

Table S1. New York City Health Department 4-HPMZ Patient Inclusion and Exclusion Criteria.

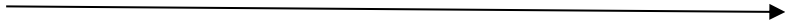
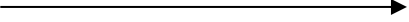
Inclusion Criteria: ▪ Aged ≥ 12 years old. ▪ Body weight ≥ 40 kilograms. ▪ Patients with pulmonary tuberculosis (TB) caused by organisms that are not known or presumed to have drug resistance to INH, RIF, PZA, FQ. ○ Patients can begin this regimen empirically pending susceptibilities. ▪ Extrapulmonary lymphatic and pleural sites only. ▪ Patients with HIV infection who have CD4 > 100 and are receiving efavirenz as part of Antiretroviral Therapy (ART). ▪ <i>rpoB</i> negative. ▪ Patients who are available for at least 4 months of treatment. ▪ Patient agrees to daily Directly Observed Therapy (DOT). ▪ Status of acid-fast bacilli (AFB) smear baseline ○ Smear-negative, culture-positive. ○ Smear-negative with high suspicion of tuberculosis. ○ Smear-positive, culture-positive. ▪ Patient not receiving medications that have clinically relevant drug to drug interactions with the regimen. ▪ No history of prolonged QTc interval or use of QTc-prolonging meds.	Exclusion Criteria: ▪ Body weight < 40 kilograms. ▪ Received >30 days of TB therapy. ▪ Children under 12 years of age. ▪ Patients with history of prolonged QT syndrome or concurrent use of one or more QT-prolonging medications. ▪ Extrapulmonary disease- Bone TB, Central Nervous System (CNS), disseminated TB, Pericardial. ▪ Patients who are presumed to have resistance or are known to have mutations in INH, PZA, RIF or FQ. Specific targets should include but are not limited to the following: ○ INH: the <i>inhA</i> (promoter region), <i>katG</i> and <i>fabG1</i> ○ RIF: RRDR of <i>rpoB</i>, codon 170 (previously 176) in <i>rpoB</i> and codon 491 (previously 572) in <i>rpoB</i> ○ PZA: <i>pncA</i> ○ FQs: <i>gyrA</i> ▪ Patients receiving medications with known clinically relevant drug-drug interactions with RPT, MOX, INH, or PZA; or patients infected with a baseline <i>Mycobacterium tuberculosis</i> isolate known or suspected to be resistant to INH, PZA, rifampin (RIF), or fluoroquinolones. ▪ Women who are pregnant or are lactating mothers.
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Figure S1. New York City Health Department 4-HPMZ Physician Job Aid*.

4-HPMZ Regimen	
INITIAL MEDICAL EVALUATION:	
1. Assess eligibility of the patient:	
INCLUSION CRITERIA ▪ Aged ≥ 12 years old. ▪ Body weight ≥ 40 kilograms. ▪ Patients with pulmonary TB caused by organisms that are not known or presumed to have drug resistance to INH, RIF, PZA, FQ. ○ Patients can begin this regimen empirically pending susceptibilities. ▪ Extrapulmonary lymphatic and pleural sites only. ▪ Patients with HIV infection who have CD4 > 100 and are receiving efavirenz as part of ART. ▪ <i>RpoB</i>-negative.	INCLUSION CRITERIA ▪ Patients who are available for at least 4 months of treatment. ▪ Patient agrees to daily DOT. ▪ Status of AFB smear baseline ○ Smear-negative, culture-positive. ○ Smear-negative with high suspicion of TB. ○ Smear-positive, culture-positive. ▪ Patient not receiving medications that have clinically relevant drug to drug interactions with the regimen. ▪ No history of prolonged QTc interval or use of QTc prolonging meds.
2. Explain the criteria for enrollment and offer 4-HPMZ.	
3. Educate the patient regarding the regimen and possible side effects.	
4. Write orders for:	
○ Baseline CBC, chem screen and hepatitis panel and HCG for women of childbearing age ○ For rifapentine, the first order should be written for 14 days with 1 refill. If patient tolerates the medications, the nurse will provide the patient with the remaining 2 weeks of medication. ○ INH, PZA, and MOX will be prescribed for 1 month.	
5. Document reasons for not prescribing the regimen, including patient refusal or other reasons in the assessment and plan section of the medical record:	
○ Physician medical judgment- indicate justification. ○ No RPT available. ○ Pill burden too large. ○ Patient refused DOT. ○ Patient refused regimen- indicate patient's current regimen. ○ Patient unable to do video DOT due lack of equipment, technology, or inability to do it. ○ Other- explain.	
FOLLOW-UP MEDICAL EVALUATION:	
1. Patient should have monthly visit.	
2. Assess the patient for adverse events.	
3. Ask the patient about new medications they are taking.	

4. Order follow-up CBC and chem-screen panel for patients whose baseline testing is abnormal and for others at risk for liver disease.
5. Re-order INH, RPT, MOX and PZA medication at each visit.

