

# Experience with Pyrazinamide and Rifampin Regimens for Latent TB Infection

**Krista Powell, MD, MPH**

Co-Project Officer, National Surveillance for Severe Adverse Events Associated with LTBI Treatment

Lead, Outbreak Investigations Team  
Surveillance, Epidemiology, & Outbreak Investigations Branch  
CDC, Division of TB Elimination

## **Background**

- ❑ **Targeted testing and treatment of latent tuberculosis infection (LTBI) is a key component of TB elimination**
- ❑ **Isoniazid (INH) has been mainstay of treatment since 1960s**
- ❑ **Toxicity concerns and long duration of treatment have limited use of INH to cure LTBI**
  - Need for shorter, safer alternatives

## **Short-Course Alternative**

- ❑ **Lecour et. al (1989): short-course preventive therapy using 2 months of rifampin (RIF) and pyrazinamide (PZA) in mice**
- ❑ **RIF and PZA have recognized potential for toxicity during treatment for TB disease**
- ❑ **In standard combination therapy, RIF may exacerbate INH toxicity**
- ❑ **PZA associated with**
  - Dose-related toxicity
  - Worsening of liver injury in combination with other hepatotoxic drugs
  - Most hepatotoxic potential?

## **Short-Course Alternative**

- ❑ **1998–2000: results published for three randomized treatment trials of 2 months of RIF-PZA (RIF 600 mg, PZA 25–50 mg/kg) versus 6–12 months of INH among human subjects with HIV infection**
  - RIF-PZA was as effective as 6–12 months of INH
  - RIF-PZA was better tolerated
  - Better treatment completion with RIF-PZA
- ❑ **RIF-PZA trials among human subjects with HIV infection did not identify significant risk of toxicity**
- ❑ **October 1998: CDC recommended RIF-PZA to treat LTBI in patients with HIV infection**

## New Recommendation, 2000

- ❑ **Apr 2000: Guidelines for targeted testing & treatment by ATS and CDC**
- ❑ **Introduction of RIF-PZA as alternative, short-course regimen, expanding recommendation to individuals without HIV infection**

### Strength of recommendations

Regimen	HIV (+)	HIV(-)
9 months INH (daily)	A (II)	A (II)
6 months INH (daily)	C (I)	B (I)
<b>2 months of RIF-PZA</b>	<b>A (I)</b>	<b>B (II)</b>
4 months RIF (daily)	B (III)	B (II)

# Reports of Severe Toxicity Within Months of New Recommendations

- **Apr 2001: CDC publishes report in MMWR, soliciting reports of severe liver injury associated with LTBI treatment**

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## **Fatal and Severe Hepatitis Associated With Rifampin and Pyrazinamide for the Treatment of Latent Tuberculosis Infection — New York and Georgia, 2000**

One of the recommended treatments for latent tuberculosis infection (LTBI) is a 9-month regimen of isoniazid (INH); a 2-month regimen of rifampin (RIF) and pyrazinamide (PZA) is an alternative in some instances. In September 2000, a man in New York died of hepatitis after 5 weeks of RIF-PZA, and in December, a woman in Georgia was admitted to a hospital because of hepatitis after 7 weeks of this regimen. This report summarizes the findings of the investigations of these incidents, which underscore the need for clinical monitoring for adverse effects in all patients receiving treatment for LTBI.

CDC. Fatal and severe hepatitis associated with rifampin and pyrazinamide for the treatment of latent tuberculosis infection — New York, and Georgia, 2000. MMWR 2001;50(15):289–291.

## Summary of CDC's Approach

- ❑ **Challenge: small case numbers to assess associations**
- ❑ **Approach: "Emergency" surveillance system**
  
- ❑ **Challenge: lack of denominator data to estimate incidence and risk ratios**
- ❑ **Approach: Cohort study**

# **“Emergency” Surveillance System**

- ❑ **In response to reports of RIF-PZA-associated adverse events, CDC created an emergency surveillance system for adverse events associated with LTBI treatment**
  - CDC IRB: urgent public health response, not human subjects research
- ❑ **Case definition: liver injury leading to hospitalization or death of a patient being treated for LTBI with RIF-PZA**
- ❑ **On-site investigations**
  - Review of medical records
  - Interviews with health care providers, patients, families



