Treatment of Tuberculosis

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Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature
  - 6 mo (26 wk) is the MINIMUM duration of Rx
  - 6 mo regimens require rifampin throughout and PZA for the first 2 months
  - Intermittent regimens (2-3x/wk):
    - Not as effective as daily dosing
    - GIVEN by DOT ONLY
    - Drug susceptible isolate
    - Regimen contains INH and rifampin

Antituberculosis Drugs
(ATS/CDC/IDSA)

- First-Line drugs (RIPE)
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol
  - Pyrazinamide

  *Not FDA approved for TB

- Second-Line Drugs
  - Cylcoserine
  - Ethionamide
  - Levofloxacin*
  - Moxifloxacin*
  - PAS
  - Streptomycin
  - Amikacin/Kanamycin
  - Capreomycin
  - Bedaquiline
  - Delamanid
  - Pretomanid

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- First-Line drugs (RIPE)
  - Isoniazid
  - Rifampin
  - Rifapentine
  - Rifabutin*
  - Ethambutol — weaker
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- Second-Line Drugs
  - Cylcoserine — CNS disturbance
  - Ethionamide — GI disturbance-weaker drug
  - Levofloxacin*
  - Moxifloxacin*
  - PAS — GI disturbance-weaker drug
  - Streptomycin
  - Amikacin/Kanamycin — Injections-renal/otic injury
  - Capreomycin
  - Bedaquiline — Expensive, basis of MDR treatment
  - Delamanid — Not FDA Approved
  - Pretomanid — Newly approved

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

- General conclusions from the literature:
  - Without PZA - minimum duration is 9 months
  - Without rifampin - minimum duration is 12 months (up to 18-24 months)
  - Streptomycin and ethambutol (EMB) are approximately equivalent in effect (BUT concern about increasing Streptomycin resistance among foreign born leads to preference of EMB for initial therapy)
  - If the patient does not convert to culture negative or has a cavity after 2 months of appropriate treatment, extend to 9 months

Why Give Ethambutol?

- A four drug regimen is recommended until susceptibility tests are reported
- If treatment is being initiated after drug susceptibility tests are known and the organisms are susceptible, ethambutol is not necessary
- Ethambutol can be stopped as soon as the lab reports an isolate susceptible to INH & rifampin.

ATS recommendations for treatment of tuberculosis

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	*
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	*
							Lesser

Monitoring patients on Treatment for TB

- Pyridoxine (Vitamin B6) for patients taking INH who have:
  - HIV, diabetes, poor diets, malnutrition, are pregnant
- Monthly visits for symptom and toxicity screens
- Monthly labs (CBC, CMP) for at-risk patients
  - Comorbid conditions (HIV, diabetes)
  - Pregnant
  - Having toxicity due to medications

Therapy for TB Disease in Children

- Start 4-drug therapy (a change from 2006 Red Book)
  - INH, rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB); INH/RIF are the backbone of therapy
- Use PZA only during 1st 2 months for susceptible TB
- Stop EMB once culture results known, if have pan-susceptible TB
  - This is your insurance in case you have drug-resistant TB
- Anticipate minimum 6 month therapy, may need to extend it to longer periods, especially for extensive, CNS or bone disease
- Can dose BIW or TIW after first 2 weeks of daily dosing
- ***Always*** administered by directly observed therapy (DOT)

2021 Red Book

Monitoring Children on TB Treatment

- Routine vitamin B_6 not necessary except breast-feeding, pregnant adolescents, poor diet
  - Vitamin B_6 doses 1-2 mg/kg
- Risk of drug toxicity very low
- Monitor clinical signs
  - regular clinical visits (4-6 wks)
  - patient education at every visit
  - Weigh at least monthly and increase dose as needed
- Routine blood work not necessary unless
  - symptoms
  - risk factors for toxicity
- Monitor and reinforce adherence

Active TB During Pregnancy

- Diagnosis:
  - If you are suspecting TB in a pregnant woman, shield the abdomen and get a CXR. You could be saving 2 lives
- Treatment:
  - INH, Rifampin, Ethambutol x 9 months
    - Stop ethambutol if susceptible to INH and rifampin
  - PZA is regarded as safe by most countries in world (only US and Australia don't). Discuss the benefits of treatment with the patient and strongly consider adding to the regimen
- Follow carefully for hepatotoxicity
  - During pregnancy
  - Three months postpartum

Aren’t there any new options?

