Effectiveness of Isoniazid Treatment for Latent Tuberculosis Infection among Human Immunodeficiency Virus (HIV)–Infected and HIV–Uninfected Injection Drug Users in Methadone Programs

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Injection drug users (IDUs) were heavily affected by the tuberculosis (TB) resurgence in New York City in the 1990s. We assessed the effectiveness of screening for latent TB infection in methadone users and of selective treatment with isoniazid. Risk for future TB was classified as low or high on the basis of tuberculin, anergy, and HIV test results. The cohort of 2212 IDUs was followed up for a median of 4.2 years; 25 IDUs, of whom 20 (80%) were infected with human immunodeficiency virus (HIV), developed TB. In an adjusted Cox proportional hazards model of high-risk IDUs, the risk of TB was associated with HIV infection (HR 10.3; 95% CI, 3.4–31.3); receipt of <6 months of isoniazid therapy (HR 7.6; 95% CI, 1.02–57.1); a CD4+ T lymphocyte count of <200 cells/mm³ (HR 6.6; 95% CI, 1.7–25.9); and tuberculin positivity (HR 4.0; 95% CI, 1.6–10.2). Treatment with isoniazid was beneficial in HIV-infected, tuberculin-positive IDUs.

Due to a high burden of HIV infection and ongoing tuberculosis (TB) transmission, injection drug users (IDUs) were heavily affected by the TB resurgence in New York City in the 1990s [1–5]. We report the results of TB prevention efforts among individuals attending 6 methadone treatment programs in New York City between 1 January 1993 and 31 December 1995. Our analysis focused on 3 primary hypotheses: first, that HIV-infected individuals were at greater risk for TB than were HIV-uninfected participants; second, that treatment with isoniazid for ≥6 months significantly reduced the risk of TB disease; and, third, that tuberculin positivity was a more significant risk factor for TB disease than was cutaneous anergy.

METHODS

In 1990, the Centers for Disease Control and Prevention (CDC; Atlanta, GA) funded HIV-related TB prevention projects throughout the United States to provide isoniazid treatment for latent TB infection (LTBI) to individuals at high risk for TB disease. The TB Control
In the Multitest cell-mediated immunity (CMI) device (Merieux Institute) using 8 tines, which included 7 recall antigens (old tuberculin) and a methylated bovine serum albumin (MBSA) control. Anergy results were read within 48–72 h of testing. Participants were considered to be anergic if they had a negative TST result and no reaction in excess of 2 mm induration to any of the antigens utilized [6]. Participants who remained TST-negative were retested annually.

Participants were classified as being at high risk for developing TB if, at the time of initial assessment, they had a positive TST result (i.e., either a documented history of a TST result with an induration of ≥5 mm in diameter or a TST result with an induration of ≥5 mm at risk assessment) or had cutaneous anergy (with either HIV infection or an unknown HIV status). Low-risk participants were defined as those with a negative TST result who were not infected with HIV. Participants who had tuberculin conversions during the follow-up period retained the classification identified on initial risk-assessment.

At the time of enrollment, all high-risk participants received a complete medical evaluation by physicians at the methadone programs, including a viral hepatitis screening, and liver function and transaminase tests. Isoniazid therapy was prescribed to eligible high-risk participants; all participants who were prescribed isoniazid therapy were examined monthly. Participants with HIV-infection or an unknown HIV-status who had positive TST results or were anergic were prescribed 12 months of isoniazid therapy. HIV-uninfected participants who had positive TST results were prescribed 6 months of isoniazid therapy. Treatment was provided under direct nurse observation and was administered with methadone and 25 mg of pyridoxine (i.e., vitamin B6) q.d.; nurses recorded doses as either “taken” or “missed.” Participants were prescribed isoniazid as either a daily regimen (300 mg q.d.) or an intermittent regimen (900 mg 2 times per week or 600 mg 3 times per week). A course of treatment was considered complete if 95% of prescribed doses were taken within 3 months before or after the date of expected completion.

