NTCA PROVIDER GUIDANCE

A 4-Month Regimen to Treat Pulmonary Tuberculosis: Isoniazid, Rifapentine, Moxifloxacin, and Pyrazinamide (HPMZ)

What is the 4-month HPMZ Regimen for treatment of drug susceptible TB?

The HPMZ regimen consists of an **8-week intensive phase** of isoniazid (H), rifapentine (P), moxifloxacin (M), and pyrazinamide (Z) given daily, followed by a **9-week continuation phase** of isoniazid, rifapentine, and moxifloxacin given daily. The total duration of therapy is 17-weeks.

What is the medication dosage of the HPMZ regimen?

Medication	Body weight	Dose/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

The entire regimen should be administered once daily with food 7 days per week.

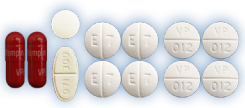
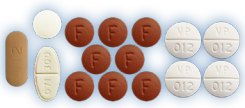
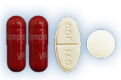
What are the advantages and disadvantages of the HPMZ Regimen?

Potential pros of the 4-month regimen

- A shorter duration of treatment for culture-positive pulmonary TB.
- Facilitates treatment completion in patients with barriers
  - planned geographic relocation, incarceration, or
  - residents in congregate or institutionalized settings
- Avoids potential for ocular toxicity with ethambutol (EMB)
- May reduce time to culture conversion

Potential cons of the 4-month regimen

- Higher pill burden
- Required to be taken with food to optimize drug absorption.
- Avoid drug-drug interactions with comedications (e.g., antacids)
- Potentially higher program cost for HPMZ regimen
- Limited long-term outcome data (12 months post-randomization)
- Potential side effects of fluoroquinolone (e.g., QT prolongation, tendonitis, effects on gut microbiota)
- Lack of data for treating extrapulmonary TB, including CNS disease and osteomyelitis

	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

Treatment interruption:

- The 56 doses of initiation phase should be administered completely within 70 days.
- The 63 doses of the continuation phase should be administered within 84 days.
- If these targets are not met, the patient should be considered to have interrupted therapy and should be managed with clinical judgment and in consultation as described in TB treatment guidelines.

Are there drug-drug interactions?

There are common interactions for isoniazid, rifapentine, and moxifloxacin:

- Isoniazid increases blood levels of phenytoin and disulfiram
- Rifapentine, similar to rifampin, decreases blood levels of oral or implanted hormonal contraceptives, warfarin, sulfonylureas, methadone, suboxone, some anti-hypertensives and steroids.
- Some cardiac medications and certain antiretroviral drugs may have serious drug-drug interactions.
- Moxifloxacin interacts with other medications that are QTc prolonging. Please see additional information on use of moxifloxacin under Programmatic Consideration (Page 2).
- **Please check drug-drug interactions**

Possible adverse events (AEs) with HPMZ

Mild to moderate:

Continue to monitor, discontinue if needed

- Joint pain
- Tendonitis
- LFTs ≥ 3-5X ULN
- Rash
- Fever
- Pruritis
- Nausea
- Vomiting

Moderate to Severe:

Recommend discontinuing treatment

- Hypersensitivity
- Hypotension, mild to profound syncope/fainting
- Dizziness
- Life threatening syndromes (fever, chills HA, dizziness and musculoskeletal pain)
- Thrombocytopenia
- Shortness of breath, wheezing, acute bronchospasm
- Urticarial petechiae, purpura
- Conjunctivitis
- Angioedema and shock
- Chest pain/angina, palpitations, or cardiac arrhythmias
- Elevated liver function tests (LFTs) ≥ 5X ULN

Patient checklist before starting HPMZ

- ✔ Age ≥ 12 years
- ✔ Weight > 40 kg
- ✔ If HIV-positive, CD4>100 cells/mm^3, please see NTCA FAQ for additional HIV treatment recommendations.
- ✔ Negative pregnancy test if of childbearing age
- ✔ Not breastfeeding
- ✔ Baseline laboratory values: serum creatinine < 2.0, potassium ≥ 3.5 meq/L, Hgb ≥ 7.0 g/dL, platelets ≥ 100,000/mm^3, LFTs ≤ 2X upper limit of normal
- ✔ No suspected or documented extrapulmonary TB
- ✔ No history of taking TB drugs within past 6 months
- ✔ Medication review with no drug–drug interactions with HPMZ
- ✔ Rapid molecular detection of drug resistance from initial specimen should be ordered if available
- ✔ Patient can be started on the HPMZ regimen while awaiting drug susceptibility test (DST) results, including for fluoroquinolones

Programmatic Considerations for HPMZ

Case management:

- Ensure drug supply available for full 17-week course
- Discuss pill burden and need for once-daily dosing
- Medications taken 7 days a week and DOT/eDOT at least 5 days a week
- Monthly clinical visits
- Sputum, laboratory, and EKG monitoring when indicated
- Verify reimbursement for HPMZ by program or third party

Moxifloxacin

- Educate about food and drug interactions: Avoid taking dairy products, sucralfate, antacids, multivitamins, iron, aluminum, magnesium, or calcium within 4 hrs. before or 8 hrs. after HPMZ
- Access EKG for patients with cardiac risks per practice standards for long term moxifloxacin administration.
- Review cardiac history: This regimen is contraindicated in patients with active ischemia and/or history of arrhythmias.
- CDC does not recommend use with other medications that prolong QTc; however, some experts may choose to prescribe this regimen in patients with h/o prolonged QTc or patients on other QT-prolonging drugs with careful and appropriate EKG monitoring.

