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Challenges to initiate and complete a 4-month rifapentine-moxifloxacin TB treatment regimen

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SUMMARY

BACKGROUND: In February 2022, the U.S. Centers for Disease Control and Prevention (CDC) recommended a 4-month rifapentine-moxifloxacin based regimen (4-HPMZ) for treating drug-susceptible pulmonary TB. We describe 4-HPMZ implementation, treatment outcomes, and regimen tolerability at New York City (NYC) Health Department TB clinics.

METHODS: A multidisciplinary workgroup developed a 4-HPMZ implementation plan and protocol based on CDC patient eligibility guidance. Treatment outcomes were classified as ‘completed’ when 4-HPMZ was completed within 5 months or ‘discontinued’ when 4-HPMZ was stopped due to clinical or programmatic reasons. Adverse events (AEs) included abnormal lab results, or any medication-related concern reported by patients.

RESULTS: Between April 2022 to December 2023, 617 patients with TB visited NYC Health Department TB clinics; for 4-HPMZ, 333 (54%) were ineligible and 284 (46%) were eligible. Of the eligible patients, 40 (14%) were prescribed 4-HPMZ; of these, 36 initiated 4-HPMZ treatment, 13 (36%) completed treatment, and 23 (64%) discontinued. A total of 15 patients (42%) discontinued due to AEs.

CONCLUSION: Significant programmatic and clinical challenges were associated with initiation and completion of 4-HPMZ treatment. As a result, few patients completed treatment. Further assessment is needed to identify populations most likely to initiate and complete 4-HPMZ.

Keywords

Mycobacterium tuberculosis ; tuberculosis; treatment; public health; New York City; USA

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On February 25, 2022, the Centers for Disease Control and Prevention (CDC) issued guidance recommending a new treatment option for patients aged ≥ 12 years with drug-susceptible pulmonary TB.¹ The guidance was based on results from a multi-country, randomized controlled clinical trial study (31/A5349) which demonstrated non-inferiority of a 4-month rifapentine-moxifloxacin based-regimen (4-HPMZ) to the standard 6-month regimen in the treatment of pan-susceptible TB.² CDC recommended using the 4-HPMZ regimen consisting of 8 weeks of daily treatment with rifapentine (RPT), isoniazid (INH), pyrazinamide (PZA) and moxifloxacin (MOX), followed by 9 weeks of daily treatment with RPT, INH and MOX. In the United States (US), guidelines for the treatment of drug-susceptible TB have heretofore recommended a 6-month regimen, which consists of an intensive phase of 2 months of INH, rifampin (RIF), PZA and ethambutol (EMB) (HRZE), followed by a continuation phase of 4 months of INH and RIF (HR).³ However, shorter regimens, may have the potential to reduce length of treatment, increase adherence, and thus reduce TB incidence.^{4,5} The CDC guidance does not recommend the use of 4-HPMZ for all patients; exclusions include pregnant women, patients aged < 12 years, and patients with extrapulmonary TB,¹ consistent with the patient population in study 31/A5349² and recommendations from WHO for the use of 4-HPMZ.⁶

Despite the updated published guidelines for the treatment of TB,^{6,7} few TB programs have implemented 4-HPMZ, and only one retrospective cohort study has reported findings.⁸ That study had a small sample size with limited demographic and clinical information; widespread program adoption of 4-HPMZ was limited.⁸ Results of the study alerted public health practitioners to concerns about patient discontinuation of 4-HPMZ treatment due to AEs.⁸ We therefore sought to determine prospectively whether 4-HPMZ treatment could be effective under routine programmatic conditions with a diverse patient population. In this report, we describe 4-HPMZ implementation, treatment outcomes and regimen tolerability at New York City (NYC) Health Department TB clinics.

METHODS

A multidisciplinary workgroup comprised of clinical and program staff developed the NYC Health Department 4-HPMZ implementation plan, protocol, data analysis plan, patient educational materials, provided training, and job aides for clinical and program staff (Supplementary Data Figure S1). On April 11, 2022, NYC Health Department physicians began offering the 4-HPMZ regimen.

