National Survey to Measure Rates of Liver Injury, Hospitalization, and Death Associated with Rifampin and Pyrazinamide for Latent Tuberculosis Infection


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Background. Cases of severe and fatal liver injury were reported after a 2-month course of rifampin-pyrazinamide therapy was recommended in 2000 as an alternative to isoniazid for treatment of latent tuberculosis infection. We estimated rates of rifampin-pyrazinamide-associated liver injury and compared these with historical rates for isoniazid.

Methods. We conducted a survey of state and city tuberculosis programs and other health care settings in the United States where rifampin-pyrazinamide was prescribed. The number of rifampin-pyrazinamide therapy initiations was collected, as well as the number of occurrences of (1) asymptomatic aspartate aminotransferase serum concentration $\geq 5$ times the upper limit of normal, (2) symptomatic hepatitis (in which the patient was not hospitalized), (3) hospitalization for liver injury, (4) death with liver injury, and (5) treatment completion. We also searched a national pharmacy claims database (Verispan). Rates of these events were calculated.

Results. Among 139 programs, 110 (79%) responded; 87 (79%) had initiated rifampin-pyrazinamide therapy for a total of 8087 patients between January 2000 and June 2002. Rates per 1000 rifampin-pyrazinamide therapy initiations during this period were 25.6 (95% confidence interval [CI], 22.3–29.3) for asymptomatic aspartate aminotransferase level $\geq 5$ times the upper limit of normal and 18.7 (95% CI, 15.9–21.9) for hepatitis. Seven fatalities and 23 hospitalizations occurred, with rates of 0.9 (95% CI, 0.4–1.9) and 2.8 (95% CI, 1.8–4.3) per 1000 rifampin-pyrazinamide therapy initiations, respectively. Of 8087 patients, 64% completed rifampin-pyrazinamide therapy. The Verispan search revealed 1 rifampin-pyrazinamide–associated hospitalization (2.9 hospitalizations per 1000 rifampin-pyrazinamide therapy initiations; 95% CI, 0.1–18.4) and no deaths. Articles on the use of isoniazid therapy for latent tuberculosis infection that were published after 1990 reported fatality rates of 0.0–0.3 deaths per 1000 persons.

Conclusions. Rates of liver injury, hospitalization, and death associated with rifampin-pyrazinamide therapy exceed rates reported for isoniazid therapy. Because earlier randomized trials of rifampin-pyrazinamide lacked adequate statistical power to detect fatal events, the Centers for Disease Control and Prevention recommends that rifampin-pyrazinamide generally should not be used for treatment of latent tuberculosis infection.

Persons exposed to contagious tuberculosis (TB) may become infected with *Mycobacterium tuberculosis* and later develop TB disease. The risk of progression to TB disease is reduced through treatment of latent TB infection (LTBI) [1, 2]. The detection and treatment of LTBI is critical to the TB elimination strategy in the United States [3]. Several regimens are recommended for LTBI treatment, but isoniazid therapy administered for at least 6 months has been used for $\geq$30 years. All of these regimens are associated with adverse effects, including idiosyncratic liver injury.

Treatment of LTBI with a 2-month combination of daily or twice-weekly rifampin-pyrazinamide was recommended by the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) in April 2000 [4]. The evidence for this regimen’s
safety and efficacy came from 3 randomized clinical trials involving HIV-infected persons [5–7]. The results became the scientific basis for recommending rifampin-pyrazinamide therapy for HIV-uninfected persons. A multicenter study of the programmatic feasibility of rifampin-pyrazinamide therapy was initiated in 2000 [8], and a patient involved in this project died of liver injury [9]. Following additional reports of liver injury, revised interim guidelines were issued in mid-2001 [10]; nevertheless, adverse reactions continued [11].

LTBI and its treatment are not reportable conditions in most TB-control jurisdictions. Therefore, the number of patients who initiated rifampin-pyrazinamide therapy—and therefore, the rate of adverse events—remained unknown. We estimated the rates by surveying TB-control personnel and other health care providers about initiations of rifampin-pyrazinamide treatment and subsequent liver injuries, hospital admissions, and deaths. To determine whether adverse events resulted when other providers prescribed rifampin-pyrazinamide therapy, we also searched a linked database of commercial pharmacy claims and medical claims.

