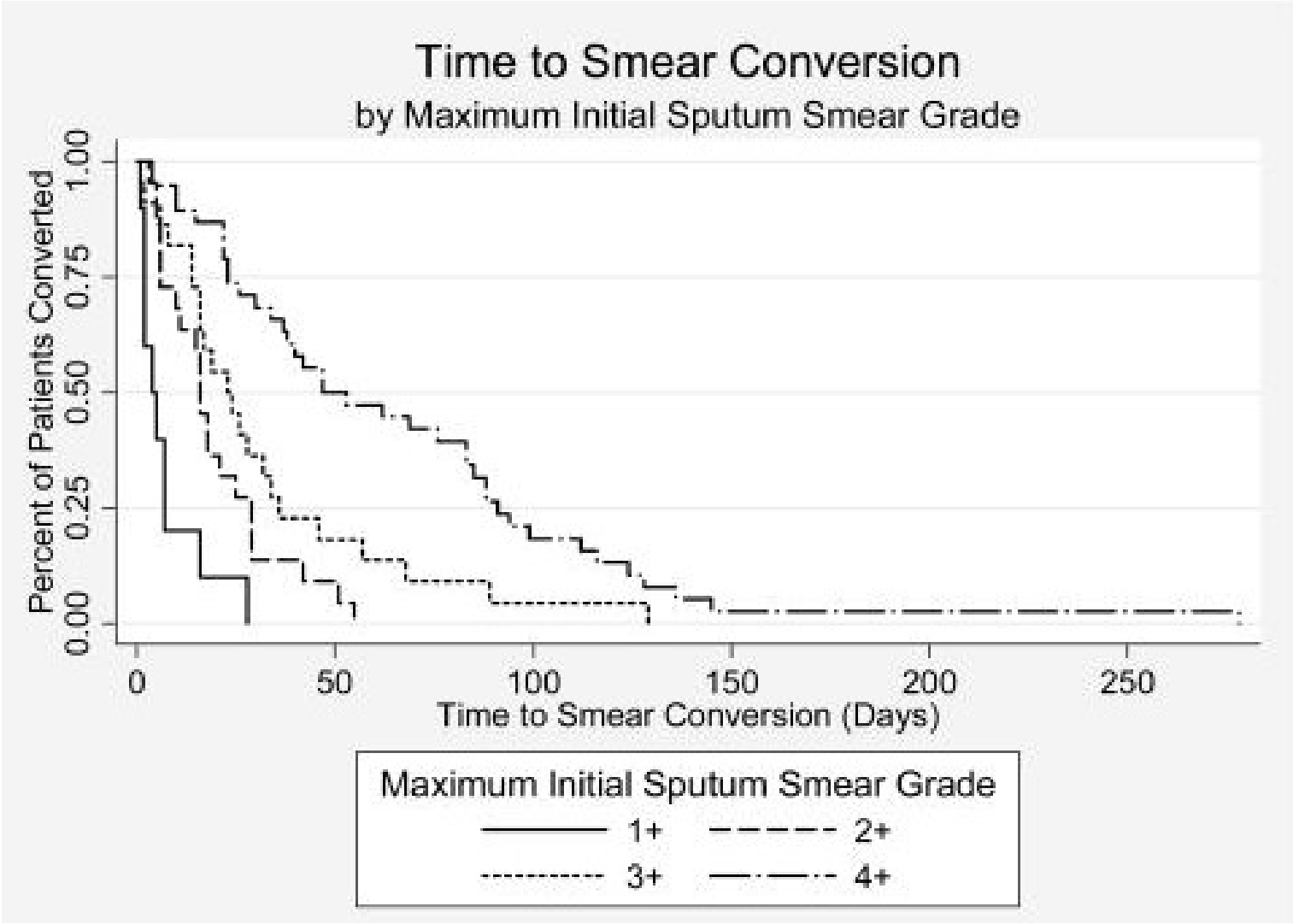
# Extending the Regimen: Risk Factors For Relapse

- If cavitary disease **AND** culture positive at 2 months…
  - extend continuation phase HR to 7 months (9 total months of treatment)
- If cavitary disease **OR** culture positive at 2 months, consider extending to 9 total months if….
  - > 10% below ideal body weight
  - Active smoker
  - Poorly controlled DM
  - HIV or other immunosuppression
  - Extensive disease on CXR

