The New England Journal of Medicine

VOLUME 337 SEPTEMBER 18, 1997 NUMBER 12

A TRIAL OF THREE REGIMENS TO PREVENT TUBERCULOSIS IN UGANDAN ADULTS INFECTED WITH THE HUMAN IMMUNODEFICIENCY VIRUS

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ABSTRACT

Background Infection with the human immunodeficiency virus (HIV) greatly increases the risk of reactivation tuberculosis. We evaluated the safety and efficacy of three preventive-therapy regimens in a setting where exposure to tuberculosis is common.

Methods We performed a randomized, placebo-controlled trial in 2736 HIV-infected adults recruited in Kampala, Uganda. Subjects with positive tuberculin skin tests (induration, ≥5 mm) with purified protein derivative (PPD) were randomly assigned to one of four regimens: placebo (464 subjects), isoniazid daily for six months (536), isoniazid and rifampin daily for three months (556), or isoniazid, rifampin, and pyrazinamide daily for three months (462). Subjects with anergy (0 mm induration in reaction to PPD and candida antigens) were randomly assigned to receive either placebo (323 subjects) or six months of isoniazid (395). The medications were dispensed monthly and were self-administered.

Results Among the PPD-positive subjects, the incidence of tuberculosis in the three groups that received preventive therapy was lower than the rate in the placebo group ($P = 0.002$ by the log-rank test). The relative risk of tuberculosis with isoniazid alone, as compared with placebo, was 0.33 (95 percent confidence interval, 0.14 to 0.77); with isoniazid and rifampin, 0.40 (0.18 to 0.86); and with isoniazid, rifampin, and pyrazinamide, 0.51 (0.24 to 1.08). Among the subjects with anergy, the relative risk of tuberculosis was 0.83 (95 percent confidence interval, 0.34 to 2.04) with isoniazid as compared with placebo. Side effects were more common with the multidrug regimens, and particularly with the regimen containing pyrazinamide. Survival did not differ among the groups, but the subjects with anergy had a higher mortality rate than the PPD-positive subjects.

Conclusions A six-month course of isoniazid confers short-term protection against tuberculosis among PPD-positive, HIV-infected adults. Multidrug regimens with isoniazid and rifampin taken for three months also reduce the risk of tuberculosis. (N Engl J Med 1997;337:801-8.)

INFECTION with *Mycobacterium tuberculosis* is the most common human infection worldwide. As the epidemic of human immunodeficiency virus (HIV) infection continues to evolve, the risk of dual infection with HIV and *M. tuberculosis* may be substantial in young adults, especially in developing countries.[1] HIV infection confers the greatest known risk for the development of tuberculosis, both for the reactivation of latent infection and for progressive primary disease.[2-5] Moreover, once active tuberculosis develops in HIV-infected persons, mortality is high, despite good clinical and microbiologic responses to antituberculous therapy.[6-11]

Preventive therapy has been proposed as a strategy to control tuberculosis in HIV-infected populations.[12-14] The potential benefit of preventive therapy was first suggested by observational studies of injection-drug users,[2,3,15,16] but these were uncontrolled studies of selected populations at high risk.[17] Data on the efficacy of preventive therapy in HIV-seronegative persons[18-22] cannot be readily extrapolated to HIV-seropositive persons, because of the confounding effects of progressive immunosuppression related to HIV infection and concern about an in-

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creased risk of drug toxicity in HIV-infected persons.[23,24] Because of the relevance of preventive therapy to the strategy for eliminating tuberculosis in the United States and the potential benefit of preventive therapy in targeted populations in resource-poor countries, in March 1993 the Uganda–Case Western Reserve University Research Collaboration began a randomized, placebo-controlled trial of three regimens of therapy to prevent tuberculosis in HIV-infected Ugandan adults who had positive skin tests with purified protein derivative (PPD). In October 1993 enrollment was expanded to include HIV-infected persons with anergy with respect to PPD and candida antigens, on the basis of new information suggesting an increased risk of tuberculosis in HIV-infected persons with anergy.[3,4]

METHODS

Study Design

The objective of this randomized, placebo-controlled clinical trial was to determine the efficacy of three daily, self-administered regimens of preventive therapy for tuberculosis in HIV-infected adults. The trial was designed to obtain at least three years of follow-up data on all enrolled subjects, with annual interim analyses to ensure timely detection of risks and benefits to the participants. All subjects gave oral informed consent before screening and enrollment in the study. The study protocol was approved by the institutional review board at the University Hospitals of Cleveland and Case Western Reserve University and by the Ugandan National AIDS Research Subcommittee.