PATIENTS AND METHODS

Passive Surveillance for Adverse Events
The initial US-published report of rifampin-pyrazinamide-associated hepatitis requested additional similar reports [9], and this request was repeated in updates [10–12]. We recorded demographic and clinical information from each report on an abstraction form. In collaboration with state and local TB-control officials, CDC epidemiologists confirmed hospitalizations and deaths with on-site reviews.

Active Surveillance for Adverse Events
In mid-2002, we retrospectively surveyed for cases of rifampin-pyrazinamide-associated liver injury and for the number of patients who initiated rifampin-pyrazinamide therapy (i.e., denominator data). This required establishing a national sampling frame of providers who prescribed rifampin-pyrazinamide.

Institutional review. The protocol for this survey underwent CDC ethics review and was deemed to be an urgent public health response and not to be human subjects research.

Sampling frame. In December 2001, we sent a letter to the directors of all of the 50 state TB programs and the 10 large city TB programs that receive federal categorical funding for TB control. The letter reviewed the public health issues and our strategy for estimating hepatitis rates [9, 10, 13]. An enclosed questionnaire requested a list of health care programs and providers prescribing rifampin-pyrazinamide. We contacted each entity to determine who should be surveyed.

Survey. In October 2002, we mailed the survey after pilot testing it in 9 states. The survey covered 3 consecutive periods: 1 January 2000–30 April 2001 (period 1, ending with the first publication of the hepatitis incidents [9]), 1 May 2001–31 August 2001 (period 2, ending with the publication of revised guidance [10]), and 1 September 2001–30 June 2002 (period 3, ending with the inception of the survey) [14]. We asked respondents to describe their setting (e.g., county jail) and to confirm which LTBI treatment regimens were used. We made 3 attempts to contact nonresponders by March 2003.

For each of the 3 periods, we requested the following aggregate counts: total number of candidates eligible for treatment of LTBI with any drug regimen; number of patients for whom daily rifampin-pyrazinamide treatment was initiated; number of patients for whom twice-weekly rifampin-pyrazinamide treatment was initiated; number of patients for whom rifampin-pyrazinamide treatment was stopped because of asymptomatic elevated serum aspartate aminotransferase (AST) levels (defined as >5 times upper limit of normal, with or without elevated serum bilirubin levels); number of patients for whom rifampin-pyrazinamide treatment was stopped because of symptoms of hepatitis (i.e., progressive onset of anorexia, nausea, vomiting, or jaundice); number patients admitted to the hospital for treatment of liver injury within 1 month after administration of the last rifampin-pyrazinamide dose; number of patients who died of liver injury (within 1 month after the last known rifampin-pyrazinamide dose was administered); and number of patients who completed rifampin-pyrazinamide therapy. Patient-specific data (e.g., sex and age) were not requested.

Pharmacy Claims Data
We searched the Verispan proprietary electronic reimbursement claims databases to determine whether rifampin-pyrazinamide-associated adverse events occurred in patients whose cases were not captured in our survey. Verispan collects a data warehouse of Health Insurance Portability and Accountability Act of 1996 compliant, standardized, patient-centric claims. For the period 1 January 2000–30 April 2002, the database contained unidentified, patient-linkable claims from 109 million patients, who contributed 2.4 billion claims (~16% of the electronic claims volume in the United States). These claims arose from ~38,000 pharmacies, ~680,000 providers, and ~4400 hospitals. Retail pharmacy prescriptions included purchases by third-party payers (including Medicare and Medicaid) and cash.

To exclude patients treated for TB disease, the search targeted prescriptions for rifampin and pyrazinamide and no other antituberculosis medications (antituberculosis medications included isoniazid, ethambutol, streptomycin, para-aminosalicylic acid, ethionamide, cycloserine, capreomycin, kanamycin, and thiacetazone). For each patient who received a prescription for rifampin-pyrazinamide, we searched for medical claims made during the period from 7 days after receiving rifampin-pyrazinamide therapy to 90 days later. Medical claims with International Classification of Diseases, Ninth Revision (ICD-9),
We maintained survey responses in a Microsoft Access database (Microsoft). A χ² test for trend was used to examine whether rifampin-pyrazinamide use (yes vs. no) was related to state-specific TB incidence (categorized as ≤3.5, 3.6–5.8, and >5.8 cases per 100,000 population) [15]. The rates of asymptomatic AST levels >5 times the upper limit of normal, hepatitis, hospitalization, and death were calculated using adverse event counts from the survey as numerators and the numbers patients who initiated rifampin-pyrazinamide as denominators. Epi-Calc2000 (Gillman and Myatt) was used for the period-specific rates during the study period.

