Novel Four Month Regimen for Drug Susceptible TB - Webcast

Lisa Armitige, MD, PhD

April 24, 2025

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

Novel Four Month Regimen for Drug Susceptible TB

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DSHS Webinar
April 24, 2025

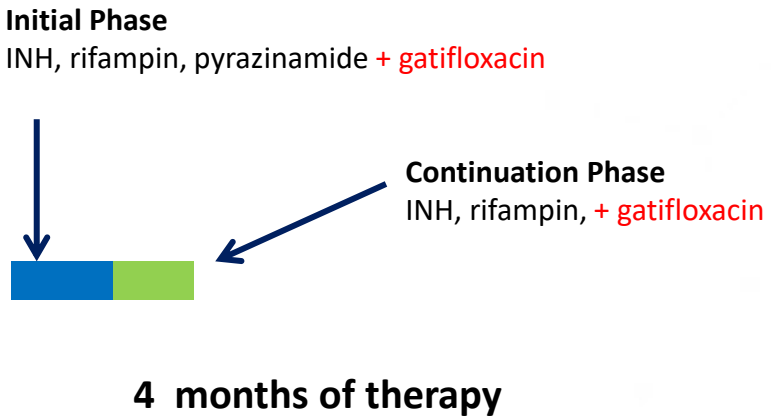
History of Treatment Shortening Regimens

OFLOTUB study

ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*



- Non-inferiority, randomized, open-label, controlled trial
- 1836 patients, 18-65 y/o, five Sub-Saharan African countries
- Avg. BMI 17.5, 27% women
- RIP + gatifloxacin (2 months), RI + gatifloxacin (2 months) vs. 6 month standard treatment
- DOT daily x 2 months, then self-administered with pill counts

N Engl J Med 2014;371:1588-1598

OFLOTUB study

Table 3. Percentages of Favorable and Unfavorable Outcomes in the Primary Efficacy Analysis and of Outcomes That Could Not Be Assessed in the Modified Intention-to-Treat Population.

Variable	Experimental Group	Control Group
	no. (%)	
Favorable outcome*	548 (79.0)	548 (82.8)
Unfavorable outcome*	146 (21.0)	114 (17.2)
By end of treatment	45 (6.5)	67 (10.1)
Study dropout	19 (2.7)	33 (5.0)†
Withdrawal of consent	8 (1.2)	8 (1.2)
Adverse event other than death	1 (0.1)	1 (0.2)
Death	5 (0.7)	9 (1.4)‡
Treatment failure	12 (1.7)	16 (2.4)
After end of treatment: recurrence of tuberculosis	* 101 (14.6)	* 47 (7.1)
Two positive cultures	86 (12.4)	33 (5.0)
One positive culture	12 (1.7)	9 (1.4)
Culture-negative or unknown status§	3 (0.4)	5 (0.8)

REMoxTB study

The NEW ENGLAND JOURNAL of MEDICINE

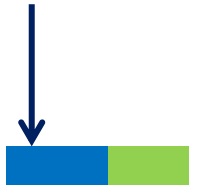
ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371 NO. 17

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

Initial Phase
INH, rifampin, pyrazinamide, moxifloxacin
moxifloxacin, rifampin, pyrazinamide, ethambutol

Continuation Phase
Same as Initial phase +
2 more months of placebo



4 months of therapy

- Randomized, double-blind, placebo-controlled, phase 3 trial
- 1931 patients, ≥18 y/o, Africa/China/India/Thailand/Malaysia/Mexico
- Moxifloxacin replacing either INH or ethambutol

REMoxTB study

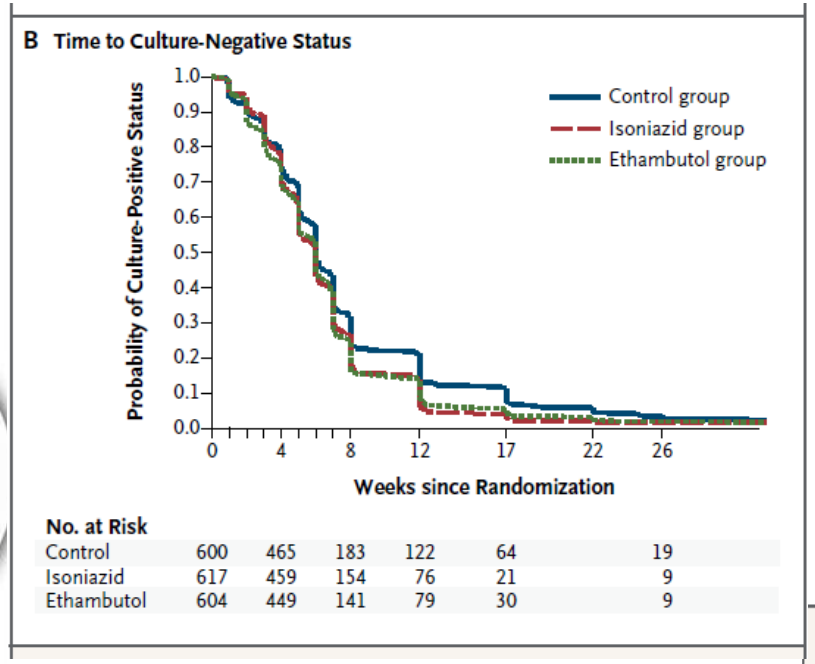


Table 2. Primary Efficacy Analysis in Per-Protocol and Modified Intention-to-Treat Populations.*

Variable	Per-Protocol Analysis				Modified Intention-to-Treat Analysis			
	Control Group (N=510)	Isoniazid Group (N=514)	Ethambutol Group (N=524)	All Patients (N=1548)	Control Group (N=555)	Isoniazid Group (N=568)	Ethambutol Group (N=551)	All Patients (N=1674)
Favorable outcome — no. (%)								
Patients with outcome	467 (92)	436 (85)	419 (80)	1322 (85)	468 (84)	436 (77)	419 (76)	1323 (79)
Follow-up								
Relapse after culture-negative status	12 (2)	46 (9)	64 (12)	122 (8)	13 (2)	46 (8)	64 (12)	123 (7)

RIFAQUIN

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Hatherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Mungofa, M.P.H., Nasir A. Shah, M.B., B.S., Simukai Zizhou, M.B., Ch.B., Lloyd Magweta, M.B., Ch.B., James Shepherd, Ph.D., Sambayawo Nyirenda, M.D., Janneke H. van Dijk, Ph.D., Heather E. Clouting, M.Sc., David Coleman, M.Sc., Anna L.E. Bateson, Ph.D., Timothy D. McHugh, Ph.D., Philip D. Butcher, Ph.D., and Denny A. Mitchison, F.R.C.P., for the RIFAQUIN Trial Team*

Initial Phase
moxifloxacin, rifampin, pyrazinamide, ethambutol

Continuation Phase
Moxi + 900 mg rifapentine BIW (4 months)
Moxi + 1200 mg rifapentine weekly (6 months)

4 Or 6 months of therapy

- Randomized, controlled trial
- 827 patients, ≥18 y/o, four African countries
- Initial phase observed health facility, standard daily dosing supervised by a relative or other person

N Engl J Med 2014;371:1599-160

RIFAQUIN

Table 2. Primary Outcome Classification According to Treatment Group for the Per-Protocol and Modified Intention-to-Treat Analyses.*

