Treatment for Tuberculosis Infection With 3 Months of Isoniazid and Rifapentine in New York City Health Department Clinics

Natalie L. Stennis, Joseph N. Burzynski, Cheryl Herbert, Diana Nilsen, and Michelle Macaraig

New York City Department of Health and Mental Hygiene, Bureau of Tuberculosis Control, Long Island City, New York

Background. Completion of treatment for tuberculosis infection (TBI) with 9 months of self-administered daily isoniazid (9H) has historically been low (<50%) among New York City (NYC) Health Department tuberculosis clinic patients. Treatment of TBI with 3 months of once-weekly isoniazid and rifapentine (3HP) administered under directly observed therapy (DOT) might increase treatment acceptance and completion.

Methods. The study population included patients diagnosed with TBI at 2 NYC Health Department tuberculosis clinics from January 2013 through November 2013. Treatment acceptance and completion with 3HP were compared with historical estimates. Treatment outcomes, side effects, and reasons for refusing 3HP were described.

Results. Among 631 patients eligible for TBI treatment, 503 (80%) were offered 3HP; 302 (60%) accepted, 92 (18%) chose other treatment, and 109 (22%) refused treatment. The most common reason for refusing 3HP was the clinic-based DOT requirement. Forty (13%) patients treated with 3HP experienced side effects—9 were restarted on 3HP, 18 switched treatment regimens, and 13 discontinued. Although treatment acceptance did not differ from historical estimates (78% vs 79%, P = .75), treatment completion increased significantly (65% vs 34%, P < .01).

Conclusions. Implementation of 3HP in 2 NYC Health Department tuberculosis clinics increased TBI treatment completion by 31 percentage points compared with historical estimates. More flexible DOT options may improve acceptance of 3HP. Wider use of 3HP may substantially improve TBI treatment completion in NYC and advance progress toward tuberculosis elimination.

Keywords. Latent tuberculosis infection; 3-month treatment; directly observed therapy; public health.

Treatment of tuberculosis infection (TBI) is recommended for individuals at increased risk of progressing to tuberculosis disease and is a key element in the strategy to eliminate tuberculosis in the United States and globally [1–3]. The standard regimen for TBI treatment in the United States is isoniazid (INH) taken daily for 6 to 9 months [4]. The length of TBI treatment and potential adverse effects of the medication are barriers to treatment completion [5]. In 2011, an estimated 66% of contacts to active tuberculosis cases in the United States completed treatment for TBI, well below the national objective of 79% [6].

New York City (NYC) is home to a diverse population of more than 8.4 million residents, 37% of whom are foreign-born [7]. Based on TBI testing results from NYC Department of Health and Mental Hygiene (DOHMH) tuberculosis clinics, an estimated 16% of NYC residents are infected with tuberculosis [8]. However, acceptance of and adherence to TBI treatment with 9 months of INH (9H) has historically been low among health department tuberculosis clinic patients, with overall treatment completion below 50% [9]. Various strategies to increase TBI treatment completion have been explored, including the use of incentives such as transportation subsidies and food coupons, directly observed therapy (DOT), and telephone monitoring [10]. However, these approaches have not been sustainable nor have they resulted in substantial improvements (NYC DOHMH, unpublished data).

In 2011, the Centers for Disease Control and Prevention (CDC) released guidelines for the use of 3 months of once-weekly isoniazid and rifapentine (3HP) for the treatment of TBI [11]. These guidelines were based on the results of an open-label, randomized trial of 3HP vs 9H. The study concluded that 3HP was as effective as 9H for the prevention of tuberculosis disease and resulted in higher treatment completion (82% vs 69%, P < .001) [12]. Based on these results and CDC recommendations, the NYC DOHMH began offering 3HP at 2 health department tuberculosis clinics in January 2013. A study of the implementation was conducted to determine the feasibility of providing 3HP, the impact of 3HP on treatment acceptance and completion, and the acceptability and tolerability of the regimen for patients.
STUDY POPULATION AND METHODS

The study population included patients diagnosed with TBI at 2 NYC Health Department tuberculosis clinics from 14 January 2013 to 6 November 2013. These clinics served more than 6000 patients in 2013 and provided tuberculosis evaluation and treatment free of charge to individuals recently exposed to an infectious tuberculosis case; patients referred by other providers; individuals seeking clearance for housing, homeless facilities, or rehabilitation centers; and newly arrived immigrants and refugees. Using 2011 data from clinic A, we estimated that 79% of patients historically initiated treatment for TBI and 34% completed treatment. An enrollment goal of 300 patients was established to detect an increase of ≥6 percentage points in treatment initiation and ≥7 percentage points in treatment completion with 80% power and 5% significance. Enrollment at clinic A began in January 2013; the study was expanded to clinic B in May 2013 to accelerate attainment of enrollment goals. Data from clinic B were not used in sample size calculations since expansion was not planned at the study onset; however, historical treatment initiation and completion for clinic B were similar to those for clinic A.