# Monitoring During Treatment

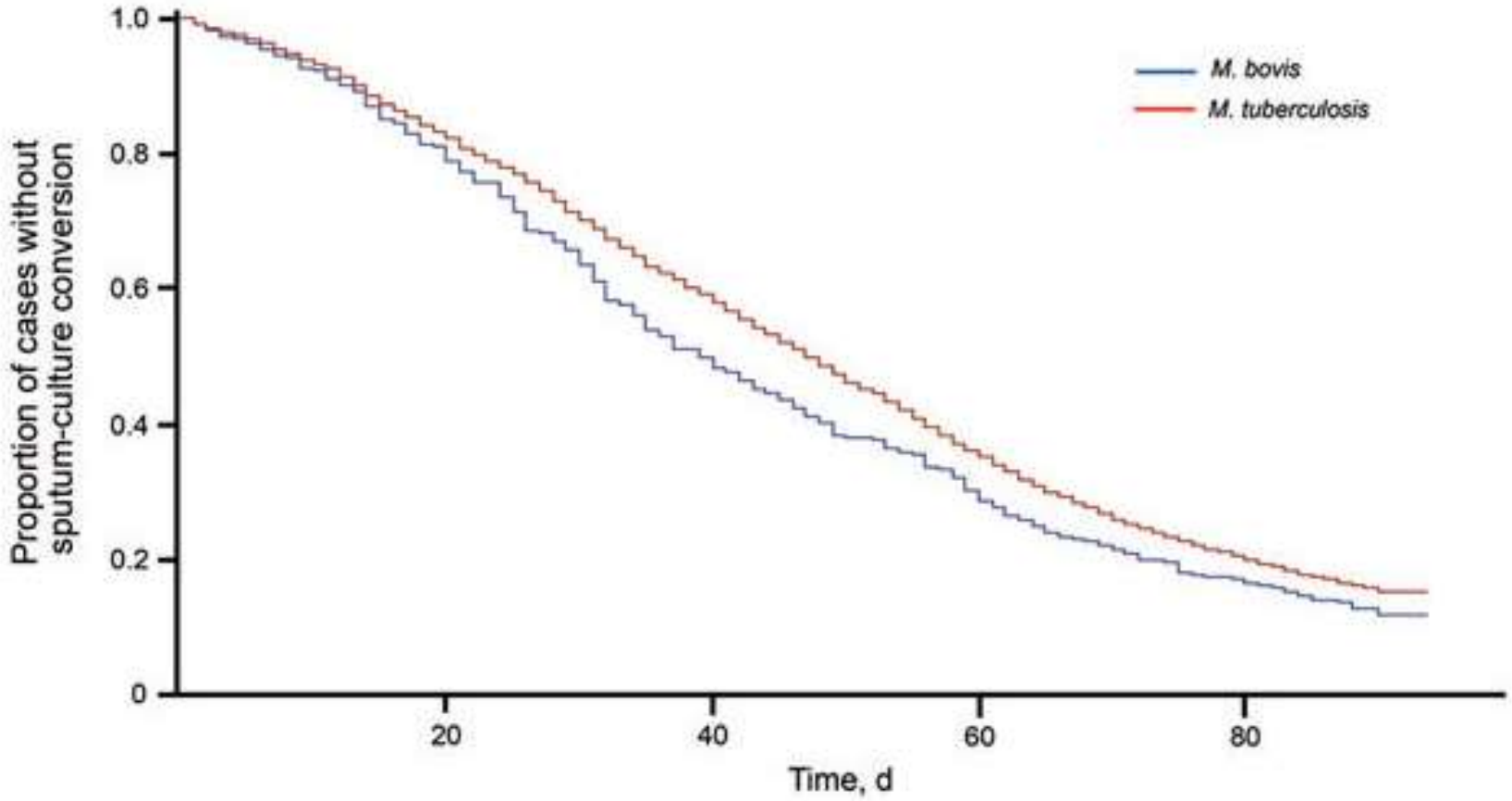
- Clinical response is variable, but my own general impression: Assuming they were ill to begin with, most patients are feeling better at 2 weeks into treatment, a lot better by 4 weeks, and back to normal (or nearly so) by 8 weeks.
- Sputum mycobacteriologic response is also variable, and dependent on initial burden of disease (next slides)

# MONITORING DURING TREATMENT: SPUTUM SMEAR CONVERSION




Horne. Infect Control Hosp Epidemiology 2010

# MONITORING DURING TREATMENT: SPUTUM CULTURE CONVERSION




Scott EID 2017

# Treatment Completion

- Based on number of doses, not duration
- Definition of completion for standard 6 month regimen:
  - Intensive phase completed in 3 months
  - Continuation phase completed in 6 months
  - So total therapy completed in 9 months
- If targets not met, manage as treatment interruption
- End of treatment counseling:
  - Inform future providers about previous TB and persistent CXR abnormalities
  - Seek medical evaluation if signs/symptoms TB recurrence

# Treatment Failure

- Definition: Culture positive at 4 months
- 90-95% of patients with drug susceptible TB will be culture negative at 3 months if on regimen with INH and RIF
- If culture positive at 3 months, look for
  - Adherence issues
  - Occult drug resistance (repeat molecular and phenotypic DST)
  - Malabsorption
  - Consider therapeutic drug monitoring
- *****Never add a single drug to a failing regimen****

# Culture Negative TB

- Culture Negative TB:
  - Clinical syndrome consistent with TB
  - Radiographic findings consistent with TB
  - Sputum AFB smear/culture negative
  - Other conditions unlikely or ruled out
  - Positive TST/IGRA (supportive, not always necessary)
  - Clinical/radiographic improvement (2 mo CXR)
- Treatment: 2 months HRZE, 2 months HR
- If didn’t get better at 2 months, stop therapy and considered them treated for LTBI