### Table 1. Distribution of latent tuberculosis infection (LTBI) treatment regimens used between January 2000 and late 2002, as reported by 110 survey respondents.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>No. (%) of survey respondents reporting any use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Daily for 9 months</td>
<td>101 (92)</td>
</tr>
<tr>
<td>Twice weekly for 9 months</td>
<td>59 (54)</td>
</tr>
<tr>
<td>Daily for 6 months</td>
<td>75 (68)</td>
</tr>
<tr>
<td>Twice weekly for 6 months</td>
<td>27 (25)</td>
</tr>
<tr>
<td>Rifampin-pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>Daily for 2 months</td>
<td>82 (75)</td>
</tr>
<tr>
<td>Twice weekly for 2 months</td>
<td>22 (20)</td>
</tr>
<tr>
<td>Rifampin, daily for 4 months</td>
<td>64 (58)</td>
</tr>
</tbody>
</table>

* The majority of programs and health care providers used multiple regimens to treat LTBI, and some used all possible regimens.

### Table 2. Distribution of survey respondents’ use of daily only, daily and twice-weekly, or twice-weekly only rifampin-pyrazinamide for treatment of latent tuberculosis infection (LTBI) and the number of treatment candidates reported to have initiated rifampin-pyrazinamide therapy, January 2000–June 2002.

<table>
<thead>
<tr>
<th>Rifampin-pyrazinamide regimen(s) used</th>
<th>No. of survey respondents</th>
<th>No. (%) of patients (n = 127,996)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily only</td>
<td>67</td>
<td>4501 (3.5)</td>
</tr>
<tr>
<td>Daily and twice-weekly</td>
<td>14</td>
<td>2545 (2.0)</td>
</tr>
<tr>
<td>Twice-weekly only</td>
<td>6</td>
<td>1041 (0.8)</td>
</tr>
<tr>
<td>Total</td>
<td>87</td>
<td>8087 (6.3)</td>
</tr>
</tbody>
</table>

### Table 3. Distribution of survey respondents’ use of daily only, daily and twice-weekly, or twice-weekly only rifampin-pyrazinamide for treatment of latent tuberculosis infection (LTBI) and the number of treatment candidates reported to have initiated rifampin-pyrazinamide therapy, January 2000–June 2002.

### RESULTS

#### Sampling frame.

All 50 state and 10 city TB programs responded to the sampling questionnaire by April 2002, and they listed 139 distinct programs or providers in 39 states as possible prescribers of rifampin-pyrazinamide. Rifampin-pyrazinamide use was not associated with states’ TB incidence for 2000 (χ² for trend, 1.357; P = .24). We distributed the survey to each of the 139 programs and providers.

#### Response to survey.

Of the 139 programs and providers, 110 (79%) responded. Respondents included local health departments (50%), local jails (20%), long-term care facilities (13%), state prisons (10%), and a range of other program types, including 3 private providers (2%). Daily isoniazid therapy administered for 9 months was offered by the greatest number of respondents, and twice-weekly rifampin-pyrazinamide therapy was offered by the fewest number (table 1). Most programs reported some rifampin-pyrazinamide use during the survey period, but only 6.3% of their LTBI-treatment candidates received rifampin-pyrazinamide (table 2).

#### Liver injury, hospitalization, death, and treatment completion.

Survey findings for liver injury, hospitalization, and death associated with rifampin-pyrazinamide therapy are summarized in table 3. Between January 2000 and June 2002, the respondents reported 207 cases of patients who stopped treatment regimens between the daily and the twice-weekly regimens. All P values are 2-sided.