Rifapentine

- Discuss FDA alert regarding nitrosamine with patient

Baseline and follow-up monitoring and evaluation for patients on HPMZ regimen

(**X** = recommended; **O** = optional)

Evaluation Types		Baseline	Intensive Phase (Total 56 doses)								Continuation Phase (Total 63 doses)								
			Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Clinical assessment and evaluation	Symptoms, medication, drug–drug interaction	X				X				X				X					X
	Weight	X				X				X				X					X
	EKG if indicated	O				O				O				O					O
Laboratory testing	CBC, Platelet, LFT, Creatinine, Potassium, Calcium, Magnesium	X				O				O				O					O
	HIV (if positive CD4 count and HIV RNA)	X																	
	Hepatitis B and C Diabetes screen	O																	
	Pregnancy test	X																	
Microbiology (Sputum)	AFB smear and culture	X	O	O	O	X				X				O					O
	Rapid molecular test	X																	
	Phenotypic drug susceptibility test	X								O									
Imaging	Chest radiograph	X								O									O
Administered medication DOT/eDOT with food ≥ 5 days/ week	Isoniazid (INH, H)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Rifapentine (RPT, P)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Moxifloxacin (MOX, M)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Pyrazinamide (PZA, Z)		X	X	X	X	X	X	X	X									
	Vitamin B6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Consultation with TB clinical experts at either local or state level, or TB Center of Excellence (COE) recommended:

- For treatment of lymph node or pleural disease.
  - Avoid using this regimen for sites such as as with CNS or bone disease
- For concerns regarding slow or incomplete clinical response or treatment failure
- For interruption in therapy or changes in drug regimen

Please refer to the full NTCA FAQ for detailed discussion of the HPMZ regimen:
https://www.tbcontrollers.org/docs/resources/4-Month-HPMZ-TB-Regimen_NTCA-FAQ.pdf

FREQUENTLY ASKED QUESTIONS (FAQs)

A 4-Month Regimen to Treat Pulmonary Tuberculosis: Isoniazid, Rifapentine, Moxifloxacin, and Pyrazinamide (HPMZ)

National Tuberculosis Controllers Association

Table of Contents

Introduction

The following Frequently Asked Questions (FAQs) address practical considerations for implementation of the 4-month isoniazid (H), rifapentine (P), moxifloxacin (M), and pyrazinamide (Z) regimen for treatment of drug-susceptible pulmonary tuberculosis (TB), as described in:

1. Dorman SE, Nahid P, Kurbatova EV, et al. "Four-Month Rifapentine Regimens with or without Moxifloxacin for TB." *N Engl J Med* 2021; 384:1705–1718 [TB Trials Consortium (TBTC) Study 31].

2. Carr W, Kurbatova E, Starks A, Goswami N, Allen L, and Winston C. "Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis—United States, 2022." *Morb Mortal Wkly Rep* (*MMWR*) 2022; 71 (8):285–289.

Throughout this document, the study will be referred to as **TBTC Study 31**, and the 4-month regimen will be referred to as **HPMZ**.

Note: *While 'RIPE' is commonly used to describe a standard regimen of "rifampin, isoniazid, pyrazinamide, and ethambutol," the abbreviation "P" more commonly refers to rifapentine in the TB scientific literature (e.g., 3HP refers to 3 months of isoniazid and rifapentine). For consistency, we use "HRZE" to refer to the standard 6-month treatment regimen.* Rifampin, rifapentine, and rifabutin are all rifamycins but have different pharmacological and pharmacokinetic properties. Rifampin or rifabutin should *not* be substituted for rifapentine in the HPMZ regimen.

General TBTC Study 31/HPMZ information

What were the main findings of TBTC Study 31?

In a multicountry, open-label, randomized controlled trial, a 4-month treatment regimen containing isoniazid (H), rifapentine (P), moxifloxacin (M), and pyrazinamide (Z) was compared to the standard 6-month regimen for the treatment of culture-positive, pan-susceptible pulmonary TB disease. Study participants were newly diagnosed with pulmonary TB and had a median age of 31 years (range 13.7–77.5 years). Eight percent were HIV-positive, and 73% had a cavity identified on chest X-ray.

On the primary outcome of TB-free survival at 12 months after the start of treatment, the 4-month treatment regimen of HPMZ was found to be non-inferior to the standard 6-month regimen. Time to stable conversion of sputum cultures was shorter in the 4-month regimen than in standard regimens.

No evidence was found of a difference in overall percentage of participants with a grade 3 adverse effect, including elevation of AST or ALT, between study groups. A slightly higher percentage (3.3%) receiving HPMZ had elevated bilirubin compared to standard care (1%). All-cause mortality was similar across study regimens.

What is the HPMZ regimen for treatment of TB disease?

The HPMZ regimen consists of an 8-week intensive phase of isoniazid (H) 300 mg, rifapentine (P) 1200 mg, moxifloxacin (M) 400 mg, and pyrazinamide (Z) at standard weight-based dosage given daily, followed by a 9-week continuation phase of daily isoniazid 300 mg, rifapentine 1200 mg, and moxifloxacin 400 mg. The total duration of therapy is 17 weeks, and for the purposes of this document is abbreviated as HPMZ. The entire regimen should be administered once daily 7 days per week. The HPMZ regimen is considered complete based on the total number of doses taken (56 intensive phase, 63 continuation phase, for a total of 119 doses taken). The 56 intensive phase doses must be completed within 70 days, and the 63 continuation phase doses must be completed within 84 days, so the entire 17-week regimen must be completed within 22 weeks.

In the TBTC Study 31 clinical trial, a portion of treatment (5 days per week) was verified through directly observed therapy (DOT). Programs implementing the regimen should consider treatment verification for at least 5 days per week through in-person DOT or digital adherence technologies, using a patient-centered approach. Some programs may consider including self-reported adherence (e.g., weekends) toward the total number of doses taken in determining treatment completion, based on local practice.

In addition to treatment verification, an individualized plan for adherence support inclusive of education, nursing support, psychological support, and/or incentives/enablers should be considered, consistent with US and international guidance on management of tuberculosis.

