

## Update: Fatal and Severe Liver Injuries Associated With Rifampin and Pyrazinamide for Latent Tuberculosis Infection, and Revisions in American Thoracic Society/CDC Recommendations—United States, 2001

THIS OFFICIAL AMERICAN THORACIC SOCIETY/CENTERS FOR DISEASE CONTROL AND PREVENTION (ATS/CDC) UPDATE WAS APPROVED BY THE ATS EXECUTIVE COMMITTEE, AUGUST 2001

During February 12–August 24, 2001, a total of 21 cases of liver injury associated with a 2-month rifampin-pyrazinamide (RIF-PZA) regimen for the treatment of latent tuberculosis infection (LTBI) was reported to CDC. These 21 cases are in addition to two previously reported RIF-PZA-associated cases (1). Cases of liver injury have occurred each year since 1999. CDC also received reports of 10 cases associated with other LTBI treatment regimens; however, risk for liver injury cannot be compared among treatment regimens in part because the number of patients treated for LTBI with each treatment regimen is unknown. This report provides preliminary information about the 21 cases associated with RIF-PZA and the revised recommendations on selecting appropriate LTBI therapy for patients and monitoring the use of RIF-PZA to treat LTBI (2). In most instances, the 9-month isoniazid (INH) regimen is preferred for the treatment of patients with LTBI. RIF-PZA may be used in selected cases and requires more intensive clinical and laboratory monitoring than previously recommended.

A case was defined as liver injury (i.e., clinical and laboratory findings consistent with hepatitis) leading to hospital admission or death of a patient being treated for LTBI with RIF-PZA. The median age of the 21 patients was 44 years (range: 28–73 years) and 12 were men. For patients in which the information was known, jaundice was reported in 15 of 18, and human immunodeficiency virus (HIV) test results were negative for all 11 who were tested. One patient had been diagnosed with hepatitis C disease at the start of RIF-PZA treatment. Three of the 21 RIF-PZA-associated cases occurred when patients received this regimen after recovering from INH-associated liver injury. One case was associated with a patient who received RIF-PZA after taking INH without problems.

Of the 21 patients with RIF-PZA-associated liver injury, 16 recovered and five died of liver failure. No patient received a liver transplant. The five patients who died had LTBI diagnosed under the current recommendations, and each had indications for RIF-PZA treatment (2). Patient 1 was a 68-year-old man who had diabetes and a positive tuberculin skin test (TST) result, patient 2 was a 62-year-old woman who had a TST conversion detected by employee screening, and patient 3 was a 36-year-old man who had a TST conversion during in-

carceration. Patient 4 was a 32-year-old woman who had emigrated from a high-prevalence country to the United States in 2000 and had a positive TST result of 20 mm induration, and patient 5 was a 34-year-old man who had emigrated from a high-prevalence country to the United States in 1988 and had a positive TST result of 22 mm induration. Patient 3 had HIV risk factors but a negative serology result; the other four did not have HIV risk factors. Patients 2, 4, and 5 were tested and had negative serology results. Patients 2 and 3 received RIF-PZA after recovering from INH-associated liver injury.

PZA dosages for the five patients were 19, 18, 23, 20, and 16 mg/kg/d (recommended dose: 15–20 mg/kg/d). After liver injury was diagnosed, all patients were tested for hepatitis A (acute), B (acute and chronic), and C. Patients 2 and 5 had serologic evidence of previous hepatitis A. Patient 5 had serologic evidence of past hepatitis B. Patient 1 had idiopathic nonalcoholic steatotic hepatitis confirmed by biopsy in 1997, and patient 3 used injection drugs and alcohol, although reportedly not during RIF-PZA treatment. Patient 2 had no risks for chronic liver disease and had neither a liver biopsy nor an autopsy. Patients 4 and 5 had autopsies; microscopic examination of the liver of patient 5 revealed acute hepatic necrosis, and results are pending for patient 4. Patients 1 and 2 were taking other medicines\* that have been associated with idiosyncratic liver injury. All five patients had onset of liver injury during the second month of the 2-month course of treatment. Patients 1 and 3 continued RIF-PZA an estimated 3 days and 14 days, respectively, after symptom onset; the exact duration of RIF-PZA treatment could not be determined for patients 2 and 4. Patient 5 developed symptoms at the completion of treatment. Patients 1, 2, 4, and 5 received 30-day supplies of RIF-PZA. Patient 3 received directly observed therapy daily, but a language barrier possibly hampered patient education and communication about symptoms. Patient 4 also may have faced a language barrier.

Reported by: State and territorial health depts. Div of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, CDC.