### Historical Rates of Isoniazid-Associated Liver Injury

Our review of published data describing liver injury associated with isoniazid therapy for treatment of LTBI spanned 3 decades [17–25]. We emphasized reports published after 1990, because these reflect more-recent practices.
rifampin-pyrazinamide therapy because of asymptomatic increase of AST levels (>5 times the upper limit of normal), a rate of 25.6 cases per 1000 rifampin-pyrazinamide therapy initiations. A total of 151 cases involved patients who stopped rifampin-pyrazinamide therapy because of symptomatic hepatitis, a rate of 18.7 cases per 1000 rifampin-pyrazinamide initiations. In 30 cases, patients were hospitalized for rifampin-pyrazinamide–associated liver injury; of these patients, 23 recovered and 7 died (table 3). The rate of death approached 1 death per 1000 initiations of rifampin-pyrazinamide therapy between January 2000 and June 2002, and the rate of hospitalization (including only those cases in which the patient recovered) was 2.8 cases per 1000 initiations of rifampin-pyrazinamide therapy between January 2000 and June 2002. The changes in rates of liver injury, hospitalization, and death across the survey periods were not significant, but treatment completion rates decreased over time.

**Daily versus twice-weekly rifampin-pyrazinamide therapy.**

Six (7%) of 87 surveyed programs reported using only twice-weekly rifampin-pyrazinamide therapy for 1041 patients (table 2). Compared with sites that used only twice-weekly rifampin-pyrazinamide therapy (among other standard regimens), the 67 sites that exclusively used daily rifampin-pyrazinamide therapy had indistinguishable rates of rifampin-pyrazinamide–associated liver injury, hospitalization, and death (table 4). Treatment completion rates were greater for the twice-weekly regimen, compared with the daily regimen (P<.001).

**Search for additional events.** Our search of the Verispan database found reimbursement claims for rifampin and pyrazinamide (excluding other antituberculosis medications) for a total of 349 patients between 1 January 2000 and 30 April 2002. This included 227 persons in period 1, 72 in period 2, and 50 in period 3. Of the 349 patients, 48 (14%) had 133 medical claims. The ICD-9 codes for these claims showed that 3 (0.9%) of the patients had conditions related to hepatitis, liver injury, serum AST level elevations, or adverse drug effects. Patients A, B, and C had “nonspecific abnormal serum enzyme levels,” “acute or unspecified hepatitis C without mention of hepatic coma,” and “nonspecific elevation of transaminase,” respectively.

Interviews with 3 treating physicians of patients A and B revealed that neither patient experienced a rifampin-pyrazinamide–associated adverse event. Interviews with physicians who treated patient C and a review of medical records confirmed that the patient was hospitalized for rifampin-pyrazinamide–associated liver injury, meeting the case definition. Thus, among 349 patients, 1 patient was hospitalized for rifampin-pyrazinamide–associated liver injury (hospitalization rate, 2.9 per 1000 cases; 95% CI, 0.1–18.4).

The Adverse Events Reporting System identified a single case of rifampin-pyrazinamide–associated liver injury involving hospitalization that was not detected by the other methods. The patient was a 32-year-old man who received a prescription for daily rifampin-pyrazinamide in February 2001. After 12

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**Table 3. Number of patients reported to have initiated rifampin-pyrazinamide therapy and occurrence of adverse reactions, hospitalizations, deaths, and completion of therapy for 3 periods during January 2000–June 2002.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Period (n=5327)</th>
<th>Period (n=1528)</th>
<th>Period (n=1232)</th>
<th>P</th>
<th>Total no. of patients (n=8087)</th>
<th>Rate or percentage (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver injury, no. of patients (rateb)</td>
<td>130 (24.4)</td>
<td>37 (24.2)</td>
<td>40 (32.5)</td>
<td>.161</td>
<td>207</td>
<td>25.6 (22.3–29.3)</td>
</tr>
<tr>
<td>AST level &gt;5 times the ULNc</td>
<td>91 (17.1)</td>
<td>36 (23.6)</td>
<td>24 (19.5)</td>
<td>.297</td>
<td>151</td>
<td>18.7 (15.9–21.9)</td>
</tr>
<tr>
<td>Hospitalization, no. of patients (rateb)</td>
<td>23 (4.6)</td>
<td>4 (2.6)</td>
<td>3 (2.4)</td>
<td>.238</td>
<td>30</td>
<td>3.7 (2.5–5.4)</td>
</tr>
<tr>
<td>By outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deathd</td>
<td>6 (1.2)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>…</td>
<td>7</td>
<td>0.9 (0.4–2.0)</td>
</tr>
<tr>
<td>Recoveryf</td>
<td>17 (3.4)</td>
<td>3 (2.0)</td>
<td>3 (2.4)</td>
<td>.509</td>
<td>23</td>
<td>2.8 (1.9–4.5)</td>
</tr>
<tr>
<td>Completed rifampin-pyrazinamide therapy, no. (%) of patientsg</td>
<td>3451 (65)</td>
<td>959 (63)</td>
<td>735 (60)</td>
<td>&lt;.001</td>
<td>5145</td>
<td>64 (63–65)</td>
</tr>
</tbody>
</table>