How does the HPMZ regimen differ from currently recommended standard TB treatment regimens?

The currently recommended standard treatment regimen for drug-susceptible TB disease consists of an intensive phase of 8 weeks of rifampin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E) , followed by a continuation phase of 18 weeks of rifampin and isoniazid; this regimen is sometimes abbreviated as HRZE (sometimes described as “RIPE”). Note that in the TB scientific literature, “P” refers to rifapentine rather than pyrazinamide; to avoid confusion, HRZE will be used in this document.[3]

The HPMZ regimen contrasts with the standard HRZE (i.e,.RIPE) regimen in the following ways:

a) this regimen is shorter than standard treatment (~4 months vs. ~6 months, respectively);
b) this regimen has a higher daily pill burden;
c) this regimen substitutes rifapentine for rifampin, includes moxifloxacin in both the intensive and continuation phases, and does not include ethambutol (*Note: whereas ethambutol may be discontinued after demonstration of pan-susceptibility in the standard treatment, moxifloxacin is continued for the duration of the 4 month course)*; and
d) this regimen has not been studied in patients with extrapulmonary TB, children, or pregnant persons.

Is the HPMZ regimen approved by the Food and Drug Administration (FDA)?

The use of rifapentine at this dose and frequency and the use of moxifloxacin have not been FDA-approved for TB treatment and are considered off-label use. While FDA approval is not a requirement for a physician using clinical judgement in prescribing medications for his or her patient, this may have third-party reimbursement implications for certain patients and programs. Rifapentine is approved at a lower dose for once-weekly dosing in continuation phase treatment of active TB disease and for latent TB infection prevention as once-weekly dosing with isoniazid (3HP) for 12 weeks. While moxifloxacin does not have an FDA-approved indication for any use in TB treatment, it is often used in the treatment of drug-resistant TB disease or following adverse drug reaction/drug intolerance.

Treatment considerations

If a patient has already been started on a standard TB treatment regimen with HRZE (i.e.,RIPE), can they be switched to HPMZ?

Patients who have been receiving TB treatment with HRZE or other antituberculous agents may be deemed appropriate candidates for HPMZ. Patients who are switched to HPMZ should receive the entire 17-week course (119 doses) to be considered completely treated; no partial "credit" should be given for patients who have already received HRZE or other antituberculous agents.

Can HPMZ be started in hospitalized patients with active pulmonary TB?

Hospitalized patients diagnosed with active pulmonary TB may have complex disease and should be carefully reviewed for comorbid illness and polypharmacy that may result in drug–drug interactions with HPMZ. Consultation with local or state TB experts is recommended to review whether HPMZ is an appropriate TB regimen for hospitalized patients and to expedite laboratory testing, including drug-susceptibility testing. Consultation with public health TB programs is also necessary to assure availability of medications and resources needed to monitor treatment appropriately and to safely complete therapy.

Can the HPMZ regimen be used in persons with extrapulmonary or disseminated TB (i.e., more than two distant sites affected, such as lungs and lymph nodes or lungs and central nervous system)?

TBTC Study 31 included participants with pulmonary disease and specifically excluded patients with central nervous system (CNS), bone, miliary, and pericardial TB. Given the lack of data for efficacy for specific manifestations of extrapulmonary TB, at present patients with only pulmonary TB are the best candidates for the HPMZ regimen.

Clinicians and programs may use individual discretion to consider use of the HPMZ regimen to treat TB in other isolated body sites that typically have paucibacillary disease or good drug absorption, including lymph node or pleural disease. However, use of this regimen for sites such as those with CNS or bone disease should be avoided, pending additional data. Consultation is recommended with a TB clinical expert at either a local or state level or at a regional CDC TB Center of Excellence (COE). https://www.cdc.gov/tb/education/tb_coe/default.htm

Can the HPMZ regimen be used for culture-negative pulmonary TB?

For the purposes of this question, culture-negative pulmonary TB is defined as patients with a clinical and/or radiographic presentation consistent with TB but with appropriately collected respiratory specimen cultures that are negative. TBTC Study 31 did not

include participants with culture-negative pulmonary TB.[1] Because culture-negative results may take several weeks to finalize, it is possible that patients may be started on HPMZ but later identified as culture-negative. In these instances, it is reasonable to continue the patient on HPMZ for the entire 17-week duration as long as the patient is improving clinically and treatment is well-tolerated.

What should be the approach if patients have slow or no microbiological, radiographic, or clinical response to HPMZ?

For concerns regarding slow or incomplete clinical response or treatment failure, consultation is recommended with a TB clinical expert at either a local or state level or at a regional CDC TB COE. Concerns about poor clinical outcomes can include lack of clinical, radiographic, or microbiological improvement (i.e., cultures remain persistently positive) at 8 weeks of treatment. In this circumstance, clinicians and programs should evaluate possible etiologies for poor clinical response and may consider options ranging from extending the continuation phase of HPMZ, switching to standard treatment regimens (e.g., HRZE), or switching to alternative regimens based on individualized circumstances. Other reasons to consider switching to alternative regimens may include, but are not limited to, drug-susceptibility testing results indicating drug resistance to isoniazid, rifamycin, pyrazinamide, or fluoroquinolones. Adjunctive therapeutic drug monitoring can be performed based on clinician and program discretion.

What if the patient requires significant interruptions to TB therapy?

The HPMZ regimen is considered complete based on the total number of doses taken (119 doses).

DURATION OF THERAPY

Intensive phase: Fifty-six (56) doses should be administered within 70 days from treatment initiation.

Continuation phase: Sixty-three (63) doses should be administered within 84 days from intensive phase completion so that the regimen is completed within 5 months. If these targets are not met, the patient should be considered to have interrupted therapy and managed as described in CDC drug-susceptible TB treatment guidelines.[3] In the TBTC Study 31 clinical trial, a portion of treatment (5 days per week) was verified through directly observed therapy (DOT). Programs implementing the regimen should consider treatment verification for at least 5 days per week through in-person DOT or digital adherence technologies, using a patient-centered approach and existing protocols. Some programs may consider including self-reported adherence (e.g., weekends) toward treatment completion, based on local practice.