We included participants who had a risk assessment performed between 1 January 1993 and 31 December 1995. We excluded high-risk participants who did not receive anergy testing within 3 months after a negative TST, as well as participants who had a prior history of TB disease or prior treatment with anti-TB medications. All participants were matched to the New York City tuberculosis case registry and the National Death Index to determine whether participants subsequently developed TB or died. Participants receiving multiple risk-assessments were counted once in the analyses and information on the first risk assessment was used. Participants were excluded if their medical records could not be found.

The period of observation for development of active TB began on the date of the first risk assessment at the methadone program and ended on the date of diagnosis of active TB disease, the date of death, or 31 December 1998, whichever was earliest. Participants were considered to have active TB disease if they met the CDC criteria for culture-confirmed TB; participants with culture-negative TB were excluded [7]. Anti-TB drug resistance was determined with either conventional or radiometric methods.

Rates of TB disease were expressed as the number of TB cases divided by the person-years (PYs) of observation. Risk of TB disease was compared by HIV status, duration of isoniazid treatment, and response to tuberculin and anergy panels by Cox proportional hazard rate ratios to account for duration of follow-up. A multivariate model with CD4+ T lymphocyte count as a covariate was also developed, with the assumption that individuals with unknown CD4+ T lymphocyte count who were HIV-uninfected had a CD4+ T lymphocyte count of >200 cells/mm³. TB rate by year of diagnosis was assessed. Analyses restricted to HIV-infected participants were also performed to determine risk of death in this group. Analyses were performed using SAS version 7 (SAS Institute) [8]. This study received ethical oversight by the institutional human subject review boards of all collaborating sites.

RESULTS

Of 3169 participants who met the study criteria, 957 (30.2%) were excluded; 919 of those excluded had incomplete medical records, 35 received prior treatment with anti-TB medications,
Table 1. Comparison of demographic characteristics of 2212 injection drug users enrolled in methadone programs (MPs) in New York City, 1993–1998, by risk of developing tuberculosis disease.

<table>
<thead>
<tr>
<th>Variable</th>
<th>High-risk group (n = 995)</th>
<th>Low-risk group (n = 1217)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>333 (33.5)</td>
<td>462 (38.0)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>662 (66.5)</td>
<td>755 (62.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>564 (56.7)</td>
<td>722 (59.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Black</td>
<td>254 (25.5)</td>
<td>177 (14.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White</td>
<td>169 (17.0)</td>
<td>312 (25.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (0.8)</td>
<td>6 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Born in the United States</td>
<td>942 (94.7)</td>
<td>1139 (93.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>40 (21–67)</td>
<td>37 (19–73)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean years enrolled in MP</td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>prior to assessment (range)a</td>
<td>3.2 (0–26)</td>
<td>2.6 (0–22)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (% of patients), unless otherwise indicated.

* No data were available on the duration of enrollment for 341 (34.3%) of the members of the high-risk group and 718 (59%) of the low-risk group.

and 3 were treated for culture-negative TB. After exclusions, 2212 participants were retained for analyses, 995 of whom were classified as being at high risk for TB disease.

Demographic characteristics of high- and low-risk groups are presented in table 1. A summary of the isoniazid treatment study is presented in figure 1, and selected clinical characteristics of individuals in the high-risk group are presented in table 2. Of the 995 high-risk participants, 373 (37.5%) were infected with HIV. Of the high-risk participants, 607 started isoniazid treatment for latent TB infection and 259 (26.1%) completed ≥6 months of treatment. None of the low-risk participants were prescribed treatment.

Participants were followed up for a median of 4.2 years (range, 0–6 years) between risk assessment and censoring.