Study Population

Between March 1, 1993, and April 20, 1995, Ugandan adults 18 years or more of age were screened for enrollment at five medical clinics and counseling centers for persons with HIV type 1 (HIV-1) infection in Kampala, Uganda. Enrollment of subjects with anergy was begun in October 1993. In the PPD-positive cohort, enrollment in the isoniazid and isoniazid-plus-rifampin groups was continued beyond the predetermined sample size to allow us to screen and enroll subjects in the anergy groups. The study's inclusion criteria were HIV infection documented by enzyme-linked immunosorbent assay, a PPD skin test showing at least 5 mm of induration after 48 to 72 hours or anergy, and a Karnofsky performance score of more than 50.[25] Anergy was defined as 0 mm of induration in reaction to both PPD and candida antigens. Candida antigens were used for skin testing because tetanus-toxoid and mumps vaccinations are not routinely used in Uganda. Only one control antigen was used, to enhance acceptance by the subject. The exclusion criteria were the presence of active tuberculosis, previous treatment for tuberculosis, use of antiretroviral drugs, a white-cell count under 3000 per cubic millimeter, a hemoglobin level under 80 g per liter, serum aspartate aminotransferase level over 90 U per liter, serum creatinine level over 1.8 mg per deciliter (160 μmol per liter), a positive urinary β-human chorionic gonadotropin test, residence more than 20 km from a project clinic, advanced HIV disease, or the presence of major underlying medical illness unrelated to HIV infection. Before entry into the trial, all the subjects were screened for active tuberculosis by a history taking and physical examination, chest radiography, sputum microscopy with the Ziehl–Neelsen stain for acid-fast bacilli, and sputum mycobacterial culture.

Intervention and Randomization

The four study groups received placebo (250 mg of ascorbic acid per day for six months); isoniazid (300 mg per day for six months); isoniazid (300 mg per day) and rifampin (600 mg per day) for three months; or isoniazid (300 mg per day), rifampin (600 mg per day), and pyrazinamide (2000 mg per day) for three months. Blocked randomization was used (in blocks of six) to assign eligible subjects to one of the study regimens. Sequentially numbered, sealed envelopes containing the treatment assignments were drawn in numerical order by a data clerk. Subjects with anergy were assigned only to the placebo and isoniazid groups by a separate, but identical, randomization process. Instruction about HIV and tuberculosis and counseling on compliance were given to all study subjects at enrollment and during follow-up clinic visits. Study nurses dispensed the medication in prepackaged envelopes containing one month of doses with oral and written instructions. A team of five experienced home health visitors traced the subjects who did not keep scheduled appointments and encouraged them to return to the clinic.

Assessment of Outcome

The primary outcome of the study was the development of tuberculosis; secondary outcomes included adverse drug reactions and mortality. The subjects were evaluated monthly during the first six months of the study and every three months thereafter. Active screening for tuberculosis was performed at all scheduled and unscheduled visits by means of a standardized evaluation of the symptoms and signs of tuberculosis; chest radiographs were obtained every six months. If tuberculosis was suspected on the basis of symptoms, signs, or the chest radiograph, three sputum specimens were obtained for mycobacterial smear and culture. Decisions to initiate antituberculous therapy for active tuberculosis were made by on-site investigators after reviewing the clinical, radiographic, and microbiologic data.

Cases of suspected tuberculosis were referred for independent review and classification by two chest physicians who were blinded to the subjects' treatment group. Subjects were selected for review if they had at least one of the following: symptoms or signs consistent with active tuberculosis, a sputum smear positive for acid-fast bacilli, a positive culture for *M. tuberculosis,* abnormal findings consistent with tuberculosis on chest radiography, or empirical therapy for tuberculosis. The reviewers independently classified suspected cases of tuberculosis according to operational definitions of the disease.[26] Definite tuberculosis was defined as culture-confirmed disease (more than five colonies of *M. tuberculosis*). Probable tuberculosis was defined as a clinical illness consistent with tuberculosis on the basis of at least two of the following findings: results of chest radiography consistent with pulmonary tuberculosis, smear of tissue or secretions positive for acid-fast bacilli, or a response to antituberculous therapy. Suspected cases that did not fulfill the criteria for definite or probable tuberculosis were not considered to be active tuberculosis.

