Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection

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Summary

Background Tuberculosis is a common complication of HIV-1 infection, especially in developing countries. Practical and effective chemoprophylaxis regimens for HIV-1-related tuberculosis are needed. Our aim was to test the efficacy of isoniazid versus rifampicin with pyrazinamide for prevention of tuberculosis in HIV-1-positive individuals.

Methods We compared the efficacy of 6 months of isoniazid with 2 months of rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1-seropositive individuals. Eligible participants were aged 16–77 years, HIV-1 seropositive, had a positive purified-protein derivative (PPD) skin test reaction of at least 5 mm, and had a normal chest radiograph. Participants were randomly assigned partially supervised twice weekly isoniazid for 24 weeks or twice weekly rifampicin and pyrazinamide for 8 weeks. Participants were followed up for up to 4 years for the development of tuberculosis and survival.

Findings Tuberculosis developed in 14 (3·8%) of 370 participants assigned isoniazid and 19 (5·0%) of 380 participants assigned rifampicin and pyrazinamide (Cox model rate ratio 1·3 [95% CI 0·7–2·7]). The Kaplan-Meier estimate of the risk of tuberculosis during the first 10 months after entry was 3·7% among participants who received rifampicin and pyrazinamide compared with 1·0% (p=0·03) among participants who received isoniazid, and 5·4% versus 5·1%, respectively (p=0·9) at 36 months after entry. Higher rates of tuberculosis were observed in people with baseline CD4 percentages (of total lymphocytes) of less than 20 (rate ratio 4·0 [95% CI 1·8–9·0]). There were no significant differences in total mortality at any time.

Interpretation Twice-weekly isoniazid preventive therapy for 6 months or rifampicin and pyrazinamide for 2 months provided similar overall protection against tuberculosis in HIV-1-infected, PPD-positive adults. The better protection among recipients of isoniazid during the first 10 months was most likely secondary to the longer duration of chemoprophylaxis. Preventive therapy for HIV-1-seropositive, PPD-positive individuals could be practical in developing countries with a once weekly clinic visit, but optimum duration of chemoprophylaxis has not been determined.

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Introduction

HIV-1 infection is a potent risk factor for reactivation of latent *Mycobacterium tuberculosis* infection. The reported annual rates of tuberculosis among HIV-1-seropositive, tuberculin-positive adults who did not receive preventive therapy have ranged from 3% to 16%.[1–4] The administration of 300 mg of isoniazid daily for 6 months or more has been shown to reduce the risk of reactivation tuberculosis by 60–90% in immunocompetent individuals,[5–10] and daily administration of isoniazid for at least 6 months in HIV-1-seropositive individuals with a positive purified-protein derivative (PPD) skin test also reduces their risk of developing reactivation tuberculosis.[3,8] WHO has recommended that people found to be seropositive for HIV-1 should be screened for tuberculosis infection with PPD and that preventive therapy should be considered for those with a positive result.[11] In most developing countries, however, the resources are not available to screen all individuals for HIV-1 and tuberculosis and provide selective preventive therapy for 12 months.[8,12] Alternatives to 12 months of isoniazid preventive therapy are needed to improve patients' compliance, to reduce the risk of isoniazid-associated hepatotoxicity,[13] and to effectively prevent isoniazid-resistant *M tuberculosis* infections. In a murine model of chronic tuberculosis infection, daily rifampicin and pyrazinamide sterilised spleen cultures in 100% of animals after 2 months, whereas isoniazid given for 6 months sterilised only 60% of spleen cultures,[14] suggesting that rifampicin and pyrazinamide could be effective for prevention of active tuberculosis in human beings.

We undertook a prospective, randomised, unmasked trial to compare the efficacy of 6 months of twice weekly isoniazid with 2 months of twice weekly rifampicin and pyrazinamide for prevention of active tuberculosis in HIV-1-seropositive and PPD-positive Haitian adults. We studied twice weekly partly supervised regimens because intermittent therapy has been shown to be effective for treatment of tuberculosis, but has not been assessed for preventive therapy,[15,16] and because non-adherence to unsupervised daily treatment is common, particularly in developing countries.[15]

Disease categories

Confirmed tuberculosis: isolation of *M tuberculosis* from sputum, blood, or lymph-node specimens in a patient with a compatible clinical illness.

Probable tuberculosis: identification of acid-fast bacilli of characteristic morphology on biopsy sample or sputum smear from participants with clinically compatible disease.