DRUG SUSCEPTIBILITY

If interruption in therapy occurs during the HPMZ regimen, confirmation of continued susceptibility to all drugs in the 4-month regimen is required **prior** to restarting this regimen.

What happens if the patient cannot tolerate HPMZ due to adverse events (symptoms or laboratory/EKG abnormalities)?

The decision to stop HPMZ and switch to a different regimen (HRZE or alternative regimen) should be based on clinician and program discretion and the individual reason for switching (e.g., intolerance to or drug-induced liver injury (DILI) caused by a particular drug, or drug resistance detected).

Individual TB drugs in the HPMZ regimen should not be switched with other individual drugs interchangeably (e.g., rifampin for rifapentine). Patients should not be given "credit" for partial completion of HPMZ if switched to a new regimen. Changes to a new regimen should be performed in consultation with TB experts at the local or state level, or regional CDC TB COE. Switches to alternative regimens are expected to alter the total duration of treatment.

Special patient populations

Can the HPMZ regimen be used in children?

TBTC Study 31 did not include participants < 12 years of age. HPMZ should not be used in children < 12 years, or persons who weigh < 40 kg, until more data is available.

Can the HPMZ regimen be used in pregnant persons?

TBTC Study 31 did not include participants who were pregnant. HPMZ should not be used in pregnant persons until more data are available. Persons who become pregnant while on the HPMZ regimen should be switched to a standard TB regimen that has more data on safety and effectiveness during pregnancy.

Can the HPMZ regimen be used in persons of childbearing age (12–50 years)?

All persons of childbearing age (12–50 years) being considered for the HPMZ regimen should be screened for pregnancy. Persons of childbearing age who are taking hormonal contraceptives should be advised to use alternative methods of contraception while taking HPMZ.

Can the HPMZ regimen be used in persons living with HIV?

There are several important drug–drug interactions particularly attributable to daily rifapentine and some antiretroviral medications, which may limit current usage of this regimen in persons with HIV. Studies are underway to evaluate the interactions between rifapentine and commonly used antiretroviral therapy (ART) regimens. Available data from Study 31 is limited to persons with HIV with CD4 counts ≥ 100

cells/μL receiving a regimen comprised of efavirenz (a non-nucleoside reverse transcriptase inhibitor) along with two nucleoside reverse transcriptase inhibitors (tenofovir plus either lamivudine or emtricitabine). Notably, ART that includes protease inhibitors or other pharmacologic enhancers (e.g., cobicistat) is expected to have significant drug-drug interactions and should be avoided. There is a lack of data to support usage with most integrase strand transferase inhibitors and other non-nucleoside reverse transcriptase inhibitors.

Pending additional data, the HPMZ regimen usage can be considered in persons living with HIV with CD4 counts ≥ 100 cells/μL who are receiving efavirenz-based therapy as part of their ART (with tenofovir disoproxil fumarate plus lamivudine or emtricitabine per study usage), and in the absence of drug–drug interactions with any other antiretroviral medications. Notably, current Department of Health and Human Services (DHHS) guidance suggests no dosage adjustment is needed when using tenofovir disoproxil (TDF) with rifapentine; due to potential for decreased concentrations of tenofovir alafenamide (TAF), current guidelines recommend they are "not coadministered unless benefits outweigh risks."[5]

Further information about drug–drug interactions with anti-TB and HIV medications is available at:

- HIV-ASSIST[4]: https://www.hivassist.com/
- DHHS Guidelines:
    - "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV."5 https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/overview
    - Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV: Mycobacterium tuberculosis infection and disease[6]: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/mycobacterium-tuberculosis-infection-and?view=full
- University of Liverpool Drug Interaction Checker[7]: https://www.hiv-druginteractions.org/checker

Can the HPMZ regimen be used in older patients?

Clinicians should perform an individual assessment based on the presence of common comorbidities in geriatric populations and consider the risk–benefit of using the HPMZ regimen compared to the standard HRZE regimen. Some important concerns include the potential for frailty (HPMZ has not been studied in participants < 40 kg), drug–drug interactions in patients on multiple medications, undiagnosed cardiac disease and risk for QT prolongation, and development of tendinopathy or tendon rupture on fluoroquinolone therapy.

Can the HPMZ regimen be used in patients with comorbid illnesses?

Each patient should undergo a comprehensive review of comorbid illnesses. While rifapentine is likely to have a similar risk of hepatotoxicity to rifampin, rifapentine also has a longer half-life. As when initiating treatment with standard HRZE therapy, patients

should be screened for history of chronic liver disease, viral hepatitis, chronic alcohol use, or use of concurrent hepatotoxic medications, and should also be monitored at least monthly for signs, symptoms, and laboratory abnormalities that would suggest drug-induced liver injury (DILI). Due to the potential for QT prolongation with usage of moxifloxacin, patients should be assessed for a history of cardiac illness with consideration for a baseline or monitoring EKG. In TBTC Study 31, cardiac disorders of grade 3 or higher were reported in three participants (0.4%) receiving HPMZ although baseline and monitoring EKGs were not done.

Can the HPMZ regimen be used in patients who report chronic alcohol use?

As when initiating treatment with standard HRZE/RIPE therapy, patients should be screened for history of chronic alcohol use and monitored for signs, symptoms, and laboratory abnormalities that would suggest concern for drug-induced liver injury (DILI). Based on individual clinical assessment, patients started on the HPMZ regimen should be counseled on the importance of abstaining from alcohol while on TB treatment and should be educated on the signs and symptoms of hepatotoxicity. Patients who indicate that they will continue alcohol intake should be monitored at least monthly for signs, symptoms, and laboratory abnormalities that would suggest DILI.