Status and Outcome	Control Regimen	4-Month Regimen	6-Month Regimen	Total
Per-protocol analysis — no.	163	165	186	514
Favorable — no. (%)	155 (95.1)	135 (81.8)	180 (96.8)	470 (91.4)
Unfavorable				
Failure (culture confirmed) — no.	2	2	0	4
Death during treatment — no.	1	0	1	2
Relapse (culture confirmed) — no.	4	19	4	27
Relapse (limited bacteriology) — no.	1	7	1	9
Culture positive when last seen — no.	0	2	0	2
Total — no. (%)	8 (4.9)	30 (18.2)	6 (3.2)	44 (8.6)
Modified intention-to-treat analysis — no.	188	193	212	593
Favorable — no. (%)	161 (85.6)	141 (73.1)	183 (86.3)	485 (81.8)
Unfavorable				
During treatment — no.				
Failure (culture confirmed)	2	2	0	4
Death	1	0	1	2
Change in treatment due to adverse event	1	2	2	5
Lost to follow-up	5	6	8	19
Inadequate treatment	2	1	3	6
Other treatment change†	10	11	10	31
After treatment — no.				
Relapse				
Culture confirmation	4	19	4	27
Limited bacteriologic confirmation‡	2	8	1	11
Death due to tuberculosis	0	1	0	1
Culture positive when last seen	0	2	0	2
Total — no. (%)	27 (14.4)	52 (26.9)	29 (13.7)	108 (18.2)

Treatment shortening regimen – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

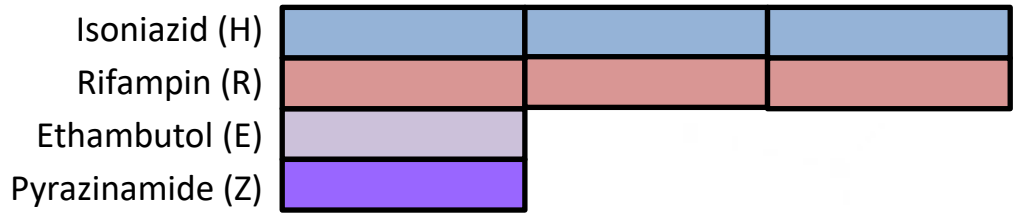
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, 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

2234 participants (194 PLHIV, 1703 with cavity on CXR)
Randomized 1:1:1 to 3 arms
Noninferiority study

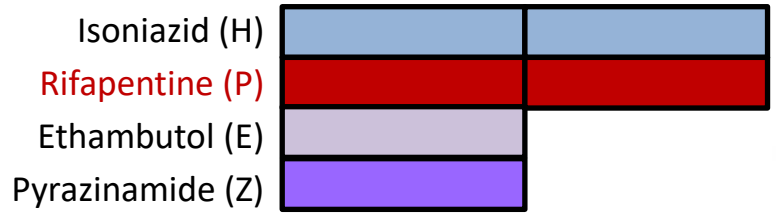
N Engl J Med 2021;384:1705-18.

Study 31/A5349

Control
(2HRZE/4HR)

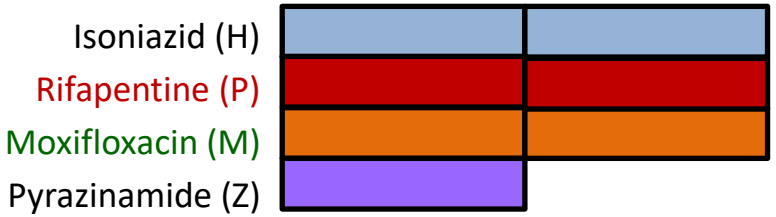


RPT
(2HPZE/2HP)



Inferior to 6 month regimen

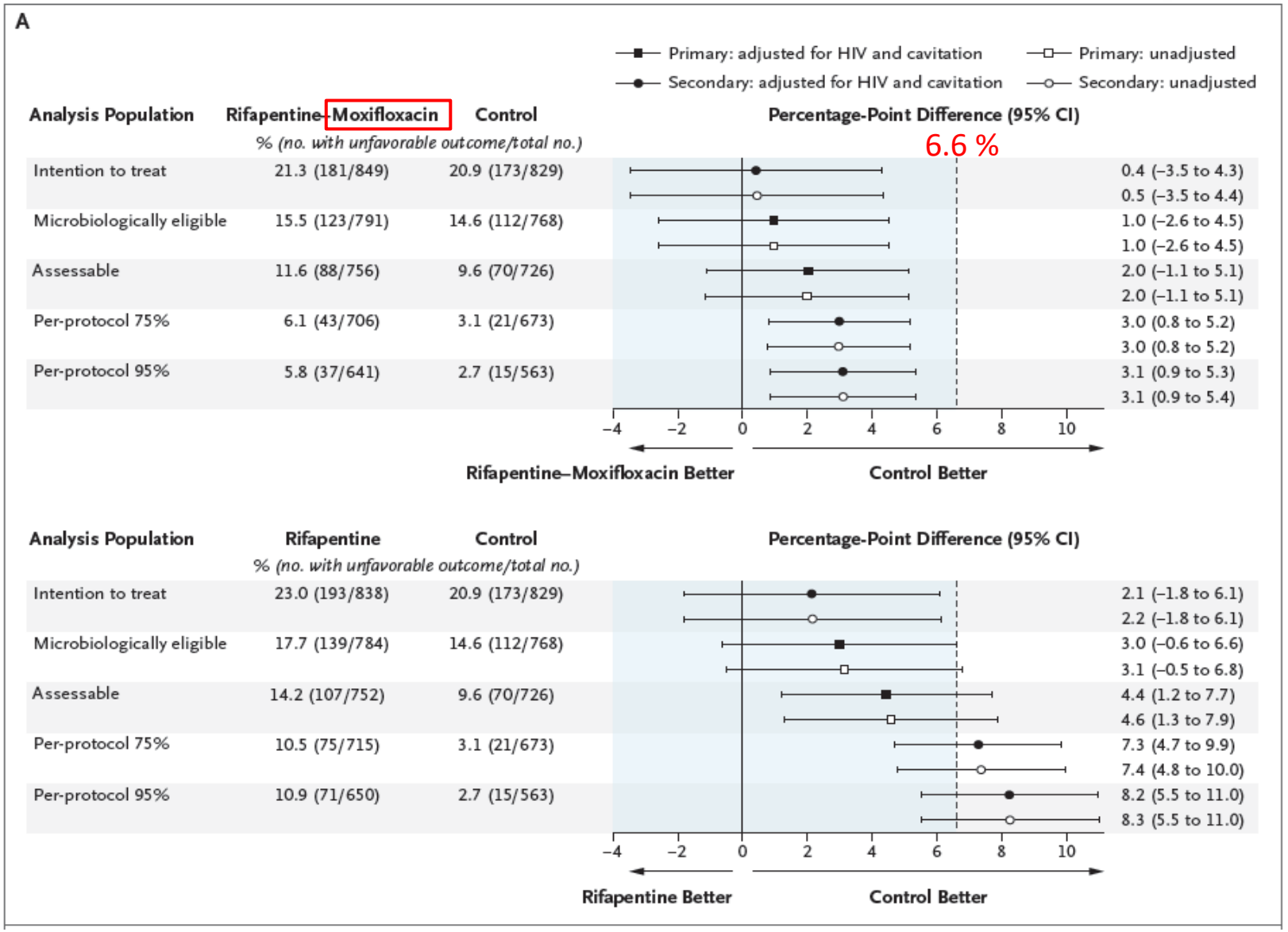
RPT/Moxi
(2HPZM/4HPM)



Notes:

- HRZE dosed at standard doses
- Dosed daily, 7 days/week, observed 5 days/week
- Rifapentine 1200 mg (8 tablets)
- Moxifloxacin 400 mg

Study 31 - Results



N Engl J Med 2021;384:1705-18

Completion

- Completion is based on the total number of doses taken
- Intensive Phase - 56 doses (8 weeks)
  - Must be taken within 70 days
- Continuation Phase – 63 doses (9 weeks)
  - Must be completed within 84 days
- Total of 119 doses taken (17 weeks)
  - Must be completed within 22 weeks

Points to Consider

- Patients want shorter regimens….that are safe and effective

- Smear conversion by 8 weeks:
  - standard regimen 63.4%
  - RPT/moxi arm 78.5%

- Study compared 4 months of RPT/moxi regimen to *6 months* of standard therapy

What does CDC say?