**NOTE.** AST, aspartate aminotransferase; ULN, upper limit of normal.

| Period (95%) | a 16 months long, period 2 was 4 months long, and period 3 was 10 months long, for a total of 30 months.
| Rate is expressed as no. of events per 1000 patients who initiated rifampin-pyrazinamide therapy.
| Patients who stopped rifampin-pyrazinamide therapy because of serum AST levels >5 times the upper limit of normal, without symptoms.
| Patients who stopped rifampin-pyrazinamide therapy because of symptoms of hepatitis (progressive onset of anorexia, nausea, vomiting, and jaundice).
| Patients who died of liver injury within 1 month after receiving their last known rifampin-pyrazinamide dose.
| Patients who were admitted to the hospital for liver injury within 1 month after their last known rifampin-pyrazinamide dose and experienced full recovery.
| Patients who successfully completed a full course of rifampin-pyrazinamide therapy. Reasons for failure to complete therapy (other than adverse events) were not ascertained by our survey.
Table 4. Number and rate of patients reported as having stopped rifampin-pyrazinamide therapy because of liver injury, hospitalization, or death in the United States during 2000–2002, by regimen.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Daily rifampin-pyrazinamide use onlya (n = 4501)</th>
<th>Twice-weekly rifampin-pyrazinamide use onlyb (n = 1041)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of patients</td>
<td>Ratec (95% CI)</td>
</tr>
<tr>
<td>Liver injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST level &gt;5 times the ULNd</td>
<td>121</td>
<td>26.9 (22.4–32.1)</td>
</tr>
<tr>
<td>Hepatitisa</td>
<td>57</td>
<td>12.7 (9.7–16.5)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>17</td>
<td>3.8 (2.3–6.2)</td>
</tr>
<tr>
<td>By outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deathf</td>
<td>4</td>
<td>0.9 (0.3–2.4)</td>
</tr>
<tr>
<td>Recoveryh</td>
<td>13</td>
<td>2.9 (1.6–5.1)</td>
</tr>
<tr>
<td>Completed rifampin-pyrazinamide therapyi</td>
<td>2679 (60)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. AST, aspartate aminotransferase; ULN, upper limit of normal.

a Program or health care provider reported no simultaneous use of twice-weekly regimens of rifampin-pyrazinamide.
b Program or health care provider reported no simultaneous use of daily regimen of rifampin-pyrazinamide.
c Rate is expressed as no. of events per 1000 patients who initiated rifampin-pyrazinamide therapy.
d Patients who stopped rifampin-pyrazinamide therapy because of serum AST levels >5 times the upper limit of normal, without symptoms.
e Patients who stopped rifampin-pyrazinamide therapy because of symptoms of hepatitis (progressive onset of anorexia, nausea, vomiting, and jaundice).
f Patients who died because of liver injury within 1 month after receiving their last known rifampin-pyrazinamide dose.
g Patient was detected by both passive and active surveillance systems. On-site investigation of this reported event (part of the Centers for Disease Control and Prevention passive surveillance system) revealed the patient to be infected with HIV.
h Patients who were admitted to the hospital for liver injury within 1 month after their last known rifampin-pyrazinamide dose and experienced full recovery.
i Patients who successfully completed a full course of rifampin-pyrazinamide therapy. Reasons for failure to complete therapy (other than adverse events) were not ascertained by our survey.

days of rifampin-pyrazinamide therapy, he was hospitalized with nausea, vomiting, fever, an AST level of 205 U/L, and an ALT level of 709 U/L. Trace-back was not possible for verifying the events and the rifampin-pyrazinamide association, and the report was excluded from our count. Five other rifampin-pyrazinamide–associated deaths recorded in the Adverse Events Reporting System (all occurring between November 2000 and May 2001) had been reported to the CDC.