Patient eligibility

Consistent with CDC guidance, eligibility criteria included patients aged ≥ 12 years with drug-susceptible pulmonary TB.¹ Eligibility criteria included patients with extrapulmonary pleural or lymphatic TB and patients with presumptive TB, as recommended in the CDC guidance under clinical considerations.¹ Patients choosing to participate were required to agree to directly observed treatment (DOT) per NYC Health Department standards⁹ (Supplementary Data Table S1). Patients were excluded if they had > 30 days of TB therapy before their first outpatient NYC Health Department clinic visit, had extrapulmonary TB

other than pleural or lymphatic, or had other exclusion criteria (Table S1) listed in the CDC recommendations.¹

Implementation

The project coordinator pre-screened patients scheduled for initial clinic visits at the NYC Health Department and informed physicians and nurses of eligible patients before clinic visits. If the patient met eligibility criteria, and if the physician decided to prescribe 4-HPMZ, the physician informed patients about potential adverse events (AEs) and DOT. Physicians' reasons for not prescribing 4-HPMZ or patients' refusals of 4-HPMZ were documented. Similar to HRZE and other regimens, 4-HPMZ was empirically prescribed to patients following NYC Health Department clinical practices.⁹ Due to the limited availability of RPT,¹⁰ physicians initially prescribed a 2-week dose of RPT, assessed the patient's 4-HPMZ tolerability, and prescribed an additional 2-week supply of RPT to patients tolerating treatment. After the initial 2 weeks of 4-HPMZ treatment, follow-up visits were scheduled monthly. During monthly follow-up visits, physicians reviewed treatment progress, assessed AEs, and medication compliance, and ordered laboratory tests. The NYC Health Department 4-HPMZ protocol did not include follow-up visits after treatment completion.

Data collection and procedures

A REDCap database^{11,12} (Version 14.0.11 Vanderbilt University, Nashville, TN, USA) hosted at the NYC Health Department was developed to collect patient eligibility information and documented by the project coordinator. Clinical data were obtained from the NYC Health Department TB clinic electronic medical record (EMR) and included all eligible patients evaluated for TB by physicians between April 2022 and December 2023. Demographic information was collected from the NYC Health Department TB electronic disease surveillance and case management system. (Maven 6.3.2, Conduent Inc, Florham Park, NJ).

Outcomes and statistical analysis

Demographic and clinical characteristics of patients prescribed 4-HPMZ (4-HPMZ patients) were compared to patients not prescribed 4-HPMZ (non-4-HPMZ patients). The reasons for not prescribing 4-HPMZ were tabulated. Additionally, we assessed the treatment outcomes of patients who were prescribed HRZE before 4-HPMZ treatment. Treatment outcomes were assessed for completion or discontinuation of 4-HPMZ treatment. Patients who moved during treatment, died (from causes unrelated to TB), had TB ruled out, or were prescribed but did not initiate 4-HPMZ treatment were excluded. Treatment outcomes were classified as 'completed' when physicians documented completion of 4-HPMZ regimen within 154 days or 5 months,¹ as 'completed late' when medication doses were administered past 154 days of treatment initiation, or as 'discontinued' when 4-HPMZ was discontinued due to AEs, loss to follow-up, low DOT compliance, or TB resistance to INH, RIF, PZA or fluoroquinolones (FQ).

AEs included abnormal lab results, or any medication-related concern reported by patients during physician visits. AEs reported during 4-HPMZ treatment were tabulated by days

on treatment before AE reports; frequency, type, and severity of AEs; clinical action in response to AEs; and treatment status after AE reports. Additionally, the proportion of patients who switched to alternative TB regimens after 4-HPMZ discontinuation due to AEs was assessed. Two NYC Health Department physicians reviewed and graded AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events.¹³ We compared the demographic and clinical characteristics of 4-HPMZ patients and non-4-HPMZ patients. Among 4-HPMZ patients, we also compared demographic and clinical characteristics with treatment outcomes (patients who completed 4-HPMZ treatment versus patients who discontinued treatment) and with AEs (patients who reported AEs versus patients who did not report AEs). R Studio (Version 4.2.3)¹⁴ was used for bivariate analyses (Fischer's exact tests, Wilcoxon ranked sum tests, and Chi-squared tests) for descriptive summaries; the significance threshold was $p=0.05$.

The NYC Health Department Institutional Review Board approved this evaluation (22–033). Data were collected as part of NYC Health Department TB program services. This activity was reviewed by the CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.