- CDC recommends the 4-month RPT-MOX regimen for treating patients
  - aged ≥12 years
  - with body weight ≥40 kg (88 lb.)
  - with pulmonary TB
  - caused by organisms that are not known or suspected to be drug-resistant
  - and who have no contraindications to this regimen

Monitoring

INH Toxicity

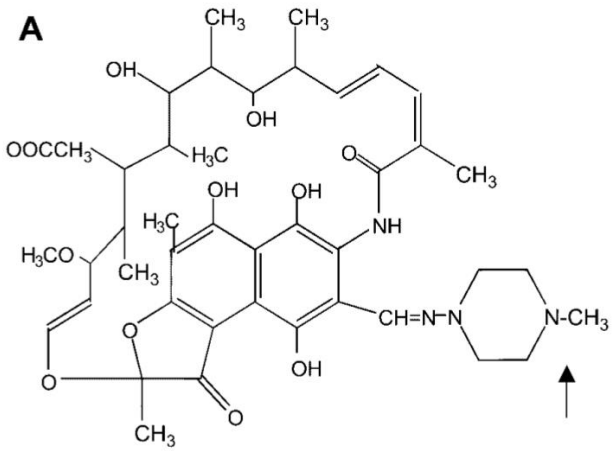
- **Transaminitis**
- **Peripheral neuropathy**
- Central Nervous System Effects: irritability, seizures, dysphoria, inability to concentrate
- Lupus-like syndrome: 20% develop antinuclear antibodies (1), < 1% develop clinical lupus erythematosus
- Hypersensitivity Reactions: fever, rash
- GI reactions (nausea, anorexia, abdominal pain)
- Drug Interactions: levodopa, phenytoin, valproic acid, carbamazepine

(1) Ann Intern Med. 1978 May;88(5):650-2.

Rifapentine

- Long acting rifamycin is highly protein bound
- Adverse effects similar to rifampin
- Resistance: *rpoB*

(1) IDSA 2016 guideline



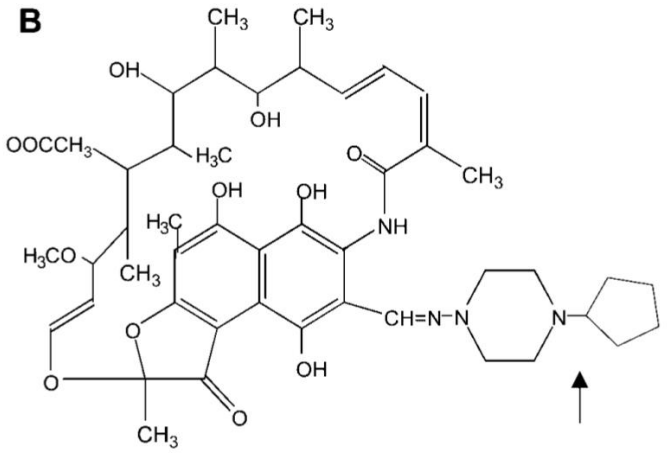


Table 1. Comparing features of rifampin versus rifapentine.

	Rifampin	Rifapentine
MIC	0.125–0.25 µg/mL	0.01–0.06 µg/mL
Half-life	2 h	15 h
Protein binding	80–85%	97–99%
Food requirement	No	Yes
Kinetic	Nonlinear (Michaelis–Menten)	Nonlinear (saturable absorption)
Hepatic enzyme induction	3-fold	4.5-fold
Flat vs. mg/kg dosing	mg/kg	Flat
Cavitary penetration	Good	Poor
Access	Global	Limited
Efficacy	Comparative efficacy at high doses is to be determined	

MIC: Minimum inhibitory concentration.

Expert Rev Clin Pharmacol. 2017 Oct;10(10):1027-1036.

Rifampin (Rifapentine) Toxicity

- **Well tolerated medication: Only 1.9% have to switch from rifampin**
- **Orange discoloration of body fluids**
- **Drug interactions** due to induction of hepatic microsomal enzymes (CYP 450)

- Cutaneous Reactions: 6%, generally self- limited

  Pruritus/flushing (usually 2-3 hours after the dose)
- Gastrointestinal symptoms: nausea, anorexia, abdominal pain
- Hepatotoxicity: nearly 0% as monotherapy, 2-3% with INH, **cholestatic**
- Hematological: Leukopenia, thrombocytopenia

Pyrazinamide (PZA) Toxicity

- **Hepatotoxicity**: Less at 25 mg/kg than 50 mg/kg
- **Gastrointestinal symptoms**: nausea and vomiting mild at standard doses.
- Non-gouty polyarthralgia: Up to 40% of patients: not an indication to stop therapy.
- **Asymptomatic hyperuricemia**: Expected (blocking excretion)
- Acute gouty arthritis: Unusual except in patients with pre-existing gout.
- Rash/dermatitis: usually self limited

Kucers' The Use of Antibiotics 7th

Fluoroquinolone Toxicity

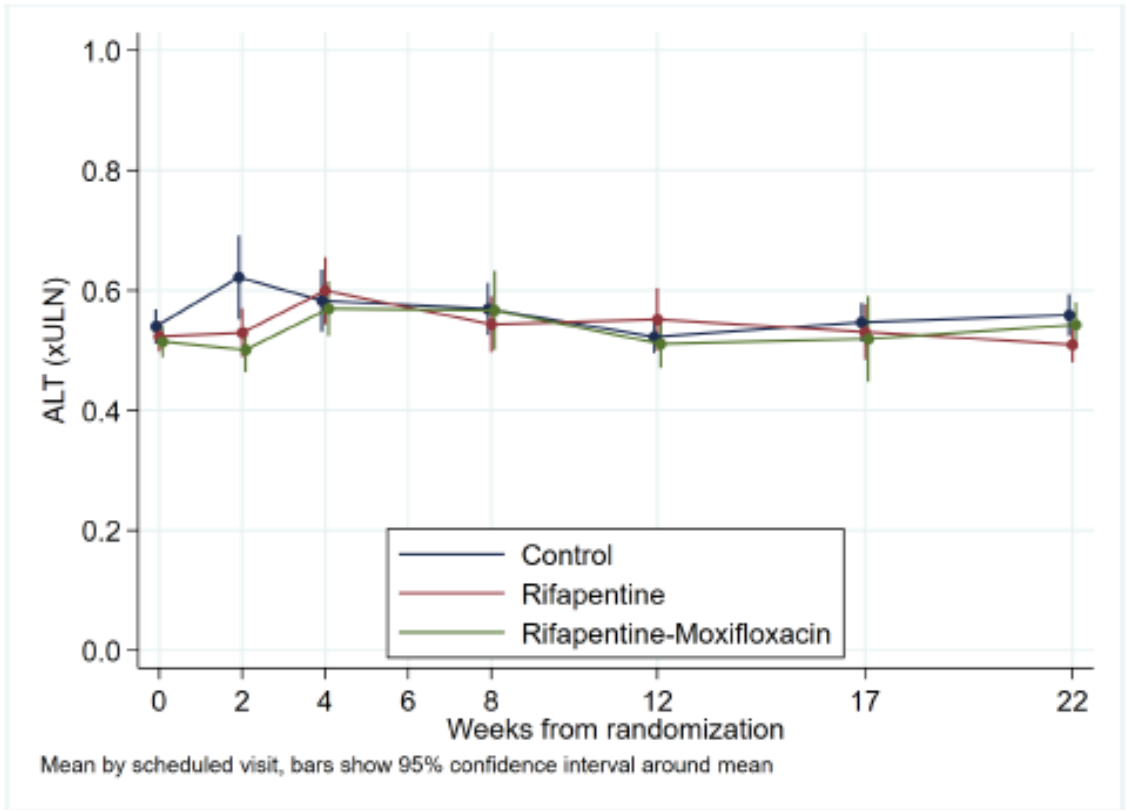
- **Gastrointestinal disturbance:** nausea/bloating 0.5-2%
- **QTc Prolongation**
  - MFX: 6.4 - 14.9 ms at Cmax
  - LFX: 6ms
- **Tendinopathy**
- LFX: higher risk of **tendinopathy** and **tendon rupture**
- **CNS toxicity**
- Psychiatric disturbance/lower seizure threshold