With the exception of some additional data collection, standard clinic operations were maintained throughout the study. All patients aged ≥12 years who were eligible were offered treatment with 3HP; those refusing 3HP were offered 9H or a rifamycin-based regimen. Patients aged <12 years were excluded from treatment with 3HP following CDC guidelines at the time [11]. Other ineligible patients included those meeting any of the exclusion criteria used in the randomized trial of 3HP [12] and patients unable to be contacted by phone to confirm DOT appointments. Patients unable to demonstrate understanding of side effects or signs and symptoms of tuberculosis disease and those without a valid address were considered ineligible for all TBI treatment. Physicians used a structured questionnaire to record patient demographics, eligibility for any TBI treatment and 3HP specifically, and whether or not

![Figure 1](cid:2016:6215242619)
patients were offered and accepted treatment with 3HP. In accordance with clinic protocols, translation services were used for patients who did not speak English.

All clinic patients scheduled for initial medical evaluation following TBI testing were provided with a 3HP fact sheet upon registration at the clinic (Supplementary Figure 1). Patients were further educated about the regimen and potential side effects by a physician during the medical evaluation and by a nurse when the first dose of medication was administered. Patients were also provided with a drug interaction card to share with other providers (Supplementary Figure 2) and a card listing potential side effects of the 3HP regimen, signs and symptoms of tuberculosis disease, and instructions for contacting a health department tuberculosis clinic physician (Supplementary Figure 3). Patients who refused all treatment for TBI or treatment with 3HP were interviewed by study facilitators using a structured questionnaire to elicit reasons for refusal (Supplementary Figure 4).

Per CDC guidelines, patients treated with 3HP were administered medication weekly under DOT at 1 of the 2 health department tuberculosis clinics to minimize improper dosing, monitor for side effects, and encourage adherence [11]. INH was administered at a dose of 15 mg/kg body weight rounded up to the nearest 50 mg or 100 mg with a maximum dose of 900 mg; rifapentine was administered at a dose of 900 mg for patients weighing >50 kg and 750 mg for those weighing ≤50 kg [11]. A dose of 3HP typically consisted of 11 pills: 6 of rifapentine, 3 of INH, and 2 of vitamin B6 (50 mg). Treatment completion was defined as receipt of ≥11 doses within 16

### Table 1. Characteristics of Health Department Tuberculosis Clinic Patients by Treatment Choice Among Those Eligible for and Offered Treatment With 3 Months of Isoniazid and Rifapentine With Directly Observed Therapy, New York City, January–November 2013