# Soliciting Reports

- ❑ **Small case numbers to assess associations, so more cases needed**
  
- ❑ **Solicitation of reports of severe liver injuries**
  - Publications in MMWR
  - Routine meetings with TB-control programs that receive federal funding for TB control
  - ATS newsletter
  - Newsletter sent to health departments and specialists in pulmonary medicine and infectious disease
  - Query of FDA's Adverse Event Reporting System

# Systematic Tracking of Liver Injuries

- ❑ **Patient demographic characteristics**
- ❑ **Indications for LTBI testing and treatment**
- ❑ **Monitoring strategy during therapy**
  - Clinical observation, laboratory testing, or both
- ❑ **Factors related to diagnosis of severe liver injury**
  - Symptoms, onset date, laboratory evaluation results
- ❑ **Risk factors for hepatitis**
  - Prior liver disease, injection drug use, alcohol use, risk factors for viral hepatitis, testing results for viral hepatitis

# **MMWR™**

## **MORBIDITY AND MORTALITY WEEKLY REPORT**

- 733 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
- 736 Impact of Targeted, School-Based Dental Sealant Programs in Reducing Racial and Economic Disparities in Sealant Prevalence Among Schoolchildren — Ohio, 1998–1999
- 738 Progress Toward Poliomyelitis Eradication — South-East Asia

### **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**

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

## **Findings, as of Aug 2001** (2<sup>nd</sup> MMWR)

- ❑ **21 patients with severe liver injury since 1999**
  - Median age 44 years (range: 28–73 years)
  - 12 men, 9 women
- ❑ **Jaundice reported in 15 of 18 patients**
- ❑ **Of 11 patients tested, none had HIV infection**
- ❑ **No patient received liver transplant**
- ❑ **Five patients died**
  - Age range: 32–68 years
  - 3 men, 2 women
  - Onset in second month of treatment

## Findings, as of Aug 2001

- ❑ **10 cases associated with other LTBI treatment regimens**
  - Risk for liver injury could not be compared in part because of lack of denominator data
  
- ❑ **Cases among persons without HIV infection were unexpected**
  - New recommendations issued to supersede previous recommendations

## **New Recommendations, Aug 2001**

- ❑ RIF-PZA should be used with caution**
- ❑ 9 months of daily INH preferred regimen**
- ❑ No more than 2-weeks supply of RIF-PZA should be dispensed**
- ❑ Clinical evaluation and laboratory monitoring (AST, bilirubin) every 2 weeks for patients receiving RIF-PZA**
- ❑ Advised against RIF-PZA for persons with underlying liver disease or previous INH-associated liver injury**
- ❑ Report severe liver injury to CDC in persons receiving any regimen for LTBI**

# **Ongoing Investigation, as of Nov 2002**

## **(3<sup>rd</sup> MMWR)**

- ❑ **After Aug 2001, CDC continued to solicit reports of adverse effects associated with RIF-PZA**
- ❑ **40 cases (8 fatal) reported as of Sep 25, 2002**
  - 23 cases (5 fatal) had been described
- ❑ **Of 17 cases not previously reported, 2 occurred in patients who initiated treatment after revision of guidelines**
  - One had contraindications, one without laboratory monitoring
- ❑ **Findings underscored previous recommendations**
  - INH is preferred regimen
  - If RIF-PZA offered, revised guidelines should be followed