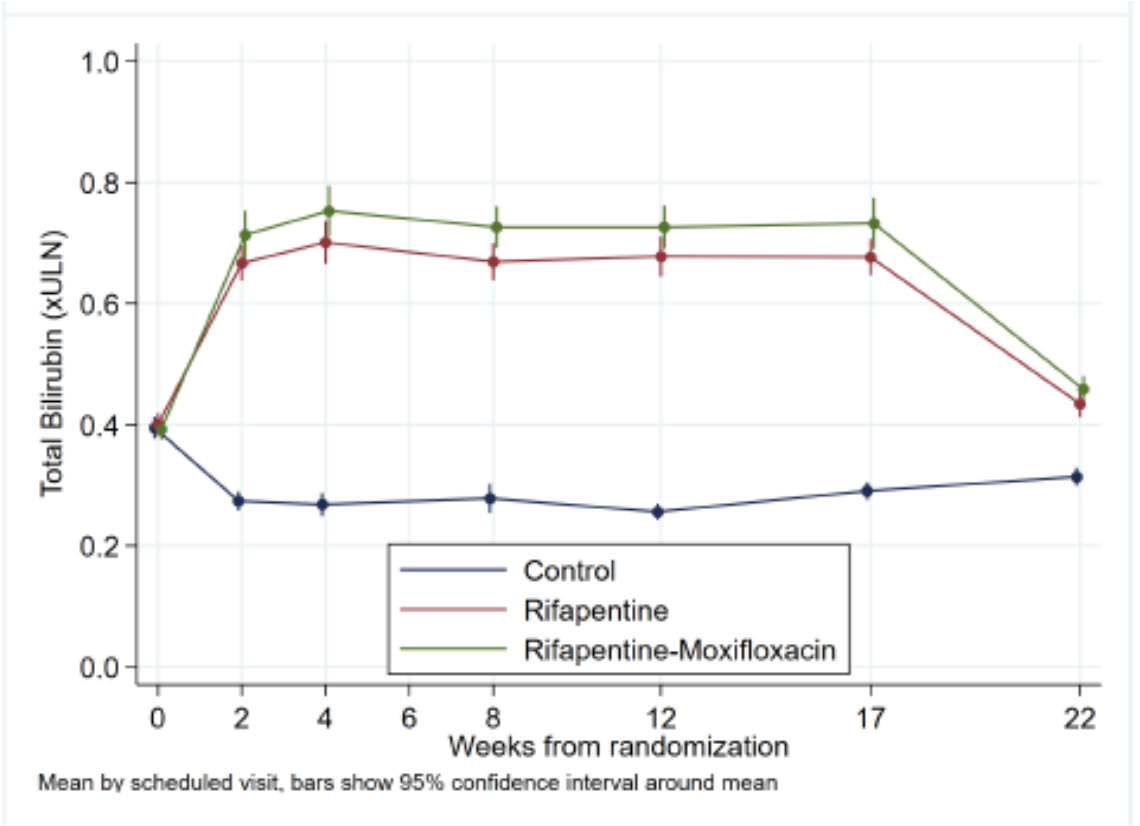
Table 3. Safety and Premature Discontinuation of Assigned Regimen.*

Variable	Control (N=825)	Rifapentine–Moxifloxacin (N=846)	Rifapentine (N=835)	Total (N=2506)
Primary safety outcome				
Grade 3 or higher adverse event — no. (%)	159 (19.3)	159 (18.8)	119 (14.3)	437 (17.4)
Percentage-point difference from control (95% CI)†	NA	−0.6 (−4.3 to 3.2)	−5.1 (−8.7 to −1.5)	NA
Secondary safety outcome				
Treatment-related grade 3 or higher adverse event — no. (%)	81 (9.8)	109 (12.9)	64 (7.7)	254 (10.1)
Percentage-point difference from control (95% CI)†	NA	3.0 (−0.0 to 6.1)	−2.2 (−4.9 to 0.6)	NA
Other safety outcomes				
Any serious adverse event — no. (%)	56 (6.8)	37 (4.4)	39 (4.7)	132 (5.3)
Death — no. (%)‡	7 (0.8)	3 (0.4)	4 (0.5)	14 (0.6)
Any adverse event resulting in discontinuation of assigned treatment — no. (%)§	7 (0.8)	16 (1.9)	11 (1.3)	34 (1.4)
Any grade 3 or higher adverse event within 28 weeks after randomization	159 (19.3)	194 (22.9)	138 (16.5)	491 (19.6)
ALT or AST level ≥5×ULN — no. (%)¶	24 (2.9)	16 (1.9)	13 (1.6)	53 (2.1)
ALT or AST level ≥10×ULN — no. (%)	9 (1.1)	4 (0.5)	5 (0.6)	18 (0.7)
Serum total bilirubin level ≥3×ULN — no. (%)‖	8 (1.0)	28 (3.3)	20 (2.4)	56 (2.2)
Hy's law criteria of ALT or AST level ≥3×ULN plus serum total bilirubin level ≥2×ULN — no. (%)	7 (0.8)	10 (1.2)	8 (1.0)	25 (1.0)
Premature discontinuation of assigned regimen in the microbiologically eligible population				
Discontinuation of assigned regimen for any reason — no./total no. (%)	61/768 (7.9)	55/791 (7.0)	37/784 (4.7)	153/2343 (6.5)
Percentage-point difference from control (95% CI)†	NA	−1.0 (−3.6 to 1.6)	−3.3 (−5.7 to −0.9)	NA

ALT and TBili - Study 31

Figure S9. Graph of mean values over time for blood alanine aminotransferase (top) and blood total bilirubin (bottom) among participants in the safety analysis population





Groups That May Not Benefit

- Patients< 12 years old and ≥75 years old
- Pregnant women – no studies
- Patients with severe liver disease – Not likely to tolerate INH and PZA
- Patients with severe renal disease – No guidance on renal dosing

Groups That May Not Benefit

- Patients with multiple medication interactions – Rifapentine works like rifampin regarding drug interactions
- The study specifically excluded patients with central nervous system (CNS), bone, miliary, and pericardial TB. Patients with extensive disease, even pulmonary, that would require 9 or more months of standard treatment – Not for bone, CNS, miliary or pericardial disease
- Tiny patients (< 88 lb.) – must weigh at least 40 kg
- Patients with long QTc syndrome – moxifloxacin can prolong QTc

Potential Challenges

Potential Challenges

- Pill burden
  - 1 INH, 8 rifapentine, 1 moxifloxacin, 1 pyridoxine (everybody gets these)
    + PZA for weight
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
  - Substitutions?
    - There is no guidance on substituting any of the drugs
  - EOT and they need more treatment?
    - There is no real guidance on how long to extend treatment
- Drug shortages! – We think we have this worked out….