Possible tuberculosis: a patient with a clinically compatible disease that responded to anti-tuberculosis therapy but no positive cultures or smears.

Lost to follow-up: participants not seen in the clinic for 6 months or more or those who could not be contacted after three consecutive visits to their home.

Methods

Non-pregnant adults aged 16–77 years were recruited from the communities of Cité Soleil and Petit Place Cazeau, Haiti. Individuals attending outpatient clinics, including contacts of patients with active tuberculosis, were approached for possible participation in the trial. Community health workers also recruited participants from the general community. Interested individuals were asked to attend a special clinic where group education regarding tuberculosis and HIV-1 infection was provided by auxiliary nurses, followed by individual pretest HIV-1 counselling. Verbal informed consent in Haitian Creole was obtained because about 80% of the population was illiterate. Individuals who gave consent had a 5-tuberculin unit PPD skin test placed on the volar surface of the forearm. Blood was taken for HIV-1 testing, posteroanterior chest radiography and physical examination were done, and the investigators ran through a brief questionnaire with the participants. Individuals were asked to return to the clinic 3–4 days later for the test results.

Skin tests were interpreted by trained nurses who measured induration by the ballpoint-pen method.[17,18] At the follow-up visit, participants were given private post-test counselling which included methods for prevention of HIV-1 acquisition if they were seronegative and methods for prevention of HIV-1 transmission if they were HIV-1-seropositive. Individuals with abnormal chest radiographs or physical findings suggestive of extrapulmonary tuberculosis were referred to the tuberculosis clinic for further evaluation and therapy.[19] Baseline social and demographic data were collected at screening and enrolment.

The protocol was approved by the review boards of Johns Hopkins University School of Hygiene and Public Health, the Centers for Disease Control and Prevention, and the Centres pour le Developpement et la Santé, Port-au-Prince, Haiti.

Criteria for participation in the trial included: age of at least 16 years, not being pregnant, PPD of at least 5 mm diameter induration, no evidence of extrapulmonary tuberculosis, a normal chest radiograph, two positive HIV-1 EIA or a rapid test for HIV-1 followed by a positive EIA, aspartate aminotransferase of less than 3 times normal upper limit, total bilirubin of less than 43 μmol/L, serum creatinine of less than 221 μmol/L, platelet count of more than 100 000/μL, white blood cell count of more than 4000/mL, weight over 25 kg, and informed consent. Participants with a negative or indeterminate western blot or who did not meet the criteria but were inadvertently enrolled were excluded from the final analysis.

A sample size of 500 was initially chosen on the basis of the following assumptions: a baseline cumulative incidence of tuberculosis in untreated people of 30%; a treatment efficacy of 50% in one treatment arm reducing incidence to 15%; an incidence of 5% or less in the other arm; and 40% loss to follow-up. Before completion of enrolment a decision was made to increase the sample size at the Cité Soleil site to 650. This was in response to concerns over loss of participants due to civil unrest associated with the overthrow of the government and the discontinuation of follow-up at the Petit Place Cazeau site because of logistical constraints. Enrolment began in April, 1990, and was completed in July, 1992.