For the period January 2000–June 2002, our survey captured 27 (73%) of the 37 known hospitalizations and deaths previously reported to the CDC through passive surveillance (figure 1). The 10 events from this period that were not captured by our survey stemmed from the 21% nonresponse rate of TB programs that had previously reported these cases to our passive surveillance system. The survey detected 4 additional cases (including 2 involving fatalities) not previously known to the CDC. One of these hospitalizations was reported from a TB program that did not report its denominator data, which excluded it from our rate estimates. The Verispan search accounted for 1 case, but that case was not included in our survey-based rate estimates. Eight cases occurred either before (3 cases) or after (5 cases) the survey window period. In summary, 50 cases (including 12 fatalities) were reported to the CDC through December 2004 and reflect events captured by both passive and active surveillance.

Historical rates of isoniazid-associated events. Early studies attributed hospitalization rates of up to 5.0 hospitalizations per 1000 treatment initiations and mortality rates as high as 1.0 death per 1000 treatment initiations to the use of isoniazid for treatment of LTBI [17, 19]. However, since 1991, studies involving >1 million persons treated with isoniazid for LTBI have reported hospitalization rates of 0.1–0.2 hospitalizations per 1000 treatment initiations (median, 0.15 hospitalizations per 1000 treatment initiations) and mortality rates of 0–0.3 deaths per 1000 treatment initiations (median, 0.04 deaths per 1000 treatment initiations) [21–25]. The highest reported isoniazid-associated hospitalization rate (0.2 hospitalizations per 1000 treatment initiations) or mortality rate (0.3 deaths per 1000 treatment initiations) and the lower limit of our 95% CIs for rifampin-pyrazinamide–associated hospitalization (1.9) and mortality rates (0.4) do not overlap. Furthermore, the lower limit of our 95% CI for rifampin-pyrazinamide–associated hospitalization rate was 9.5 times greater than the highest reported isoniazid hospitalization rate; the lower limit of our 95% CI
Figure. 1. Number of patients ($n = 50$) reported to have initiated rifampin-pyrazinamide (RZ) therapy for treatment of latent tuberculosis infection and to have subsequently been hospitalized for RZ-associated liver injury, United States, 1999–2004. Data are from passive and active (survey period, January 2000–June 2002) surveillance activities conducted by the Centers for Disease Control and Prevention (CDC). Fatalities ($n = 12$) are indicated by an x. Superscripted numbers refer to the relevant citation in the reference list. As of December 2004, no additional reports had been received by the CDC. ATS, American Thoracic Society; MMWR, Morbidity and Mortality Weekly Report.

for rifampin-pyrazinamide–associated mortality rate was 1.3 times greater than the highest reported isoniazid-associated mortality rate.

**DISCUSSION**

Treatment for LTBI is a distinctive component of the strategy to eliminate TB in the United States. TB elimination will be difficult to achieve without new LTBI treatments that are briefer, safer, and at least as efficacious as 9 months of isoniazid therapy [4]. In early 2000, the CDC/ATS introduced recommendations, endorsed by the Infectious Diseases Society of America, for use of rifampin-pyrazinamide therapy (independent of HIV infection) following studies involving mice [26, 27] and demonstration of safety and efficacy in 3 randomized clinical trials [5–7]. Rifampin-pyrazinamide therapy was attractive for HIV-infected patients with LTBI because it could be completed quickly, before starting treatment with antiretroviral agents. Although each rifampin-pyrazinamide clinical trial included adverse effect monitoring, no patients were hospitalized with rifampin-pyrazinamide–associated liver injury, and no hepatitis fatalities were reported. Recently, an analysis of serum transaminase monitoring from one of these trials showed that rifampin-pyrazinamide–associated liver injury was infrequent [28]. The reason for greater rates of rifampin-pyrazinamide–associated liver injury, hospitalization, and death on programmatic implementation of this regimen is unclear. A protective effect of HIV infection is conjectural, because comparable groups have not been studied in controlled trials [29].