Figure 1. Flow chart summarizing a study of isoniazid treatment among individuals at high risk for tuberculosis enrolled in methadone programs in New York City, 1993–1998. aProportion of 388 participants who never received treatment with isoniazid. bProportion of 607 participants who received treatment with isoniazid. cOf 298 participants who completed ≥6 months of treatment, 4 (1.5%) had treatment discontinued due to medical contraindications. TST+, positive results of a tuberculin skin test.
Table 2. Clinical characteristics at the time of initial tuberculosis (TB) risk-assessment among 995 individuals classified as being at high risk for TB, by HIV serostatus.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 373)</th>
<th>With TB (n = 20)</th>
<th>Group 1, HIV-infected</th>
<th>Group 2, HIV-uninfected</th>
<th>Group 3, unknown HIV serostatus</th>
<th>All groups (n = 995)</th>
<th>With TB (n = 25)</th>
<th>Group 1 vs. Group 2</th>
<th>Group 1 vs. Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin result at initial risk assessmenta</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>141</td>
<td>12 (8.5)</td>
<td>241</td>
<td>0</td>
<td>308</td>
<td>5 (1.6)</td>
<td>690</td>
<td>17 (2.5)</td>
<td>&lt;.001</td>
<td>.002</td>
</tr>
<tr>
<td>Anergic</td>
<td>232</td>
<td>8 (3.5)</td>
<td>...</td>
<td>...</td>
<td>73</td>
<td>0</td>
<td>305</td>
<td>8 (2.6)</td>
<td>Undefined</td>
<td>NS</td>
</tr>
<tr>
<td>Death during follow-up</td>
<td>159</td>
<td>14 (8.8)</td>
<td>13</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>206</td>
<td>14 (6.8)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of isoniazid treatmentb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>161</td>
<td>11 (6.8)</td>
<td>63</td>
<td>0</td>
<td>164</td>
<td>4 (2.4)</td>
<td>388</td>
<td>15 (3.9)</td>
<td>.03</td>
<td>NS</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>121</td>
<td>8 (6.6)</td>
<td>93</td>
<td>0</td>
<td>134</td>
<td>1 (0.8)</td>
<td>348</td>
<td>9 (2.6)</td>
<td>.009</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;6 and &lt;9 months</td>
<td>24</td>
<td>1 (4.2)c</td>
<td>58</td>
<td>0</td>
<td>39</td>
<td>0</td>
<td>121</td>
<td>1 (0.8)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;9 and &lt;12 months</td>
<td>32</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>68</td>
<td>0</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>35</td>
<td>0</td>
<td>12</td>
<td>0</td>
<td>23</td>
<td>0</td>
<td>70</td>
<td>0</td>
<td>Undefined</td>
<td>Undefined</td>
</tr>
<tr>
<td>CD4+ T lymphocyte count, cells/mm³</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>121</td>
<td>9 (7.4)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>200–&lt;400</td>
<td>71</td>
<td>1 (1.4)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>&gt;400</td>
<td>60</td>
<td>1 (1.7)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Unknown</td>
<td>121</td>
<td>9 (7.4)</td>
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<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
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</tr>
</tbody>
</table>

Note. NS, not significant; TB, tuberculosis; Undefined, undefined.

* Included testing for tuberculin and at least 2 of 3 antigens: Candida, mumps, and/or tetanus. Of anergic participants, 290 (95.1%) met this criterion.

b Included 18 patients who received ≥2 anti-TB medications for ≥2 weeks, none of whom developed TB, and for whom the duration of isoniazid therapy was as follows: <6 months, 14 patients (77.7%); 6 to <9 months, 1 patient (5.6%); 9 to <12 months, 2 patients (11.1%); and ≥12 months, 1 patient (5.6%).

c This patient completed 8 months of treatment with isoniazid.

Twenty-five participants (2.5%) in the high-risk group developed culture-confirmed TB, and 4 (16.0%) of these participants had isolates that were resistant to isoniazid, including 2 participants who had isolates that were also resistant to rifampin. Because no TB cases were observed in the low-risk group, subsequent analyses are presented for the high-risk group only.

The rate of TB in the high-risk group was 610 TB cases per 100,000 PYs (95% CI, 370–850). Of the 25 cases of TB that developed in this group, 20 (80.0%) were in HIV-infected participants (1570 cases per 100,000 PYs; 95% CI, 890–2,250). The remaining 5 cases occurred in participants with unknown HIV status (290 cases per 100,000 PYs; 95% CI, 40–540).