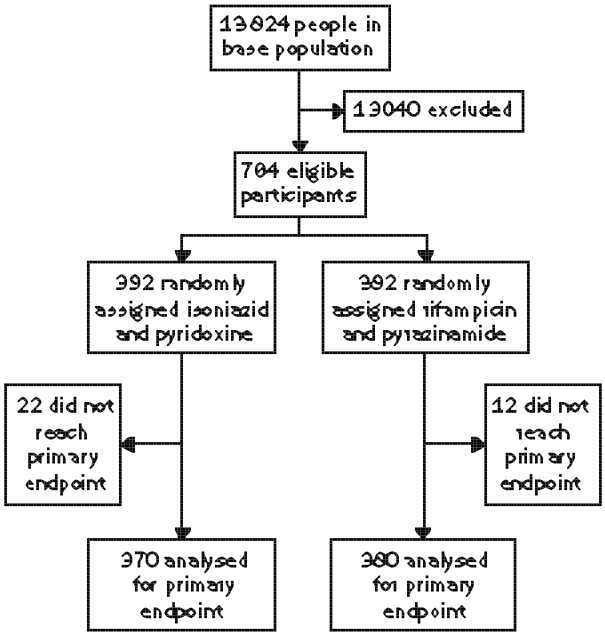

Figure 1: **Trial profile**

Randomisation

Eligible individuals were randomised by the project coordinator who opened sealed, sequentially numbered envelopes containing the assignment to treatment regimen. Random blocks of four or six allocations equally divided between regimens were used. Individuals were provided with twice weekly preventive therapy. Individuals in the isoniazid group who weighed less than 50 kg were given 600 mg isoniazid and 25 mg pyridoxine and those who weighed 50 kg or more were given 800 mg isoniazid and 25 mg pyridoxine. Pyridoxine was provided to keep to a minimum the potential complications from isoniazid in a nutritionally compromised population. Participants in the rifampicin and pyrazinamide group who weighed less than 40 kg were given 450 mg of rifampicin and 1500 mg of pyrazinamide, respectively; those who weighed 40–50 kg were given 450 mg and 2000 mg, respectively; and those who weighed more than 50 kg were given 600 mg and 2500 mg, respectively.

Participants were given two doses each week; the first dose was given under direct observation and the second dose was given to the participant in an envelope with the instruction to take it at home 3 days later. Individuals who did not return to the clinic for their appointment were visited by a home visitor and encouraged to come to the clinic. Participants were allowed up to 9 months to attend 24 weekly clinic visits and receive 48 doses of isoniazid and pyridoxine or up to 12 weeks to attend eight weekly visits and receive 16 doses of rifampicin and pyrazinamide. Adherence to the preventive therapy regimen was defined as attending at least 80% of the prescribed weekly clinic visits. As an incentive to participate, a monthly nutrition supplement of approximately 2·3 kg of beans, sugar, rice, or wheat was provided.

Adverse reaction monitoring

Physical examinations were done, and serum concentrations of creatinine, uric acid, aspartate aminotransferase, alkaline phosphatase, and bilirubin were measured at baseline. During the time medications were being administered, participants were screened weekly by a pharmacist and referred to a physician in the same clinic for examination if they had illnesses or signs or symptoms suggestive of drug toxicity (jaundice, nausea, vomiting, abdominal pain, skin rash, joint pain, changes in vision, and/or excessive malaise). Serum creatinine, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and uric acid were measured at 1 month and 2

Characteristic	Treatment		p
	Isoniazid and pyridoxine (n=370)	Rifampicin and pyrazinamide (n=380)	
Mean age (years)	31	31	0·99
Male	108 (29·2%) of 370	129 (33·9%) of 380	0·18
Married	40 (11·5%) of 348	33 (9·1%) of 361	0·30
Median years of schooling	0	0	0·38
Employed	89 (26·5%) of 336	103 (29·9%) of 344	0·35
Ever smoked	67 (18·9%) of 354	83 (22·7%) of 366	0·23
Ever drunk alcohol	9 (2·5%) of 353	26 (7·1%) of 366	0·005
Mean PPD size (mm)	11·7	11·7	0·75
Mean entry CD4	22·5%	22·2%	0·72
Mean entry CD4/CD8	0·57	0·56	0·73

PPD=purified-protein derivative.

Table 1: **Characteristics of patients at baseline by drug regimen**

months after entry for all participants and at 4 months and 6 months for participants on isoniazid. Additional liver function tests and other laboratory studies were done when indicated clinically. Individuals with results of liver function tests that showed an increase by three times the upper limits of normal values were assessed for toxicity and taken off medication while repeat tests were done.

Other tests were done: a complete blood count, including white blood cell differential, done manually, and lymphocyte subsets determination by fluorescence antibody cell sorting. Lymphocytes were stained with monoclonal antibodies, preserved in formaldehyde, and shipped to Johns Hopkins University every 1–2 weeks for analysis by fluorescence antibody cell sorting. HIV-1 EIA was done at the study site by standard methods. A latex agglutination rapid screening test was done on some individuals. Confirmation of positive screening results was by western blot done at Johns Hopkins University.

Follow-up

In addition to weekly interviews by the pharmacist, participants were seen each month by a nurse until the completion of follow-up. Participants with illnesses were referred to the clinic physicians for examination and treatment. Individuals with signs suggestive of tuberculosis (fever, persistent cough, weight loss, or unusually enlarged lymph nodes) had chest radiography and sputum collected for smears and culture on three consecutive mornings. Sputum smears were stained by the Ziehl-Neelsen method for acid-fast bacilli and with rhodamine-auramine stain for fluorescence microscopy, when available. Sputum samples were sent to the National Tuberculosis Laboratory, Port-au-Prince, for culture on Ogawa or Lowenstein-Jensen medium. After the first year of the study, the second sputum sample obtained from each participant with suspected tuberculosis was decontaminated with sodium hydroxide and stabilised with cetylpyridinium chloride and transported in batches every 2 weeks to Johns Hopkins Hospital for culture on Lowenstein-Jensen medium.

