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

An International Randomized Trial

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Context Because of problems with adherence, toxicity, and increasing resistance associated with 6- to 12-month isoniazid regimens, an alternative short-course tuberculosis preventive regimen is needed.

Objective To compare a 2-month regimen of daily rifampin and pyrazinamide with a 12-month regimen of daily isoniazid in preventing tuberculosis in persons with human immunodeficiency virus (HIV) infection.

Design Randomized, open-label controlled trial conducted from September 1991 to May 1996, with follow-up through October 1997.

Setting Outpatient clinics in the United States, Mexico, Haiti, and Brazil.

Participants A total of 1583 HIV-positive persons aged 13 years or older with a positive tuberculin skin test result.

Interventions Patients were randomized to isoniazid, 300 mg/d, with pyridoxine hydrochloride for 12 months (n = 792) or rifampin, 600 mg/d, and pyrazinamide, 20 mg/kg per day, for 2 months (n = 791).

Main Outcome Measures The primary end point was culture-confirmed tuberculosis; secondary end points were proven or probable tuberculosis, adverse events, and death, compared by treatment group.

Results Of patients assigned to rifampin and pyrazinamide, 80% completed the regimen compared with 69% assigned to isoniazid ($P < .001$). After a mean follow-up of 37 months, 19 patients (2.4%) assigned to rifampin and pyrazinamide and 26 (3.3%) assigned to isoniazid developed confirmed tuberculosis at rates of 0.8 and 1.1 per 100 person-years, respectively (risk ratio, 0.72 [95% confidence interval, 0.40-1.31]; $P = .28$). In multivariate analysis, there were no significant differences in rates for confirmed or probable tuberculosis ($P = .83$), HIV progression and/or death ($P = .09$), or overall adverse events ($P = .27$), although drug discontinuation was slightly higher in the rifampin and pyrazinamide group ($P = .01$). Neither regimen appeared to lead to the development of drug-resistant tuberculosis.

Conclusions Our data suggest that for preventing tuberculosis in HIV-infected patients, a daily 2-month regimen of rifampin and pyrazinamide is similar in safety and efficacy to a daily 12-month regimen of isoniazid. This shorter regimen offers practical advantages to both patients and tuberculosis control programs.

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C HEMOPROPHYLAXIS OF TUBERculosis in individuals with latent *Mycobacterium tuberculosis* infection is an important component of tuberculosis control.[1] Isoniazid has been proven effective in preventing tuberculosis in tuberculin-positive persons, both human immunodeficiency virus (HIV)–negative[2,3] and HIV-positive.[4-6] The American Thoracic Society and the Centers for Disease Control and Prevention (CDC) currently recommend 6 months or longer of isoniazid daily for tuberculosis preventive therapy.[7] Difficulties with isoniazid preventive therapy, however, include poor adherence,[8] hepatotoxicity,[9] and organisms with isoniazid resistance, both in the United States and globally.[10,11] Given these limitations, the development of alternative, shorter regi-

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mens for the prevention of tuberculosis has become a high priority.[12,13]

This study evaluated the safety and efficacy of a 2-month regimen of daily rifampin and pyrazinamide for prevention of tuberculosis in tuberculin-positive, HIV-infected persons (a group selected because of its high risk for reactivation of tuberculosis infection [eg, 7.9 cases per 100 person-years]).[14] The comparison regimen was 12 months of daily isoniazid, the standard at the start of the study.[8]

METHODS
Study Patients
Patients were enrolled at 15 units of the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA 004), at 33 units of the Adult AIDS Clinical Trials Group (ACTG 177), and at 5 units sponsored by the CDC. One unit each in Haiti and Brazil was also sponsored by the CDC Prevention Study Group, and 1 unit in Mexico was sponsored by the Pan American Health Organization.

Patients were required to be 13 years or older, have been diagnosed with HIV infection, have a reaction of 5 mm or more of induration to 5 U of purified protein derivative (or a documented history of a positive test), a hemoglobin level of more than 80 g/L, a neutrophil count of more than 0.75×10^9/L, platelet count of more than 50×10^9/L, total bilirubin of 42.7 µmol/L (2.5 mg/dL) or less, and aspartate aminotransferase and alkaline phosphatase levels of less than 5 times the normal level. Exclusions were clinical or radiological evidence of active tuberculosis at enrollment; current treatment with fluoroquinolones or other agents active against *M tuberculosis*; history of more than 2 months of continuous treatment with antituberculous agents; past intolerance to study medications; acute hepatitis or peripheral neuropathy; or pregnancy. The study protocol was approved by an institutional review board at each site and all patients gave written, informed consent.