**MMWR Editorial Note:** During June, tuberculosis (TB) and liver disease specialists consulted by CDC analyzed case reports and assessed current guidelines on the use of RIF-PZA and noted that the 2-month RIF-PZA regimen was well tolerated in LTBI treatment trials among HIV-infected persons (3–5). Although clinical trials of RIF-PZA did not include HIV-uninfected persons, the number of reports of severe liver injury among persons presumed or known not to be

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\*One patient was taking hydrochlorothiazide and the other was taking lisinopril, metformin, and aspirin.

infected with HIV was unexpected. CDC continues to investigate the rate and risk factors for liver injury. To reduce the risk for liver injury associated with RIF-PZA therapy, the American Thoracic Society and CDC, with the endorsement of the Infectious Diseases Society of America, have prepared recommendations that supercede previous guidelines (2).

1. The 2-month RIF-PZA treatment regimen for LTBI should be used with caution, especially in patients concurrently taking other medications associated with liver injury, and those with alcoholism, even if alcohol use is discontinued during treatment. RIF-PZA is not recommended for persons with underlying liver disease or for those who have had INH-associated liver injury. Persons being considered for treatment with RIF-PZA should be informed of potential hepatotoxicity and asked whether they have had liver disease or adverse effects from INH.
2. For persons not infected with HIV, 9 months of daily INH remains the preferred treatment for LTBI; 4 months of daily RIF is an acceptable alternative. Two months of daily RIF-PZA may be useful when completion of longer treatment courses is unlikely and when the patient can be monitored closely.
3. Available data do not suggest excessive risk for severe hepatitis associated with RIF-PZA treatment among HIV-infected persons. In a large multinational trial, HIV-infected patients treated with RIF-PZA had lower rates of serum aminotransferase (AT) elevations than those given INH alone (3). The RIF-PZA regimen also was well tolerated when given twice weekly to HIV-infected persons in Zambia and Haiti (4, 5). However, experience from trials may not translate to all clinical practice settings, and it may be prudent to use 9 months of daily INH for treatment of HIV-infected persons with LTBI when completion of treatment can be assured.
4. No more than a 2-week supply of RIF-PZA (with a PZA dose < 20 mg/kg/d and a maximum of 2 gm/d) should be dispensed at a time to facilitate periodic clinical assessments. Patients should be reassessed in person by a health-care provider at 2, 4, and 6 weeks of treatment for adherence, tolerance, and adverse effects, and at 8 weeks to document treatment completion. At each visit, healthcare providers conversant in the patient's language should instruct patients to stop taking RIF-PZA immediately and seek medical consultation if abdominal pain, emesis, jaundice, or other hepatitis symptoms develop. Provider continuity is recommended for monitoring.
5. A serum AT and bilirubin should be measured at baseline and at 2, 4, and 6 weeks of treatment in patients taking RIF-PZA. Because some side effects may occur in the second month of treatment, patients should be monitored

throughout the entire course of treatment. Asymptomatic serum AT increases are expected and usually do not require that treatment be stopped (2, 3). However, treatment should be stopped and not resumed for any of these findings: AT greater than five times the upper limit of normal range in an asymptomatic person, AT greater than normal range when accompanied by symptoms of hepatitis, or a serum bilirubin greater than normal range.

The following considerations are crucial in deciding whom to test and treat for LTBI:

1. The purpose of targeted testing is to find and treat persons who have both LTBI and high risk for TB disease (e.g., recent exposure to a contagious case) (2). Persons at low risk for developing TB and who have had a TST for other reasons, such as baseline TST of health-care workers, are not necessarily candidates for treatment if found to be infected (2).
2. Treatment is recommended for foreign-born persons from countries with a high prevalence of TB who have LTBI and who have been in the United States < 5 years (2). After 5 years, treatment decisions should be made on the same basis as other patients.
3. Because sporadic severe INH-associated liver injury still occurs, patients taking INH should be monitored as recommended (2).

CDC is collecting reports of severe liver injury (i.e., leading to hospital admission or death) in persons receiving any regimen for LTBI. Reports are being analyzed to assess contributing factors. Report possible cases to the Division of Tuberculosis Elimination; telephone (404) 639-8116.

#### References\*

1. CDC. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection—New York and Georgia, 2000. *MMWR* 2000;50:289–291.
2. American Thoracic Society, CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Resp Crit Care Med* 2000; 161:S221–S247.
3. Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide versus isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. *JAMA* 2000;283:1445–1450.
4. Mwinga A, Hosp M, Godfrey-Faussett P, et al. Twice weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS* 1998;12:2447–2457.
5. Halsey NA, Coberly JS, Desormeaux J, et al. Randomized trial of isoniazid versus rifampin and pyrazinamide for the prevention of tuberculosis in HIV-1 infection. *Lancet* 1998;351:786–792.

\*All *MMWR* references are available on the Internet at <http://www.cdc.gov/mmwr>. Use the search function to find specific articles.