Blood cultures for mycobacteria were introduced in the second year of the study. Organisms were identified as *M tuberculosis* by standard biochemical techniques.[20] Individuals with unusually enlarged lymph nodes suspected to be tuberculous were encouraged to have a lymph-node biopsy or fine-needle aspiration. Participants were treated for tuberculosis (on the basis of sputum smears, chest radiographs, clinical signs, and symptoms) with a thrice weekly regimen of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months followed by 4 months of isoniazid and rifampicin.[19]

Suspected tuberculosis cases were classified into disease categories by three physicians who had no knowledge of prophylaxis regimen (panel). The primary outcome was the hazard rate ratio for the entire study period for individuals on rifampicin and pyrazinamide compared with those on isoniazid.

Characteristic	Lost to follow-up (n=85)	Not lost to follow-up (n=665)	p
Mean age (years)	29	31	0·02
Male	27 (32%) of 85	210 (31·6%) of 665	1·0
Married	13 (16%) of 81	60 (9·6%) of 628	0·07
Median years of schooling	4	0	0·0001
Employed	19 (36%) of 53	173 (27·6%) of 627	0·21
Ever smoked	15 (18%) of 82	135 (21·2%) of 638	0·66
Ever drunk alcohol	3 (4%) of 81	32 (5·0%) of 638	0·79
Mean PPD size (mm)	11·6	11·7	0·74
Mean entry CD4	22·2%	22·4%	0·91
Mean entry CD4/CD8	0·67	0·55	0·03
BCG scar	34 (40%) of 84	309 (47·2%) of 655	0·30
Thrush at entry	2 (2%) of 83	17 (2·6%) of 662	1·0

PPD=purified-protein derivative.

Table 2: **Characteristics of participants by follow-up status**

Percentage treatment visits completed	Number of participants	
	Isoniazid and pyridoxine*	Rifampicin and pyrazinamide*
100%	173 (46·8%)	264 (69·5%)
80–99%	30 (8·1%)	17 (4·5%)
50–79%	53 (14·3%)	45 (11·8%)
0–49%	114 (30·8%)	54 (14·2%)
Total	370 (100%)	380 (100%)

*p<0·0001 for comparison of adherence at cutpoints of 50%, 80%, or 100% of treatment visits completed.

Table 3: **Adherence rates by drug regimen**

Statistical analyses

Intention-to-treat analyses were done for all outcomes based on assigned treatment regimen. Baseline characteristics of participants were compared by use of continuity-corrected χ^2 tests, Fisher's exact test, and the Kruskal-Wallis test, as appropriate. The cumulative incidence of tuberculosis and survival probabilities were estimated by the Kaplan-Meier method and the results of the treatment groups were compared by Greenwood's variance estimator. Hazard ratios were determined with Cox proportional hazards models with fixed covariates; the time-related interaction was evaluated with a time-varying covariate. The time line for the survival analysis methods began at enrolment, and responses were censored at the earliest of: loss-to-follow-up, death (for the tuberculosis outcome), and end of 10 months since enrolment or end of study, depending on the analysis. Follow-up at the Petit Place Cazeau study site was terminated prematurely, with the result that 52 of the 750 eligible participants in the trial did not have time to complete their drug regimen before the clinic was closed. These participants (35 on isoniazid and 17 on rifampicin and pyrazinamide) were excluded from the calculation of adherence rates but included in all other intention-to-treat analyses. SAS software version 6.11 (Cary, NC, USA) and SPSS software version 6.0 were used for all analyses.