Study Design and End Points
Patients were randomized to receive 300 mg/d of isoniazid with 50 mg/d of pyridoxine hydrochloride for 12 months or 600 mg/d of rifampin (or 450 mg/d for those who weighed less than 50 kg) and 20 mg/kg of pyrazinamide per day for 2 months. Patients who did not receive the study drug continuously were encouraged to complete a 6-month course if in the isoniazid arm and a 60-day course if in the rifampin and pyrazinamide arm.

The study was designed to enroll 2000 patients with follow-up for an average of 36 months. The study, as designed, had a power of 80% to detect a 35% difference (12% vs 7.8%) at 36 months in the risk of tuberculosis (2-sided α level, .05) between treatment groups. The rate of expected tuberculosis was based on prior data on the development of tuberculosis in HIV-infected persons[14] and on the efficacy of isoniazid.[1] It was assumed that 5% of patients in each group would crossover to the other treatment group outside of the protocol, and that 10% in each group would die or become lost to follow-up without tuberculosis. A stratified 1:1 randomization with permuted blocks was used, with the study unit as the stratification factor.

The primary end point was active tuberculosis, confirmed by *M tuberculosis* culture from any source. Cultures and susceptibility tests were performed at participating certified laboratories. Secondary end points were the combination of confirmed and probable tuberculosis, adverse events, and death. The diagnosis of probable tuberculosis required clinical evidence; specimens positive by smear test for acid-fast bacilli were insufficient for a diagnosis of tuberculosis.

Death and clinical progression of HIV disease were also reported. Clinical progression was defined as the first occurrence of an acquired immunodeficiency syndrome (AIDS)–defining condition[15] or as a recurrence of *Pneumocystis carinii* pneumonia, esophageal candidiasis, herpes simplex infection, disseminated herpes zoster, or septicemia due to nontyphoidal salmonella. Progression of HIV disease was not reliably diagnosed in Haiti.

Follow-up
Treatment was usually self-administered. Study visits for both treatment groups were scheduled at months 1, 2, 3, 6, 9, and 12, and then every 6 months thereafter. All patients received follow-up regardless of study drug status until the close of the study. At months 1 and 2, a complete blood cell count, uric acid, aspartate aminotransferase, total bilirubin, and alkaline phosphatase levels

Table 1. Baseline Characteristics of the Study Patients*

Characteristic	Rifampin and Pyrazinamide (n = 791)	Isoniazid (n = 792)	P Value
Women	29.2	27.8	.54
Mean age, y	36.9	37.7	.78
Race or ethnicity			
Black or Haitian	51.7	50.9	
Latino	35.0	35.1	.98
White or other	13.3	14.0	
History of injection drug use	33.2 (775)	37.6 (785)	.30
Male homosexuality or bisexuality	33.6 (787)	31.9 (786)	.52
Karnofsky score <90	7.5 (789)	8.6 (790)	.47
Prior AIDS diagnosis	6.2	7.8	.24
Median CD4 cell count, $\times 10^6$/L	454 (777)	427 (779)	.28
Use of antiretroviral drugs	35.8	36.8 (791)	.71
Purified protein derivative induration			
5-9 mm	11.8	10.7	
≥10 mm	45.0	46.0	.80
Historical positive	43.2	43.3	

*Where some patients are missing data, the number with data available is noted in parentheses. Values are expressed as percentages unless otherwise indicated. AIDS indicates acquired immunodeficiency syndrome.

were measured; and at all follow-up visits, clinical assessment was performed. Patients thought to have active tuberculosis were studied by chest radiography, sputum evaluation, and other tests. Adverse events were categorized using the Division of AIDS Table for Grading Severity of Adult Adverse Experiences.