# Adjusting The Standard Regimen: Mono-resistance or intolerance

- Without INH:
  - RZE + FQ for 6 months
- Without PZA:
  - 9 months HR with initial use of EMB white waiting for DST

Curry Center Drug Resistant TB Survival Guide
Nahid ATS/CDC/ERS/IDSA 2019

# NEW 4 MONTH REGIMEN: HPMZ

ORIGINAL ARTICLE

## Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

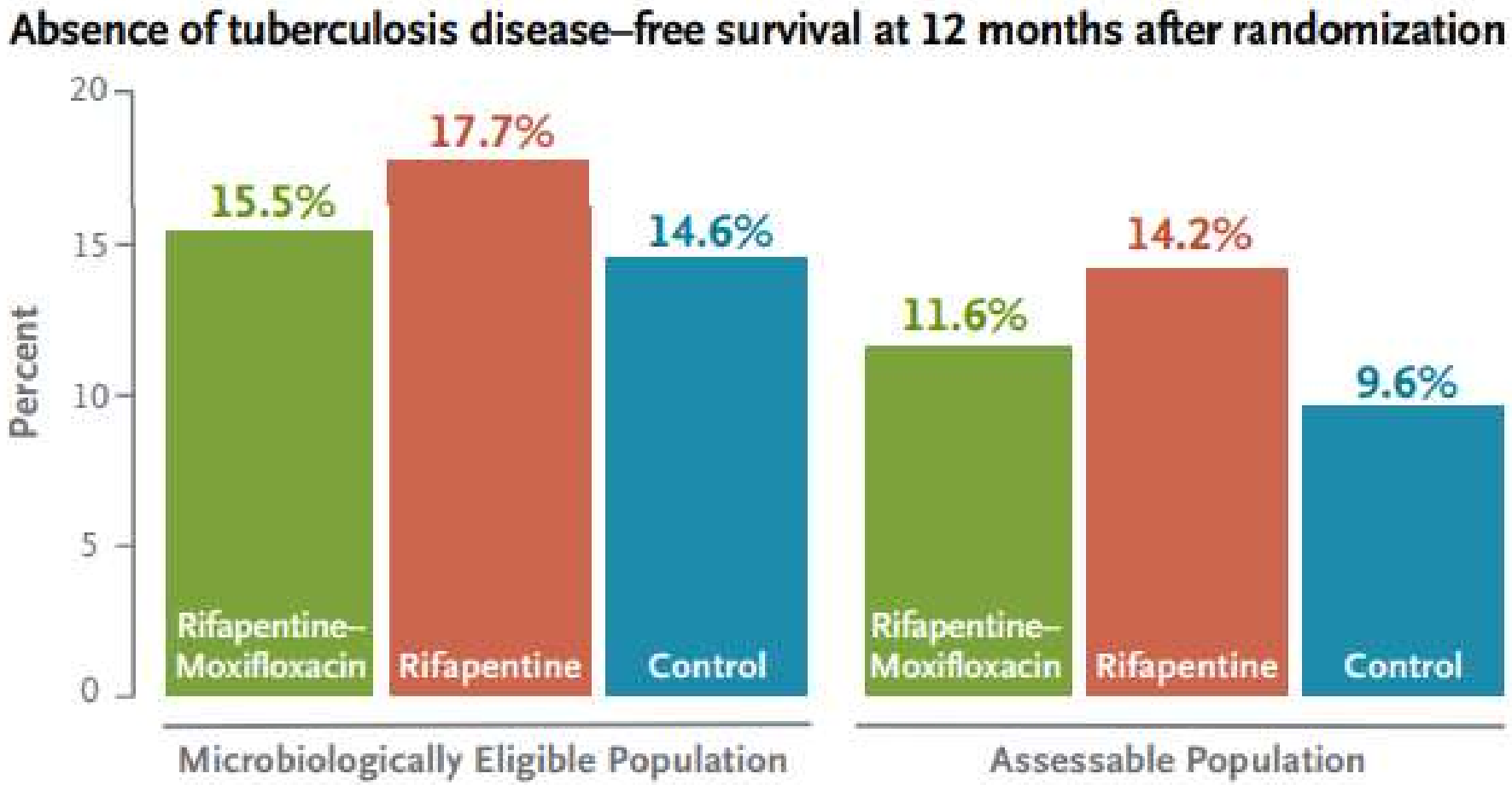
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Dorman et al NEJM 2021

