

# Rifampin and pyrazinamide for 2 months prevented TB in patients with HIV infection who had a positive tuberculin test result

Gordin F, Chaisson RE, Matts JP, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. An international randomized trial. *JAMA*. 2000 Mar 15;283:1445-50.

## QUESTION

For patients with HIV infection who have a positive tuberculin test result, are rifampin and pyrazinamide for 2 months as safe and efficacious as 12 months of isoniazid (INH) for preventing tuberculosis (TB)?

## DESIGN

Randomized (allocation concealed\*), unblinded, controlled trial with mean follow-up of 37 months.

## SETTING

AIDS treatment centers in the United States, Mexico, Haiti, and Brazil.

## PATIENTS

1583 patients (72% men, mean age 37 y, 51% black) who had HIV infection and a reaction of  $\geq 5$  mm of induration to 5 U of purified protein derivative. Inclusion criteria were hemoglobin level  $> 80$  mg/L, neutrophil count  $> 0.75 \times 10^9/L$ , platelet count  $> 50 \times 10^9/L$ , total bilirubin  $\leq 42.7$   $\mu\text{mol/L}$ , and aspartate aminotransferase and alkaline phosphatase levels  $< 5$  times the normal level. Exclusion criteria were current active TB, current use of fluoroquinolones or other agents active against TB, history of  $> 2$  months of anti-TB agents, past intolerance to study drugs,

acute hepatitis, peripheral neuropathy, or pregnancy. 93% completed the study.

## INTERVENTION

791 patients were allocated to rifampin, 600 mg/d (450 mg/d if body weight  $< 50$  kg), and pyrazinamide, 20 mg/kg of body weight per day for 2 months (RIF-PZA). 792 patients were allocated to INH, 300 mg/d, and pyridoxine hydrochloride, 50 mg/d for 12 months.

## MAIN OUTCOME MEASURES

The main outcome measure was culture-proved active TB. Secondary outcomes were confirmed for probable TB, death, adverse effects, and progression of HIV infection.

## MAIN RESULTS

The groups did not differ for rates of confirmed TB, confirmed or probable TB,

death (Table), death or TB, progression of HIV infection, or adverse effects (12% for RIF-PZA vs 11% for INH,  $P = 0.3$ ).

## CONCLUSION

Rifampin and pyrazinamide for 2 months were as effective as isoniazid for 12 months in preventing TB in patients with HIV infection who had a positive tuberculin test result.

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\*See Glossary.

## Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis (TB) in patients with HIV infection who were positive for tuberculin testing†

Outcomes at mean 37 mo	Rifampin	Isoniazid	Adjusted RRR (95% CI)	P value
Confirmed TB	2.4%	3.3%	33% (-24 to 67)‡	0.2
Confirmed or probable TB	3.5%	3.7%	5% (-61 to 44)‡	0.8
Death	18%	20%	13% (-11 to 31)‡	0.3

†Abbreviations defined in Glossary.

‡RRRs were adjusted for baseline variables and calculated using time-to-event data.

## COMMENTARY

The World Health Organization estimates that one half of the 34 million persons with HIV infection worldwide are coinfecting with *Mycobacterium tuberculosis* and that TB is the principal cause of death in up to one third of persons dying of HIV infection (1). INH, currently the first-line prevention agent for reactivation TB in persons with HIV infection is problematic because of poor adherence to 12-month therapy, hepatotoxicity, and increasing resistance to INH therapy.

In this international randomized controlled trial, Gordin and colleagues showed that crude rates of TB were lower in the RIF-PZA group than in the INH group, and the RIF-PZA group had a higher treatment completion rate despite a higher rate of nausea and vomiting. Adverse effects, which include hepatitis, led to discontinuation in 1.4% of patients in the RIF-PZA group and 3.3% in the INH group.

Because the median CD4+ count of study patients was 454, only 36% were taking antiretroviral agents. Rifampin is generally contraindicated for patients who are taking protease inhibitors because it

accelerates the metabolism of these antiretroviral agents, resulting in subtherapeutic levels. Despite this limitation, the success of this 2-month regimen is welcome news to patients, clinicians, and public health officials, particularly because RIF-PZA did not select for resistant strains of *M. tuberculosis*. In fact, the U.S. Centers for Disease Control and Prevention has endorsed the 2-month RIF-PZA daily regimen in persons with HIV infection and has recently recommended it for prevention of TB in persons without HIV infection.

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## Reference

1. World Health Organization. Groups at Risk: WHO Report on the Tuberculosis Epidemic. Geneva: World Health Organization; 1996.