Title

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Journal

Open Forum Infectious Diseases, 11(4)

ISSN

2328-8957

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Publication Date

2024-04-01

DOI

10.1093/ofid/ofae178

Peer reviewed

Open Forum Infectious Diseases

MAJOR ARTICLE

Experience With Four-Month Rifapentine and Moxifloxacin–Based Tuberculosis Treatment in San Francisco

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Background. A multicountry randomized controlled trial has demonstrated that pan-susceptible pulmonary tuberculosis (TB) can be successfully treated with a 4-month regimen of daily isoniazid, rifapentine, moxifloxacin, and pyrazinamide (HPMZ). We piloted HPMZ in San Francisco (SF) using a modified version of the US Centers for Disease Control and Prevention HPMZ treatment guidelines.

Methods. In this retrospective cohort, patients consecutively referred to SF TB clinic were evaluated for HPMZ eligibility based on preestablished inclusion/exclusion criteria. All underwent evaluation and management according to national recommendations. We reviewed the medical records of those initiated on HPMZ.

Results. From August 2021 to December 2023, 30 (18.8%) of 160 patients diagnosed with active TB met HPMZ inclusion criteria; of these, 22 (13.8%) started HPMZ. The median age (range) was 32.5 (14–86) years, 17 (77.3%) were otherwise healthy, and 19 (86.4%) had pulmonary TB, including 7 (36.8%) with cavitary disease. Eighteen (81.8%) patients had an adverse event, with 11 (50%) prematurely discontinuing HPMZ; the most common adverse events were vomiting, elevated transaminases, and rash. To date, 9 (40.9%) have completed treatment, with most achieving criteria for cure. One patient was diagnosed with possible TB recurrence and restarted standard TB treatment.

Conclusions. Our experience, with half of patients to date prematurely discontinuing HPMZ, illustrates the challenge of extrapolating findings from TB clinical trials commonly conducted in high-incidence, non-US settings to US clinical practice. Further experience may help identify best practices for implementing HPMZ, including identifying predictors of which patients may be most likely to benefit from and tolerate this regimen.

Keywords. tuberculosis; treatment; short-course; 4-month; SF.

For >4 decades, standard treatment recommendations for pan-susceptible pulmonary tuberculosis (TB) have included 4-drug antituberculous therapy for a duration of 6 months, with extension to 9 months for cavitary disease and positive cultures at completion of 2 months of therapy [1]. Recently, a multicountry randomized controlled trial (Tuberculosis Trials Consortium [TBTC] Study 31/AIDS Clinical Trials Group [ACTG] A5439) showed that it is possible to cure high-burden, pan-susceptible pulmonary TB in 4 months using a regimen of daily isoniazid, pyrazinamide, and 2 new components: rifapentine and moxifloxacin (HPMZ) [2]. When compared with standard therapy with isoniazid, rifampin, pyrazinamide, and ethambutol (HRZE), HPMZ was noninferior, including with respect to negative sputum cultures at month 12 after start of treatment (88.6% compared with 86.8%, respectively) [2].

The programmatic feasibility of HPMZ treatment has not been studied in the United States. Standard 4-drug treatment with HRZE can be associated with adverse events (AEs); in San Francisco (SF), 35.4% of patients (46.2% in those aged ≥65 years) experience AEs during treatment, including gastrointestinal symptoms, hepatotoxicity, and rash [1, 3]. High-dose rifapentine is currently used for treatment of latent infection with *M. tuberculosis* (Mtb) with once-weekly dosing and has a similar AE profile to rifampin (nausea and vomiting, elevated serum transaminases, and rash) [4]. However, few data beyond those from Study 31/A5349 are available on AEs when rifapentine is given at a higher flat daily dose of 1200 mg. Moxifloxacin has been recommended for treatment of multidrug-resistant

Received 16 January 2024; editorial decision 19 March 2024; accepted 23 March 2024; published online 26 March 2024

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https://doi.org/10.1093/ofid/ofae178