Dosing Recommendations for 4-HPMZ

Medication	Body Weight, kg	Daily Dose
Rifapentine 150 mg tablet 	> 40 kg	1,200 mg = 8 tablets
Moxifloxacin 400 mg tablet 	> 40 kg	400 mg = 1 tablet
Isoniazid 300 mg tablet 	> 40 kg	300 mg = 1 tablet
Pyrazinamide 500 mg tablets 	≥ 40 - 55 kg	1,000 mg = 2 tablets
	≥ 55-75 kg	1,500 mg = 3 tablets
	> 75 kg	2,000 mg = 4 tablets
Medication ^A	Initiation Phase 8 weeks 56 doses	Continuation Phase 9 weeks 63 doses
Rifapentine		
Moxifloxacin		
Isoniazid ^B		
Pyrazinamide		

^A Medications should be administered with food; ^B Pyridoxine (vitamin B6) 25 mg day should be given with isoniazid to all patients.

The pills above illustrate back & front of the medication.

Adapted: Carr, W., Kurbatova, E., Starks, A., Goswami, N., Allen L., Winston, C. (Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022) Morbidity and Mortality Weekly Report 2022; 71 (p. 285-289)

	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 Photos courtesy of George Lee, RN	9 weeks  Isoniazid Rifapentine Moxifloxacin Vitamin B6

*Job Aids were also available for Nurses & Case Managers.

Photo courtesy of George Lee, RN National Tuberculosis Controllers Association.

Adapted; Carr, W., Kurbatova, E., Starks, A., Goswami, N., Allen L., Winston, C. (Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen.

Table S2. Demographic and clinical characteristics of patients who completed or discontinued TB treatment with 4-HPMZ at NYC Health Department TB clinics, April 2022- December 2023.

Variable	Patients completed TB treatment with 4-HPMZ, N = 13 ^A	Patients discontinued TB treatment with 4-HPMZ, N = 23 ^A	p-value ^B
Age (Median [IQR])	32 (28, 58)	37 (28, 66)	0.48
Age Groups			0.17
12-17	1 (7.7%)	1 (4.3%)	
18-44	6 (46%)	12 (52%)	
45-64	5 (38%)	3 (13%)	
65+	1 (7.7%)	7 (30%)	
Sex			0.21
Female	1 (7.7%)	7 (30%)	
Male	12 (92%)	16 (70%)	
Birthplace			0.61
Non-US Born	11 (85%)	21 (91%)	
US Born	2 (15%)	2 (8.7%)	
Site of Disease			0.50
Extrapulmonary	1 (7.7%)	1 (4.3%)	
Pulmonary	10 (77%)	15 (65%)	
Pulmonary and Extrapulmonary	2 (15%)	7 (30%)	
DOT adherence ^C	92 (88, 95)	88 (63, 100)	0.98
Positive sputum smear ^D	10 (83%)	14 (64%)	0.43
Chest X-ray result ^D			0.28
Abnormal cavitary	6 (50%)	5 (23%)	
Abnormal non-cavitary	6 (50%)	15 (68%)	
Normal X-ray	0 (0%)	2 (9.1%)	
Diabetes	3 (23%)	4 (17%)	0.69
Hypertension	4 (31%)	4 (17%)	0.42
Hyperlipidemia	2 (15%)	2 (8.7%)	0.61
Coronary artery disease	1 (7.7%)	1 (4.3%)	>0.9
Other comorbidities ^E	3 (23%)	6 (26%)	>0.9
Other non-TB medications	4 (31%)	11 (48%)	0.32
^A Median (IQR); n (%), ^B Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test; ^C Patients were required to have at least 5 doses of 4-HPMZ with DOT to be included; ^D Patients with pulmonary TB diagnosis, and both extrapulmonary and pulmonary TB diagnosis; ^E Other comorbidities reported by the patients included: gout, gastritis, asthma, anemia, hypercalcemia, hyperparathyroidism, COPD, cerebral vascular accident, emphysema, and allergies to dust.			

Table S3. Patients first reported adverse event during 4-HPMZ treatment at NYC Health Department TB clinics, April 2022-December 2023.

Signs and Symptoms of Adverse Events Reported ^{A,B}	Grade 1 or 2 AEs ^C N = 21	Grade 3 AEs ^C N = 2
Gastro-intestinal (GI) issues	17 (81%)	2 (100%)
Nausea	9 (53%)	0 (0%)
Vomiting	5 (29%)	0 (0%)
Diarrhea	2 (12%)	0 (0%)
Abdominal pain	2 (12%)	2 (100%)
Other GI (e.g., bloating, GERD ^D)	6 (35%)	0 (0%)
Rash	4 (19%)	0 (0%)
Dizziness	3 (14%)	0 (0%)
Loss of appetite	3 (14%)	0 (0%)
Fatigue	2 (10%)	0 (0%)
Other pain (e.g., leg, shoulder)	2 (10%)	0 (0%)
Other signs and symptoms reported ^E	5 (24%)	0 (0%)

^A First AE report by patients (N=23) to the physician; ^B Patients (n=13) reported concomitant signs and symptoms. Multiple signs and symptoms reported on the same day were recorded as one AE report; ^C Grading was done according to the National Cancer Institute Common Terminology Criteria for AE; ^D Gastroesophageal reflux disease; ^E Other signs and symptoms reported included: insomnia, night sweats, weight loss, lesion in eye and skin discoloration.