# Cohort Study, Aug 2003

## (4<sup>th</sup> MMWR)

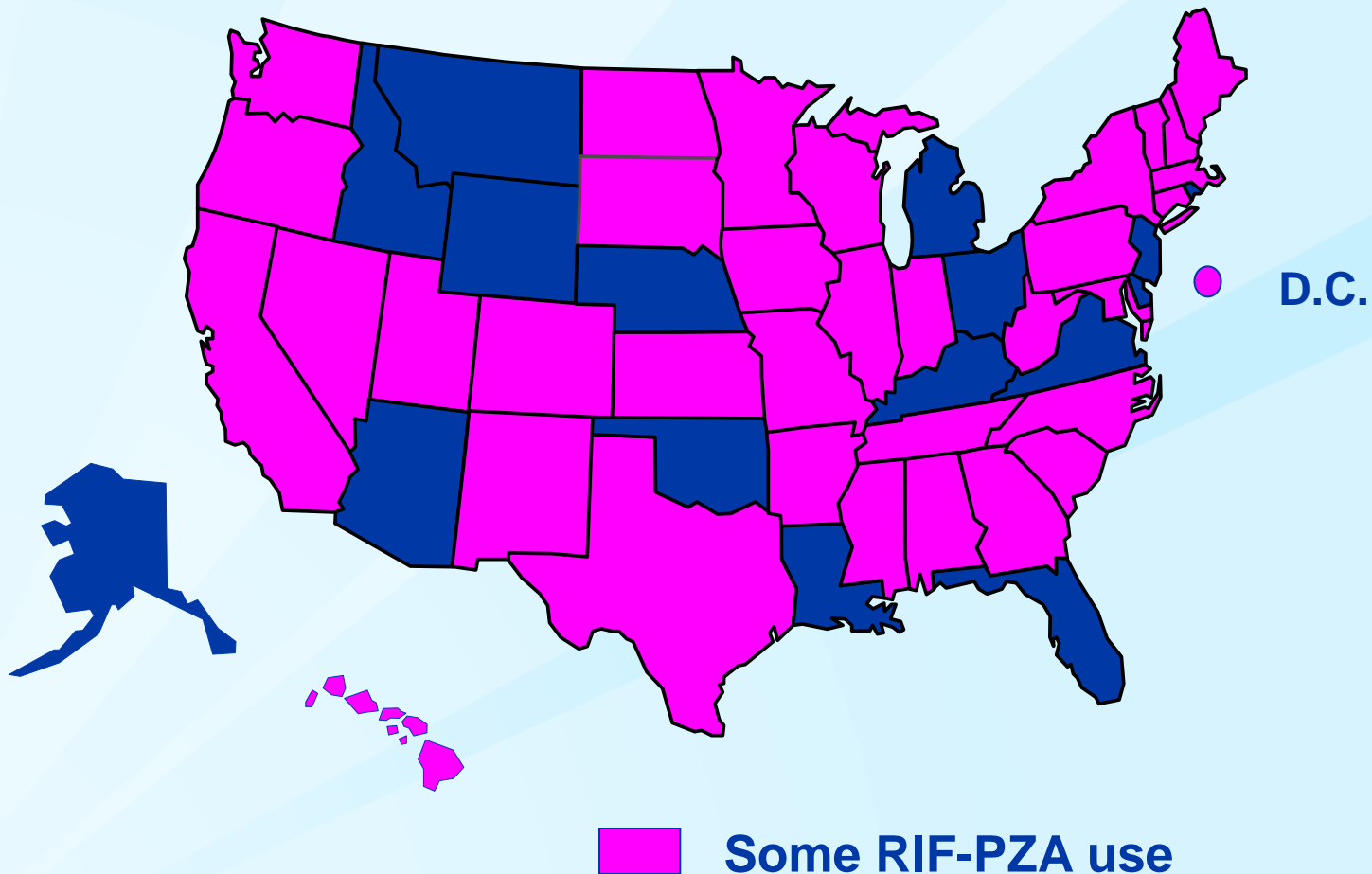
- ❑ **Surveillance data had led to revised recommendations, but total number initiating treatment unknown**
  - → Unable to estimate incidence ratios or risk ratios
- ❑ **CDC conducted a two-phase retrospective cohort study to estimate rates of liver injury associated with RIF-PZA**
- ❑ **Inclusion criteria**
  - Patients received treatment of LTBI during Jan 2000–Jun 2002, AND
  - Data for these patients were reported to CDC through Jun 6, 2003



## Two-Phase Cohort Study

- ❑ **Phase I: questionnaire to TB-control programs in 12 large cities and 50 states**
  - Dec 2001: Asked programs to identify programs and health care providers prescribing RIF-PZA for LTBI treatment (all responded)
  - Feb 2002: CDC staff called programs and 150 providers that had been identified to confirm use of RIF-PZA
  
- ❑ **Phase II: second questionnaire to 150 health-care providers, requesting aggregate cohort data for Jan 2000–Jun 2002**
  - 109 (78%) had responded by Jun 6, 2003

# States Reporting Some RIF-PZA Use, as of Feb 2002



Source: Vernon A. Hepatotoxicity issues: TB treatment regimens with moxifloxacin + PZA, without INH. Presented in London, United Kingdom, October 2004.