Treatment shortening regimen – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

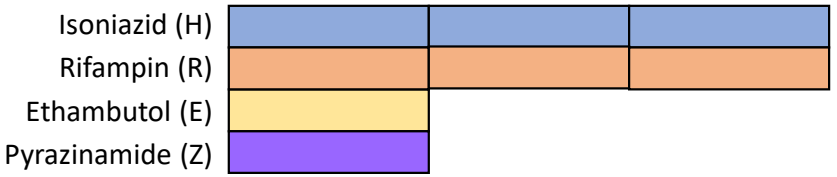
S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott,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

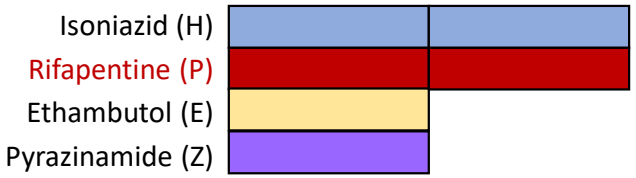
N Engl J Med 2021;384:1705-18.

Study 31/A5349

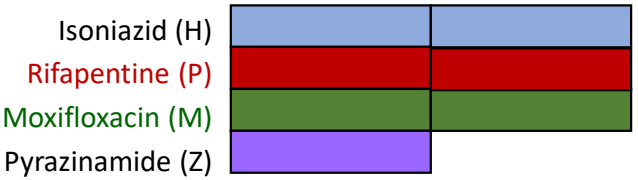
Control
(2HRZE/4HR)



RPT
(2HPZE/2HP)



RPT/MOX
(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

Safety and Efficacy Study 31/A5349

TABLE 1. EFFICACY AND SAFETY OUTCOMES IN S31/A5349

	EFFICACY		SAFETY	
Regimen	**Favorable outcomes**	**Unfavorable outcomes**	**Grade 3 or higher AEs**	**All-cause mortality**
Control (2HRZE/4HR)	90.4% (656/726)	9.6% (70/726)	19.3% (159/825)	0.8% (7/825)
RPT-MOX (2HPZM/2HPM)	88.4% (668/756)	11.6% (88/756)	18.8% (159/846)	0.4% (3/846)

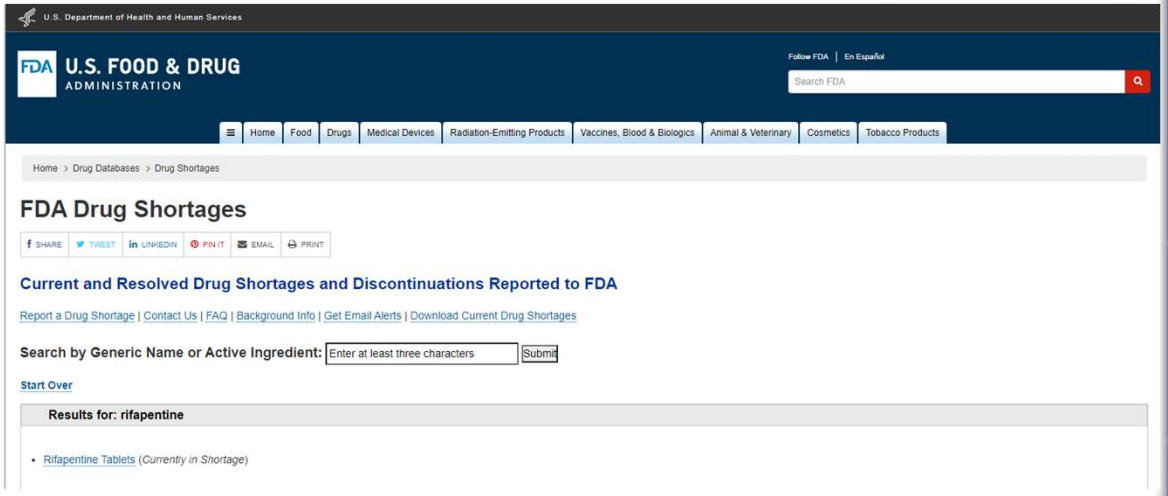
TABLE 2. EFFICACY AND SAFETY OUTCOMES IN S31/A5349 AMONG PLHIV