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3 Months of Isoniazid and Rifapentine With Directly Observed Therapy, n (%)</th>
<th>Other Treatment, n (%)</th>
<th>Refused Treatment, n (%)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>302</td>
<td>92</td>
<td>109</td>
<td>. . .</td>
</tr>
<tr>
<td>Male sex</td>
<td>154 (51)</td>
<td>32 (35)</td>
<td>45 (41)</td>
<td>.01</td>
</tr>
<tr>
<td>Median age, y (interquartile range)</td>
<td>33 (22, 45)</td>
<td>31 (23, 44)</td>
<td>40 (30, 52)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>US bornc</td>
<td>70 (23)</td>
<td>19 (21)</td>
<td>23 (21)</td>
<td>.85</td>
</tr>
<tr>
<td>English as primary language</td>
<td>128 (42)</td>
<td>40 (44)</td>
<td>54 (50)</td>
<td>.43</td>
</tr>
<tr>
<td>Educational attainmentd</td>
<td>66 (22)</td>
<td>17 (19)</td>
<td>16 (15)</td>
<td>.25</td>
</tr>
<tr>
<td>Less than high school</td>
<td>71 (23)</td>
<td>31 (23)</td>
<td>40 (30, 52)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>High school or higher</td>
<td>216 (71)</td>
<td>70 (76)</td>
<td>80 (73)</td>
<td>.68</td>
</tr>
<tr>
<td>Unknown</td>
<td>20 (7)</td>
<td>5 (5)</td>
<td>13 (12)</td>
<td>.14</td>
</tr>
<tr>
<td>Employedd</td>
<td>82 (27)</td>
<td>29 (32)</td>
<td>22 (20)</td>
<td>.17</td>
</tr>
<tr>
<td>Human immunodeficiency virus status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>1 (&lt;1)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Negative</td>
<td>161 (53)</td>
<td>43 (47)</td>
<td>43 (39)</td>
<td>.04</td>
</tr>
<tr>
<td>Unknown</td>
<td>140 (46)</td>
<td>49 (53)</td>
<td>66 (61)</td>
<td>.03</td>
</tr>
<tr>
<td>Tuberculosis risk category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population riskc</td>
<td>187 (62)</td>
<td>48 (52)</td>
<td>73 (67)</td>
<td>.09</td>
</tr>
<tr>
<td>Medical riskf</td>
<td>56 (19)</td>
<td>23 (25)</td>
<td>26 (24)</td>
<td>.28</td>
</tr>
<tr>
<td>Contact with a tuberculosis case</td>
<td>42 (14)</td>
<td>16 (17)</td>
<td>1 (1)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Other</td>
<td>17 (6)</td>
<td>5 (5)</td>
<td>9 (8)</td>
<td>.59</td>
</tr>
<tr>
<td>Treatment outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed treatment</td>
<td>196 (65)</td>
<td>42 (46)</td>
<td>. . .</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Lost</td>
<td>31 (10)</td>
<td>23 (25)</td>
<td>. . .</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Refused</td>
<td>26 (9)</td>
<td>22 (24)</td>
<td>. . .</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Switched treatment</td>
<td>18 (6)</td>
<td>0 (0)</td>
<td>. . .</td>
<td>.01</td>
</tr>
<tr>
<td>Discontinued due to side effects</td>
<td>13 (4)</td>
<td>0 (0)</td>
<td>. . .</td>
<td>.04</td>
</tr>
<tr>
<td>Other</td>
<td>18 (6)</td>
<td>4 (4)</td>
<td>. . .</td>
<td>.80</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>. . .</td>
<td>.23</td>
</tr>
</tbody>
</table>

a Among patients taking other treatment, 89 (97%) were treated with isoniazid and 3 (3%) were treated with a rifamycin-based regimen.
b P values compare overall differences by treatment choice. P values were calculated using the Pearson χ² or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous data.
c US born includes patients born in the United States, Puerto Rico, and other United States territories.
d Based on patient self-report.
e Population risk includes individuals at increased risk of tuberculosis infection due to demographic and social risk factors including birth outside of the United States, homelessness, and drug or alcohol use.
f Medical risk includes individuals at increased risk of tuberculosis infection due to recent conversion of a test for tuberculosis infection, diabetes, immunosuppressive conditions, or treatment with immunosuppressive drugs.
Patients treated with 3HP were questioned about side effects at weekly DOT visits and were referred to a physician if any were reported. During monthly medical evaluations, physicians evaluated all patients, regardless of treatment regimen, for side effects, adverse reactions, and contraindications. Patients treated with 3HP were asked about 25 specific side effects of INH and rifapentine using a structured questionnaire (Supplementary Figure 5). Data on eligibility for and acceptance of 3HP, reasons 3HP was refused, and side effects information were entered into a database by study facilitators. Basic patient demographics and records of DOT visits were transferred from the health department tuberculosis clinic electronic medical record system to the study database. The database was regularly reviewed by study investigators to ensure data quality. When data were missing, chart reviews were conducted to improve data completeness.

The proportions of study patients initiating and completing 3HP were compared with historical data from clinic A using 1-sample binomial tests. Bivariate associations between treatment eligibility, acceptance, outcomes, and patient characteristics by treatment choice and completion were compared using the Pearson $\chi^2$ or Fisher exact test for categorical variables and the Wilcoxon rank-sum test for continuous data. All tests were performed using 5% significance. Analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, North Carolina). This study was considered to be a public health program evaluation that is not research by the NYC DOHMH Institutional Review Board and did not undergo review.

**RESULTS**

From January 2013 through November 2013, 631 patients diagnosed with TBI and eligible for treatment were evaluated for 3HP eligibility at 2 NYC Health Department tuberculosis clinics (Figure 1). Of these, 514 (81%) were eligible for treatment with 3HP; the most common reasons for ineligibility were age <12 years (53%) and contraindication based on drug interactions (13%). Almost all eligible patients (98%) were offered treatment with 3HP. Among those offered 3HP, 302 (60%) accepted treatment, 92 (18%) chose other treatment, and 109 (22%) refused treatment. The majority of patients (97%) who chose other treatment received 9H; 3 patients were treated with a rifamycin-based regimen. The overall proportion accepting treatment for TBI (78%) was no different from historical estimates (79%, $P = .75$).