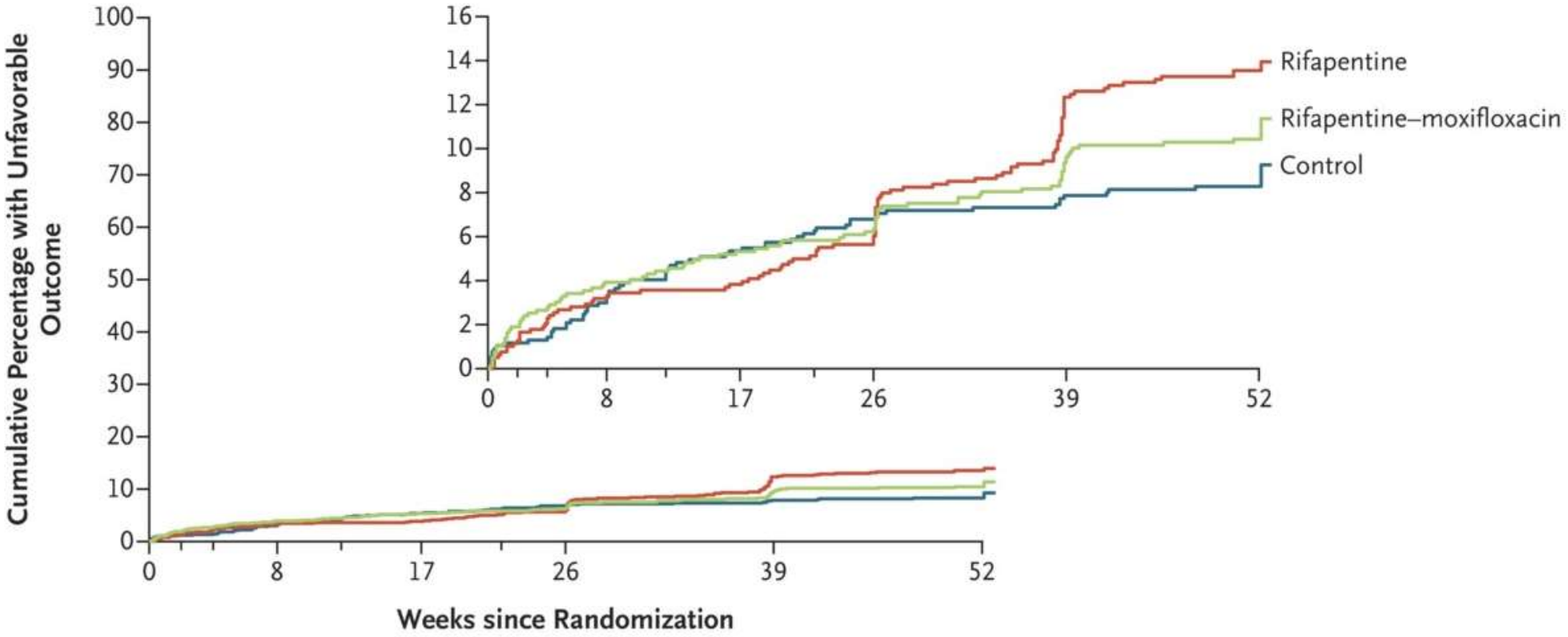
# STUDY 31

- Open label randomized trial in 13 countries
- N=2343 with pulmonary TB sensitive to HR + FQ
  - 73% had cavitary disease on CXR
- Primary Outcome: TB free survival at 12 months
- Randomized to:
  - Standard regimen arm
    - 8 weeks HRZE, then 16 weeks HR
  - Rifapentine (1200 mg) daily arm
    - 8 weeks HPZE, then 9 weeks HP
  - Rifapentine (1200 mg) and moxifloxacin daily arm
    - 8 weeks HPMZ, then 9 weeks HPM

# STUDY 31


Absence of tuberculosis disease–free survival at 12 months after randomization
Percent
20
15
10
5
0
15.5%
17.7%
14.6%
11.6%
14.2%
9.6%
Rifapentine–Moxifloxacin
Rifapentine
Control
Rifapentine–Moxifloxacin
Rifapentine
Control
Microbiologically Eligible Population
Assessable Population

# STUDY 31




- Unfavorable outcomes: Positive MTB sputum culture after treatment, died, withdrew or lost to follow up, had a positive sputum culture when last seen, died from TB during follow up, received additional treatment for TB

# STUDY 31

- 4 month regimen including rifapentine and moxifloxacin was deemed non-inferior (non-inferiority margin 6.6%)