## Results of Cohort Study

- ❑ **48 reports of severe liver injury (11 fatalities) detected through passive surveillance, including 30 cases detected in phase II**
  - Two persons who died had HIV infection
  - 33 (69%) cases occurred in second month
- ❑ **7,737 patients began RIF-PZA for LTBI treatment**

## Results of Cohort Study (N=7,737)

Event	Number	Rate per 1,000 treatment initiations (95% confidence interval)	
Discontinued RIF-PZA because of AST >5 times upper limit of normal	204	26.4	(22.8–30.0)
Discontinued RIF-PZA because of hepatitis symptoms	146	18.9	(17.4–20.4)
Hospitalization	30	3.0	(1.8–4.2)
Death	7	0.9	(0.2–1.6)

CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection — United States, 2003. MMWR 2003;52(31):735–739.

## Implications of Findings, Aug 2003

- ❑ **Rates of severe liver injury and death with RIF-PZA higher than reported rates with INH**
  - For INH, hospitalization rates of 0.1–0.2 (median 0.15) and mortality rates of 0–0.3 per 1,000 (median 0.04) (based upon historical data)
  
- ❑ **→ In combination of these with other data, group of TB experts convening in May 2003 suggested revised recommendations**

## Revised Recommendations, Aug 2003

- ❑ **RIF-PZA should never be offered to patients who**
  - Concurrently take other medications associated with liver injury
  - Drink excess alcohol, even if discontinued during treatment
  - Have underlying liver disease
  - Have history of INH-associated liver injury

### Revised strength of recommendations

Regimen	HIV (+)	HIV(-)
9 months INH (daily)	A (II)	A (II)
6 months INH (daily)	C (I)	B (I)
<b>2 months of RIF-PZA</b>	<b>A (I) → D (II)</b>	<b>B (II) → D (II)</b>
4 months RIF (daily)	B (III)	B (II)

CDC. Update: adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection — United States, 2003. MMWR 2003;52(31):735–739.

# Summary of Surveillance Data, Oct 1998–Mar 2004

- ❑ **50 cases (12 fatalities)**
  - Liver injury attributable to RIF-PZA for all
- ❑ **Median age 44 years (range: 17–72 years)**
  - 32 (64%) male
- ❑ **5 patients referred for liver transplantation, but none received**
  - 2 died, 3 recovered
- ❑ **31 (62%) monitored according to guidelines**
  - 9 of whom died
- ❑ **Six patients, including 2 who died, without risk factors**

