

## Rifampin and Pyrazinamide vs Isoniazid for Prevention of Tuberculosis in HIV-Infected Persons

### CITATION

Gordin F, Chaisson RE, Matts JP, Miller C, et al. Rifampin and Pyrazinamide vs Isoniazid for Prevention of Tuberculosis in HIV-Infected Persons. An International Randomized Trial. *JAMA* 2000; 283(11):1445-50

### RESEARCH QUESTION

How effective is a 2-month regimen of daily rifampin and pyrazinamide compared to a 12-month regimen of daily isoniazid in preventing tuberculosis in HIV infected individuals?

### THE STUDY DESIGN

Randomised, open-label, controlled trial

### STUDY SETTING

Outpatient clinics in the United States, Mexico, Haiti, and Brazil  
Written informed consent; Ethics approval obtained  
September 1991 – May 1996 with follow-up through October 1997

### PARTICIPANTS

Included: Patients 13 years and older, diagnosed as being HIV infected and having a reaction of 5mm or more of induration to 5 U of PPD ( or a documented history of a positive test). Hemoglobin level of > 80g/L, neutrophil count >  $0.75 \times 10^9/L$ , platelet count >  $50 \times 10^9/L$ , total bilirubin of  $42.7 \mu\text{mol/L}$  or less and aspartate aminotransferase and alkaline phosphatase levels of less than 5 time the normal level

Excluded: Clinical or radiological evidence of active tuberculosis at enrolment; current treatment with fluoroquinolones or other agents active against *M tuberculosis*, history of > 2months treatment with antituberculous agents, past intolerance to study medications, acute hepatitis or peripheral neuropathy or pregnancy.

### INTERVENTIONS

Patients were randomised to receive 300mg/d of isoniazid with 50mg/d of pyridoxine hydrochloride for 12 months or 600mg/d rifampin (or 450mg/d if weight below 50kg) and 20mg/kg of pyrazinamide per day for two months.

### OUTCOMES

Primary: Active tuberculosis, confirmed by *M tuberculosis* culture from any source

Secondary: The combination of confirmed and probable tuberculosis, adverse events and death.

**RISK OF BIAS** (Risk Scale: Low – Moderate – High)

#### **SELECTION BIAS: Moderate**

Open-label study – no concealment of allocation.

A stratified 1:1 randomisation with permuted blocks were used, the study unit, i.e. study clinic, was used as stratification factor. Size of permuted blocks not stated. Baseline characteristics similar for both groups at treatment allocation.

#### **PERFORMANCE BIAS: Moderate**

Controlled trial with Isoniazid used as the control regimen.

Treatment was self-administered.

No blinding reported

#### **DETECTION BIAS: Moderate**

Investigators aware of assignment – no blinding reported. Tuberculosis confirmed by *M tuberculosis* culture from any source.

### ATTRITION BIAS: Low

In the statistical analysis, primary analyses were performed on intention to treat principle. Loss to follow up very low.

|                     | Rifampin / Pyrazinamide | Isoniazid  |
|---------------------|-------------------------|------------|
| Started             | 791                     | 792        |
| Completed study     | 729 (92%)               | 739 (93%)  |
| Completed Treatment | 636 (80%)               | 544 (69%)  |
| Loss to follow-up   | 62 (7,83%)              | 53 (6.69%) |

Loss to follow-up: In the rifampin / pyrazinamide group 10.1% patients and in the isoniazid group 9.2% patients were lost to follow-up for development of active tuberculosis at the end of the study. After censoring for tuberculosis, death, and loss to follow-up the mean follow-up was 37.2 months in the rifampin / pyrazinamide group and 36.8 months in the isoniazid group.

Calculating loss to follow-up using the data in Figure 1, page 1447, there is a difference from results reported in the text.

### STUDY FINDINGS

1583 Patients were randomized: 1128 in United States; 157 in Haiti; 117 in Brazil; and 181 in Mexico. Of those randomised 791 were assigned to rifampin/pyrazinamide group and 792 to isoniazid group.

|   | Rifampin / Pyrazinamide<br>N=791 | Isoniazid<br>N = 792 | Unadjusted RR<br>(95% CI) | Adjusted RR<br>(95% CI) |
|---|----------------------------------|----------------------|---------------------------|-------------------------|
| Event   | No. of cases                     | No. of cases         |                           |                         |
| Tuberculosis (confirmed)                      | 19                               | 26                   | 0.72 (0.40-1.31)          | 0.67 (0.36-1.24)        |
| Tuberculosis (confirmed of probable)          | 28                               | 29                   | 0.96 (0.57-1.61)          | 0.95 (0.56-1.61)        |
| Death   | 139                              | 159                  | 0.87 (0.69-1.09)          | 0.87 (0.69-1.11)        |
| Death or tuberculosis (confirmed or probable) | 148                              | 172                  | 0.86 (0.69-1.07)          | 0.86 (0.68-1.08)        |
| Progression of HIV disease of death           | 192                              | 224                  | 0.83 (0.69-1.01)          | 0.84 (0.69-1.03)        |

### ADVERSE EVENTS

One case of grade 4 hepatitis in a patient receiving rifampin + pyrazinamide vs 2 amongst those on isoniazid. Abnormal liver function test results, which were grade 4 or resulted in discontinuation of drugs, were recorded for 11 in rifampin + pyrazinamide patients vs 26 in isoniazid group.

### COMMENTS

The results showed that a 2-month regimen of daily rifampin and pyrazinamide is safer and similar in efficacy compared to a standard 12-month regimen of isoniazid in preventing tuberculosis in patients who are HIV infected and have a positive tuberculin test result.

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