Results

The trial profile is shown in figure 1. 13 824 individuals were screened for participation in the trial including 10% of the adult population in Cité Soleil. Of those screened, 961 (7·0%) were HIV-1-seropositive and had a PPD reaction of at least 5 mm, a normal chest radiograph, and no signs or symptoms of active tuberculosis. Among this eligible population, 784 (81·6%) gave consent and were enrolled in the trial (665 at the Cité Soleil site and 119 at Petit Place Cazeau). At the primary study site (Cité Soleil), 242 (2·3%) of the screened adults were found to have active tuberculosis and were provided with the WHO-recommended treatment.[17,19] 34 (4·3%) of the 784 individuals enrolled were excluded from the final analysis because they were found to be HIV-1 negative or indeterminate by western blot (n=23), have had a PPD reaction of less than 5 mm (n=10), or an initial chest radiograph that was subsequently found to be abnormal (n=1). 22 of the

	Isoniazid and pyridoxine* (n=370)	Rifampicin and pyrazinamide* (n=380)	Total (n=750)
Culture confirmed	5	10	15
Sputum smear or histology positive	2	5	7
Clinically compatible with response to tuberculosis	7	4	11
Total	14	19	33

*Overall p=0·21.

Table 4: **Tuberculosis in study participants by chemoprophylaxis regimen**

individuals excluded were in the isoniazid group and 12 in the rifampicin and pyrazinamide group (p=0·11). Inclusion of these individuals in the final analyses did not result in any significant differences in the findings. The HIV-1 seropositivity rates, tuberculin skin test results, and the results of the chest radiographs have been described elsewhere.[17,18]

The two study groups were similar at baseline except that a slightly higher percentage of individuals who received rifampicin and pyrazinamide reported some lifetime use of alcohol (table 1). 68% of participants were female, the mean age was 31 years, and median years of schooling was zero. The mean baseline CD4 lymphocyte percent was 22·3.

Of the 750 eligible participants, 38 (10·3%) of 370 on isoniazid, and 47 (12·4%) of 380 on rifampicin and pyrazinamide were lost to follow-up before the completion of the study (p=0·43). The median follow-up was 2·5 years. Active follow-up was discontinued in September, 1992, at Petit Place Cazeau because of unexpected decreases in funding and in June, 1994, at the primary study site. There were no incident tuberculosis cases at the Petit Place Cazeau, and only four deaths. Individuals who were lost to follow-up were similar to the remaining study participants with regard to sex, marital status, smoking history, presence of BCG scar, baseline β-2 microglobulin, PPD size, and percentage CD4 at enrolment (table 2). Participants lost to follow-up, however, had a slightly lower mean age (29 *vs* 31 years, p=0·02), a higher median number of years of school (4 *vs* 0, p<0·001), and a higher enrolment CD4:CD8 ratio (0·67 *vs* 0·55, p=0·03) than participants who were followed throughout the trial. Longitudinal determinations of percentage CD4 showed no important difference in the last CD4 values of participants between the two arms: 21·5% for participants on rifampicin and pyrazinamide compared with 20·7% for those on isoniazid (p=0·3), when accounting for time since entry.

There were no significant differences between the number lost to follow-up in the isoniazid group compared with the rifampicin and pyrazinamide group.

Adherence

Higher rates of adherence to treatment were noted for individuals on rifampicin and pyrazinamide than for isoniazid recipients for all cut-off points (50%, 80%, or 100% of study regimen taken; table 3). Adherence was strongly associated with duration of treatment. Virtually identical proportions of patients dropped out during the first 2 months of treatment when all patients were taking medication. When analysed by the time since starting preventive therapy, no significant difference was noted in adherence to either regimen.

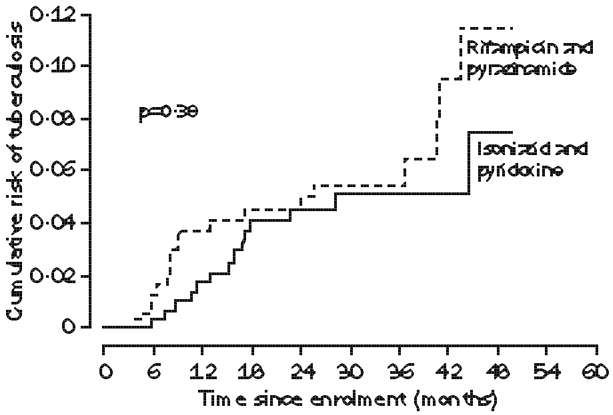

Figure 2: **Kaplan-Meier plot of proportions of patients developing confirmed, probable, or possible tuberculosis by treatment regimen**

Tuberculosis and related illnesses

14 (3·8%) participants on isoniazid and 19 (5·0%) on rifampicin and pyrazinamide developed tuberculosis as diagnosed by positive culture, sputum smear, histology, or clinical response to therapy (table 4). An additional six participants on isoniazid and four on rifampicin plus pyrazinamide developed symptoms suggestive of tuberculosis, but diagnoses were not completed before death or loss to follow-up so active tuberculosis could not be confirmed. Sensitivity analysis indicated the results would be unlikely to be materially affected by a defective assignment of disease status. The overall time to tuberculosis was not significantly different between the two groups (figure 2).