Figure 2. Tuberculosis (TB) case rates and 95% CIs (brackets) among tuberculin-positive or anergic participants, by HIV serostatus and duration of isoniazid treatment. Squares, all HIV-infected participants; diamonds, tuberculin-positive HIV-infected participants; stars, anergic HIV-infected participants; triangles, participants with unknown HIV serostatus; circles, HIV-uninfected participants. PYs, person-years.
At highest risk for TB disease were HIV-infected, tuberculin-positive or anergic individuals with <6 months of treatment, with a case rate of 2130 per 100,000 PYs (95% CI; 1190–3070), compared with those participants with unknown HIV status who received <6 months of treatment (380 cases per 100,000 PYs; 95% CI, 50–710) (figure 2). Among HIV-infected individuals with a positive TST result, the rate of TB decreased from 3520 cases per 100,000 PYs (95% CI; 1480–5560) for individuals receiving <6 months of isoniazid therapy to 500 cases per 100,000 PYs (95% CI; 440–1360) in individuals receiving ≥6 months. One participant developed TB after completing 8 months of treatment with isoniazid; this individual was HIV-infected, had a positive TST result, and had a CD4+ T lymphocyte count of <200 cells/mm³. Among HIV-infected participants, regardless of the duration of treatment, the highest TB case rate (8890 per 100,000 PYs; 95% CI, 2620–15170) occurred among individuals with a positive TST result and with a CD4+ T lymphocyte count of <200 cells/mm³ (figure 3). Sixty-two percent of HIV-infected participants were receiving anti-HIV monotherapy concurrently with isoniazid therapy.

Not shown in the figures is the finding that, among HIV-infected participants who completed <6 months of isoniazid treatment, the highest TB rates occurred in 1993 and decreased steadily through 1998. From 1993 to 1995, the TB rate in HIV-infected participants with <6 months of isoniazid treatment was 2420 cases per 100,000 PYs (95% CI; 1280–3560) compared with 110 per 100,000 PYs (95% CI; 50–270) among participants diagnosed from 1996 to 1998.

Crude and adjusted risks of TB disease are presented in table 3. In addition, we performed a multivariate analysis (not shown in the tables) with TB disease as the outcome variable and adjusted for the same variables as in the former model, with the addition of CD4+ T lymphocyte count. The following variables were associated with TB disease: HIV-infection (HR 10.3; 95% CI, 3.4–31.3), <6 months of isoniazid (HR, 7.6; 95% CI, 1.02–57.1), CD4+ T lymphocyte count of <200 cells/mm³ (HR, 6.8; 95% CI, 1.7–25.9), unknown CD4+ T lymphocyte count (HR, 3.8; 95% CI, 1.1–13.9), and tuberculin positivity (HR, 4.0; 95% CI, 1.6–10.2).

We also examined death by any cause as an outcome variable, among HIV-infected individuals only, using a multivariate model that included CD4+ T lymphocyte count, TB disease, isoniazid treatment, and positive TST results as covariates (not shown).
shown in table). Greater risk of mortality was associated with CD4+ T lymphocyte count of <200 cells/mm³ (HR, 3.5; 95% CI, 2.2–5.4), TB disease (HR, 3.4; 95% CI 1.7–6.7), and <6 months of isoniazid therapy (HR, 2.4; 95% CI, 1.4–4.2).

DISCUSSION

In this study, relatively high rates of TB disease were found among individuals who had evidence of infection with both Mycobacterium tuberculosis and HIV. The highest rate was seen among individuals with TB and HIV infection and a CD4+ T lymphocyte count of <200 cells/mm³. This rate was 200 times greater than that seen in the New York City adult population during this study’s follow-up period of 1993–1998 [9]. Second, the TB rate among IDUs with dual TB and HIV infection was significantly reduced with the provision of isoniazid treatment. In this study, the rate of isoniazid resistance among patients with TB (16%) was not higher than expected [9].