TB and as a second-line drug for fluoroquinolone-susceptible TB [5]. Fluoroquinolones, including moxifloxacin, are associated with multiple AEs and US Food and Drug Administration black box warnings, including tendonitis, tendon rupture, irreversible peripheral neuropathy, and central nervous system effects [6]. In February 2022, the US Centers for Disease Control and Prevention (CDC) and the National TB Coalition of America (NTCA) provided guidance on best practices for implementation of HPMZ in US populations [7,8]. The San Francisco Department of Public Health (SFDPH) TB clinic evaluates and manages all patients with active TB residing in SF. SF has a relatively high TB incidence (6.9 per 100 000 population, compared with a US TB incidence of 2.2 per 100 000 population in 2022) and has an older TB patient population, with a median age (range) of 61 (14–89) years [9]. In this report, we describe our experience piloting HPMZ using a modified version of the CDC/NTCA guidelines for the treatment of active TB.

METHODS

In this retrospective cohort, we reviewed medical records of patients with TB at the SFDPH TB clinic initiated on HPMZ. All patients underwent TB diagnostic evaluation according to national recommendations [1]. SFDPH TB clinicians evaluated patients consecutively referred to the TB clinic for HPMZ eligibility based on preestablished inclusion and exclusion criteria congruent with those recommended by the CDC and NTCA (Table 1) [7, 8]. Clinicians were able to, at their discretion, exclude patients who were assessed as clinically unstable (eg, hospitalized or with abnormal laboratory values not outlined in the CDC and NTCA guidance) or had difficulty communicating their understanding of the importance of adherence, frequent monitoring, and reporting of AEs. Each patient underwent counseling with a clinician regarding the regimen, pill burden, duration, and possible adverse events (AEs) of HPMZ compared with HRZE. Because the pilot was conducted during a national shortage of rifapentine, patients were only recruited if a full course of rifapentine was available at the time of treatment initiation [10]. Patients expressing interest in HPMZ were initiated on once-daily dosing under directly observed therapy (DOT) with isoniazid 300 mg, rifapentine 1200 mg, moxifloxacin 400 mg, and pyrazinamide 20–25 mg/kg for 8 weeks, followed by 9 weeks of isoniazid 300 mg, rifapentine 1200 mg, and moxifloxacin 400 mg.

All patients underwent chest radiography at baseline. Three sputum specimens were collected for acid-fast bacilli (AFB) smear and culture, with 1 sputum specimen tested by the Xpert MTB/RIF assay. Specimens that were AFB smear– or culture-positive were also sent to the California Department of Public Health Microbial Diseases Laboratory for pyrosequencing (PSQ) to screen for resistance-conferring mutations for isoniazid, rifamycins, and fluoroquinolones. Monitoring studies during and after HPMZ treatment are listed in Table 1. Patient management decisions while on HPMZ were left to individual provider discretion. In general, if patients developed moderate or severe AEs, HPMZ was discontinued, and the patient was switched to standard HRZE treatment. When liver function tests were abnormal, HPMZ therapy was continued if the patient was asymptomatic and transaminases and/or total bilirubin were <3 times the upper limit of normal. Participants were classified as having treatment failure if any of the following events occurred during TB treatment: (1) death due to TB, (2) persistently culture-positive sputa for Mtb throughout treatment, or (3) clinical or radiographic worsening attributed to TB. If TB clinicians had concern for treatment failure, patients were considered for extending HPMZ to 6 months or longer or switching to standard HRZE.

The 4-month regimen was considered complete when 119 doses were administered (including 5 days a week by DOT as per the CDC recommendations [11]). All patients were monitored after end of treatment (EOT) for recurrence at 3, 6, and 12 months with clinician visits, which included symptom review, chest radiography, and collection of 2 sputum samples for AFB smear and culture testing. Participants were classified as having disease recurrence if any of the following events occurred after EOT: (1) death due to TB, (2) ≥1 positive sputum culture for *Mtb* after EOT, or (3) initiation of additional treatment for TB based on clinical discretion including new symptoms or new or worsening radiographic changes.

We extracted data including symptomatology, clinical course, regimen changes, laboratory results, and treatment-related AEs. We assessed AEs using the Common Terminology Criteria for Adverse Events (CTCAE); the CTCAE grades AEs on a scale of 1 to 5, with grades 1, 2, 3, and 4 indicating mild, moderate, severe, and life-threatening AEs, respectively, and grade 5 indicating death related to an AE [12].