- 4 month regimen including rifapentine only was not

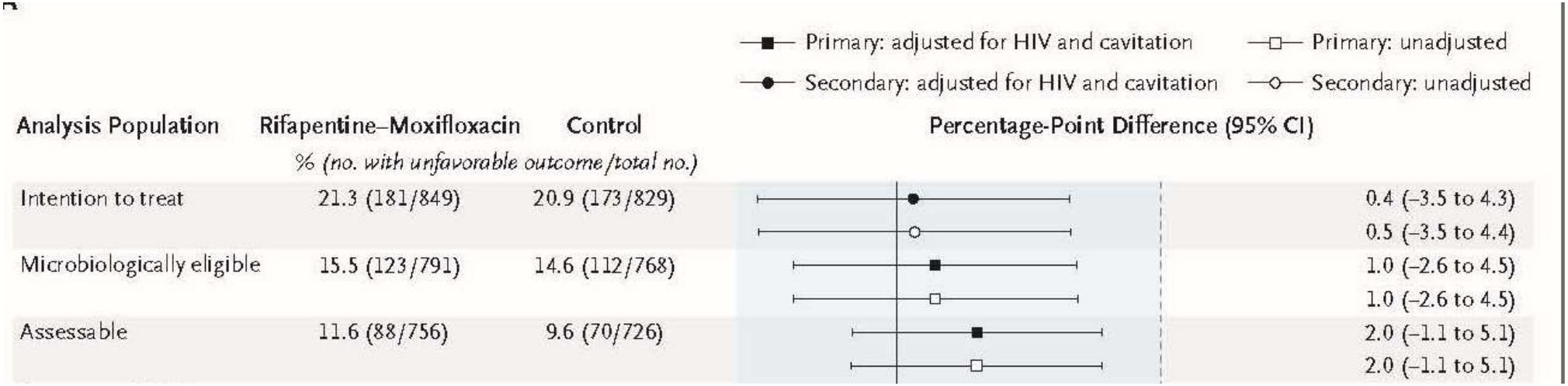
# STUDY 31

- Other important findings
  - Earlier time to culture conversion in HPMZ compared to standard regimen
  - No significant difference in grade 3 or higher adverse effects
  - Grade 3 or higher cardiac adverse effects in 0.4% of HPMZ arm; no EKG monitoring was done
- Study did not include EPTB, children, pregnant

# Slow Local Adoption

- Logistical concerns:
  - Up front molecular DST for MFX not available
  - Rifapentine shortage
- Efficacy concerns
  - Efficacy concerns? See next slide
  - Issues with comparator group: 37% in standard regimen were culture positive at 8 weeks, but protocol did not include extension to 9 months
- BUT: We are currently evaluating how to implement HPMZ as our preferred regimen for eligible patients

# 4 month regimen data




| Analysis Population | Rifapentine–Moxifloxacin | Control | Percentage-Point Difference (95% CI) |
|---|---|---|---|
| | *% (no. with unfavorable outcome/total no.)* | | |
| Intention to treat | 21.3 (181/849) | 20.9 (173/829) | 0.4 (–3.5 to 4.3) |
| | | | 0.5 (–3.5 to 4.4) |
| Microbiologically eligible | 15.5 (123/791) | 14.6 (112/768) | 1.0 (–2.6 to 4.5) |
| | | | 1.0 (–2.6 to 4.5) |
| Assessable | 11.6 (88/756) | 9.6 (70/726) | 2.0 (–1.1 to 5.1) |
| | | | 2.0 (–1.1 to 5.1) |

RFP-Moxi better

HRZE better

| Analysis Population | Rifapentine | Control | Percentage-Point Difference (95% CI) |
|---|---|---|---|
| | *% (no. with unfavorable outcome/total no.)* | | |
| Intention to treat | 23.0 (193/838) | 20.9 (173/829) | 2.1 (–1.8 to 6.1) |
| | | | 2.2 (–1.8 to 6.1) |
| Microbiologically eligible | 17.7 (139/784) | 14.6 (112/768) | 3.0 (–0.6 to 6.6) |
| | | | 3.1 (–0.5 to 6.8) |
| Assessable | 14.2 (107/752) | 9.6 (70/726) | 4.4 (1.2 to 7.7) |

RFP better

HRZE better

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 71 / No. 8
February 25, 2022

# Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

Wendy Carr, PhD[1]; Ekaterina Kurbatova, MD[1]; Angela Starks, PhD[1]; Neela Goswami, MD[1]; Leeanna Allen, MPH[1]; Carla Winston, PhD[1]

- CDC recommends this as a treatment option for those age >=12 with body weight > 40 kg and drug susceptible pulmonary TB
- Administer once daily with food (at least 5 of 7 DOT)
- Up front molecular and phenotypic DST recommended for all drugs used (including MFX)
- Not recommended if QTc is prolonged or on other drugs causing QTc prolongation

# Question

Which of the following is a possible side effect from TB therapy?

A. Hepatic failure
B. Permanent reduction in vision
C. Gout
D. Thrombocytopenia
E. Neuropathy
F. Anaphylaxis
G. All of the above

# First Line TB Medication Side Effects

- Common (~5-18% require regimen adjustment)
- Can be severe
  - Drug induced liver injury (PZA>INH>RIF)
  - Permanent reduction in vision (EMB)
  - Hypersensitivity reaction (RIF)
- General principals:
  - Goal is to kill the TB bugs without causing significant harm or long-term side effects
  - Minor side effects managed symptomatically
  - Major side effects: Drugs stopped, likely offending agent avoided (may require drug challenge to identify culprit)