Treatment choice among patients eligible for and offered 3HP was associated with patient sex, age, human immunodeficiency virus (HIV) status, and tuberculosis risk category (Table 1). Men and HIV-uninfected individuals were more likely to receive treatment with 3HP, and the median age of patients who refused treatment was significantly higher than of those selecting either 3HP or other treatment. No associations were found between treatment choice and birth in the United States, speaking English as a primary language, education, or employment. The majority of patients offered treatment with 3HP fell into the population risk category, meaning they had increased risk of progressing to tuberculosis disease due to demographic
or social risk factors such as foreign birth, homelessness, or drug and alcohol abuse. Fifty-nine of the 503 patients offered 3HP (12%) had known exposure to an individual with tuberculosis or prior skin testing positive for tuberculosis, although only 12.5% of the patients who chose to refuse 3HP had a known exposure. Among patients who refused all treatment, the most common reasons were not sick (n = 109) or did not need treatment (n = 76; Figure 2). Among the 92 patients who chose another treatment, the most common reasons for refusing 3HP were the clinic-based DOT requirement (n = 81) and concerns about taking time away from work, child care, or other household responsibilities (n = 71).

Overall, 65% of patients treated with 3HP completed treatment with this regimen (Table 1). This was significantly higher than the estimated 34% of health department tuberculosis clinic patients historically completing treatment for TBI (P < .01) and the 46% of patients receiving other therapies who completed treatment (P < .01). Of the 106 patients who did not complete 3HP treatment, 68% discontinued within the first 3 weeks after treatment initiation. The most common outcomes for patients who did not complete treatment with 3HP were loss to follow-up (n = 31), refusal (n = 26), and switching treatment (n = 18). Thirteen patients treated with 3HP were lost to follow-up after their first DOT visit. A higher proportion of patients receiving other treatment refused to continue or were lost to follow-up compared with those receiving 3HP (P < .01). Compared with those who completed 3HP, patients who did not complete 3HP or switched treatment were more likely to be born in the United States (31% vs 19%, P = .02) and to have educational attainment of high school or higher (86% vs 64%, P < .01; Table 2).

Forty patients treated with 3HP experienced side effects (Table 3). Median time from treatment initiation to side effects onset was 3 weeks. The most common side effects were nausea (n = 10), rash/itching (n = 10), abdominal pain (n = 9), and fatigue (n = 9). Among patients experiencing side effects, 8 (20%) completed treatment with 3HP, 18 (45%) switched to another treatment, 13 (33%) discontinued treatment, and 1 (3%) was lost to follow-up after continuing on 3HP. Side effects were generally comparable for patients who did and did not complete 3HP treatment, with the exception of 5 patients with elevated liver function test results, none of whom completed treatment with 3HP; 2 of these patients switched treatments, 2 discontinued treatment, and 1 was lost to follow-up. One patient experienced minor liver injury (liver enzymes greater than 3 times the upper limit of normal) that resolved quickly. This patient had a history of alcohol abuse, prompting the provider to discontinue all treatment. No other patients experienced measurable toxicity.

**DISCUSSION**

The effectiveness of 9H is limited by its lengthy duration, resulting in poor treatment completion [9, 13, 14]. The 3HP regimen, shown to be noninferior to 9H, offers an advancement in TBI treatment by reducing treatment length and increasing adherence [12]. While implementation of 3HP did not increase...
TBI treatment initiation in the health department tuberculosis clinics, the majority of patients who were offered 3HP chose this regimen. Moreover, treatment completion with 3HP improved substantially to 65%. The net effect of 3HP was to increase the proportion of patients completing TBI treatment by 31 percentage points compared with historical estimates.

More than 80% of patients included in the study were eligible for 3HP, but only 78% of eligible patients initiated treatment. Previous work has found that patients’ attitudes toward TBI treatment, including beliefs about the effectiveness of medications and the perceived risk of developing tuberculosis disease, influence treatment acceptance [15]. We similarly found that the majority of patients refusing all treatment for TBI did not believe that they needed treatment. The introduction of 3HP alone could not address these barriers to treatment acceptance. Other studies have found that individuals who are knowledgeable about tuberculosis are more likely to accept treatment and that educational interventions effectively influence patients’ decisions about treatment [16, 17]. Additional work is needed to better understand and improve TBI treatment acceptance.