Patient Consent

The analysis of routinely collected SFDPH TB Clinic data was reviewed and approved by the Human Subjects Review Committee of the University of California, San Francisco (IRB #21-34264). The analysis did not include factors necessitating patient consent.

RESULTS

From August 1, 2021, to December 31, 2023, 160 patients residing in SF were started on treatment for newly diagnosed active TB. Two patients were not considered for HPMZ due to a rifapentine shortage at the time of diagnosis. Of the remainder, 128 (81.0%) did not meet CDC/NTCA criteria for HPMZ eligibility with ≥1 exclusion criterion; the most common reasons included clinician discretion that the patient was clinically

Table 1. San Francisco Department of Public Health TB Clinic: Active TB Treatment With the Four-Month HPMZ Regimen

Baseline criteria
- Patient must be a San Francisco resident and able to be followed at SFDPH TB clinic for the duration of the HPMZ treatment course (17 wk or 119 doses);
- Patient is clinically stable based on TB clinician assessment;
- Patient communicates:
  - Understanding of the pros and cons of the HPMZ regimen;
  - Understanding of the importance of taking daily medication with directly observed therapy ≥5 d/wk;
  - Understanding of importance of adherence to clinic visits and regular monitoring including the following studies:
    - Imaging: chest x-ray at initiation of treatment, 8 wk of treatment, and 17 wk (end of treatment);
    - Sputum collection weekly until acid-fast bacilli–negative and at weeks 2, 4, 8, and 17;
    - Complete blood count and complete metabolic panel (including liver function tests) at weeks 2, 4, 8, 12, and 17; AND
    - Post end-of-treatment follow-up: chest x-ray and sputa × 2 (for AFB smear and culture) at months 3, 6, and 12.
  - Agreement to report any drug-related adverse events during treatment.
- Before initiation of treatment, assess that San Francisco rifapentine supply is adequate to complete a 17-week course (119 doses).

Inclusion criteria
- Age range ≥12 y;
- Weight ≥40 kg;
- Only pulmonary, pleural, or lymph node disease;
- If started on TB treatment, has been on standard therapy for <21 d;
- If HIV-positive, CD4 >100 cells/mm^3 (see antiretroviral therapy caveats in exclusion criteria);
- No history of end-stage liver disease or chronic active hepatitis;
- No chronic medications that have drug–drug interactions with HPMZ drugs;
- Serum creatinine <2.0 or CrCl ≥30 mg/dL;
- Potassium ≥3.5 meq/L;
- Hgb ≥7.0 g/dL;
- Platelets ≥100 000/mm^3;
- LFTs ≤2× upper limit of normal;
- Negative pregnancy test for women of childbearing age (12–55 y);
- Baseline EKG without Qtc prolongation (using Friderica correction Qtc <450 ms [men] or <470 ms [women][a]).

Exclusion criteria
- Suspected or documented extrapulmonary TB other than pleural or lymph node (eg, central nervous system, bones, joints, pericardial, gastrointestinal, peritoneal, genito-urinary, or miliary TB);
- Mono- or multidrug resistance (either previously known or identified on pyrosequencing or drug susceptibility testing);
- Pregnant or breastfeeding;
- Receiving HIV medications that include protease inhibitors, integrase inhibitors, entry and fusion inhibitors, or non-nucleoside reverse transcriptase inhibitors other than efavirenz;
- History of prolonged Qt syndrome, arrythmia, recent ischemic heart disease, or structural heart disease; and/or
- Concurrent use of Qt-prolonging medication (eg, clarithromycin, quinidine, fluconazole, antipsychotics: haloperidol, chlorpromazine; anti-emetics: ondansetron and domperidone, etc.).

Abbreviations: EKG, electrocardiogram; HPMZ, isoniazid, rifapentine, moxifloxacin, and pyrazinamide; LFTs, liver function tests; SFDPH, San Francisco Department of Public Health; TB, tuberculosis.