RESULTS

Between April 2022 and December 2023, 617 patients with confirmed or presumptive TB visited NYC Health Department TB clinics. Of 617 patients, 333 (54%) were ineligible for 4-HPMZ treatment and 284 (46%) were eligible (Figure 1). Of 333 ineligible patients, 217 (65%) had been prescribed TB medications for >30 days. Additionally, 46 (14%) were ineligible due to an extrapulmonary site of TB disease other than pleural or lymphatic. Other reasons for ineligibility were specific to TB medications (17%, 56/333), i.e., known drug resistance before the initial clinic visit, medication contraindication (e.g., hyperbilirubinemia), or medication intolerance (e.g., PZA intolerance). Patient characteristics such as age <12, pregnancy, or weight <40 kilograms accounted for 4% (14/333) of ineligibility.

Eligibility for 4-HPMZ

Of 244 eligible patients who were not prescribed 4-HPMZ, 164 (67%) did not have documented reasons for why 4-HPMZ was not prescribed in their records, therefore we are unable to report this data. The remaining 80 (33%) had documented reasons. Of these, 62 (78%) were not prescribed due to physician decision, 10 (13%) patients refused due to the high number of pills in the regimen, and 8 (10%) refused to change from HRZE to 4-HPMZ (Figure 1). Among 62 patients not prescribed due to physician decision, 42% (26/62) had multiple medical conditions (e.g., cancer, cardiopulmonary disease, renal insufficiency), 16% (10/62) were tolerating HRZE treatment, 15% (9/62) were having AEs on current TB treatment, 8% (5/62) were having potential drug interactions, 5% (3/62) were of older age, 5% (3/62) had received TB medications in the previous year before initiating TB treatment, and 10% (6/62) had other reasons.

Patient demographic and clinical characteristics

Among 284 eligible patients, 40 (14%) were prescribed 4-HPMZ and 244 (86%) were not prescribed (Table 1). Compared to non-4-HPMZ patients, 4-HPMZ patients were younger (median age 38 [IQR: 29, 61] vs 52 [IQR: 32, 67], $p=0.047$) had a greater proportion of sputum-smear-positive pulmonary TB (66% [25/38] vs 36% [75/211], $p<0.001$), and fewer 4-HPMZ patients had comorbidities (28% [11/40] vs 45% [110/244], $p=0.037$). While not statistically significant, 4-HPMZ patients had no hepatitis (0% [0/40] vs 7% [17/244], $p=0.14$), a greater proportion had a cavitory CXR (29% [11/40] vs 14% [29/244], $p=0.072$), and a smaller proportion were prescribed other non-TB medications (38% [15/40] vs 53% [130/244], $p=0.064$) compared to non-4-HPMZ patients.

Treatment outcomes

Among the 40 4-HPMZ patients, 3 (7.5%) were later determined not to have active TB and 1 (2.5%) refused to initiate 4-HPMZ. Among the remaining 36, 13 (36%) completed treatment with 4-HPMZ and 23 (64%) discontinued 4-HPMZ treatment (Table 2). Among 13 patients who completed 4-HPMZ treatment, three completed in 4 months, seven within 5 months, and three after 5 months: one had treatment extended due to poor adherence, one had treatment extended due to lack of improvement in chest X-ray (CXR), and one had treatment extended due to AE associated with PZA. Median days of 4-HPMZ treatment for those who completed treatment ($n=13$) was 135 days (IQR: 122, 157), see Figure 2. Of the remaining 23 who discontinued 4-HPMZ, the median duration of 4-HPMZ treatment was 28 days (IQR: 14, 77). Among those who completed TB treatment with 4-HPMZ, most (85%, 11/13) were between the ages of 18 and 64 (Supplementary Data Table S2). Among eight 4-HPMZ patients aged >65 , seven (88%) discontinued treatment, six due to reported AEs (e.g., nausea, abdominal pain, elevated LFTs) and one due to lack of significant improvement in CXR after nearly 4 months. Among the 13 patients who completed 4-HPMZ, 46% (6/13) initiated HRZE (20 median days [IQR: 14, 27.5]) before 4-HPMZ treatment. Similarly, 43% (10/23) of patients who discontinued 4-HPMZ initiated HRZE (19 median days [IQR: 15.5, 21.8]) before 4-HPMZ treatment.