Data Analysis

The treatment groups were compared with χ^2 or Fisher exact tests for categorial variables and with t and Wilcoxon rank sum tests for continuous variables. Time-to-event analyses were performed with proportional-hazards regression to estimate risk ratios (RRs). The assumption of proportionality was not formally tested. Patients lost to follow-up were censored at the last time they were known to be event-free. Analyses were stratified by geography: United States, Haiti, Brazil, and Mexico. Both unadjusted and adjusted analyses were performed for tuberculosis, mortality, and progression of HIV disease. The adjusted analyses used the baseline variables in TABLE 1. Primary analyses were performed on an intention-to-treat basis. All P values were 2-sided.

Safety and efficacy data were reviewed periodically by an independent data and safety monitoring board, who used the Lan-DeMets method as a guideline for early stopping.[16]

RESULTS
Study Patients

Enrollment was conducted from September 1991 to May 1996, with 791 pa-

tients assigned rifampin and pyrazinamide, and 792 assigned isoniazid with pyridoxine hydrochloride (FIGURE 1). All patients were followed up through October 1997. There were 1128 patients in the United States (603 from the Northeast), 157 in Haiti, 117 in Brazil, and 181 in Mexico. The baseline characteristics of the study groups were similar (Table 1). Of the patients, 51% were black, 35% Latino; 28% were women; mean age was 37 years (range, 16-70 years). Overall, the median CD4 cell count at entry was 436×10^6/L (interquartile range, 274-621×10^6/L), and 7% of the patients had AIDS. A current, positive purified protein derivative test was documented for 57% of the patients, and a historic positive for the remainder.

Treatment and Follow-up

In the rifampin and pyrazinamide group, 636 (80%) of 791 patients completed treatment, and 544 (69%) of 792 patients in the isoniazid group completed treatment ($P<.001$). Adverse events led to discontinuation of the study drug in 10% of the patients in the rifampin and pyrazinamide group and in 6% of the patients in the isoniazid group ($P = .01$).

At the end of the study, 10.1% of the rifampin and pyrazinamide patients and 9.2% of the isoniazid patients were lost to follow-up for development of tuberculosis. With censoring for tuberculosis, death, and loss to follow-up, the mean duration of follow-up was 37.2 months in the rifampin and pyrazinamide group and 36.8 months in the isoniazid group.

Despite the smaller sample size, there was little loss of statistical power because the person-years of follow-up was close to that in the original design.

Tuberculosis, Survival, and HIV

TABLE 2 shows the rates of tuberculosis, death, and progression of HIV disease with the associated unadjusted and adjusted RRs. Confirmed tuberculosis developed in 19 (2.4%) of 791 patients in the rifampin and pyrazinamide group (16 of 563 in the United States, 3 of 78 in Haiti, 0 of 91 in Mexico, and 0 of 59 in Brazil) and in 26 (3.3%) of 792 patients in the isoniazid group (23 of 565 in the United States, 2 of 79 in Haiti, 1 of 58 in Brazil, and 0 of 90 in Mexico). The rates of tuberculosis per 100 patient-years of follow-up were 0.8 and 1.1, respectively, for the rifampin and pyrazinamide and isoniazid groups; RR, 0.72 (95% confidence interval, 0.40-1.31; $P = .28$); the wide confidence interval was due to few events. FIGURE 2 shows cumulative rates of confirmed tuberculosis. Table 1 lists subgroups examined;

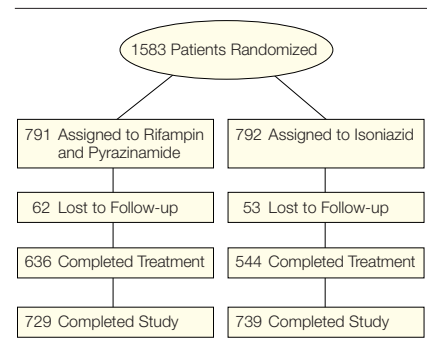**Figure 1.** Participant Flow Through the Study