	EFFICACY				SAFETY			
Regimen	**Favorable outcomes**		**Unfavorable outcomes**		**Grade 3 or higher AEs**		**All-cause mortality**	
	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-	HIV+	HIV-
Control (2HRZE/4HR)	84.7% (50/59)	90.8% (605/666)	15.3% (9/59)	9.2% (61/666)	21.4% (15/70)	19.1% (144/755)	2.9% (2/70)	0.7% (5/755)
RPT-MOX (2HPZM/2HPM)	91.4% (53/58)	88.1% (615/698)	8.6% (5/58)	11.9% (83/698)	13.9% (10/72)	19.3% (149/774)	0% (0/72)	0.4% (3/774)

https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

Challenges

- Pill burden
- Tolerability (versus safety, efficacy)
- Familiarity with the regimen
- Drug shortages



The NEW ENGLAND JOURNAL of MEDICINE

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

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

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

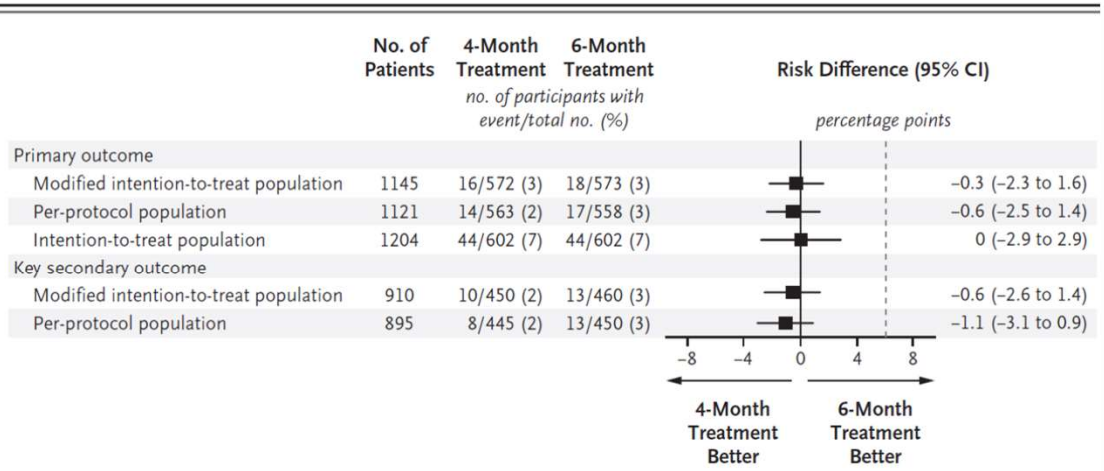


Figure 2. Unadjusted Analysis of the Primary Efficacy and Key Secondary Outcomes in the Trial Populations.

Table 2. Primary Efficacy Analysis (Modified Intention-to-Treat Population).*

Outcome	4-Month Treatment (N=572)	6-Month Treatment (N=573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			percentage points	
Unfavorable status — no. (%)	16 (3)	18 (3)	−0.4 (−2.2 to 1.5)	−0.3 (−2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		

Drug resistant TB

- INH resistance is about 9% and rifampin resistance is about 0.9% in the US
- Never (ever!) stop PZA and EMB until you have susceptibilities (even if the patient has had 2 months of them)!
- INH-resistant TB: rifampin, PZA, EMB + a fluoroquinolone, 6-9 months
- PZA-resistant TB: M. bovis? INH, rifampin for 9 months, ?EMB for 2 months?
- MDR or rifampin resistant disease: call an expert!

So What Happened with the Family?

- The mother's and father's isolates came back INH-resistant!
- INH was stopped in all of the patients and replaced with moxifloxacin (the 17 month old got levofloxacin)
- The 3 year old was taking 3HP for TB infection, he was changed to rifampin (since there was INH resistance)

Questions?

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Or

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