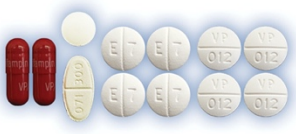
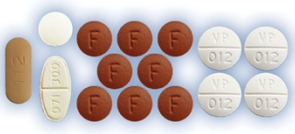
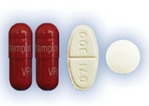
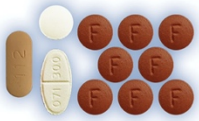
Medication considerations

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

What is the medication dosage and pill burden of the HPMZ regimen compared to the standard 6- or 9-month HRZE regimen?

While the duration of HPMZ is shorter than the 6 months of HRZE, the pill burden in the example, for a person weighing >75 Kg, the standard HRZE therapy includes 12 pills daily for the first 8 weeks followed by 4 pills daily for the duration of treatment. Alternatively, the same person on the HPMZ regimen would take 15 pills daily for the first 8 weeks followed by 11 pills daily for the next 9 weeks. Patients should be educated on the difference in pill burden, which may affect both tolerance and adherence. See photos below (both regimens pictured include one extra pill of vitamin B6).

	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

Should the HPMZ regimen be taken with food?

The CDC recommends that the HPMZ regimen be taken once daily with food. Clinicians should perform a thorough medication review, including over-the-counter products. Patients should be educated that the HPMZ regimen should *not* be taken with dairy products, sucralfate, antacids, or multivitamins or supplements containing iron, aluminum, magnesium, or calcium within 4 hours before or 8 hours after taking HPMZ. This provision is due to the impact of such agents on fluoroquinolone absorption.

What if rifapentine is not available? Can a different rifamycin (rifampin or rifabutin) be substituted?

The TBTC Study 31 authors utilized rifapentine at a high dose (1200 mg daily) based largely on its efficacy in animal studies. It is unknown if substitution with an alternative rifamycin would achieve similar clinical outcomes. Consequently, rifampin or rifabutin should *not* be substituted for rifapentine in the HPMZ regimen until more data are available. There is an active clinical trial evaluating the role of high-dose rifampin in a 4-month TB disease regimen, with results expected to come out at the end of 2022.[9]

What if moxifloxacin is not available or too expensive? Can a different fluoroquinolone (e.g., levofloxacin) be used?

TBTC Study 31 evaluated only one fluoroquinolone—moxifloxacin—in the HPMZ regimen. Until further data are available, moxifloxacin is considered the drug of choice when using HPMZ. The efficacy of substituting levofloxacin for moxifloxacin as part of the HPMZ regimen is currently unknown. Moxifloxacin was selected for TBTC Study 31 due to an increased in-vitro activity against *Mycobacterium tuberculosis* compared to other fluoroquinolones such as levofloxacin. In clinical studies, TB outcomes have appeared to be similar for both moxifloxacin and levofloxacin. When moxifloxacin is either not available or a patient has contra-indications to moxifloxacin therapy, clinicians and programs can consider substituting levofloxacin for moxifloxacin on a case-by-case basis as part of the HPMZ regimen. Consultation is strongly recommended with a TB clinical expert at either the local or state level, or a regional CDC TB Center of Excellence (COE).

Are there concerns with nitrosamine impurities recently reported in rifapentine?

The Food and Drug Administration (FDA) recently discovered elevated levels of nitrosamines, which are potential carcinogens, in rifampin and rifapentine. We are not aware of any data showing an association between cancer and use of rifamycins in humans. However, we are also not aware of any rigorous studies that have looked for this association.

In order to preserve the availability of rifampin and rifapentine for treating tuberculosis, the FDA has increased the maximal allowable daily limits of these contaminants temporarily for rifampin and rifapentine distributed in the US. Rifabutin has not been affected by this problem.

A risk–benefit statement by FDA supports the continued use of the currently approved once-weekly rifapentine for treatment of TB disease. While nitrosamine content for an individual lot of drug generally is not available, exposure to this contaminant may be significantly increased with the high-dose daily rifapentine used in this regimen, although the duration is short. The presence of nitrosamine impurities in rifapentine and rifampin should be discussed with patients who are to be prescribed either of these drugs as part of shared decision-making and case management. More information about nitrosamine impurities and rifamycin drugs is available at[10]: https://www.treatmentactiongroup.org/wp-content/uploads/2021/02/nitrosamine_faq_for_people_taking_TPT.pdf

Are there drug-drug interactions?

There are common interactions for isoniazid, rifapentine, and moxifloxacin:

- Isoniazid increases blood levels of phenytoin and disulfiram
- Rifapentine, similar to rifampin, decreases blood levels of oral or implanted hormonal
- contraceptives, warfarin, sulfonylureas, methadone, suboxone, some anti-hypertensives and steroids.
- Some cardiac medications and certain antiretroviral drugs may have serious drug-drug
- interactions.
- Moxifloxacin interacts with other medications that are QTc prolonging. Please see additional information on use of moxifloxacin under Programmatic Consideration
- Please check drug-drug interactions

Possible adverse events (AEs) with HPMZties recently reported in rifapentine?

Mild to moderate: Continue to monitor, discontinue if needed

- Joint pain
- Tendonitis
- LFTs ≥ 3-5X ULN
- Rash n Fever n Pruritis
- Nausea
- Vomiting

Moderate to Severe: Recommend discontinuing treatment

- Hypersensitivity
- Hypotension, mild to profound syncope/fainting
- Dizziness
- Life threatening syndromes (fever, chills HA, dizziness and musculoskeletal pain)

- Thrombocytopenia
- Shortness of breath, wheezing, acute bronchospasm
- Urticarial petechiae, purpura
- Conjunctivitis
- Angioedema and shock
- Chest pain/angina, palpitations, or cardiac arrhythmias
- Elevated liver function tests (LFTs) ≥ 5X ULN

Laboratory evaluation and other monitoring parameters

Is EKG monitoring recommended with the HPMZ regimen?