Table 2. Rates of Events and Risk Ratios*

Event	Rifampin and Pyrazinamide (n = 791)		Isoniazid (n = 792)		Unadjusted RR (95% CI)	P Value	Adjusted† RR (95% CI)	P Value
	No. of Cases	Rate per 100 Person-Years	No. of Cases	Rate per 100 Person-Years				
Tuberculosis (confirmed)	19	0.8	26	1.1	0.72 (0.40-1.31)	.28	0.67 (0.36-1.24)	.20
Tuberculosis (confirmed or probable)	28	1.2	29	1.2	0.96 (0.57-1.61)	.87	0.95 (0.56-1.61)	.83
Death	139	5.7	159	6.5	0.87 (0.69-1.09)	.23	0.87 (0.69-1.11)	.27
Death or tuberculosis (confirmed or probable)	148	6.2	172	7.3	0.86 (0.69-1.07)	.17	0.86 (0.68-1.08)	.18
Progression of HIV disease or death	192	9.2	224	11.1	0.83 (0.69-1.01)	.06	0.84 (0.69-1.03)	.09

*CI indicates confidence interval; RR, risk ratio; and HIV, human immunodeficiency virus.
†Adjusted for baseline variables in Table 1.

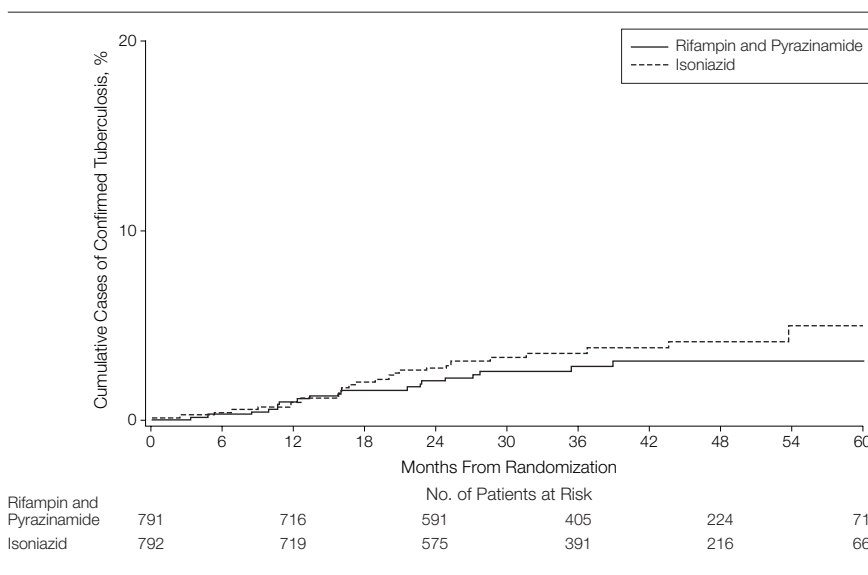**Figure 2.** Cumulative Percentage With Confirmed Tuberculosis According to Treatment

No. of Patients at Risk

Rifampin and Pyrazinamide	791	716	591	405	224	71
Isoniazid	792	719	575	391	216	66

Table 3. Results of Susceptibility Testing

	Rifampin and Pyrazinamide	Isoniazid
Pansusceptible	15	20
Isoniazid monoresistance	1	2
Rifampin monoresistance	0	0
Multidrug resistance*	2	1
Other resistance†	1	1
Not done	0	2
Total	19	26

*All 3 patients had resistance to both rifampin and isoniazid. In the rifampin and pyrazinamide group: 1 person also had resistance to pyrazinamide, ethambutol and kanamycin and 1 person also had resistance to ethambutol. In the isoniazid group: 1 person also had resistance to streptomycin.
†The person in the rifampin and pyrazinamide group had resistance to rifampin and ethambutol and the person in the isoniazid group had resistance to streptomycin.

no significant differences existed between the rifampin and pyrazinamide group and the isoniazid group.

In an analysis comparing the 636 persons who completed rifampin and pyrazinamide with the 544 who completed isoniazid, the case rates of tuberculosis were similar (0.6 vs 0.8; RR, 0.84 [95% confidence interval, 0.39-1.78]; P = .65). Completers had a lower rate of tuberculosis compared with noncompleters for both rifampin plus pyrazinamide (0.6 vs 1.6; RR, 0.42; P = .08) and isoniazid (0.8 vs 2.1; RR, 0.36; P = .01).