# TB Medication Side Effects

| ISONIAZID (INH) (2 of 2) | |
|---|---|
| **Special circumstances** | **Use in pregnancy/breastfeeding:** Safe during pregnancy; safe during breastfeeding (both baby and mother should receive pyridoxine supplementation). Up to 20% of the infant therapeutic dose will be passed to the baby in the breast milk.<br>**Use in renal disease:** No dose adjustment for renal failure, but pyridoxine supplementation should be used.<br>**Use in hepatic disease:** May exacerbate liver failure. Use with caution.<br>**Drug Interactions:** Isoniazid is a CYP3A4 inhibitor. INH may increase the concentrations of certain cytochrome P450 enzyme substrates, including phenytoin and carbamazepine. |
| **Adverse reactions** | Hepatitis (age-related).<br>Peripheral neuropathy.<br>Hypersensitivity reactions.<br>Other reactions, including optic neuritis, arthralgias, CNS changes, drug-induced lupus, diarrhea, and cramping with liquid product. |
| **Contraindications** | **Patients with high-level INH resistance** who have failed an INH-containing regimen should not receive INH. |
| **Monitoring** | **Clinical monitoring of all patients on INH is essential.** Routine laboratory monitoring is not recommended for patients receiving INH monotherapy. For patients receiving multiple TB drugs or other hepatotoxic drugs, or with underlying liver disease (including viral hepatitis), baseline liver function testing is recommended. Follow-up liver function testing is determined by baseline concerns and symptoms of hepatotoxicity. Therapeutic drug monitoring is recommended only for patients suspected of having malabsorption or treatment failure. Monitor concentrations of phenytoin or carbamazepine in patients receiving those drugs (increases phenytoin concentrations and risk of hepatotoxicity with carbamazepine), especially when undergoing INH monotherapy. Rifampin tends to lower concentrations of these drugs and balance effect of INH. |
| **2012 wholesale cost**<br>30-day supply, 60-kg person | $1 (outpatient public health pricing)<br>$3 (community hospital) |

- Excellent Resource: Curry Center Drug Resistant TB Survival Guide. Chapter 5: Medication Fact Sheets
- Available free online
- Recently updated

# TB Medication Side Effects

| Adverse Reaction | Drugs* |
|---|---|
| Rash | PZA, INH, RIF, EMB |
| Gastrointestinal intolerance | PZA, RIF > INH, EMB |
| Liver toxicity | PZA, INH, RIF > MFX |
| Peripheral neuropathy | INH>MFX |
| Optic neuritis | EMB |
| Gout | PZA |

*Listed in order of most likely offending agent

Slide c/o Lisa Chen

# Drug Induced Liver Injury (DILI)

# Drug Induced Liver Injury (DILI)

- Most common severe adverse reaction from HRZE
- Symptoms: anorexia, nausea/vomiting, abdominal pain, malaise, pruritis, jaundice (late finding)
- Caused by: PZA > INH > RIF> MFX
- Risks: Underlying liver disease, alcohol abuse, older age, hepatotoxic medications, pregnancy and up to 3 months postpartum, HIV

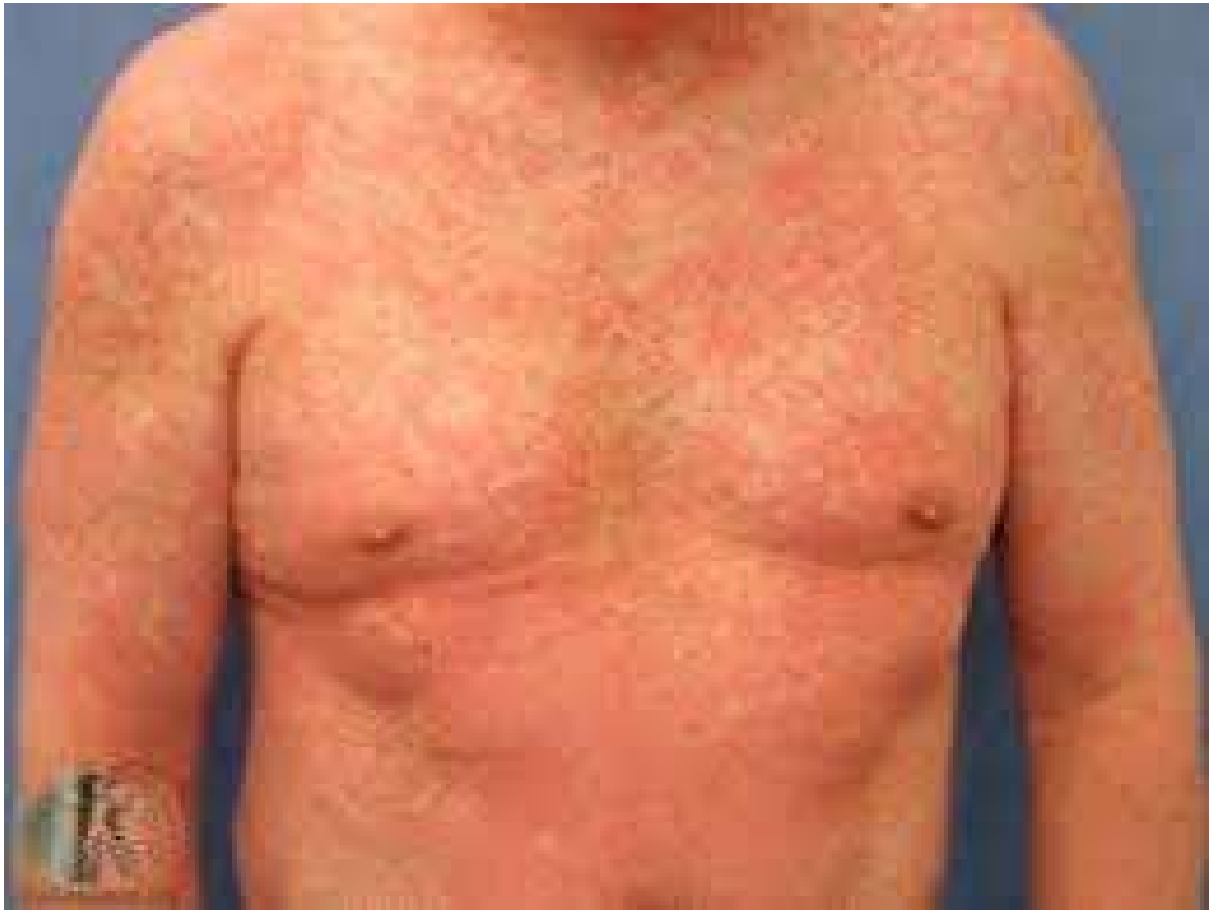
# Drug Induced Liver Injury (DILI)