# Summary of Surveillance Data, Oct 1998–Mar 2004

## □ Risk factors for hepatitis

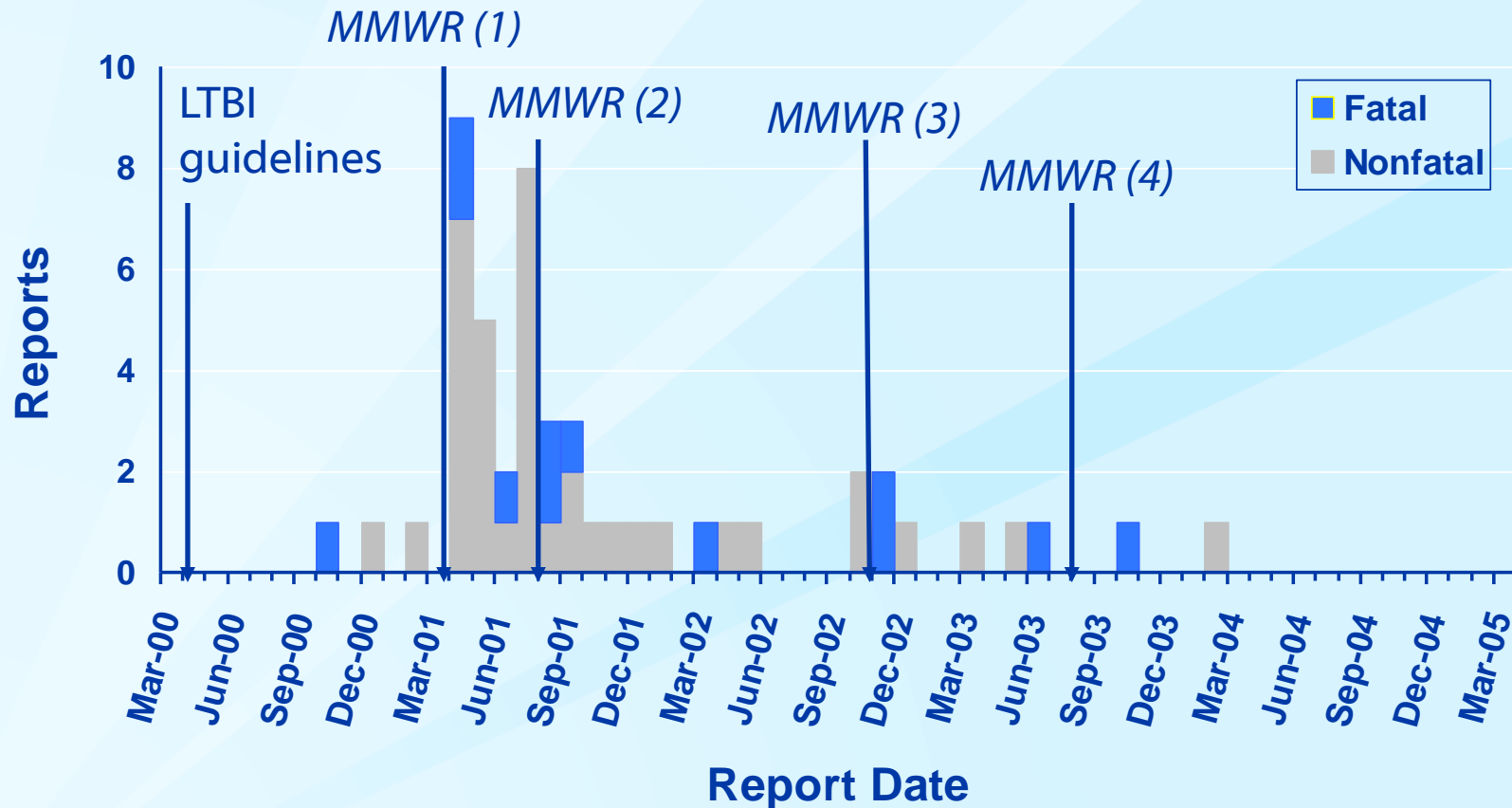
- 34 (71%) of 48 with alcohol use
- 33 (66%) of 50 taking additional hepatotoxic medications
- 7 (16%) of 43 with antibodies to hepatitis C virus
- 3 (14%) of 22 tested for HIV with positive results (two died)
- 1 (2%) of 45 with chronic hepatitis B

## □ Patients who died tended to be older and took greater numbers of hepatotoxic medications

- Median age, 52 years vs. 42 years ( $p=0.05$ )
- Median number of medications, 4 vs. 2 ( $p=0.05$ )



# Liver Injury Associated with RIF-PZA by Date of Report to CDC, United States (n=50)



Manangan L. National surveillance for severe adverse events for severe adverse events associated with latent tuberculosis infection. Presented November 2006.

## Conclusions

- ❑ **RIF-PZA was not associated with excess toxicity during trials of HIV-infected patients (cannot exclude rare events)**
- ❑ **Unexpected liver injury occurred quickly among persons without HIV infection after uptake of new guidelines**
- ❑ **Surveillance provided useful data to revise guidelines, but additional study was needed to estimate event rates**
  - LTBI is not a reportable condition
  - Number of persons initiating treatment unknown outside of studies
- ❑ **3 years after the initial recommendation, RIF-PZA was no longer recommended**

## Current Status

- ❑ **Surprisingly little further understanding of cause, despite obvious association with intact cellular immunity (i.e., HIV negative) and lack of a perceived problem in treatment of TB disease with PZA**
- ❑ **CDC has continued to collect reports of any severe adverse event associated with any LTBI treatment regimen**
- ❑ **No reports of severe liver injury with RIF-PZA since Mar 2004 (but regimen is not much used)**
  - 2004–2008: 17 events (10 investigated), associated with INH

- **Local providers should report possible severe adverse events to their respective health departments and to the Food and Drug Administration's MedWatch.**
- **State health departments should report these events to CDC's Division of Tuberculosis Elimination (e-mail: [LTBIdrugevents@cdc.gov](mailto:LTBIdrugevents@cdc.gov)).**

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

E-mail: [cdcinfo@cdc.gov](mailto:cdcinfo@cdc.gov) Web: <http://www.cdc.gov>

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.