The primary study outcome, the hazard rate ratio (HR) for the entire study period, for individuals on rifampicin and pyrazinamide compared with those on isoniazid was 1·3 (95% CI 0·68–2·70). In the first 10 months after enrolment (the time allowed for completion of the isoniazid regimen) the cumulative risk of tuberculosis was higher among those on rifampicin and pyrazinamide than those on isoniazid (3·7% *vs* 1·0%, risk ratio [RR] 3·7, p=0·03). The annualised risk of developing tuberculosis in the 36 months after randomisation was 1·8% for participants taking rifampicin and pyrazinamide and 1·7% for those on isoniazid with cumulative 36-month risks 5·4% and 5·1%, respectively (RR 1·1, p=0·90). The rate ratios before and after 10 months were significantly different according to a Cox-model test of interaction (p=0·05).

Participants who developed tuberculosis had lower baseline CD4 percentages and CD4/CD8 ratios and were more likely to be men than those who did not

Characteristic	Tuberculosis (n=33)	No tuberculosis (n=717)	p
Mean age (years)	32	31	0·46
Male	16 (49%) of 33	221 (30·8%) of 717	0·05
Married	2 (7%) of 29	71 (10·3%) of 689	0·76
Median years of schooling	2	0	0·27
Employed	10 (33%) of 30	182 (28·0%) of 650	0·54
Ever smoked	8 (27%) of 30	142 (20·6%) of 690	0·49
Ever drunk alcohol	3 (10%) of 30	32 (4·6%) of 689	0·17
Mean PPD size (mm)	12·5	11·7	0·18
Mean entry CD4	18·6%	22·5%	0·05
Mean entry CD4/CD8	0·36	0·57	0·01
Drug=isoniazid	14 (44%) of 32	356 (49·7%) of 717	0·48

PPD=purified-protein derivative.

Table 5: **Characteristics of participants who developed and did not develop tuberculosis**

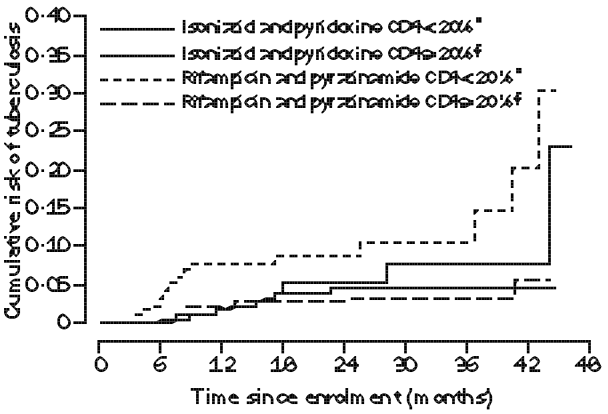

Figure 3: **Kaplan-Meier plot of proportions of patients developing tuberculosis by treatment regimen and initial CD4 lymphocyte percentage**

*p=0·17 for treatment among those with CD4 <20%; †p=0·33 for treatment among those with CD4 ⩾20%.

(table 5). Of the 27 participants who developed tuberculosis for whom there were baseline data on percentage CD4, 18 had baseline concentrations of less than 20%. A Cox proportional hazards analysis adjusted for treatment regimen showed that having a baseline percentage CD4 lymphocytes less than 20 (HR 4·0, 95% CI 1·8–9·0), a baseline CD4/CD8 ratio less than 0·5 (4·4, 1·7–11·8), and being male (2·3, 1·2–4·6) were associated with the subsequent development of tuberculosis. The rate ratio for men, however, dropped from 2·3 to 1·3 after adjustment for baseline percentage CD4. Among participants with baseline CD4 less than 20%, the rate ratio for individuals on rifampicin versus those on isoniazid was 2·0, whereas the rate ratio was 0·5 for those with CD4 lymphocytes of at least 20% (figure 3, p=0·11 for test of interaction). Individuals who were aged 30 years or older, who had a PPD of less than 10 mm, or who had no BCG scar were somewhat, but not significantly, more likely to develop tuberculosis than younger participants, participants with PPD reactions of 10 mm or more, or those with BCG scars. However, only 25% of participants had less than 50% adherence. Thus, there was little power to examine the association between adherence and tuberculosis incidence.