Among patients who started treatment for TBI, 3HP was preferred over alternative treatment options. Though patients were not asked why they selected 3HP over another treatment, the shorter treatment duration of 3HP likely played a role. Treatment choice was associated with patient age and sex but not with patients’ social characteristics. More than 85% of patients who chose another treatment over 3HP cited the clinic-based DOT requirement as a deterrent and more than one-third mentioned the large pill burden. While DOT is known to improve treatment adherence, it can be inconvenient and intrusive for patients [18, 19]. In response to these findings, the NYC DOHMH has initiated a study of 3HP using video-based DOT [20]. In addition, the CDC Tuberculosis Trials Consortium is currently evaluating the safety and efficacy of self-administered 3HP [21]. Offering patients self-administration or alternative monitoring options, such as DOT in a location of their choosing or via video conferencing, and reformulating 3HP medications to reduce pill burden may increase 3HP acceptance.

Treatment completion among clinic patients treated with 3HP (65%) was nearly double historical estimates but was lower than the 82% observed in the multicenter clinical trial [12]. This discrepancy reflects the reality of treating patients in a large, diverse health department tuberculosis clinic rather than in a controlled study. Implementing 3HP in this setting without adjusting clinic practices revealed some important challenges. Clinic staff initially expressed some hesitation about the new regimen. These concerns were overcome through efforts to educate staff about the potential benefits to both patients and clinic operations. Treatment completion was also likely impacted by some inconsistent follow-up of patients who missed DOT appointments, resulting from staff adjusting to weekly rather than daily DOT schedules and prioritizing follow-up of patients with tuberculosis disease. These challenges highlight important operational changes that were required when 3HP was introduced outside of a study setting. Of note, treatment completion in our study was not impacted by side effects of 3HP. Side effects were generally mild, and only 13 patients (4%) permanently discontinued 3HP treatment due to side effects. Treatment with 3HP was discontinued for 1 patient with a history of alcohol abuse who experienced minor liver injury that resolved quickly; no other patients experienced measurable toxicity.

While the expected increase in treatment completion with 3HP makes it a promising option, the costs of the regimen may limit widespread adoption. In NYC, study initiation was delayed by nearly 9 months until the cost of rifapentine was reduced by 70%. Despite this price decrease [22], the cost of 3HP is still approximately 3 times the cost of 9H. Additionally, while treatment of TBI is a key strategy for tuberculosis elimination in the United States, CDC funding to tuberculosis programs under cooperative agreements does not support TBI treatment, limiting the ability of US tuberculosis programs to achieve the national objective of >79% treatment completion among high-risk individuals [23, 24]. Further reductions in the cost of rifapentine are needed to make this regimen widely accessible. In addition, while computational modeling results suggest that 3HP is cost effective compared with 9H, further work is needed to determine the potential cost-savings of using 3HP in practice [25].

Health department tuberculosis clinic patients are not representative of the overall NYC population; as such, our results may not be generalizable. Individuals exposed to a person with tuberculosis disease tend to have higher treatment completion rates for TBI [9]. Only 12% of the study population had known exposure to an individual with tuberculosis disease, which may have resulted in underestimates of potential increases in treatment completion with 3HP. As an observational study, this analysis relied on historical and concurrently observed data rather than a controlled comparison group to measure increases in treatment acceptance and completion. Recent changes in health department tuberculosis clinic policies to focus resources on high-risk populations may have impacted treatment acceptance and completion in the absence of 3HP. However, it is unlikely that these changes account for the near doubling in treatment completion that was observed. Finally, patients’ reasons for discontinuing treatment were not collected; a better understanding of these factors is needed to inform future interventions.

This report describes the implementation of 3HP in a high-volume public health setting. Implementation of 3HP was integrated into the health department tuberculosis clinics’ existing infrastructure, allowing us to evaluate the use of 3HP in a real-world, nonstudy setting. The questionnaire used to collect reasons why patients did not choose 3HP is unique to this study and provided important insights about patient attitudes toward this regimen.
CONCLUSIONS

The implementation of 3HP at 2 NYC Health Department tuberculosis clinics was successful and resulted in increased treatment completion. Additional work is needed to better understand and address barriers to TBI treatment acceptance. More flexible DOT options may improve acceptance of 3HP. The cost of rifapentine must be further reduced in order to make 3HP more accessible. Wider use of 3HP may substantially improve TBI treatment completion in NYC and advance progress toward tuberculosis elimination.

Supplementary Data


Consisting of data provided by the author to benefit the reader, the posted materials are not copylefted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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