Drug susceptibility testing was performed on all 19 isolates of *M tuberculosis* in the rifampin and pyrazinamide

group and in 24 of the 26 isolates in the isoniazid group (**TABLE 3**). Rifampin resistance was detected in 3 individuals treated with rifampin and pyrazinamide, and in 1 treated with isoniazid. There were no cases of rifampin monoresistance. In each treatment group, 3 individuals had isolates resistant to isoniazid.

In the rifampin and pyrazinamide group, 139 (18%) of 791 patients died compared with 159 (20%) of 792 patients in the isoniazid group (RR, 0.87; P = .23). In the rifampin and pyrazinamide group, 192 (24%) of 791 died or had progression of HIV disease, compared with 224 (28%) of 792 patients in the isoniazid group (RR, 0.83; P = .06).

Adverse Events

At least 1 reportable adverse event occurred in 97 patients receiving rifampin and pyrazinamide vs 83 patients receiving isoniazid (**TABLE 4**; P = .27). One case of grade 4 hepatitis occurred in a patient receiving rifampin and pyrazinamide, while there were 2 cases among isoniazid recipients. Not included in Table 4 were 90 cases of suspected hepatitis that did not result in study drug discontinuation in the rifampin and pyrazinamide group, and 107 cases in the isoniazid group. Abnormal liver function test results, which were grade 4 or that resulted

in study drug discontinuation, occurred in 11 rifampin and pyrazinamide patients and in 26 isoniazid patients (P = .02). Patients taking rifampin and pyrazinamide experienced a small, statistically significant increase in nausea, vomiting, and narcotic withdrawal. Also, 52 patients in the rifampin and pyrazinamide group and 2 in the isoniazid group had uric acid values of grade 3 or higher (713.8 μmol/L; P<.001).

COMMENT

This study found that a 2-month course of daily rifampin and pyrazinamide is similar in safety and efficacy to a standard 12-month course of isoniazid for preventing tuberculosis in individuals with HIV infection and a positive tuberculin test result. Adherence to rifampin and pyrazinamide was superior and rates of toxicity were low in both groups, although discontinuation was slightly higher in the rifampin and pyrazinamide group. There was no evidence that rifampin and pyrazinamide selected for resistant strains of *M tuberculosis*.

The prevention of tuberculosis in people with HIV infection has both clinical and public health importance. Globally, tuberculosis is the principal cause of death in up to one third of people dying who have HIV infection.[17] Even in patients with HIV whose tuberculosis is effectively treated, subsequent mortality is high, reflecting the impact that active tuberculosis has on HIV replication and the natural history of HIV disease.[18,19] Tuberculosis is the one opportunistic infection occurring in people with HIV that readily infects people with whom they come in contact, potentially resulting in institutional and community outbreaks of disease.[20,21]

Isoniazid has been shown to be effective in reducing the occurrence of tuberculosis in tuberculin-positive HIV-infected persons.[3-6,22-24] Based on these data, 9 to 12 months of isoniazid has been recommended for patients who are both HIV- and tuberculin-positive.[7,25,26] This longer duration is recommended because HIV infection is the most potent risk factor for reactivation of latent tuberculosis,[27] and because 12 months of isonia-

zid was proven to be more effective than 6 months in preventing tuberculosis in persons with fibrotic lung disease.[28]

Isoniazid preventive therapy is effective, but several limitations have been identified. First, compliance with a 9- to 12-month course of therapy is difficult because patients receive the medication, not for an active illness, but for prevention of an illness. Only about half of those beginning preventive therapy complete a 6-month regimen.[29] A second concern is isoniazid-related hepatitis, which is occasionally fatal.[30] Third, isoniazid is also associated with peripheral neuropathy,[4,7] which is of concern because of the increased occurrence of peripheral neuropathy in HIV-infected persons. Finally, the effectiveness of isoniazid may decrease as isoniazid-resistant strains of *M tuberculosis* become more common.[10,11]