Adverse events

For each symptom suggestive of possible adverse reactions to study medications, the reported rates were significantly (p<0·001) higher for the week preceding the initiation of preventive therapy than the rates reported during the first 8 weeks of therapy. During the first 8 weeks of prophylaxis the rates of reported diarrhoea and stomach pain were higher for participants who received isoniazid and pyridoxine than for those on rifampicin and pyrazinamide. There were no other significant differences in reported symptoms. The rates of abnormal (over three times normal) serum creatinine, uric acid, bilirubin, alkaline phosphatase, or aspartate aminotransferase during the first 8 weeks of therapy were very low (1–3%) and did not differ significantly by drug regimen. All abnormal test results were found to be normal upon repeat testing. No participant had any serious adverse reactions, and study medications were not discontinued because of adverse events in any participant.

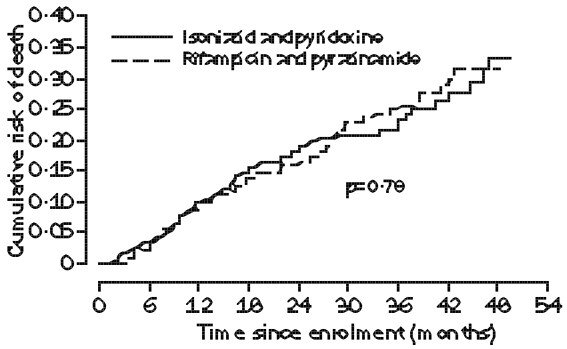

Figure 4: **Kaplan-Meier plot of all-cause mortality by treatment regimen**

M tuberculosis *susceptibility testing*

Susceptibility testing on *M tuberculosis* isolates from seven participants who developed tuberculosis revealed that two were resistant to isoniazid. One isolate was reported to be resistant to isoniazid, rifampicin, pyrazinamide, streptomycin, and ethambutol, but this patient also had a simultaneously obtained isolate from blood that was reportedly susceptible to all drugs tested and he responded to the standard treatment regimen. We believe that the susceptibility test results from the sputum isolate were due to a laboratory error. This pattern of antimicrobial resistance is similar to the 15% isoniazid and 2% rifampicin resistance found in 180 *M tuberculosis* isolates from other tuberculosis patients in the same population who had not received preventive therapy.[19]

Mortality

Of the 750 participants, 143 (19·1%) were known to have died, of whom 72 had received isoniazid and 71 had received rifampicin and pyrazinamide (p=0·85). The analysis of time to death revealed no significant differences or trends at any point during the study (figure 4). The annualised risk of death over the first 36 months of follow-up was 9·1%.

Discussion

Our study shows that isoniazid given twice a week for 6 months and rifampicin and pyrazinamide given twice a week for 2 months had similar efficacy in the prevention of tuberculosis in HIV-1-infected adults living in an area endemic for tuberculosis. The 24% lower risk of developing tuberculosis in patients on isoniazid represents only an absolute reduction of 1·2%, a difference that is not statistically or clinically significant. Fewer than 5% of patients in either study arm developed tuberculosis over a mean follow-up of 2·5 years, and the Kaplan-Meier probability of tuberculosis at 3 years after entry was 5% in both groups. The treatments were well tolerated, and there was no difference in all-cause mortality between the two treatment regimens.

During the first 10 months after enrolment, patients assigned isoniazid had a lower probability of developing tuberculosis than did patients assigned to rifampicin and pyrazinamide. In addition, no patient in either group developed tuberculosis during the first 3 months, or while receiving active therapy. Because patients assigned to rifampicin and pyrazinamide were only treated for 2 months, breakthrough cases after treatment ended could occur sooner than in patients receiving 6 months of

isoniazid. Although patients treated with isoniazid had a lower initial risk of tuberculosis, a catch-up phenomenon occurred in the second year of follow-up so that overall rates were not significantly lower in this group. Breakthrough tuberculosis cases might have been a result of reactivation of latent infection, or reinfection with a new tuberculosis strain resulting in primary disease.[21] Longer treatment with either of the two regimens used in this trial might have resulted in even lower rates of tuberculosis. In the USA, 12 months of isoniazid therapy is now recommended for HIV-1-infected individuals with a positive tuberculin skin test. Additional studies comparing long duration (lifetime) prophylaxis with short-course rifampicin and pyrazinamide in HIV-1-infected individuals should clarify this issue.