Pill Burden

- 1 INH, 8 rifapentine, 1 moxifloxacin, 1 pyridoxine (everybody gets these) + PZA for weight

What is the medication dosage of the HPMZ regimen?

Medication	Body weight	Dose per day
Isoniazid (INH, H)	> 40 kg (88 pounds)	300 mg
Rifapentine (RPT, P)	> 40 kg (88 pounds)	1200 mg
Moxifloxacin (MOX, M)	> 40 kg (88 pounds)	400 mg
Pyrazinamide (PZA, Z)	40–<55 kg (88–121 pounds)	1000 mg
	>55–75 kg (121–165 pounds)	1500 mg
	> 75 kg (> 165 pounds)	2000 mg

Pill Burden

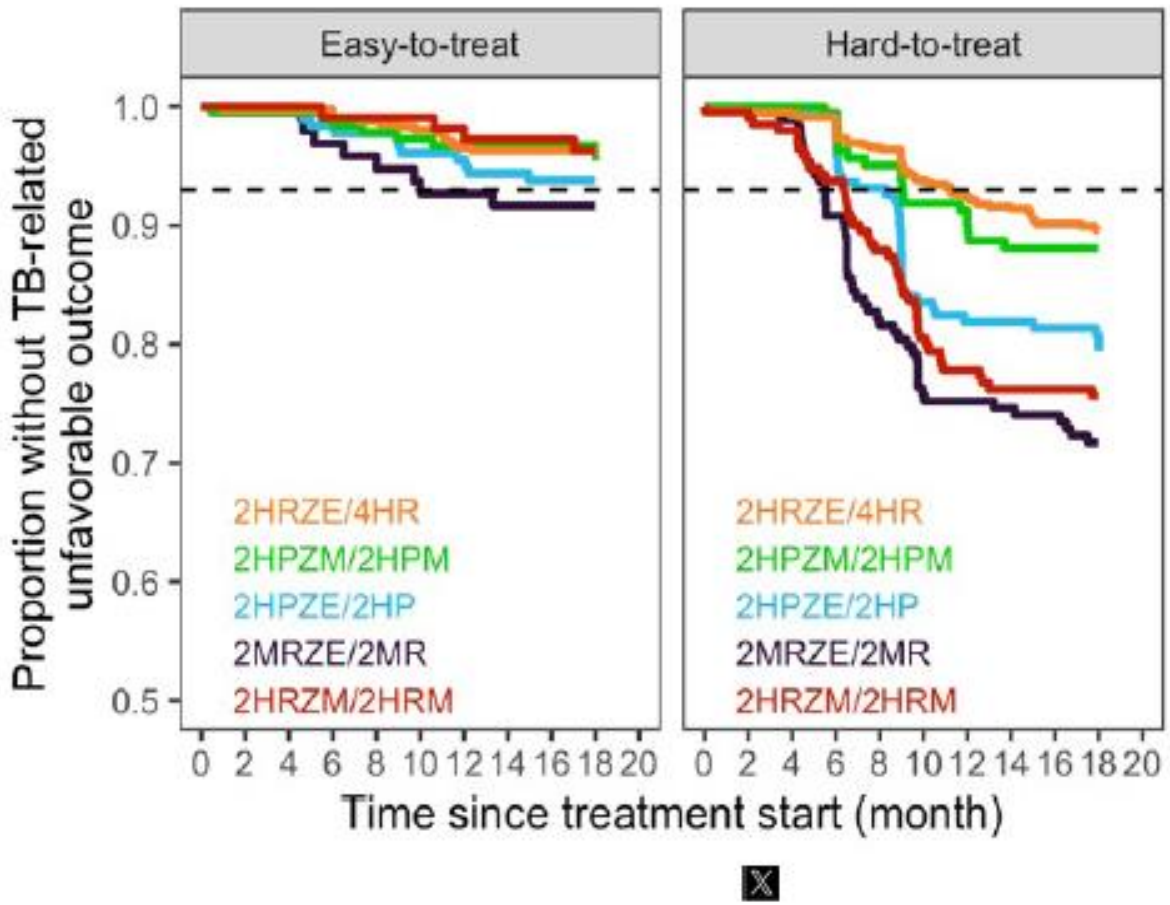
	Standard Regimen (HRZE) >75Kg	Short course regimen (HPMZ) >75Kg
Intensive Phase	8 weeks  Isoniazid Rifampin Pyrazinamide Ethambutol Vitamin B6	8 weeks  Isoniazid Rifapentine Moxifloxacin Pyrazinamide Vitamin B6
Continuation Phase	16-28 weeks  Isoniazid Rifampin Vitamin B6	9 weeks  Isoniazid Rifapentine Moxifloxacin Vitamin B6

Photos courtesy of George Lee, RN

What if……?

- What if the patient was started on RIPE, can you switch to HPMZ?
  - If the patient has been on RIPE for an extended period and is tolerating the regimen, do you really want to switch?
  - Does the patient want to switch?
  - You cannot give ‘credit for prior doses’ from another regimen. You need to do the entire 17 weeks of HPMZ regardless of prior treatment
- The cultures don’t grow
  - Continue for the full 4 months of HPMZ if the patient is responding to treatment.
  - If the patient is not responding to treatment, stop therapy and reassess