During the treatment phase, the subjects were screened for adverse events at all scheduled monthly visits or unscheduled visits. Medical officers recorded the type and grade of reaction with a standard grading system for drug toxicity in HIV-infected persons.[27] The medical officers and study subjects could not be formally blinded to the treatment because of the discoloration of body fluids produced by rifampin; however, the medical officers were instructed to perform the clinical examination and record the findings without reference to the treatment code, and they did not have access to the results of urinary testing. Mortality was assessed through interviews with family members or review of hospital records when available. Autopsies were not performed. The date of death and reports of prominent symptoms at the time of death were also obtained from family members.

Measurements

Demographic and clinical information was obtained through standardized interviews and physical examination. At the time of screening, venous blood was collected for enzyme-linked immunosorbent assay testing for HIV-1, complete blood and differential counts (Coulter T540 system, Coulter Electronics, Hialeah,

Fla.), and serum creatinine and aspartate aminotransferase measurements. HIV infection was documented by enzyme-linked immunosorbent assay (Recombigen HIV-1 env and gag ELISA, Cambridge BioScience, Worcester, Mass.); 1 in 10 HIV-1–positive and 1 in 25 HIV-1–negative serum samples, according to enzyme-linked immunosorbent assay, underwent confirmatory testing by HIV-1 Western immunoblotting (BioRad Novapath, Hercules, Calif.). At the time of screening, all the subjects underwent Mantoux skin testing with 5 tuberculin units of PPD (Tubersol, Connaught Laboratories, Swiftwater, Pa.) and 0.1 ml of candida antigen (*Candida albicans* allergic extract, Berkeley Biologics, Berkeley, Calif.; 1:50 final concentration). After 48 to 72 hours, experienced observers recorded the results of each skin test in millimeters. Posteroanterior chest radiographs were obtained at base line and at six-month intervals during follow-up.

Before randomization, at least one sputum specimen was collected if the subject was able to produce sputum. All sputum specimens were digested, concentrated, and stained for acid-fast bacilli by the Ziehl–Neelsen method at the Uganda Tuberculosis Investigations Bacteriological Unit in Wandegeya. Sputum smears were graded according to the number of acid-fast organisms seen on light microscopy.[28] Specimens were cultured for *M. tuberculosis* on Lowenstein–Jensen slants, incubated at 37°C in air, and examined weekly for eight weeks or until positive results were seen.

Compliance with the prescribed regimen was assessed by the subject's attendance at scheduled visits, urinary testing for isoniazid metabolites (Mycodyn Uritec, DynaGen, Cambridge, Mass.), and self-reports. Ninety-seven subjects in the three treatment groups were randomly selected for unscheduled tests for urinary isoniazid metabolites performed at home between clinic appointments at the beginning of the third month of preventive therapy.

Statistical Analysis

The intention-to-treat approach was used to analyze the data for the primary and secondary end points of tuberculosis, adverse drug reactions, and mortality. The incidence of tuberculosis was estimated by the person-year method; the cumulative proportion was estimated for adverse drug reactions and death. Efficacy was estimated as the relative risk (with 95 percent confidence intervals) of tuberculosis in the treatment groups as compared with the placebo group. The sample size was calculated separately for the PPD-positive and anergy cohorts to achieve a power of 80 percent to detect a reduction of 67 percent in the incidence of tuberculosis with an overall type I error of 5 percent. The sample size was adjusted for expected mortality and losses to follow-up. The target sample size for each treatment or placebo group was 410 for the PPD-positive cohort and 500 for the anergy cohort.

A global test of significance was performed with the log-rank statistic to compare the cumulative incidence of tuberculosis in the treatment groups with that in the placebo group. The nominal significance level, according to the Lan–DeMets error-spending function,[29] was 0.032 when adjusted for a second interim analysis in which 47 of 56 expected events (84 percent) had occurred in the PPD-positive subjects. Three pairwise comparisons were then made between each active-treatment group and the placebo group. The type I error for these pairwise comparisons was adjusted for multiple comparisons by using the nominal significance level from the global test to obtain an adjusted type I error of 0.011 for each comparison, preserving the overall, study-wide type I error of 0.05. A similar procedure was used to adjust the significance level for the subjects with anergy.