A trial by Pape and colleagues[9] in a nearby community compared 12 months of daily isoniazid and pyridoxine with pyridoxine alone (ie, no treatment) in HIV-1-seropositive Haitian adults. The rate of tuberculosis in PPD-positive patients treated with isoniazid was 1·7 per 100 person-years of follow-up. This finding is similar to the results seen in the PPD-positive patients treated with either regimen in our study. In patients who were not given prophylaxis in Pape's trial, the rate of tuberculosis was 10·0 per 100 person-years. In an observational study in the USA, rates of tuberculosis among PPD-positive HIV-1-infected adults were 1·6 cases per 100 person-years for participants who took isoniazid for at least 6 months, and 4·7 cases per 100 person-years for those who did not.[3] Both regimens in our trial seemed to reduce the risk of tuberculosis in latently infected adults with HIV-1-infection. The rifampicin and pyrazinamide combination was more active in an animal model of chronic tuberculosis infection[14] than isoniazid alone, but our trial demonstrated relative equivalence of the two regimens. More recent animal studies have suggested that intermittently administered rifampicin is less active in chronic tuberculosis infection than rifampicin given daily.[22]

The use of a short course of rifampicin and pyrazinamide to prevent tuberculosis was associated with improved compliance, a key element in the success of preventive interventions.[23] Although some tuberculosis experts have expressed concern that the use of rifampicin for preventive therapy could contribute to increased resistance to this drug, giving the drug in combination with pyrazinamide substantially reduces this risk. Also, the rifampicin and pyrazinamide combination could provide effective prophylaxis for patients infected with isoniazid-resistant *M tuberculosis*.[24,25]

The annual mortality in this trial was 9·1%, a rate that is high given the baseline CD4 cell concentrations in our patients. Having a lower CD4 concentration was predictive of dying, as was being male. Pape and co-workers[8] showed a survival advantage associated with tuberculosis preventive therapy in HIV-1-infected individuals, presumably related to both decreased tuberculosis mortality and the prevention of immune activation by tuberculosis that can upregulate HIV-1 replication and hasten progression of HIV-1 disease.[26,27] The patients in this study had similar overall rates of mortality and tuberculosis, irrespective of treatment arm. Our patients did not have access to antiretroviral therapy, which is known to prolong life in HIV-1-infected patients in developed countries. Although we cannot rule out that some participants could have died from undiagnosed tuberculosis, most patients had sputum, blood, or lymph-node cultures for detection of *M tuberculosis* during their terminal illnesses.

Tuberculosis morbidity and mortality are increasing and tuberculosis has become one of the most common causes of death in people with HIV-1 infection in many developing countries.[12] Traditional control strategies consisting primarily of case findings and treatment (and to a lesser extent BCG vaccination) may be inadequate in countries with a high burden of HIV-1 infection.[29] Combining community-wide tuberculosis and HIV-1 screening followed by short-course tuberculosis prophylaxis for HIV-1-infected and tuberculosis-infected individuals may be an effective approach for controlling epidemic tuberculosis.[30,31]

Contributors

Neal Halsey was the principal investigator who had primary responsibility for the design and oversight of all personnel and preparation of the final manuscript. Jacqueline Coberly, Lawrence Moulton, Michael Johnson, Reginald Boulos, Richard Chaisson, Lawrence Geiter, and Julio Desormeaux participated in the planning and implementation of the study design and methodology. Jacqueline Coberly had primary responsibility for data management and did initial interim analyses and participated in the trial data analysis. Julio Desormeaux supervised all field medical activities. Phyllis Losikoff, Joan Atkinson, Mireil Contave, Homer Davis, and Erica Johnson supervised various aspects of the field implementation and ongoing monitoring of the study including the medical management of adverse reactions and patient evaluation for tuberculosis. Lawrence Moulton was the principal statistician responsible for the final data analyses. Lawrence Geiter and Robin Huebner provided technical support and advice throughout the trial. Reginald Boulos and Julio Desormeaux had direct supervision over all the Haitian staff responsible for implementing the trial. Richard Chaisson provided medical and technical advice. Neal Halsey, Jacqueline Corberly, Lawrence Moulton, Lawrence Geiter, and Richard Chaisson participated in the final manuscript preparation.

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