Moxifloxacin is a QT-prolonging agent. In TBTC Study 31, baseline EKGs were not performed, and there were very few known or reported cardiac adverse effects.[1] In TBTC Study 31, cardiac disorders of grade 3 or higher occurred in three participants (0.4%) receiving HPMZ. Current CDC guidance does not recommend routine baseline EKGs or periodic EKG monitoring.[2] In many clinic settings, EKG monitoring and review may not be routine practice and/or may not be readily available.

All patients being considered for the HPMZ regimen should undergo a baseline risk assessment and evaluation for underlying cardiac disease and/or the need for EKG monitoring. Patients should be asked about history of congenital prolonged QT syndrome or family history of sudden death, prior drug-induced QTc prolongation, arrhythmia, hypothyroidism, electrolyte imbalances, structural and functional heart disease, or concurrent use of any QT-prolonging medications. In general, patients with any history of arrhythmia, chronic electrolyte abnormalities, recent/active cardiac ischemia or arrhythmias, or who are taking any other drugs known to increase QTc should not be considered candidates for the HPMZ regimen. A full list of QT-prolonging agents is available at[11]: https://www.crediblemeds.org/index.php/login/dlcheck

Clinicians and programs may also want to take into account the patient's age (e.g., older persons may be more likely to have underlying cardiac disease) when considering treating with the HPMZ regimen.

Clinicians and TB programs should follow their existing protocols regarding EKGs and fluoroquinolone use. If EKG monitoring is performed, patients should receive a baseline EKG and a repeat EKG 1 or 2 weeks after starting the HPMZ regimen if indicated. Follow-up EKG monitoring should be considered by the provider based on risks. Most experts would not recommend starting a fluoroquinolone if the QTc is > 500 ms; many experts recommend using the Fridericia correction for QTc. Several additional references are available to assist with EKG monitoring.[10]

What are the recommendations for monitoring for adverse events with the HPMZ regimen?

- Baseline and monthly clinical and laboratory monitoring should be performed, including initial and follow-up symptom screening, sputa microbiology, and chest radiographs.
- Screening laboratories prior to start of treatment should also include HIV, complete blood count (CBC) with platelets, basic metabolic panel (to include creatinine, K+, Ca+, Mg+), liver function tests (AST, ALT, total bilirubin, and alkaline phosphatase), and pregnancy testing for persons of childbearing age;

optional Hepatitis B, Hepatitis C, and hemoglobin A1C (HbA1c) are also recommended.

- A review of potential drug–drug interactions with HPMZ and chronic medications should be performed before and during treatment regimen.
- History of cardiac risk factors and EKG should be taken (based on clinician/program discretion as discussed above).
- Follow-up monthly laboratory testing is recommended and should include liver function tests, CBC with platelet count, and monitoring for electrolyte abnormalities (potassium, calcium, and magnesium).
- In addition to baseline testing, CDC recommends that monthly testing of sputa for AFB smear and culture should be performed for patients on HPMZ until two consecutive specimens are smear- and culture-negative. For patients who have positive AFB smears at the time of diagnosis, more frequent smears may be obtained for assessment of response to treatment and transmission risk.

Therapeutic drug monitoring can be considered (based on clinician/program discretion, testing availability, and treatment indications).

What if patient develops abnormal labs during treatment?

The following advice is taken from CDC's FAQs: "Protocol had an inclusion criterion for potassium only (serum or plasma potassium level greater than or equal to 3.5 mEq/L). Calcium and magnesium levels were not tested in the trial. When a patient has abnormal test results at baseline, the physician should consider the risks and benefits of using the 4-month rifapentine-moxifloxacin regimen, accounting for possible cardiac conduction abnormalities and underlying heart disease."

Can the HPMZ regimen be initiated if my local reference or commercial laboratory does not offer fluoroquinolone drug susceptibility testing (DST)?

TBTC Study 31 only included participants with culture-confirmed pulmonary TB with known pan-susceptibility, including to fluoroquinolones. Based on limited data, the estimated prevalence of drug resistance to fluoroquinolone in the US is ~1%–2%. Acceptable DST methods include culture-based susceptibility testing *or* rapid molecular methods such as pyrosequencing or whole genome sequencing; molecular testing through local or state health TB program may produce quick results and is strongly recommended.

The HPMZ regimen should be used only if fluoroquinolone DST results are known or are ordered and pending.

CDC's TB Elimination Laboratory (TBLab@cdc.gov) can assist with identifying laboratories to perform this testing for TB programs that intend to implement the HPMZ regimen, although turnaround time may vary—check with your local or state health TB program .

Should the patient await results of fluoroquinolone drug susceptibility test (DST) before starting the HPMZ regimen?

Patients can be started on the HPMZ regimen while awaiting DST results, including for fluoroquinolones. Some commercially available rapid molecular testing assays (i.e., the Gene Xpert MTB/RIF assay [Cepheid, Sunnyvale, California]) identify mutations associated with rifampin resistance, which will also predict rifapentine resistance. Other rapid molecular assays that provide data on presence of mutations indicating resistance to isoniazid, pyrazinamide, or fluoroquinolones may also be available in some labs. Consultation with your local or state level, or regional CDC COE is recommended.

TB programmatic considerations

What is the difference in cost between this regimen and the cost of standard HRZE treatment?

Public sector clinics procuring medications for patients may find that, at current 340B government pricing, the cost for the HPMZ regimen is higher than for standard HRZE. Prices may be different for those programs and clinics unable to access 340B government pricing. Costs for patients may also differ (higher or lower) when patients obtain medications through the private sector or individual insurance plans.