RESULTS

Between March 1, 1993, and April 20, 1995, 9095 subjects were screened and 2736 were enrolled in the study. Of the 9095 persons screened for the study, 4306 did not complete the base-line evaluation and 2053 were ineligible for the study. Persons screened for the study were not eligible for one or more of the following reasons: active tuberculosis (smear- or culture-positive; 185 subjects), HIV-seronegative or indeterminate (703), failure to return for skin testing (28), PPD-negative (374), abnormal chest radiograph (884), previous history of tuberculosis or use of preventive therapy (96), poor performance status (233), pregnancy (160), age greater than 50 years (223), or residence more than 20 km from project clinic (226). Information on the progress of subjects through follow-up is available elsewhere.*

In both the PPD-positive and the anergy cohorts, the treatment groups were balanced at base line in terms of demographic factors, performance status, and the results of laboratory tests (Table 1). During follow-up, the numbers of subjects who withdrew from the study, moved out of the study area, or could not be located for unknown reasons did not differ significantly among the study groups. The mean number of scheduled visits, unscheduled visits due to illness, and chest radiographs per person did not differ significantly among the groups. Urine tests for isoniazid metabolites were performed in 1754 subjects in the treatment groups (90 percent), and 75 percent of the results were positive; the results did not differ significantly among the treatment groups. Of the 97 subjects randomly selected for a single spot check at home between clinic appointments, 78 (80 percent) tested positive for isoniazid metabolites. The subjects with positive results on the spot test had a higher proportion of positive tests at the regular monthly visits than the subjects with negative tests (82 percent vs. 46 percent, $P<0.001$).

At the second interim analysis, in December 1995, isoniazid alone was found to reduce the risk of tuberculosis by 67 percent in HIV-infected adults with positive tuberculin skin tests, although there was no significant difference in mortality among treatment groups. Because the benefit of preventive therapy with isoniazid satisfied conservative criteria for statistical significance, the study investigators and officials at the Centers for Disease Control and Prevention, the funding agency for the study, concurred that preventive therapy with isoniazid should be offered to the subjects randomly assigned to the placebo group.

Tuberculosis

In the PPD-positive cohort, 138 subjects met the criteria for new cases of tuberculosis after a mean

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TABLE 1. CHARACTERISTICS OF THE STUDY SUBJECTS.*

CHARACTERISTIC	PPD-POSITIVE COHORT				ANERGY COHORT	
	PLACEBO (N=464)	ISONIAZID (N=536)	ISONIAZID, RIFAMPIN (N=556)	ISONIAZID, RIFAMPIN, PYRAZINAMIDE (N=462)	PLACEBO (N=323)	ISONIAZID (N=395)
Male sex (%)	31	31	29	34	31	32
Mean age (yr)	30	29	29	29	30	30
Karnofsky performance score	91	91	91	91	90	90
Body-mass index†	22.2	22.1	22.6	22.3	22.9	21.9
PPD skin test (mm of induration)	14	14	13	14	0	0
Previous herpes zoster or thrush (%)	25	25	25	27	33	35
Absolute lymphocyte count (per mm^3)	2200	2300	2300	2200	2000	2100
Hemoglobin (g/liter)	126	125	127	126	125	123
Person-years of observation	616	645	680	577	327	355
Completion of trial (%)	89	88	86	80	85	86

*Categorical values were compared by the chi-square test for homogeneity; continuous values were compared by analysis of variance. PPD denotes a tuberculin skin test with purified protein derivative.

†The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

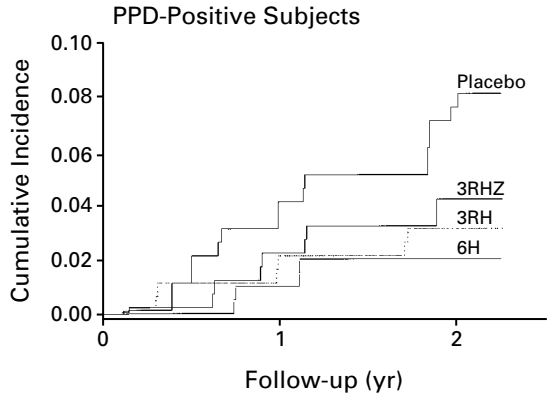
follow-up of 15 months. Forty-seven cases of tuberculosis (24 definite and 23 probable) were observed. In this cohort, the cumulative incidence of tuberculosis was greater in the placebo group than in the treatment groups ($P=0.002$ by the log-rank test) (Fig. 1A). In separate pairwise comparisons of individual treatment regimens with placebo (Table 2), the relative risk of tuberculosis with isoniazid alone was 0.33, a statistically significant value. A similar effect was found with the isoniazid and rifampin group as compared with the placebo groups; the relative risk was 0.40, but in this comparison, the effect narrowly failed to meet the prespecified adjusted level of significance. The relative risk of tuberculosis with the three-drug regimen was 0.51, and the estimate of the effect was of borderline statistical significance. The relative risks of tuberculosis in the treatment groups as compared with the placebo groups remained unchanged for isoniazid and isoniazid with rifampin in a proportional-hazards regression model after adjustment for age, sex, body-mass index, hemoglobin level, white-cell count, Karnofsky performance score, history of HIV-related infection, and presence of chronic diarrhea or weight loss. After this adjustment, the relative risk with the three-drug regimen decreased to 0.43 and was of borderline statistical significance ($P=0.03$).