[a]Based on criteria outlined in the USAID/KNCV/ChallengeTB. Guide for QTc monitoring and management of drug-resistant TB patients with QT-prolonging agents. Available at: https://www.challengetb.org/publications/tools/pmdt/Guidance_on_ECG_monitoring_in_NDR_v2.pdf.

unstable (32, 25.0%; including patient ultimately dying [14], requiring hospitalization [9], having severe illness requiring intensive care [7], or in hospice due to concurrent malignancy [2]); presence of extrapulmonary disease outside of lymph nodes or pleura (28, 21.9%; including spine [4], eye [4], peritoneal/omental [4], gastrointestinal [3], skin [3], bone [2], genitourinary [2], central nervous system [2], joint [1], pericardial [1], retroperitoneal [1], and intrathoracic [1]); history of end-stage liver disease or baseline elevated serum transaminases (13, 10.2%); documented adverse event to pyrazinamide, isoniazid, or rifamycin while on HRZE before switch to HPMZ (13, 10.2%); known drug–drug interaction with a rifamycin and chronic medications (10, 7.8%); isoniazid monoresistance (6, 4.7%); and end-stage renal disease on hemodialysis (6, 4.7%).

The remaining 30 patients were offered the option of HPMZ treatment. Eight patients declined; the reasons cited included the high pill burden (5) and concern about being treated with a new, nonstandardized short-course regimen (3), leaving 22 patients who were included in the present analysis (Table 2).

The median age of patients who started HPMZ (range) was 32.5 (14–86) years. Seventeen (77.3%) patients were healthy without a known comorbidity; others had diabetes mellitus (3, 13.6%), chronic liver disease (2, 9.1%), chronic alcohol use (2, 9.1%), and chronic lung disease (1, 4.5%).

Patients were diagnosed with pulmonary TB (19, 86.4%), lymph node TB (2, 9.1%), and isolated pleural TB (1, 4.5%). Among those with pulmonary disease, 9 (47.4%) had multilobar disease, and 7 (36.8%) had cavitary disease identified on chest radiograph. Microbiology showed that 12 (63.2%) were AFB smear–positive (6 with numerous AFB on initial smear); PSQ of these specimens did not show mutations concerning for resistance. Thirteen (68.4%) were Xpert MTB/RIF–positive without rifampin resistance, and 15 (78.9%) were culture-positive for Mtb; drug susceptibility testing showed that all Mtb isolates were pan-susceptible. Two

Table 2. HPMZ Treatment Outcomes in San Francisco, August 1, 2021–December 31, 2023

	Total
No. patients started on active TB treatment	160
No. patients offered HPMZ based on inclusion/exclusion criteria	30 (18.8)[a]
No. patients started on HPMZ	22 (13.8)[b]
Median age (range), y	32.5 (14–86)
Male	11/22 (50)
Comorbid illness[c]	
Previous healthy	17/22 (77.3)
Diabetes mellitus	3/22 (13.6)
Chronic liver disease	2/22 (9.1)
Alcohol use disorder	2/22 (9.1)
Chronic lung disease	1/22 (4.5)
TB disease site[d,e]	
Pulmonary	19/22 (86.4)
Unilobar disease	10/19 (52.6)
Multilobar/bilateral disease	9/19 (47.4)
Cavitary	7/19 (36.8)
Pleural only	1/22 (4.5)
Lymph node	2/22 (9.1)
Microbiology, pulmonary disease site	
Acid-fast bacilli smear–positive	12/19 (63.2)
Xpert MTB/RIF–positive	13/19 68.4)
Culture-positive	15/19 (78.9)
Adverse events	
Any adverse event	18/22 (81.8)
Mild (CTCAE grade 1)[f]	7/22 (38.9)
Gastrointestinal (nausea and/or vomiting)	4/22 (18.2)
Rash	2/22 (9.0)
Myalgias	1/22 (4.5)
Moderate (CTCAE grade 2)[f]	10/22 (45.5)
Gastrointestinal (nausea and/or vomiting)	5/22 (22.7)
Nausea and/or vomiting with liver function test values >3× upper limit of normal	2/22 (9.1)
Dermatologic	2/22(9.1)
Dizziness, flushing, palpitations, anxiety	1/22 (4.5)
Severe (CTCAE grade 3)[f]	1/22 (4.5)
Syncope, weakness, nausea, electrolyte abnormality	1/22 (4.5)
HPMZ treatment discontinued due to adverse event(s)	11/22 (50.0)
Median time to first adverse event occurrence (range), d	4.3 (1–63)
Median time to HPMZ cessation (range), d	10.5 (3–70)
Cases who completed HPMZ treatment	9/22 (40.9)
Median time to HPMZ treatment completion (range), d	126 (120–198)
Treatment failure[g]	0/22 (0)[h]
Possible disease recurrence[i]	1/22 (4.5)[j]