LESSONS FROM THE DS PHASE 3 TRIALS



Control

Successful 4-month regimen

Failed

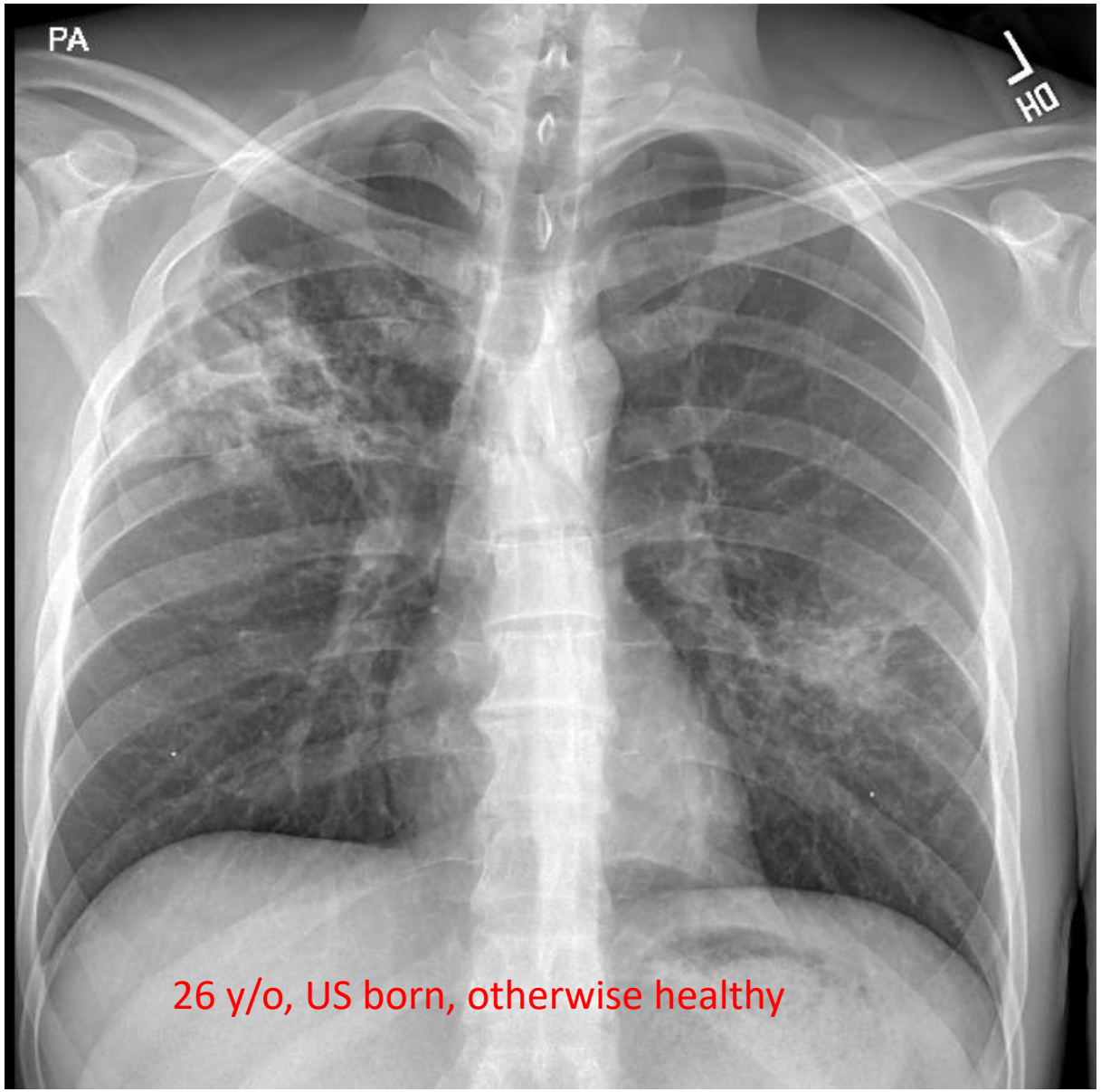
Failed

Failed

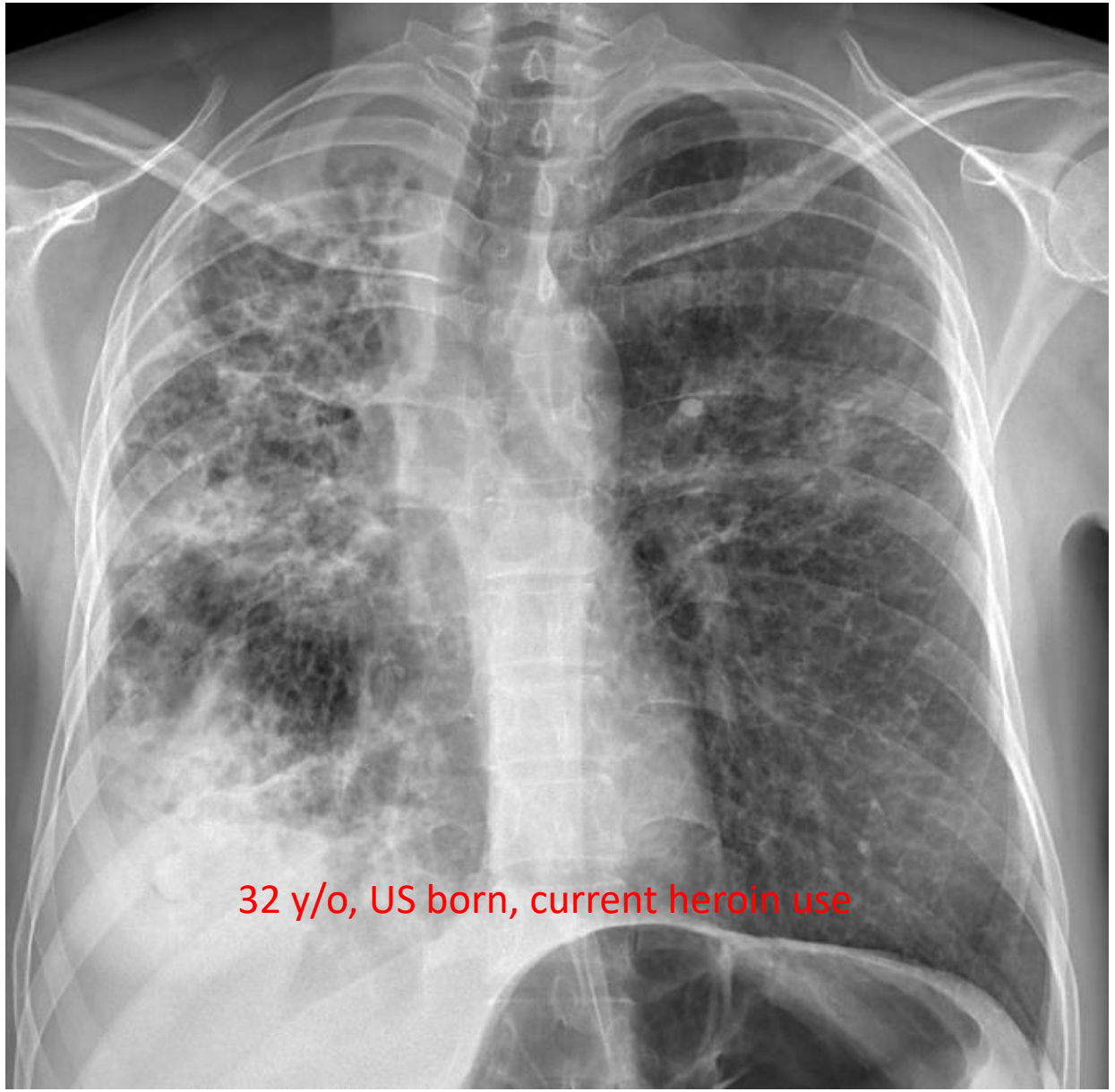
Phase 3 clinical trials failed because of inadequate response
In hard-to-treat patients

(Imperial et al. 2018)