What are the advantages and disadvantages of the HPMZ Regimen*

Potential pros of the 4-month regimen

- May be preferred by some patients that prioritize shorter overall treatment duration over larger pill burden, for personal, social, or other individualized considerations
- Shorter duration of treatment than standard HRZE therapy, particularly for uncomplicated pulmonary TB
- May facilitate treatment completion in patients with barriers to longitudinal availability (e.g., planned geographic relocation, incarceration), or whose TB disease poses a risk to others (e.g. residents in congregate or institutionalized settings)
- Avoids potential for ocular toxicity with ethambutol (EMB)
- May reduce time to culture conversion

Potential cons of the 4-month regimen

- Higher pill burden compared to standard HRZE regimen
- Considerations for administration with food and avoidance of some comedications (e.g., antacids) to optimize drug absorption
- Rifamycins, including high-dose daily rifapentine, may have significant drug interactions, particularly with many currently recommended antiretrovirals for people with HIV.
- Program cost is likely to be higher per treatment regimen if paying 340B prices to procure medications (driven by rifapentine); individual program or patient costs may differ based on payor sources, particularly in the private sector or with insurance reimbursements.
- Long-term outcome data when using this regimen are limited (12 months).
- Overall, HPMZ was non-inferior (2% difference [95% CI—2.6, 4.5]) to standard regimens with respect to composite unfavorable outcomes; however, among unfavorable outcomes, a higher proportion of individuals (4.3%) with HPMZ had evidence of relapse/failure than HRZE (1.4%) after week 17.
- Considerations for potential side effects of inclusion of fluoroquinolone in the HPMZ regimen compared to standard HRZE regimen (e.g., QT prolongation, tendonitis, effects on gut microbiota)
- There is a lack of data for usage in many forms of extrapulmonary TB, including CNS disease and osteomyelitis.

** Pros and cons may change over time and vary by program.*

TB Program — Patient Checklist

PATIENT NAME_____**CASE/MEDICAL RECORD #:** _____

PROVIDER: _____

1. Confirm patient meets minimal recommended criteria for starting HPMZ:

- ☐ Age ≥ 12 years
- ☐ Weight > 40 kg
- ☐ If HIV-positive, CD4 > 100 cells/mm3; if on ART, the regimen is efavirenz-based and does not contain protease inhibitors, integrase inhibitors, entry/fusion inhibitors or non-nucleoside reverse transcriptase inhibitors other than efavirenz.** (See FAQ HIV section).
- ☐ Negative pregnancy test if of childbearing age (12–55 years).
- ☐ Not breastfeeding
- ☐ Baseline laboratory values: serum creatinine < 2.0, potassium ≥ 3.5 meq/L, Hgb ≥ 7.0 g/dL, platelets ≥ 100,000/mm3, liver function tests ≤ 2X upper limit of normal
- ☐ No suspected or documented extrapulmonary TB (See FAQ)
- ☐ No history of taking TB drugs within past 6 months
- ☐ Medication review with no drug–drug interactions with HPMZ
- ☐ Rapid molecular detection of drug resistance from initial specimen should be ordered if available
- ☐ Patient can be started on the HPMZ regimen while awaiting drug susceptibility test (DST) results, including fluoroquinolones

2. Programmatic Cosiderations for HPMZ

Case management

- ☐ Ensure drug supply available for full 17-week course
- ☐ Patient and provider have discussed pill burden (see photo).
- ☐ Medication taken for 7 days a week and DOT/eDOT arranged for medication administration at least 5 days/week
- ☐ Clinical (monthly) visits arranged
- ☐ Sputum monitoring arranged
- ☐ Laboratory monitoring arranged
- ☐ EKG monitoring arranged, when indicated
- ☐ Verify reimbursement for HPMZ by program or third party

Rapid molecular detection of drug resistance from initial specimen or drug susceptibility testing of isolate after culture growth of *Mycobacterium tuberculosis*:

- ☐ Fluroquinolone-susceptible (culture-based or absent gyrA / gyrB mutation)
- ☐ Rifampin-susceptible (culture-based or absent rpoB mutation)
- ☐ Isoniazid-susceptible (culture-based or absent inhA or katG mutation)
- ☐ Pyrazinamide-susceptible (culture-based or absent pncA mutation)

***May change over time based on available infrmation on drug-drug interactions*

Moxifloxacin

- ☐ Patient educated that HPMZ should *not* be taken with dairy products, sucralfate, antacids, or multivitamins or supplements containing iron, aluminum, magnesium, or calcium within 4 hours before or 8 hours after taking HPMZ
- ☐ Review cardiac comorbidities: history of structural or functional cardiac disease including active ischemic disease, arrhythmias (especially bradyarrhythmias), or prolonged QTc at baseline.
- ☐ Access EKG for patients with cardiac risks per practice standards for long term moxifloxacin administration: baseline and monthly. Baseline QTc < 500.
- ☐ Review concurrent medications that prolong QTc intervals.
- ☐ CDC does not recommend use with other medications that prolong QTc; however, some experts may choose to prescribe this regimen in patients with h/o prolonged QTc or patients on other QT-prolonging drugs with careful and appropriate EKG monitoring.

Rifapentine

- ☐ Patient and provider have discussed FDA alert regarding increased nitrosamine burden.