- Definition:
  - ALT > 3 times ULN with symptoms
  - ALT > 5 times ULN without symptoms
- Patterns:
  - Elevated ALT/AST: PZA, INH, RIF
  - Cholestatic (elevated alk phos and bili): RIF

# DILI Management

- Rule out other causes (viral hepatitis, alcohol, other meds, biliary tract disease)
- Severe (ie ALT >500):
  - Stop RIPE. No further PZA or INH
  - Start “liver sparing regimen”
  - Consider retrying RIF once ALT < ~ 2 times ULN
- Mild/moderate:
  - Stop RIPE
  - Once ALT < 2 times ULN, sequential drug challenge at ~3-7 day intervals: RIF (+/- EMB) → INH → +/- PZA
  - If cholestatic pattern, consider different sequence
- More on this in Dr. Narita’s cases later today

# Rash



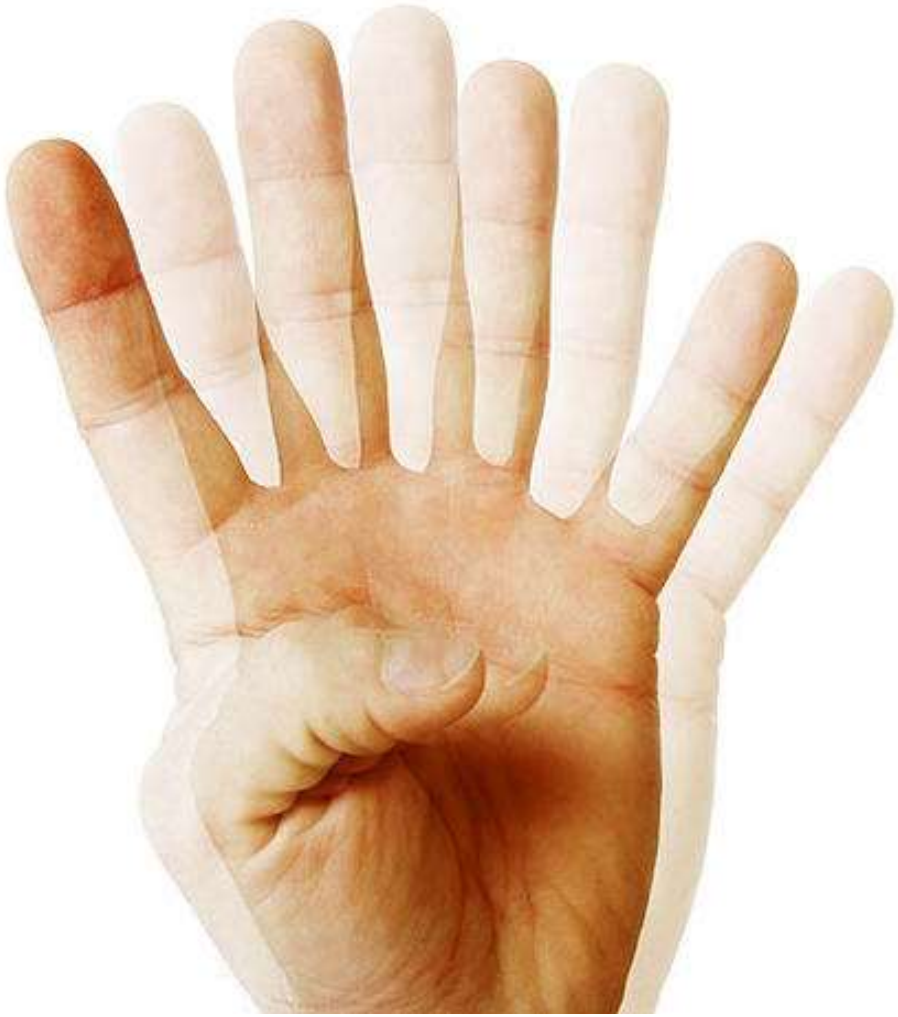
# Rash

- All TB meds can cause rash
- Minor rash: Manage symptomatically (ie antihistamine)
- Signs of more severe rash:
  - Mucous membrane involvement suggests **SJS/TEN**
  - Fever, CBC abnormalities (eosinophilia, anemia, thrombocytopena), renal failure, transaminitis suggests potential **hypersensitivity reaction**
  - Petechial rash suggests **thrombocytopenia from RIF**
  - Urticaria, airway involvement suggests **anaphylactic reaction**

# Rash

- If concerned, check safety labs (CBC, Cr, LFTs) and hold medications