The case rate for participants with dual TB and HIV infection and with <6 months of treatment was 3-fold lower than that reported in a similar study by Selwyn et al. [3] covering the years 1988–1990. The most likely reasons for this difference are the longer follow-up period and larger sample size in our study, as well as a decrease in TB rates in the community as a result of an improved TB control program in New York City. TB rates similar to those seen in the Selwyn study are seen in developing countries where there is a high prevalence of HIV infection and where effective TB control programs are not in place [10–12]. Prior to strengthening of the TB control program, <50% of patients with TB completed treatment. Due in large part to a treatment completion rate of >85%, TB case rates declined steadily among both IDUs and HIV-infected individuals since that time [9, 13]. In addition, advances in HIV treatment, starting in 1996, likely accelerated a decline in TB rates [14].

Participants with HIV infection and cutaneous anergy had a significantly lower risk for TB disease than HIV-infected participants with positive TST results. Similar results were reported by Gordin et al. [15]. This suggests that the benefits of isoniazid treatment for HIV-infected individuals with positive TST results are far greater than for HIV-infected individuals with anergy.

No TB cases were observed in participants with ≥9 months of isoniazid treatment, which is the current CDC treatment recommendation [16]. Participants with low CD4+ T lymphocyte counts had a higher risk of TB disease, but receiving ≥6 months of isoniazid therapy provided an 8-fold increase in protection from TB disease. This suggests that low CD4+ T lymphocyte counts may have diminished the full protection conferred by 6 months of isoniazid therapy. However, some level of protection was still observed.

Despite intensive case-management, a surprisingly small proportion of the high-risk participants received ≥6 months of isoniazid. Medical contraindications were common in this group. Such contraindications may be more likely among IDUs because viral hepatitis and other illnesses are more prevalent in this population [17, 18]. Of participants with no medical contraindications, one-fifth refused treatment. Of those who started treatment, 41% did not adhere to therapy; receipt of methadone was not contingent on ingestion of isoniazid.

Shorter courses of treatment for LTBI, or a vaccine, would be of tremendous value to individuals at high risk for TB disease. However, safer and more-effective alternatives to isoniazid are not yet readily available. A 2-month regimen of rifampin and pyrazinamide administered to HIV-infected individuals was found to be as effective as isoniazid therapy, with similar rates of adverse reactions [19, 20]. However, a study of a similar regimen administered to individuals not infected with HIV reported 16 cases of severe liver damage and 5 deaths in <1 year of observation [21]; therefore, these regimens should be used with caution. Furthermore, rifampin therapy is contraindicated with several antiretroviral drugs, though rifabutin may be substituted to reduce interactions with selected anti-HIV agents [22]. No vaccine is available that demonstrates a long-term immune response in preventing TB disease [23].

Several factors limited our data and analysis. Complete medical records could be obtained from the methadone programs for only 71.1% of the eligible individuals in our cohort. One-third of HIV-infected participants did not have CD4+ T lymphocyte counts available; our analysis suggests that many individuals in this group may have had low CD4+ T lymphocyte counts, because they had a significantly higher risk of TB disease than did those with high CD4+ T lymphocyte counts. Virus load tests were not yet available for most HIV-infected participants during this study period. We did not have information on antiretroviral therapy received after the cessation of treatment with isoniazid, and the introduction of highly active antiretroviral therapy (HAART) in 1996 may have reduced immunosuppression in the HIV-infected population [24–26]. Nonetheless, over a lifetime, the benefits of isoniazid treatment for tuberculin-positive, HIV-infected individuals will be even greater as increased use of HAART increases life-expectancy.

In summary, our study showed that ≥6 months of isoniazid treatment prevented TB in HIV-infected individuals in methadone programs. Targeted tuberculin testing of HIV-infected IDUs in methadone programs should be actively supported. Among those who are tuberculin positive, intensive patient management—and possibly incentives—until the completion of treatment will be essential, particularly among those with low CD4+ T lymphocyte counts [27]. The availability of regimens with fewer hepatic side effects than those of isoniazid therapy would also allow a greater number of such high-risk
individuals to receive treatment for TB infection and would contribute to TB prevention efforts.

Acknowledgments

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References