Table S4. Demographic and clinical characteristics of patients with and without reported adverse events while taking 4-HPMZ at NYC Health Department TB clinics, April 2022-December 2023.

Variable	Patients who reported adverse events N = 23 ^A	Patients who did not report adverse events N = 13 ^A	p-value ^B
Age (Median [IQR])	45 (32, 64)	30 (25, 53)	0.084
Age Groups			0.27
12-17	0 (0%)	2 (15%)	
18-44	11 (48%)	7 (54%)	
45-64	6 (26%)	2 (15%)	
65+	6 (26%)	2 (15%)	
Sex			0.68
Female	6 (26%)	2 (15%)	
Male	17 (74%)	11 (85%)	
Birthplace			0.12
Non-US Born	22 (96%)	10 (77%)	
US Born	1 (4.3%)	3 (23%)	
Site of Disease			0.50
Extrapulmonary	1 (4.3%)	1 (7.7%)	
Pulmonary	15 (65%)	10 (77%)	
Pulmonary and Extrapulmonary	7 (30%)	2 (15%)	
DOT adherence ^C	91 (68, 100)	93 (71, 96)	0.90
Positive sputum smear ^D	16 (73%)	8 (67%)	0.71
Chest X-ray result ^D			0.62
Abnormal cavitory	6 (27%)	5 (42%)	
Abnormal noncavitory	14 (64%)	7 (58%)	
Normal Xray	2 (9.1%)	0 (0%)	
Diabetes	7 (30%)	0 (0%)	0.034
Hypertension	6 (26%)	2 (15%)	0.68
Hyperlipidemia	3 (13%)	1 (7.7%)	>0.9
Coronary artery disease	1 (4.3%)	1 (7.7%)	>0.9
Other comorbidities ^E	6 (26%)	3 (23%)	>0.9
Other non-TB medications	12 (52%)	3 (23%)	0.089
^A Median (IQR); n (%); ^B Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test; ^C Patients were required to have at least 5 doses of 4-HPMZ with DOT to be included; ^D Patients with pulmonary TB diagnosis, and both extrapulmonary and pulmonary TB diagnosis; ^E Other comorbidities reported by the patients included: gout, gastritis, asthma, anemia, hypercalcemia, hyperparathyroidism, COPD, cerebral vascular accident, emphysema, and allergies to dust.			

Table S5. Patients with type of adverse events that led to discontinuation of 4-HPMZ.

Patient who Discontinued 4HPMZ	Last Adverse Event (AE)	Final TB Regimen
1	Rash	INH and EMB
2	Night sweats, flushing, paresthesia	RIF and INH
3	Rash (pruritic)	RIF and INH
4	Gastro-intestinal (GI) issues and rash	RIF and EMB
5	GI issues	RIF and MOX
6	Elevated LFTs and acute cholecystitis	RIF and EMB
7	GI issues, fatigue, dizziness	RIF and INH
8	GI issues, dizziness, rash	RIF and INH
9	Elevated LFTs	RBT and INH
10	Rash and facial swelling ^A	RIF and INH
11	Body pain	RIF and INH
12	Muscle pain	RIF and INH
13	GI issues and muscle pain	RIF and INH
14	GI issues	RIF and INH
15	GI issues	RIF and INH

^A Patient had rapid facial swelling and was the primary reason for discontinuation. Other patients who had concomitant AEs did not have a primary AE for discontinuation.

Abbreviations: Isoniazid (INH), Rifampin (RIF), Ethambutol (EMB), Rifabutin (RBT), Moxifloxacin (MOX).

Table S6. TB regimens prescribed after 4-HPMZ was discontinued due to adverse events.

TB Regimen after 4-HPMZ ^A	Final TB regimen	Completed TB Treatment (N=15)
RIF, INH, PZA, EMB	RIF and INH	4 (27%)
RIF, INH, PZA, EMB	RIF and EMB	1 (7%)
RIF, INH, and PZA	RIF and INH	3 (20%)
RIF, INH, and PZA	RIF and MOX	1 (7%)
RIF, INH, and EMB	RIF and INH	1 (7%)
RIF and INH	RBT and INH	1 (7%)
RIF and INH	RIF and EMB	1 (7%)
RIF and INH	RIF and INH	1 (7%)
RIF and EMB	RIF and INH	1 (7%)
RIF and EMB	INH and EMB ^B	1 (7%)

^A Initial regimen after 4-HPMZ patient was discontinued due to adverse events. Initial regimens may be different than regimens for which patients completed TB treatment; ^B Patient ultimately could not tolerate a rifamycin based regimen.

Abbreviations: Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA), Ethambutol (EMB), Rifabutin (RBT), Moxifloxacin (MOX).