- Sequential drug challenge (q 2-3 days, in order of drug importance): RIF → INH → PZA → EMB

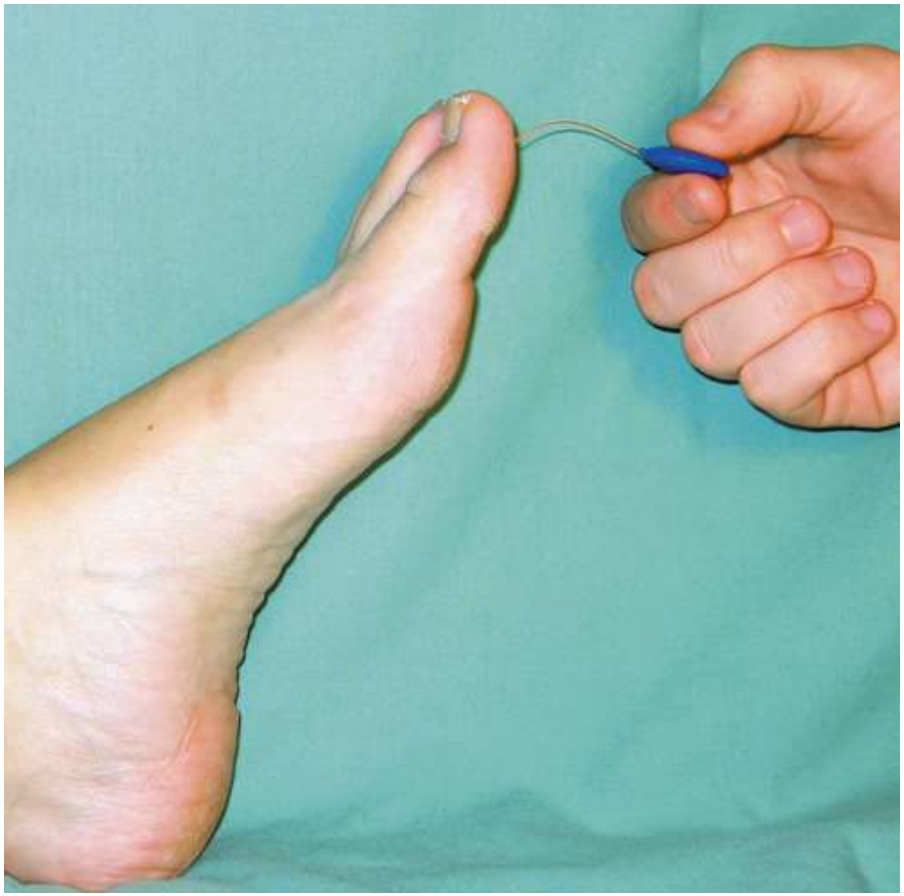
# Optic Neuritis



# Optic Neuritis

- Cause: EMB
- Onset: Usually after > 1 month of EMB, but can occur within days
- Change in visual acuity or red-green color blindness
- Challenging to differentiate DM related eye symptoms from EMB toxicity
- Ophtho consult if severe or persists

# Peripheral Neurotoxicity



# Peripheral Neurotoxicity

- Symptoms: symmetric, length dependent numbness/tingling (no motor symptoms)
- Meds: INH, FQs
- Risk factors indicating B6: DM, alcohol, pregnancy, infants, HIV, malnutrition, renal failure, elderly
- If signs/symptoms of neuropathy, can try increasing B6 dose (but caution that this can rarely actually make neuropathy worse)

# Resources

- ATS/CDC/IDSA 2016 Treatment Guidelines
  - https://www.cdc.gov/tb/publications/guidelines/treatment.htm
- Curry Center Drug Resistant TB Survival Guide
  - https://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
- NTCA document on HPMZ
  - https://www.tbcontrollers.org/resources/hpmz-4-month-regimen/
- WA state TB ECHO
  - https://doh.wa.gov/you-and-your-family/illness-and-disease-z/tuberculosis-tb/training-and-education/tb-echo
- Curry Center Warmline
  - https://www.currytbcenter.ucsf.edu/consultation

# Questions?