When the analysis was restricted to definite, culture-confirmed cases of tuberculosis among the PPD-positive cohort, the relative risk of tuberculosis with isoniazid was 0.22 (95 percent confidence interval, 0.06 to 0.77) and with isoniazid and rifampin, 0.14 (95 percent confidence interval, 0.03 to 0.62), whereas the efficacy with isoniazid, rifampin, and pyrazinamide was unchanged.

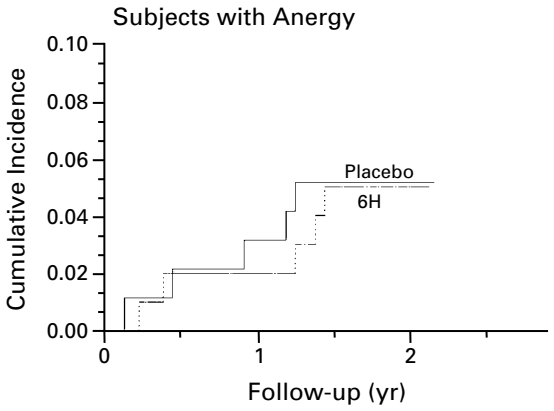
In the anergy cohort, 66 subjects met the criteria for the blinded, independent review after a mean of 12 months of observation. Nineteen cases of definite (9 cases) or probable (10 cases) tuberculosis were detected. The cumulative incidence of tuberculosis was similar in the placebo and isoniazid groups ($P=0.68$ by the log-rank test) (Fig. 1B). The relative risk of tuberculosis in the isoniazid group was 0.83 (Table 2), but the wide confidence intervals did not exclude the hypothesis of no difference in incidence rates. In a proportional-hazards regression analysis adjusted for age, sex, body-mass index, hemoglobin level, white-cell count, Karnofsky performance score, history of HIV-related infection, and presence of diarrhea, the relative risk of tuberculosis in the isoniazid group as compared with the placebo group declined to 0.75, but the confidence intervals remained wide. The relative risk of definite tuberculosis was 0.75 (95 percent confidence interval, 0.20 to 2.79).

Adverse Drug Reactions

A total of 304 adverse events were reported in 279 subjects during the course of therapy in all study groups, including the placebo groups. The frequency of any reported adverse event in the PPD-positive cohort was greater in the treatment groups than in the placebo group, and it was greatest in the group receiving the regimen containing pyrazinamide (Table 3). Treatment was discontinued in 43 subjects.



Study Group			
Placebo	464	288	104
6H	536	280	88
3RH	556	306	109
3RHZ	462	282	87



Study Group			
Placebo	323	167	8
6H	395	155	13

Figure 1. Cumulative Incidence of Tuberculosis among PPD-Positive Subjects (Upper Panel) and Subjects with Anergy (Lower Panel), According to Study Group.

For PPD-positive subjects, the incidence rates of tuberculosis in the groups receiving preventive therapy were lower than the rate in the placebo group ($P=0.002$ by the log-rank test). For subjects with anergy, the incidence rates of tuberculosis did not differ between the placebo and isoniazid groups ($P=0.68$ by the log-rank test). 6H denotes patients receiving isoniazid for six months, 3RH patients receiving isoniazid and rifampin for three months, and 3RHZ patients receiving isoniazid, rifampin, and pyrazinamide for three months. The numbers below the graphs are the numbers of subjects at risk.