Abbreviations: AFB, acid-fast bacilli; CDC, Centers for Disease Control and Prevention; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; EOT, end of treatment; HPMZ, isoniazid-rifapentine-moxifloxacin-pyrazinamide; NAAT, nucleic acid amplification test TB; TB, tuberculosis.

[a]One hundred thirty patients were excluded. Two patients were not started on HPMZ due to a rifapentine shortage at the time of TB treatment start. Reasons for exclusion in the remaining 128 included clinician assessment that the patient was clinically unstable (32; including patient ultimately dying [14], requiring hospitalization [9], having severe illness requiring intensive care [7], or in hospice due to concurrent malignancy [2]); presence of extrapulmonary disease outside of lymph nodes or pleura (28; including spine [4], eye [4], peritoneal/omental [4], gastrointestinal [3], skin [3], bone [2], genito-urinary [2], central nervous system [2], joint [1], pericardial [1], retroperitoneal [1], and intrathoracic [1]); history of end-stage liver disease or baseline transaminitis (13); documented previous adverse events to pyrazinamide, a rifamycin, or isoniazid (13); known drug–drug interaction with a rifamycin and chronic medications (10); presence of isoniazid monoresistance (6); end-stage renal disease on hemodialysis (6); pyrosequencing results not available (3); multidrug resistance (3); HIV infection on non-efavirenz-based antiretroviral therapy (3); prior TB treatment (2); plans to move out of the United States during TB treatment (2); structural heart disease (2); gout with contraindication to pyrazinamide (2); aged <12 years (1); pregnancy (1); and confirmed *Mycobacterium bovis* infection (1).

[b]Eight patients declined due to the HPMZ regimen pill burden (5) or expressed concerns about taking a new nonstandard TB regimen (3).

[c]Patients may have >1 of the comorbidities listed. The patients with chronic liver disease included those with stable chronic hepatitis B (1) and Gilberts syndrome (1).

[d]Site(s) of TB disease were classified according to criteria defined by the CDC Report of Verified Case of TB definitions [13]. For pulmonary sites, this was defined as TB disease inside the lung structure, including lung parenchyma abnormalities identified on chest radiograph and/or by respiratory specimen positive by laboratory testing for TB. For pleural sites, this was defined as TB disease in the pleural space outside the lungs, including pleural effusion or thickening identified on chest radiograph and/or pleural fluid specimen positive by laboratory testing for TB.

[e]Radiographic interpretations of pulmonary TB were not mutually exclusive (eg, a patient could have both cavitary and multilobar/bilateral disease).

[f]All adverse events were graded on a scale of 1–5 according to the CTCAE [12], available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5×11.pdf. The table notes the highest grade adverse event diagnosed for an individual patient. No patients were diagnosed with a grade 4 (life-threatening consequences; urgent intervention indicated) or grade 5 (death) adverse event.

[g]Treatment failure was defined as the following events occurring during TB treatment: (1) death due to TB; (2) clinical or radiographic worsening attributed to TB; or (3) persistently culture-positive sputa for *Mycobacterium tuberculosis* throughout treatment.

[h]One patient was extended to a total treatment duration of 180 doses due to overgrowth of rapidly growing nontuberculous mycobacteria (*M. perigrinum*) on several sputa, making it difficult to determine whether culture conversion to negative happened within 60 doses. Sputa were collected at a hospital where a confirmed outbreak of *M. perigrinum* in an ice machine was occurring.

[i]Disease recurrence was defined as any of the following events occurring after TB treatment completion (119 doses): (1) death due to TB; (2) ≥1 positive sputum culture for *M. tuberculosis* after EOT; or (3) initiation of additional treatment for TB based on clinical discretion including new symptoms or new or worsening radiographic changes.