Adverse events

Among 36 patients who initiated 4-HPMZ, 23 (64%) reported a collective total of 35 AEs (Table 3). Median time from treatment initiation to first AE was 12 days (IQR: 6, 14). The most common first reported AEs were gastro-intestinal (GI) (83%, 19/23) (Supplementary Data Table S3). Of the 23 with AEs, 12 (52%) reported two AEs during 4-HPMZ treatment and 11 (48%) reported one AE. Eighteen (78%) patients had Grade 1 or 2 AEs, and five (22%) patients had Grade 3 AEs. Of the 35 AEs reported, 19 (54%) were gastro-intestinal and Grade 1 or 2. Of five patients with Grade 3 AEs, two patients presented to hospital due to extreme abdominal pain, two patients had liver function tests (LFTs) >5 times the upper limit of normal, and one patient had facial swelling. Patients with Grade 3 AEs had symptoms resolved after discontinuing 4-HPMZ: four switched to alternative TB regimens (HRZE [$n=2$] and RIF and INH [$n=2$]); one had elevated LFTs, restarted 4-HPMZ, and completed treatment in 7 months.

Patients who did not report AEs did not have diabetes (0% [(0/13) vs 30% [7/23], $p=0.034$) (Supplementary Data Table S4). More patients with reported AEs were prescribed other non-TB medications in comparison to those who did not report AEs (52% [12/23] vs 23% [3/13], $p=0.089$). Patients who reported AEs had an older median age (45 [IQR: 32–64] vs 30 [IQR: 25–53], $p=0.084$), and 52% ($n=12$) vs 31% ($n=4$) were ≥ 45 years, compared to those who did not report AEs. Four of five patients who reported Grade 3 AEs were ≥ 60 years. Among the 23 who reported AEs, five (22%) completed 4-HPMZ treatment, 15 (65%) discontinued 4-HPMZ due to AEs, one (4%) discontinued due to low DOT compliance, one (4%) discontinued due to a physician decision because patient's weight was near 40 kilograms, and one (4%) was re-challenged with 4-HPMZ but discontinued due to PZA resistance and lack of improvement in CXR after 4 months of treatment. Among the 15 who discontinued due to AEs, 7 (46%) had GI-related issues documented in their report (Supplementary Data Table S5). All were switched to a different rifamycin-containing regimen; all completed treatment and 14 (93%) completed a rifamycin-based regimen (Supplementary Data Table S6).

DISCUSSION

The New York City Health Department was one of the first TB programs to implement 4-HPMZ treatment,¹⁵ although more than half (54%) of the patients who visited NYC Health Department TB clinics were ineligible for 4-HPMZ, primarily due to current TB diagnosis with >30 days of treatment prior to the first clinic visit. Few eligible patients (14%) were prescribed 4-HPMZ, as physicians expressed concerns about offering 4-HPMZ because the patient was tolerating current TB treatment, had comorbidities or older age, or refused. In NYC, most patients are diagnosed and initiate TB treatment while hospitalized. One way to increase 4-HPMZ uptake in NYC would be for the initiation of the regimen while hospitalized. Initiation of the regimen would require increased education to hospital-based providers and to have RPT available in hospital pharmacies. During this implementation, procurement of RPT was not a barrier in NYC Health Department clinics as we were able to obtain RPT.

In this evaluation, more than half of the patients (64%) who initiated 4-HPMZ discontinued treatment, and 42% of patients who started 4-HPMZ discontinued due to AEs. By comparison, discontinuation of treatment due to AEs is much less commonly seen in treatment with HRZE.^{16,17} All patients who discontinued 4-HPMZ were initially switched to a rifamycin-based regimen. While there are no guidelines on use of alternative regimens after discontinuation of 4-HPMZ, physicians used clinical judgment to determine the appropriate regimen and length of treatment. Compared to 4-HPMZ patients who did not report AEs, 4-HPMZ patients who reported AEs were older, had more diabetes, and were more frequently prescribed other non-TB medication. Comparing eligible patients in this present evaluation to participants of study 31/A5349, patients in this evaluation were older with a median age of 38 (29, 61) vs 31 (14.6–72.5) years.² Older age and comorbidities are commonly associated with reported AEs.^{18–20} Our patients developed low grade AEs early in treatment which necessitated discontinuation of 4-HPMZ. Most AEs reported were consistent with known AEs of the individual drugs in the 4-HPMZ regimen, with gastro-intestinal complaints being the most common^{21–23}. The proportion of Grade 3 AEs

in our study (14%) was comparable to that of study 31/A5349 (18%)². However, many of our patients with lower grade AEs did not complete treatment. High rates of treatment discontinuation due primarily to AEs have been reported by the San Francisco TB program, which had many similarities to ours.⁸ While the numbers are small, the relative high number of AEs reported by the San Francisco program and by our program that prompted discontinuation of 4-HPMZ treatment affirms AEs as cause for concern. Other reasons for discontinuing treatment, such as poor adherence, may highlight the need for programmatic solutions.