These concerns with isoniazid preventive therapy have led to the study of short-course, rifampin-based regimens. In a study of HIV-infected individuals in Uganda, Whalen et al[6] compared 3 daily regimens to a placebo: 3 months of isoniazid and rifampin; 3 months of isoniazid and rifampin and pyrazinamide; and 6 months of isoniazid. Both of the rifampin-based regimens appeared effective in preventing tuberculosis. Two other groups[31,32] have examined rifampin and pyrazinamide regimens for the prevention of tuberculosis in purified protein derivative–positive, HIV-infected persons. Both groups used rifampin and pyrazinamide twice weekly for 2 months in a study in Haiti[32] and for 3 months in Zambia.[31] In the Haiti study, the rifampin and pyrazinamide arm had a tuberculosis rate of 1.8 per 100 person-years; in Zambia, the rate was 2.7. Both rates were slightly higher than those in the respective arms that received 6 months of isoniazid. In contrast, in the present study, patients received daily rifampin and pyrazinamide, resulting in a tuberculosis rate of only 0.8, a rate lower than the comparative group, which received isoniazid for the full recommended duration (12 months). Greater confidence in the results of the present study is also secured by the study's larger sample size and longer follow-up.

Table 4. Proportion of Patients Who Developed Reportable Adverse Events*

Adverse Event	Rifampin and Pyrazinamide (n = 791)	Isoniazid (n = 792)	P Value
At least 1†	12.3	10.5	.27
At least 1 at grade 4 or higher	5.6	7.3	.18
Study drug permanently discontinued	9.5	6.1	.01
Abnormal liver function tests	1.4	3.3	.02
Hepatitis	0.8	0.4	.34
Peripheral neuropathy	0.1	0.5	.37
Skin rash	1.4	0.6	.14
Neutropenia	0.8	0.4	.34
Nausea and/or vomiting	1.9	0.1	<.001
Narcotic withdrawal	1.5	0.0	<.001

*Values are expressed as percentages.
†Adverse events were considered reportable if they were classified as at least grade 4 (potentially life-threatening) or above on a scale of 1 to 5 (with grade 5 denoting death) and not considered to be due to the progression of human immunodeficiency virus disease, or if they led to the permanent discontinuation of a study drug irrespective of the severity of the event. They were recorded while the patient was taking the study medication and for 8 weeks after its discontinuation.

The 2-month rifampin and pyrazinamide regimen offers advantages over the 12 months of isoniazid, despite the similar efficacy of the 2 regimens. Because of the shorter duration, there was a higher completion rate; this has practical implications in time savings for both patients and staff. Rates of rifampin resistance are lower than isoniazid resistance in almost all areas of the world[10,11]; therefore, the rifampin-containing regimen is potentially of greater value where drug-resistant isolates are a concern, although it will be important to continue to monitor for rifampin resistance.

The use of preventive chemotherapy is a major component of the tuberculosis control plan of the United States[1] and is being more widely applied in other regions of the world.[33] Ten years ago, a shorter, safer, and more economical alternative to isoniazid preventive therapy was deemed important in eliminating tuberculosis from the United States.[12] This study has demonstrated that the 2-month regimen is similar in safety and efficacy to a 12-month regimen in providing tuberculosis prevention in HIV-infected populations. Furthermore, this study has shown that, for both of these regimens, completion of therapy is key to achieving maximum reduction in tuberculosis risk. The results of this trial provided the basis for the revised CDC guidelines that endorsed the 2-month regimen of daily rifampin and pyrazin-amide for the treatment of latent tuberculosis in HIV-infected persons[26] (twice-weekly rifampin and pyrazinamide was not recommended for this population). The study data were also pivotal in providing the basis for the new recommendations in development from the American Thoracic Society and CDC on use of this regimen in persons without HIV infection (D. Cohn, MD, oral communication, January 2000). Preliminary information indicates that this new regimen is highly cost-effective when given to persons with latent tuberculosis infection who are at high risk of active disease.[34] The challenge now is to educate both physicians and patients about this new treatment and to determine how it may be most effectively implemented.