The most common reason for stopping therapy was the development of rash or pruritus (25 subjects), followed by nausea and vomiting (8 subjects). The frequency of rash increased from less than 1 percent in the placebo group to 5.8 percent in the group receiving three drugs ($P<0.001$ by chi-square test for trend). No cases of Stevens–Johnson syndrome were reported. Arthralgias were more common in the treated groups than with placebo (1.5, 2.8, 3.1, and 10.8 percent of subjects in the groups receiving placebo, isoniazid, isoniazid with rifampin, and isoniazid with rifampin and pyrazinamide, respectively). Paresthesias were more common in the group receiving isoniazid, rifampin, and pyrazinamide than in the placebo group (6.5 percent vs. 2.4 percent, $P<0.001$) but were reported with similar frequency in the groups receiving isoniazid and isoniazid with rifampin (2.4 and 3.1 percent, respectively).

Seven cases of clinical hepatitis were detected by medical officers during the routine evaluations. Of the 1631 subjects whose serum aspartate aminotransferase levels were measured during therapy, 65 had elevated levels. Fifty-two of these subjects had peak elevations of 135 U per liter or lower. Of the 13 subjects with values greater than 135 U per liter, 6 were subjects with anergy who were receiving isoniazid; 5 were PPD-positive subjects receiving isoniazid, rifampin, and pyrazinamide; 1 was a PPD-positive subject receiving isoniazid; and 1 was a PPD-positive subject receiving placebo.

Mortality

During follow-up, there were 399 deaths: 237 among PPD-positive subjects and 162 among subjects with anergy. The overall mortality rate was greater in the anergy cohort than in the PPD-positive cohort ($P=0.001$). The proportion surviving at one year was 0.78 in the anergy cohort and 0.90 in the PPD-positive cohort ($P=0.001$ by the log-rank test). When the analysis was stratified according to the presence of anergy, there was no significant difference between placebo and each treatment with regard to either the mortality rate or the cumulative proportion of deaths ($P>0.2$ by the log-rank test) in either the PPD-positive cohort or the anergy cohort (Table 4). Of the 66 subjects in whom tuberculosis developed, 13 died, for a cumulative mortality rate of 20 percent.

DISCUSSION

In this randomized, placebo-controlled clinical trial of therapy to prevent tuberculosis in HIV-infected Ugandan adults, self-administered isoniazid taken daily for six months reduced the risk of tuberculosis by 67 percent in subjects with positive PPD skin tests (induration, $\geq$5 mm). This level of short-term protection was achieved with a minimum of adverse effects. The efficacy of isoniazid in this study

TABLE 2. INCIDENCE OF DEFINITE OR PROBABLE TUBERCULOSIS ACCORDING TO STUDY GROUP AND RELATIVE RISK OF TUBERCULOSIS.*

GROUP	DEFINITE OR PROBABLE TUBERCULOSIS		CRUDE RELATIVE RISK (95% CI)	P VALUE†	ADJUSTED RELATIVE RISK (95% CI)‡
	NO. OF CASES	RATE§			
PPD-positive cohort¶					
Placebo	21	3.41	1.0		1.0
Isoniazid	7	1.08	0.33 (0.14–0.77)	0.01	0.32 (0.14–0.76)
Isoniazid, rifampin	9	1.32	0.40 (0.18–0.86)	0.02	0.41 (0.19–0.89)
Isoniazid, rifampin, pyrazinamide	10	1.73	0.51 (0.24–1.08)	0.08	0.43 (0.20–0.92)
Anergy cohort					
Placebo	10	3.06	1.0		1.0
Isoniazid	9	2.53	0.83 (0.34–2.04)	0.68	0.75 (0.30–1.89)

*CI denotes confidence interval. The relative risk is as compared with the placebo group.

†The P values were determined with the Wald chi-square statistic. The nominal critical value was 0.011, adjusted for the second interim analysis and multiple comparisons with placebo.

‡The relative risks have been adjusted for age, sex, white-cell count, hemoglobin level, Karnofsky performance score, body-mass index, history of HIV-related infection, and presence of chronic diarrhea by Cox proportional-hazards regression analysis.

§The rate is the number of cases per 100 person-years.

¶PPD-positive denotes a positive tuberculin skin test with purified protein derivative.

TABLE 3. CUMULATIVE INCIDENCE OF ADVERSE EVENTS, GRADE OF REACTION IN STUDY SUBJECTS, AND FREQUENCY OF DISCONTINUATION OF THERAPY ACCORDING TO STUDY GROUP AND THE PRESENCE OR ABSENCE OF CUTANEOUS ANERGY.