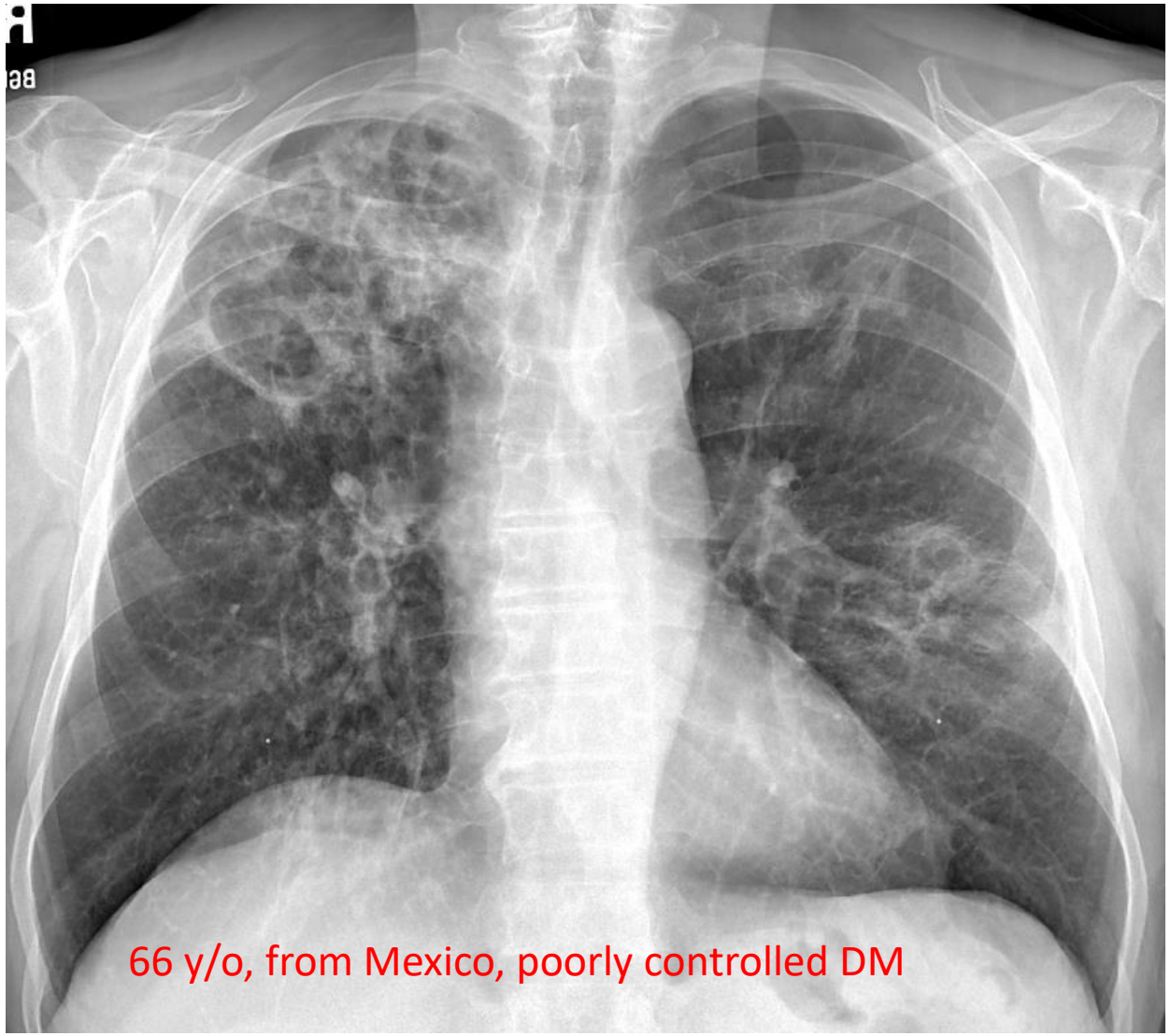
From Barbara Seaworth, MD



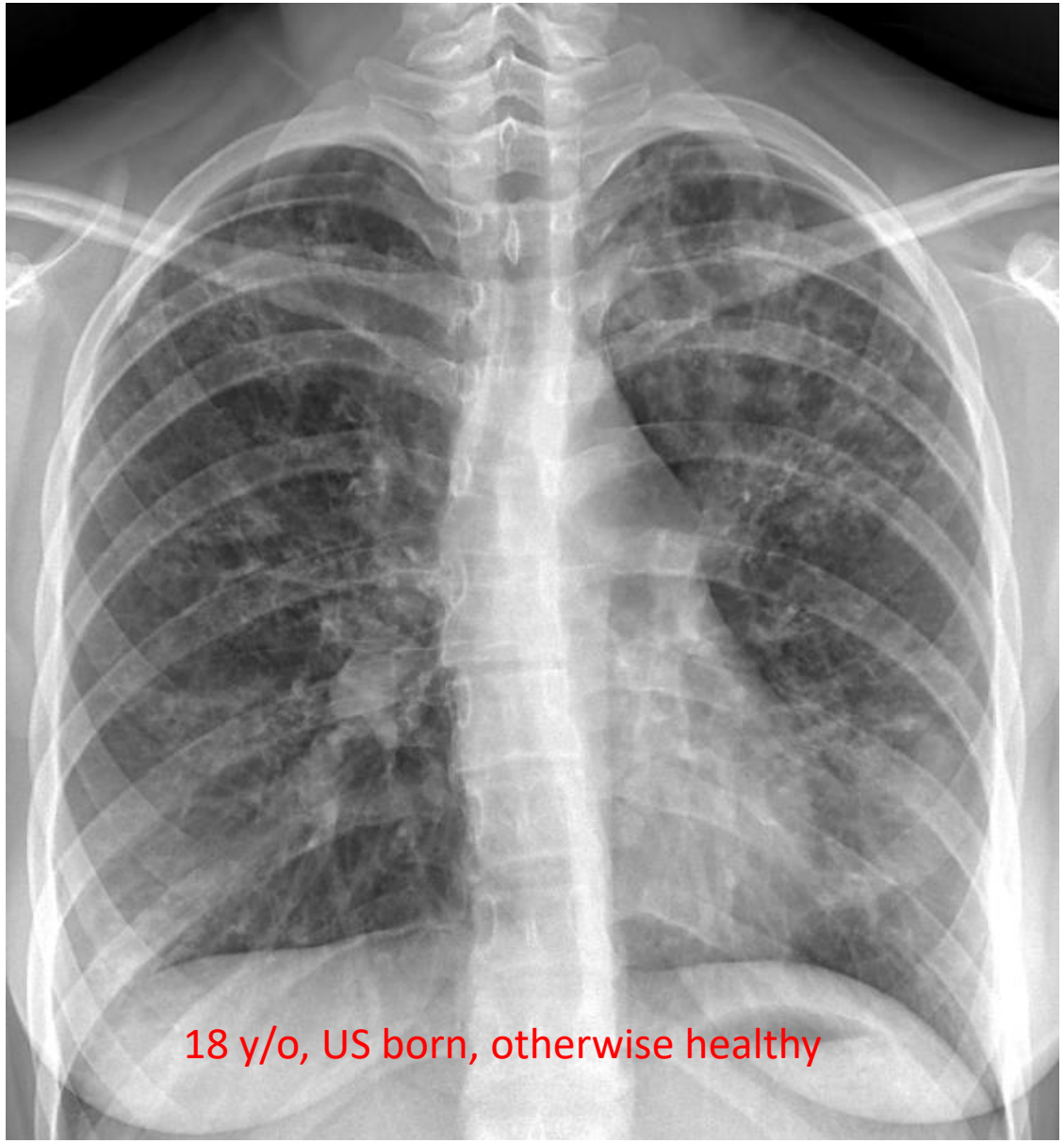
26 y/o, US born, otherwise healthy



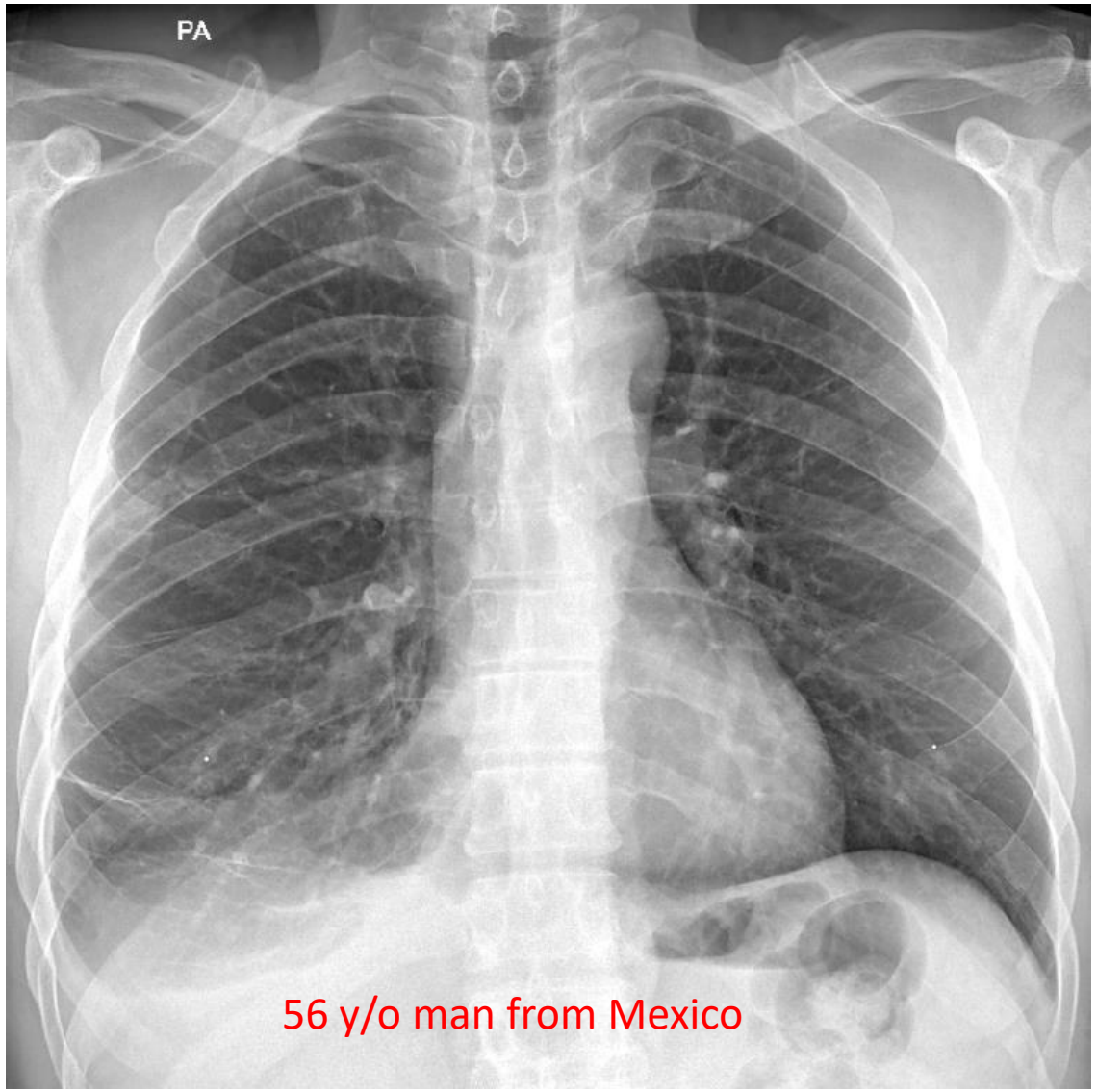
32 y/o, US born, current heroin use



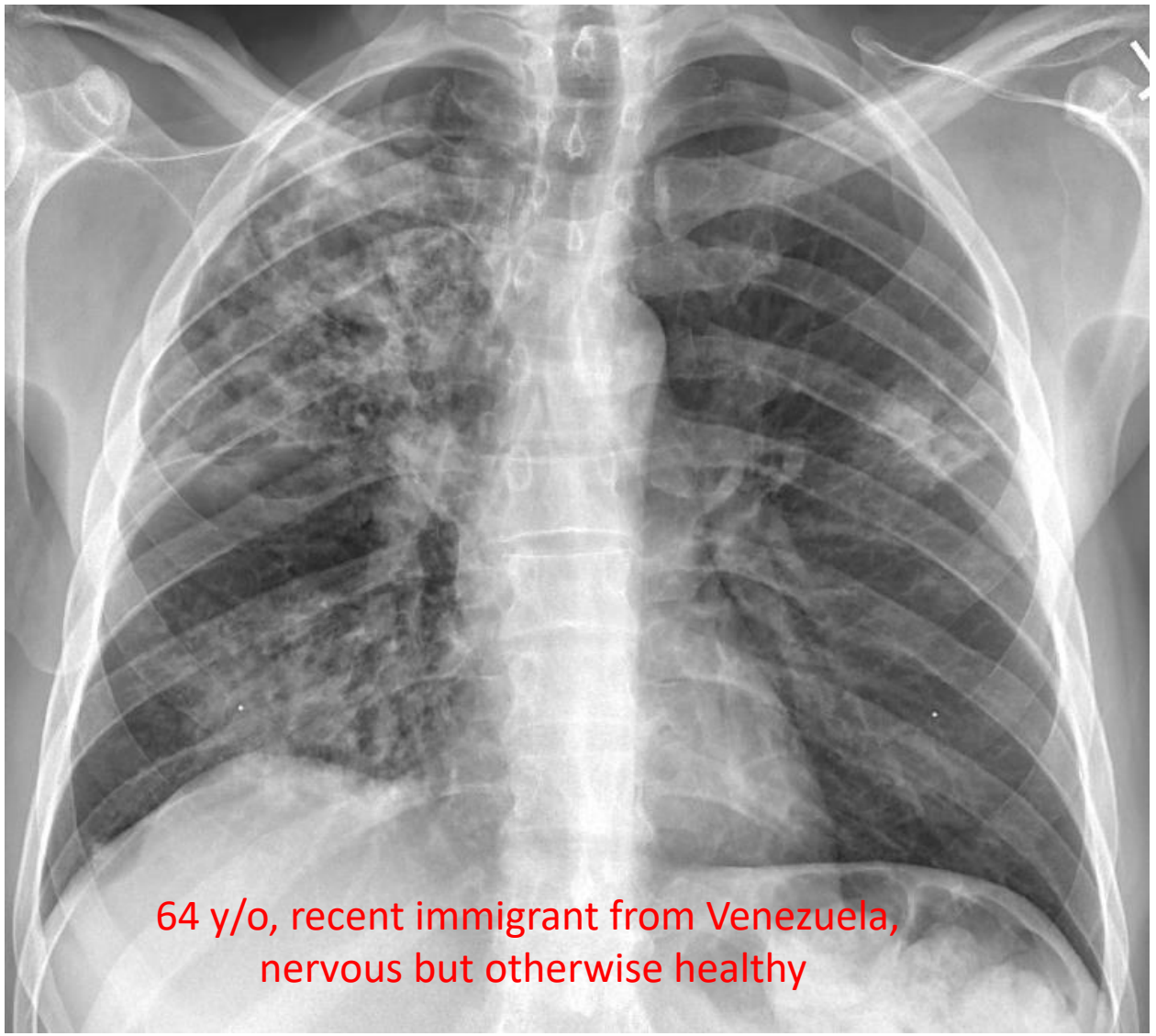
66 y/o, from Mexico, poorly controlled DM



18 y/o, US born, otherwise healthy



56 y/o man from Mexico



64 y/o, recent immigrant from Venezuela,
nervous but otherwise healthy

As we roll out ‘newer, better’,
we must remember:

(As Dr. Seaworth points out)

One size does not fit all!

Questions?

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