[j]One patient at 6 months post-EOT was treated for a second time with standard 4-drug therapy with isoniazid, rifampin, ethambutol, and pyrazinamide based on clinical judgment; the patient experienced cough, reversion to new AFB smear–positive sputa, and had new infiltrates on chest CT. The infiltrates had resolved at 2-month follow-up chest CT. Nine finalized sputa AFB cultures were negative for *Mtb*.

(9.1%) patients with pulmonary disease were culture-negative; both were later assessed at 2 months after treatment initiation as not having active TB based on clinical, radiographic, and culture results.

Of the 22 patients, 18 (81.8%) had any AE; the most common mild (CTCAE grade 1) AE was nausea. Eleven (50%) prematurely discontinued HPMZ, including 10 due to moderate (CTCAE grade 2) AEs, including vomiting only (5), nausea and vomiting with elevated serum transaminases (2), rash (2), dizziness, flushing, palpitations and anxiety (1), and 1 patient with a severe (CTCAE grade 3) AE that included syncope, weakness, nausea, and hypokalemia (K = 2.5 meq/mL) leading to a fall and subsequent hospitalization. Fourteen (63.6%) patients had hyperbilirubinemia after start of HPMZ with a high of 5.8 mg/dL; most hyperbilirubinemia was asymptomatic, although 1 patient stopped HPMZ due to vomiting with

associated elevated serum transaminases. The median duration of HPMZ before onset of AEs and stopping HPMZ due to AEs (range) was 4.3 (1–63) days and 10.5 (3–70) days, respectively. The median age of those stopping HPMZ prematurely due to AEs (range) was 43 (23–86) years. All 4 patients aged >50 years stopped HPMZ early due to AEs, with a median time to first adverse event (range) of 7.5 (2–24) days and HPMZ cessation of 20.5 (3–70) days.

Nine (40.9%) patients to date have completed HPMZ treatment. The median duration of HPMZ (range) was 126 (120–198) days; 1 patient was extended because several early sputa cultures were contaminated and overgrown with a rapidly growing nontuberculous *Mycobacterium* spp. (*M. perigrinum*), making it challenging to assess culture conversion to negative. Three and 4 patients completed the 6- and 12-month post-EOT follow-up assessments, respectively. At 6 months post-EOT, 1 patient with a presumed low burden of disease at the time of diagnosis (smear-negative sputa and noncavitary unilobar disease on chest radiograph) developed new cough and a new AFB smear–positive sputum examination. Chest radiograph showed an unchanged nodular cluster in the left upper lobe, but chest computed tomography (CT) revealed new infiltrates. Nine AFB cultures were finalized as negative; PSQ showed no resistance-conferring mutations. The patient was treated conservatively for possible TB recurrence with HRZE for culture-negative TB as per CDC guidelines [1]. The infiltrates resolved at 2-month follow-up chest CT.

DISCUSSION

We found that of all patients evaluated and started on active TB treatment over a 25-month period in SF, >80% did not meet recommended CDC/NTCA inclusion criteria for treatment with HPMZ. This is likely because the recommended criteria approximated those of Study 31/A5349 and excluded patients who were severely ill, had extrapulmonary TB, or had many comorbid conditions [2]. In contrast, in SF in 2022, ∼47% of active TB patients were hospitalized or died at the time of TB diagnosis, 31.6% had extrapulmonary TB, and ∼70% of active TB patients had a diagnosis of ≥2 chronic comorbidities (J. Louie, unpublished data) [9]. Of the 22 SF patients who were started on HPMZ, 8 have completed treatment, with most achieving successful markers of clinical, microbiologic, and radiographic cure at the end of treatment, including 5 with baseline cavitary disease. To date, we have not diagnosed any treatment failures while on HPMZ. Of the 9 who have completed 6 months of post-EOT follow-up, we identified 1 possible case of recurrence by clinical and radiographic parameters that necessitated restart of TB treatment, but without culture confirmation of Mtb recurrence.