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REFERENCES

1. American Thoracic Society. Control of tuberculosis in the United States. *Am Rev Respir Dis*. 1992; 146:1623-1633.
2. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. *Adv Tuberc Res*. 1970;17:28-106.
3. Wilkinson D. Drugs for preventing tuberculosis in HIV-infected persons [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 1999; issue 4.
4. Smieja MJ, Marchetti CA, Cook DJ, Smaill FM. Isoniazid for preventing tuberculosis in non-HIV-infected persons [Cochrane Review on CD-ROM]. Oxford, England: Cochrane Library, Update Software; 1999; issue 4.
5. Pape JW, Jean SS, Ho JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. *Lancet*. 1993;342:268-272.
6. Whalen CC, Johnson JL, Okwera A, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med*. 1997;337:801-808.
7. Bass JB, Farer LS, Hopewell PC, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med*. 1994;149:1359-1374.
8. O'Brien RJ, Perriëns JH. Preventive therapy for tuberculosis in HIV infection. *AIDS*. 1995;9:665-673.
9. Byrd RB, Horn BR, Solomon DA, Griggs GA. Toxic effects of isoniazid in tuberculosis chemoprophylaxis. *JAMA*. 1979;241:1239-1241.
10. Moore M, Onorato IM, McCray E, Castro KG. Trends in drug-resistant tuberculosis in the United States, 1993-1996. *JAMA*. 1997;278:833-837.
11. Pablos-Mendez A, Ravigione MC, Laszlo A, et al. Global surveillance for anti-tuberculosis-drug resistance, 1994-1997. *N Engl J Med*. 1998;338:1641-1649.
12. Centers for Disease Control. A strategic plan for the elimination of tuberculosis in the United States. *MMWR Morb Mortal Wkly Rep*. 1989;38(suppl 3):1S-25S.
13. Iseman MD. Less is more. *Am Rev Respir Dis*. 1989;140:1187.
14. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. *N Engl J Med*. 1989;320:545-550.
15. Centers for Disease Control and Prevention. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep*. 1987;36(suppl 1):1S-15S.
16. Lan KG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrica*. 1983;70:659-663.
17. World Health Organization. *Groups at Risk: WHO Report on the Tuberculosis Epidemic*. Geneva, Switzerland: World Health Organization; 1996.
18. Goletti D, Weissman D, Jackson RW, et al. Effect of *Mycobacterium tuberculosis* on HIV replication. *J Immunol*. 1996;157:1271-1278.
19. Whalen C, Horsburgh CR, Hom D, LaHart C, Simberkoff M, Ellner J. Accelerated course of human immunodeficiency virus infection after tuberculosis. *Am J Respir Crit Care Med*. 1995;151:129-135.
20. Edlin BR, Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N Engl J Med*. 1992;326:1514-1521.
21. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *N Engl J Med*. 1992;326:231-235.
22. Selwyn PA, Sckell BM, Alcabes P, et al. High risk of active tuberculosis in HIV-infected drug users with cutaneous anergy. *JAMA*. 1992;268:504-509.
23. Guelar A, Gatell JM, Verdejo J, et al. A prospective study of the risk of tuberculosis among HIV-infected patients. *AIDS*. 1993;7:1345-1349.
24. Moreno S, Miralles P, Diaz MD, et al. Isoniazid preventive therapy in human immunodeficiency virus-infected persons. *Arch Intern Med*. 1997;157:1729-1734.
25. Centers for Disease Control and Prevention. 1997 USPHS/IDSA guidelines for the prevention of opportunistic infections in person infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep*. 1997;46(RR-12):10-12.
26. Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR-20):1-58.
27. Rieder HL, Cauthen GM, Comstock GW, Snider DE Jr. Epidemiology of tuberculosis in the United States. *Epidemiol Rev*. 1989;11:79.
28. International Union Against Tuberculosis, Committee on Prophylaxis. Efficacy of various durations of isoniazid preventive therapy for tuberculosis. *Bull World Health Organ*. 1982;60:555-564.
29. Centers for Disease Control and Prevention. *1995 Tuberculosis Program Management Reports*. Atlanta, Ga: Centers for Disease Control and Prevention; 1995.
30. Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths. *Am Rev Respir Dis*. 1992;145:494-497.
31. Mwinga AG, Hosp M, Godfrey-Faussett P, et al. Twice-weekly tuberculosis preventive therapy in HIV infection in Zambia. *AIDS*. 1998;12:2447-2457.
32. Halsey NA, Coberly JS, Desormeaux J, et al. Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. *Lancet*. 1998;351:786-792.
33. De Cock KM, Grant A, Porter JDH. Preventive therapy for tuberculosis in HIV-infected persons. *Lancet*. 1995;345:833-836.
34. Rose DN. Short-course prophylaxis against tuberculosis in HIV-infected persons. *Ann Intern Med*. 1998;129:779-786.