Table 1. Baseline and follow-up monitoring and evaluation for patients on HPMZ regimen (X = recommended; O = optional)

Evaluation Types		Baseline	Intensive Phase (Total 56 doses)[a]								Continuation Phase (Total 63 doses)[b]								
			Week 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Clinical assessment and evaluation	Symptoms, medication, drug–drug interaction[c]	X				X				X				X					X
	Weight[d]	X				X				X				X					X
	EKG if indicated[e]	O				O				O				O					O
Laboratory testing	CBC, Platelet, LFT, Creatinine, Potassium, Calcium, Magnesium[f]	X				O				O				O					O
	HIV (if positive CD4 count and HIV RNA)[g]	X																	
	Hepatitis B and C[h] Diabetes screen[i]	O																	
	Pregnancy test[j]	X																	
Microbiology (Sputum)	AFB smear and culture[k]	X	O	O	O	X				X				O					O
	Rapid molecular test[l]	X																	
	Phenotypic drug susceptibility test[m]	X								O									
Imaging	Chest radiograph[n]	X								O									O
Administered medication[a,b] DOT/eDOT with food ≥ 5 days/ week[o]	Isoniazid (INH, H)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Rifapentine (RPT, P)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Moxifloxacin (MOX, M)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Pyrazinamide (PZA, Z)		X	X	X	X	X	X	X	X									
	Vitamin B6		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Modified from Morb Mortal Wkly Rep (MMWR) 2022; 71(8):285–289.

Abbreviations: HPMZ = 4-month isoniazid, rifapentine, moxifloxacin, and pyrazinamide; AFB = acid-fast bacilli; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; CXR = chest radiograph; DOT = directly observed therapy; DST = drug susceptibility testing; EKG = electrocardiogram; INH = isoniazid; MOX = moxifloxacin; PZA = pyrazinamide; RIF = rifampin; RPT = rifapentine.

[a]The 56 doses of initiation phase should be administered completely within 70 days. If this target is not met, the patient should be considered to have interrupted therapy and should be managed as described in TB treatment guidelines.

[b]The 63 doses of the continuation phase should be administered within 84 days. If this target is not met, the patient should be considered to have interrupted therapy and should be managed as described in TB treatment guidelines.

[c]Review medical history and medications for drug-drug interactions. HPMZ regimen is contraindicated in patients with active ischemia and/or history of arrhythmias. Adherence, improvements in tuberculosis symptoms, and medication adverse effects should be assessed:
-Tuberculosis symptoms (e.g., cough, fever, fatigue, or night sweats).
-Medication adverse effects (e.g., jaundice, dark urine, nausea, vomiting, abdominal pain, diarrhea, anorexia, dizziness, seizures, fever, rash, malaise, neuropathy, arthralgia, tendinopathy, heart palpations, irregular heartbeat, weakness, or syncope).

[d]Weight should be monitored monthly to assess response to treatment; adjust PZA dose if needed.

[e]EKG should be performed in patients with cardiac risks per practice standards for long term moxifloxacin administration.

[f] Baseline and follow-up laboratory monitoring based on clinical indication and baseline abnormalities. Follow-up liver function tests Should be conducted if baseline abnormalities are detected at baseline, symptoms consistent with hepatotoxicity develop, or patients chronically consume alcohol, take other potentially hepatotoxic medications, or have viral hepatitis or history of liver disease, HIV infection, or previous drug-induced liver injury.

[g]HIV testing in all patients; CD4 lymphocyte count and HIV RNA load testing if HIV infection.

[h]Hepatitis screening for all patients in accordance with CDC guidelines. Patients with hepatitis B or C risk factors or elevated baseline liver function tests should be tested for these viruses. Hepatitis C screening: https://www.cdc.gov/mmwr/volumes/69/rr/rr6902a1.htm.

[i]Fasting glucose or hemoglobin A1c (Hb A1C) for patients with risk factors for diabetes according to the American Diabetes Association, including age > 45 years; body mass index > 25 kg/m^2; first-degree relative with diabetes; and race/ethnicity of African American, Asian, Hispanic, American Indian, Alaska Native, or Hawaiian Native or other Pacific Islander. For patients with diabetes, glucose monitoring is indicated: https://professional.diabetes.org/content-page/practice-guidelines-resources.

[j]Persons who can become pregnant should be advised to use a barrier contraceptive method or nonhormonal intrauterine device or abstain from heterosexual intercourse during treatment.

[k]Sputum smear and culture should be obtained at baseline, then weekly until three consecutive specimens are AFB smear–negative, and then monthly until two consecutive specimens are culture-negative.

[l]At least one baseline specimen should be tested by rapid molecular resistance testing for INH, RPT, MOX, and PZA.

[m]Drug susceptibility for at least INH, RIF, PZA, and fluoroquinolones (preferred fluoroquinolone is MOX) should be obtained. DST testing (rapid molecular preferred) should be repeated if patient's culture remains positive after 2 months (8 weeks) of treatment.

[n]CXR should be obtained at baseline for all patients and at month 2 if baseline cultures are negative. End-of-treatment CXR is optional.

[o]Medications should be taken 7 days a week and directly observed therapy in-person or via electronic platform be done at least 5 days a week

List of acronyms and abbreviations

3HP	3-month weekly isoniazid and rifapentine for latent TB infection
HPMZ	Isoniazid-rifapentine-moxifloxacin-pyrazinamide
ART	Antiretroviral therapy
BMI	Body mass index
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CNS	Central nervous system
COE	Center of Excellence
DHHS	Department of Health and Human Services
DILI	Drug-induced liver injury
DOT	Directly observed therapy
DST	Drug susceptibility test
eDOT	Electronic (digital) directly observed therapy
EKG	Electrocardiogram
FDA	Food and Drug Administration
H	Isoniazid
HbA1c	Hemoglobin A1c
HIV	Human immunodeficiency virus
HRZE	Isoniazid, rifampin, pyrazinamide, ethambutol (standard 6-month TB treatment)
INH	Isoniazid
M	Moxifloxacin
MOX	Moxifloxacin
MTB	*Mycobacterium tuberculosis*
P	Rifapentine
PZA	Pyrazinamide
R	Rifampin
RIF	Rifampin
RIPE	Rifampin, isoniazid, pyrazinamide, ethambutol (standard 6-month TB treatment)
RPT	Rifapentine
TB	Tuberculosis
TBTC	Tuberculosis Trial Consortium
Z	Pyrazinamide

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