GROUP	CUMULATIVE INCIDENCE OF REPORTED ADVERSE EVENTS	GRADE OF REACTION			DISCONTINUATION OF THERAPY
		MILD	MODERATE	SEVERE	
	number (percent)				
PPD-positive cohort*					
Placebo	23 (5.0)	23 (5.0)	0	0	1 (0.2)
Isoniazid	60 (11.2)	56 (10.4)	4 (0.7)	0	3 (0.6)
Isoniazid, rifampin	54 (9.7)	48 (8.6)	6 (1.1)	0	13 (2.3)
Isoniazid, rifampin, pyrazinamide	114 (24.7)	101 (21.9)	12 (2.6)	1 (0.2)	26 (5.6)
Anergy cohort					
Placebo	22 (6.8)	22 (6.8)	0	0	0
Isoniazid	31 (7.8)	29 (7.3)	2 (0.5)	0	0

*PPD-positive denotes a positive tuberculin skin test with purified protein derivative.

was similar to the efficacy of 71 percent found in a randomized clinical trial of isoniazid in Haiti,[30] but the current study addressed some of the methodologic issues raised about the Haitian study.[31] In particular, the current analysis was based on a larger number of cases of tuberculosis, with half the cases confirmed by sputum culture. The incidence rates of tuberculosis were lower in the current study than in the Haitian study, perhaps as a result of the stricter entry criteria used to exclude subjects with active tuberculosis. Nevertheless, the consistent findings of these two studies, in addition to the preliminary reports of other clinical trials,[32,33] support the validity of the observed protective effect. The duration of this effect, however, remains to be established, since variability in the annual risk of infection among populations may affect the risk of tuberculosis after preventive therapy has been completed, especially in persons with advanced immunosuppression.

The current study extends previous observations by evaluating the safety and efficacy of two multidrug, three-month regimens, isoniazid and rifampin

TABLE 4. MORTALITY RATE AND CUMULATIVE PROPORTION OF DEATHS ACCORDING TO STUDY GROUP.

GROUP	DEATHS	MORTALITY RATE*	RELATIVE RISK (95% CI)†	P VALUE
	no. (%)			
PPD-positive cohort‡				
Placebo	64 (13.8)	10.2	1.0	
Isoniazid	58 (10.8)	8.9	0.9 (0.6–1.2)	0.44
Isoniazid, rifampin	57 (10.3)	8.3	0.8 (0.5–1.2)	0.25
Isoniazid, rifampin, pyrazinamide	58 (12.6)	9.8	0.96 (0.7–1.4)	0.83
Anergy cohort				
Placebo	76 (23.5)	22.3	1.0	
Isoniazid	86 (21.6)	23.5	1.05 (0.77–1.42)	0.77

*The mortality rate is the number of deaths per 100 person-years. Total person-years for the PPD-positive cohort were as follows: placebo, 625; isoniazid, 652; isoniazid and rifampin, 689; and isoniazid, rifampin, and pyrazinamide, 589. Total person-years for the anergy cohort were as follows: placebo, 340; and isoniazid, 367.

†CI denotes confidence interval.

‡PPD-positive denotes a positive tuberculin skin test with purified protein derivative.

and isoniazid, rifampin, and pyrazinamide. These regimens substantially reduced the risk of tuberculosis, but the reduction did not reach the conservative level of statistical significance. These regimens were included in the trial because of the greater sterilizing activity of rifampin,[34] with or without pyrazinamide, and because of the potential for improved compliance with shorter regimens.[19] In addition, fixed-dose combinations of these drugs are available. The slight difference in efficacy between the two- and three-drug regimens may be due to the greater frequency of adverse events associated with the use of pyrazinamide and its possible effect on compliance.

In this study, there was evidence of a small benefit of preventive therapy with isoniazid in subjects with anergy, but the confidence intervals were wide and did not rule out the null hypothesis. The reason isoniazid did not confer the same degree of protection in the subjects with anergy is unclear. We speculate that subjects with anergy may be at greater risk than PPD-positive subjects for primary failure of preventive therapy because of drug malabsorption[35-37] or other host factors associated with advanced disease. Alternatively, exogenous reinfection with progressive primary disease may occur because of the more advanced degree of immunosuppression.

The safety of isoniazid as preventive therapy in HIV-seronegative persons may not be readily extrapolated to HIV-seropositive persons, because of the enhanced drug hypersensitivity associated with HIV infection.[4,23,24] In the current trial, no serious toxic effects were reported with six months of isoniazid, and the rate of clinical hepatitis was similar to that observed in HIV-seronegative persons of similar age.[38] Other side effects, such as rash, arthralgias, and paresthesias, were detected more frequently in the treatment groups than in the placebo groups and were more common in subjects receiving the regimen containing pyrazinamide. Because medical officers were not blinded to the subjects' treatment assignments, it is possible that this observed difference resulted from detection or reporting bias. Nonetheless, since these regimens are intended to prevent tuberculosis in asymptomatic or minimally symptomatic persons at risk, the treatment should not produce unacceptable side effects. Although the reported side effects were not severe, they may have led to higher rates of noncompliance or to the withdrawal of therapy by physicians.