These preliminary results are encouraging, although difficult to compare with Study 31/A5349, which was a noninferiority trial with different end points and metrics of success. For example, Study 31/A5349's sample size calculations were based on an assumption that 15% of participants would have an unfavorable outcome (including TB-related outcomes such as TB-related death, failure to achieve culture conversion by EOT, or clinical diagnosis of TB recurrence leading to re-initiation of treatment), which is much higher than the usual TB treatment failure or recurrence rates of <1% in SF with standard HRZE therapy (J. Louie, unpublished data) [2]. The trial design also assumed that a number of patients would be lost to follow-up and used a time point for success of 12 months after start of treatment (8 months after EOT); in contrast, in SF most patients are able to maintain close to 100% adherence, and treatment success is measured at 12 months after the EOT [2]. More data are needed to better understand how outcomes in HPMZ-treated patients in the United States will compare to the Study 31/A5349 findings.

Our results are notable for the high proportion of patients who experienced a treatment-related AE compared with Study 31/A5349. This is likely due to the different safety outcomes measured. In Study 31/A5349, while participants were monitored for all AEs (CTCAE grade 1–5), only severe AEs (CTCAE grade 3 or higher) were used as a primary safety end point [2]. In the participants randomized to HPMZ, 18.8% had any CTCAE grade 3–5 AE; common AEs included blood and lymphatic system disorders (7.2%) and hepatobiliary disorders (4.6%) [2]. In contrast, in our SF clinic setting even mild to moderate AEs (CTCAE grade 1–2) may affect treatment adherence [3]. Over 80% of our patients experienced any AE; the most common were moderate (CTCAE grade 2), including rash, nausea, and vomiting. While only 1.9% of HPMZ patients in Study 31/A5349 required a change in treatment because of AEs, half of SF patients had AEs that required premature discontinuation of HPMZ, including all 4 patients aged >50 years. It is unlikely that SFDPH clinicians and nurse case managers were biased to assess AEs and hold TB treatment in HPMZ patients compared with patients on standard HRZE. The standard protocol in the SFDPH TB clinic is to hold TB treatment regardless of the regimen for any patients with symptoms that the patient reports as debilitating or affecting activities of daily life, or abnormal laboratory values that meet certain thresholds (eg, CTCAE grade 2 or higher). Deducing which drugs may be causing AEs may be difficult with multidrug TB therapy. In a 5-year review of SF TB patients, 26.2% had treatment-related AEs resulting in drug discontinuation, including due to pyrazinamide (21.5%), a fluoroquinolone (16.9%), a rifamycin (7.3%), and isoniazid (5.9%); older patients were significantly more likely to have treatment-related AEs [3].

Our experience illustrates the challenge of extrapolating clinical trial findings to routine clinical practice. By necessity, many randomized controlled trials studying new TB drugs and regimens are conducted in high-burden countries to recruit participants in large enough numbers to power analysis of study

outcomes. Clinical trial exclusion criteria, which are designed to ensure enrollment of a trial population likely to permit assessment of the primary outcome(s), may restrict the generalizability of findings even in large, pragmatic Phase 3 trials. As a result of these factors, participant demographics, comorbidities, chronic medications, and associated drug–drug interactions may differ from those common in resource-rich settings. Furthermore, protocol-defined or investigator-led thresholds for discontinuing medications due to AEs are likely different than in US programmatic settings.

While our number of patients started on HPMZ to date is small and the medical complexity of patients seen at the SFDPH TB clinic may differ from other centers, the incidence of AE we observed suggests that there may be challenges to widespread implementation of this regimen, particularly in an older population with multiple comorbidities. At the same time, the impact of shortening treatment duration for a disease that has historically required treatment of 6 months or longer, particularly for those with cavitary disease, may be substantial, including reducing the need for clinical and public health resources required for medical management, laboratory testing, and DOT. Further experience in the United States may help identify how best to practically implement HPMZ, including identifying predictors of which patients are most likely to benefit from and tolerate this regimen.

Acknowledgments

We thank the SFDPH Tuberculosis clinic staff for their diligent care of our patients, with special acknowledgement to Rebecca Abelman, Christopher Berger, Gabriel Chamie, Jose Gonzales, Stephen Goodman, Michelle Huang, Min Naing Ma Khine, George Lee, Ana Li, Talibah Miller, Gloria Perez, Haiyan Ramirez-Batlle, and Ann Schraufnagel.

Potential conflicts of interest. All authors: no reported conflicts.

Financial support. This study was funded by the San Francisco Department of Public Health.

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