In our evaluation, the low number of patients prescribed 4-HPMZ largely reflected those already tolerating standard TB treatment before arriving to the NYC TB clinics and/or lack of desire of the patients and physicians to switch to 4-HPMZ. For our population, a potential mechanism to increase uptake of this new shorter regimen may be to offer 4-HPMZ when treatment is initiated in hospital. Because 4-HPMZ is currently not often prescribed, the sample size for this evaluation was limited.

CONCLUSION

Although a small group of patients completed treatment with 4-HPMZ, this evaluation uncovered significant programmatic and clinical challenges associated with initiating and completing this regimen. While most patients in NYC receive HRZE, 4-HPMZ will continue to be offered to select populations such as patients not available to complete treatment within six months or at risk for not completing for other reasons. Further assessment is needed to determine populations most likely to initiate and complete 4-HPMZ, as more real-world evidence will be needed to optimally operationalize use of this new treatment regimen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

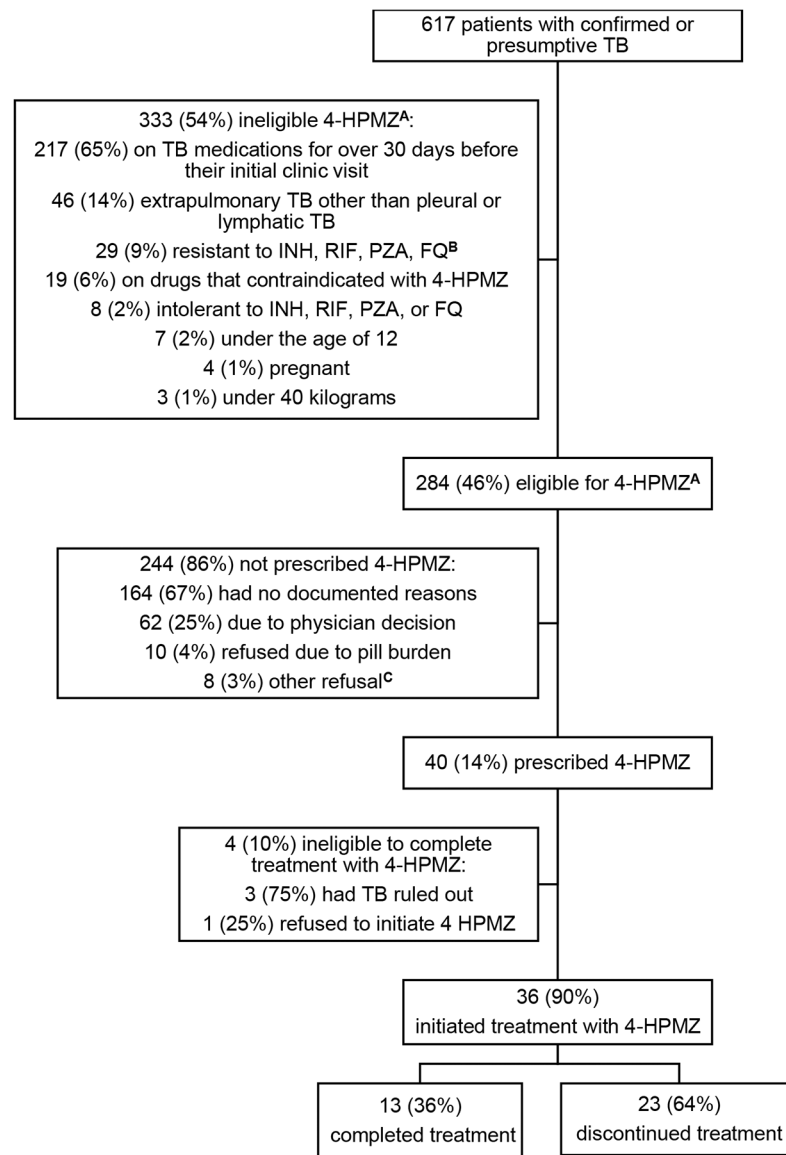
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**Figure 1.**

Patient eligibility, screening, and treatment outcomes for 4-HPMZ at New York City Health Department TB clinics, April 2022–December 2023.