The 3 randomized trials had 2 limitations for detecting adverse events. The persons included in these 3 trials (all of whom were HIV-infected and most of whom were residents of developing countries) experienced substantial mortality from AIDS during follow-up: 139 (19%) [5], 71 (18%) [6], and 68 (19%) [7] fatalities were reported among patients treated with rifampin-pyrazinamide. Although the majority of these deaths occurred after rifampin-pyrazinamide treatment, each trial reported at least 1 death during treatment. The overall number of patients treated with rifampin-pyrazinamide in each trial was relatively limited (791, 380, and 360 patients, respectively), and deaths could have been unrecognized as being adverse events attributable to rifampin-pyrazinamide unless each death had been thoroughly investigated, particularly those deaths that occurred during the treatment period. Furthermore, an absence of severe liver injury in the 3 trials may have been a consequence of inadequate statistical power to detect this rare outcome.

After initial reports of severe liver injury associated with rifampin-pyrazinamide, some investigators asserted that such injury was less likely with the twice-weekly regimen [30, 31]. The use of a lower pyrazinamide dosage (mean dosage of 30 mg/kg twice-weekly versus a recommended dosage of 50 mg/kg twice-weekly) used in one trial may explain a low incidence of hepatotoxicity and a high treatment-completion rate [30].
As noted by the authors of that report [30], the efficacy of the lower pyrazinamide dosage has not been demonstrated.

With 2 exceptions [30, 31], our findings are consistent with those of reports of programmatic experiences with rifampin-pyrazinamide (table 5) [32–39]. The rates of treatment termination (expressed as the number of events per 1000 rifampin-pyrazinamide initiations) after either elevated AST levels >5 times the upper limit of normal or symptomatic hepatitis have been at least as high as our current estimates. In 3 reports of hospitalization for rifampin-pyrazinamide–associated liver injury [33, 36, 38], the rates (5, 14, and 18 hospitalizations per 1000 rifampin-pyrazinamide initiations, respectively) exceed the rate estimate from our survey (3.9 hospitalizations per 1000 rifampin-pyrazinamide initiations). The lowest reported rate of elevated AST levels >5 times the upper limit of normal was among HIV-infected persons [31]. Even if rifampin-pyrazinamide were less hepatotoxic in persons infected with HIV, the risk still warrants caution; among the 12 rifampin-pyrazinamide–associated fatal liver injuries investigated by the CDC, 2 were in HIV-infected patients [10–12].

Our strategy has limitations. First, the sampling frame we established in 2002 included few private health care providers. However, because most LTBI treatment candidates in the United States probably receive a diagnosis and are treated in the public sector, it is unlikely that numerous private-sector patients were missed. The Verispan search, which includes mostly private-sector patients, detected only 349 patients nationwide who were treated with rifampin-pyrazinamide during the surveyed period. Second, the reasons that physicians chose rifampin-pyrazinamide therapy instead of isoniazid therapy might confound the comparison of rates of liver injuries, especially if the physicians were concerned about giving isoniazid to patients who might have been more susceptible to hepatotoxicity. Finally, a major limitation of aggregate data is that patient-specific characteristics cannot be examined for their effects. Our findings provide minimal insight into mechanisms of rifampin-pyrazinamide–associated hepatotoxicity. However, our rate estimates for liver injury and hospitalization were similar for the daily and twice-weekly rifampin-pyrazinamide regimens (table 3). This is an important finding, because previous data were insufficient for this comparison.

Our survey did not pursue adverse events associated with other LTBI treatments, particularly those associated with isoniazid therapy. This was a trade-off in the survey design. Our need to balance between conducting a concise survey about rifampin-pyrazinamide treatment and conducting a more lengthy survey that would also include isoniazid therapy was debated during planning. On the basis of the pilot survey, a shorter survey designed to increase response rate prevailed. However, through publications [9–11] and presentations at meetings, the CDC requested reports of any liver injuries leading to hospitalization or death associated with all LTBI regimens. Five reports of death due to isoniazid–associated liver injury (CDC, unpublished data) were received within the same period (January 2000–June 2002) in which 10 reports of rifampin-pyrazinamide–associated deaths were received. At least 3 decades of literature describing isoniazid–associated hepatotoxicity exist, and substantially more programmatic experience with isoniazid has accumulated than with rifampin-pyrazinamide.