In this study, short-term survival did not differ significantly between the placebo and treatment groups in either the PPD-positive or the anergy cohort. If the survival benefit of preventive therapy is conferred through a reduction in the tuberculosis-related case fatality rate, then the use of isoniazid in the PPD-positive cohort prevented 14 cases of tuberculosis and approximately 3 deaths, assuming a case fatality rate of 20 percent. Thus, a large, randomized clinical trial of preventive therapy would be needed to detect a clinically important reduction in the relative risk of cause-specific mortality from tuberculosis. However, the absolute difference in the mortality rates observed in this study between PPD-positive subjects receiving isoniazid and those receiving placebo may indicate important public health benefits in terms of survival if preventive therapy is used widely in HIV-infected persons. The conclusions regarding survival are limited, however, because the average duration of follow-up was short.

The implications of the findings of this study depend on the setting and the target population for preventive therapy. In the United States, where the annual risk of infection and the incidence of tuberculosis are in general low, preventive therapy in dually infected patients is both a standard medical practice and central to tuberculosis control. In developing countries, where dual infection is common and continued exposure to infectious cases of tuberculosis is likely, preventive therapy provides benefit to the individual patient, at least for a short time, but the effect on tuberculosis control remains to be established.

Supported by a cooperative agreement with the Centers for Disease Control and Prevention (ADEPT/HIV-Related Tuberculosis Demonstration Project, U78/CCU506716-04) and by a training grant from the Fogarty International Center at the National Institutes of Health (AIDS International Training and Research Program, TW-00011-08).

We are indebted to the following members of the study team: administration — L. Gary, M. Kasujja, S. Kibende, M. Manning, A. Nakayiza, and P. Nasige; counselors and interviewers — G. Bwamiki, R. Byaruhanga, and R. Galiwango; data managers — P. Bajaneza, D. Gwatudde, S. Katabalwa, J.B. Mukasa, M. Odie, C. Opit, G. Olupot, and A. Turyamureba; dispensers — A. Aben-

akyo and L. Ndegemu; drivers — E. Kaggwa, H. Kabymera, G. Lumumba, R. Mukasa, and L. Oryema; filing — G. Bukenya, A. Mulyabintu, and B. Nansubuga; health educators — W. Bagundirire and M. Mwanje; home health visitors — K. Kataliwa, M. Kato, J. Mulabbi, and J. Nakibali; laboratory — K. Edmonds, P. Kataaha, S. Kabengera, J. Okiror, E. Piwowar, B.S. Tugume, and R.S. Wallis; medical officers — W. Bukulu, F. Byekwaso, A. Gasasira, P. Kyambadde, H. Luzze, A. Mateega, F. Mubiru, C. Mukulu, and R. Odeke; microbiology — T. Aisu, E. Hatanga, and A. Morrissey; nurses — J. Kayungirizi, C. Kiramba, M. Mulindwa, G. Nalugwa, A. Rwamucece, and G. Tumusiime; radiology — A. Adongo and E. Katende; study coordinator — P. Langi; and tuberculin skin testers — G. Mpalanyi, P. Nasozzi, S. Nyole, and G. Wasswa. We are also indebted to S. Okware, Ministry of Health; M.G. Alwano-Edyegu, director, AIDS Information Centre; F. Engwau-Adatu, head of the Ugandan National Tuberculosis and Leprosy Programme; and the clients and staff of the following organizations: AIDS Information Centre; Joint Clinical Research Center, the AIDS Support Organization, Mulago Branch; the Post-HIV Test Club, Kisenyi; Good Samaritan Counseling Centre; HIV/AIDS Clinics of St. John's, Rubaga, and Nsambya Hospitals, Kampala, Uganda; Drs. E. Villarino, A. Vernon, P. Smith, and R. O'Brien and Mr. L. Geiter of the Centers for Disease Control and Prevention for their scientific contributions to the study design and analysis; to Drs. T.M. Daniel and F. van der Kuyp for their independent review of incident cases of tuberculosis; and to the subjects who participated in the trial.

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