^A4-HPMZ 4-month TB treatment regimen with rifapentine, isoniazid, pyrazinamide and moxifloxacin; ^BPatients with TB organism resistant to isoniazid, rifapentine, pyrazinamide, or fluoroquinolones; ^CPatients who had other refusal were on HRZE and did not want to change from their current regimen.

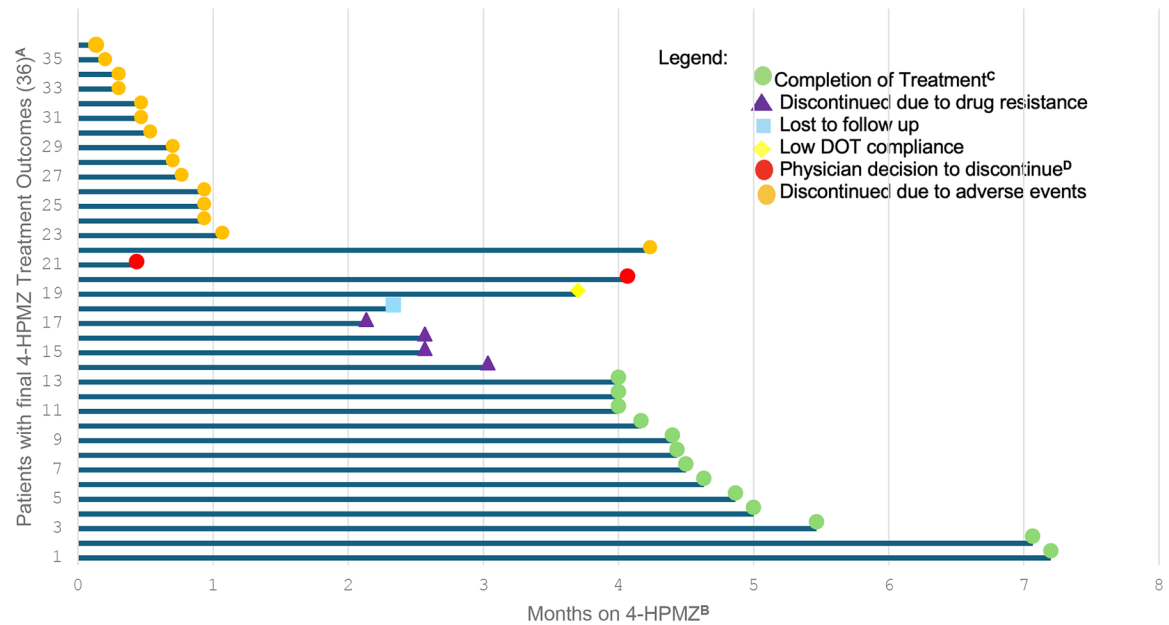


Figure 2.

4-HPMZ (4-month TB treatment regimen with rifapentine, isoniazid, pyrazinamide and moxifloxacin) outcomes by months on treatment.

^A Each symbol represents a patient who initiated treatment with 4-HPMZ; ^B Each month on the x-axis represents 30 days of treatment with 4-HPMZ; ^C Completed all doses of 4-HPMZ treatment; ^DPhysician decision to discontinue: one patient's borderline weight nearing 40 kilograms, one lacked improvement in chest X-ray after nearly 4 months of treatment. Patient #22, who discontinued due to AEs after 4 months of treatment, experienced AEs early on treatment and physician planned on extending treatment before patient had acute cholecystitis and 4-HPMZ was discontinued.

Table 1.

Demographic and clinical characteristics of eligible patients who were prescribed versus not prescribed 4-HPMZ at NYC Health Department TB Clinics, April 2022–December 2023.