One wonders whether the rates of liver injury, hospitalization, and death when rifampin-pyrazinamide is used for treatment of LTBI exceed those of the combination of rifampin-pyrazinamide with isoniazid for treatment of TB disease. Others

### Table 5. Patients given rifampin-pyrazinamide therapy for treatment of latent tuberculosis infection, frequency of adverse events, and completion rates, as reported from operational studies in the United States, 2001–2003.

<table>
<thead>
<tr>
<th>Report</th>
<th>Rifampin-pyrazinamide regimen, no. of patients</th>
<th>Adverse events, no. of patients (ratea)</th>
<th>Completion rate, % of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>Twice weekly</td>
<td>Hepatitis</td>
</tr>
<tr>
<td>Bock et al. [32]</td>
<td>168</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Chaisson et al. [30]b</td>
<td>0</td>
<td>489</td>
<td>0</td>
</tr>
<tr>
<td>Jasmer et al. [34]</td>
<td>307</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Lee et al. [33]</td>
<td>148</td>
<td>0</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Leung et al. [35]</td>
<td>40</td>
<td>0</td>
<td>6 (150)</td>
</tr>
<tr>
<td>McNeil et al. [36]</td>
<td>110</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Narita et al. [31]</td>
<td>0</td>
<td>135</td>
<td>0</td>
</tr>
<tr>
<td>Priest et al. [38]</td>
<td>0</td>
<td>423</td>
<td>13 (31)</td>
</tr>
<tr>
<td>Stout et al. [37]</td>
<td>78</td>
<td>35</td>
<td>5 (60)</td>
</tr>
</tbody>
</table>

**NOTE.** This table excludes 1 non–US-based report. AST, aspartate aminotransferase; NA, data not available or could not be determined from the report. ULN, upper limit of normal.

a Numbers in parentheses indicates rate (no. of events per 1000 rifampin-pyrazinamide treatment initiations).
b A lower-than-recommended dosage of pyrazinamide was used (median dosage, 30 mg/kg twice weekly).
have speculated on this [33-40], but there is no clear answer. It is possible that fatal liver injury associated with treatment of TB disease may occur at the same rate as it did associated with rifampin-pyrazinamide treatment of LTBI, but current surveillance systems do not allow a useful comparison.

This study and others provided the basis for the updated CDC/ATS recommendation, endorsed by the Infectious Diseases Society of America, that rifampin-pyrazinamide generally should not be used to treat LTBI, regardless of HIV-infection status [12]. The reservoir of LTBI among persons in the United States will continue to generate TB cases. Until the advent of new options that are briefer, safer, and more efficacious, 9 months of isoniazid therapy remains the preferred treatment for LTBI [40]. Adherence to this prolonged regimen for an asymptomatic condition is challenging, and this justifies the ongoing search for improvements [29, 41-43].

Acknowledgments

We thank the National TB Controllers Association for their assistance with the survey. The approach used to address this public health emergency would not have been successful without the care and attention paid to this effort by state and local TB controllers. We are also grateful for the efforts of the Rifampin-Pyrazinamide Survey Team, including Dr. McKenzie Andre, Phyllis Cruise, Beverly Devoe, Heather Duncan, Dr. Reubin Granich, Dr. Connie Haley, Darryl Hardee, Dr. Jane Kelly, Dr. Ram Koppaka, Dr. Phil LoBue, Dr. Farah Parvez, Dr. Renee Ridzon, Frank Romano, Dr. Philip Spradling, and Dr. Kevin Winthrop. We also thank the following for their expert opinion during the review, interpretation, and discussion of these data: Dr. Henry Blumberg, Dr. Richard Chaisson, Dr. David Cohn, Dr. Stefan Goldberg, Dr. Robert Jasmer, Dr. Masa Narita, Dr. Charles Nolan, Dr. Richard O'Brien, and Dr. Dixie Snider.

Financial support. This project was funded by the CDC, US Public Health Service, Department of Health and Human Services.

Potential conflicts of interest. All authors: no conflicts.

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