Variable	Patients not prescribed 4-HPMZ, N=244 ^A	Patients prescribed 4-HPMZ, N = 40 ^A	p-value ^B
Age (median [IQR])	52 (32,67)	38 (29,61)	0.047
Age groups			0.015
12–17	0 (0%)	2 (5%)	
18–44	94 (39%)	20 (50%)	
45–64	77 (32%)	10 (25%)	
65+	73 (30%)	8 (20%)	
Sex			0.36
Female	85 (35%)	11 (28%)	
Male	159 (65%)	29 (72%)	
Birthplace			0.51
Non-US born	227 (93%)	36(90%)	
US born	17 (7.0%)	4 (10%)	
Site of disease			0.33
Extrapulmonary	32 (13%)	2 (5%)	
Pulmonary	169 (69%)	29 (72%)	
Pulmonary and extrapulmonary	43 (18%)	9 (22%)	
Positive sputum smear ^C	75 (36%)	25 (66%)	<0.001
Chest X-ray result ^C			0.072
Cavitary consistent with TB	29 (14%)	11 (29%)	
Non-cavitary consistent with TB	170 (80%)	25 (66%)	
Not consistent with TB	13 (6.1%)	2 (5.3%)	
Known positive HIV status	2 (1.0%)	0 (0%)	>0.9
Diabetes	52 (21%)	7 (18%)	0.58
Hepatitis	17 (7.0%)	0 (0%)	0.14
Hypertension	51 (21%)	8 (20%)	0.90
Hyperlipidemia	28 (11%)	4 (10%)	>0.9
Coronary artery disease	9 (3.7%)	1 (2.5%)	>0.9
History of cancer	11 (4.5%)	0 (0%)	0.37
Other comorbidities ^D	110 (45%)	11 (28%)	0.037
Other non-TB medications	130 (53%)	15 (38%)	0.064

^A Median (IQR); n (%);

^B Wilcoxon rank sum test; Fisher's exact test; Pearson's Chi-squared test;

^C Includes patients started on TB treatment because of a presumptive pulmonary TB diagnosis. TB was later ruled out in some patients and treatment was discontinued;

^D Other comorbidities refer to medical conditions reported at the first visit, not already listed in the table.

US = United States.

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Table 2.

Outcomes of treatment with 4-HPMZ (4-month TB treatment regimen with rifapentine, isoniazid, pyrazinamide and moxifloxacin).

Outcomes ^A	N = 36 (%)
Completed 4-HPMZ treatment ^B	13 (36%)
Completed all doses within 5 months	10 (77%)
Completed all doses >5 months	3 (23%)
Discontinued 4-HPMZ treatment	23 (64%)
Discontinued due to adverse events	15 (65%)
Discontinued due to TB resistant to INH, RPT, PZA or FQ ^C	4 (17%)
Discontinued due to lost to follow up	1 (4%)
Discontinued due to low DOT adherence	1 (4%)
Discontinued due to physician decision ^D	2 (9%)

^A Of 40 patients prescribed 4-HPMZ, 3 were determined to not have TB, one did not initiate treatment after 4-HPMZ prescribed;

^B Documented completion of 4-HPMZ doses within 154 days or 5 months;

^C Four patients were discontinued due to TB resistance: two were resistant to INH, one to PZA, and one to FQ;

^D Physician decision to discontinue: 1 patient's weight was nearing 40 kilograms, one lacked improvement in chest X-ray after nearly 4 months of treatment.

Table 3.

Reported adverse events by NYC Health Department TB clinic patients treated with 4-HPMZ (4-month TB treatment regimen with rifapentine, isoniazid, pyrazinamide and moxifloxacin).

Signs and Symptoms of Adverse Events Reported ^{A,B}	Grade 1 or 2 ^C AE N = 30	Grade 3 ^C AE N = 5
Gastro-intestinal (GI) issues	19(63%)	2(40%)
Nausea	9(47%)	0(0%)
Vomiting	5(26%)	0(0%)
Diarrhea	2(11%)	0(0%)
Abdominal pain	3(16%)	2(100%)
Other GI (e.g., bloating, GERD ^D)	7(37%)	0(0%)
Rash	7(23%)	0(0%)
Elevated liver function tests ^E	4(13%)	2(40%)
Dizziness	4(13%)	0(0%)
Fatigue	3(10%)	0(0%)
Other body pain (e.g., leg, shoulder)	4(13%)	0(0%)
Loss of appetite	3(10%)	0(0%)
Other signs and symptoms reported ^F	9(30%)	1(20%) ^G

^A 23 patients reported a total of 35 AEs, and 12 (52%) patients reported two AEs. No Grade 4 AEs were reported;

^B Patients (n=14) 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 Elevated liver function tests were Grade 3 if >5 times the upper limit of normal;

^F Other signs and symptoms reported included: insomnia, night sweats, flushing, paresthesia, acute cholecystitis, eye and skin discoloration, facial edema, eye lesion, weight loss, gout;

^G Rapid facial swelling.