

# Isoniazid preventive therapy for tuberculosis in HIV-1-infected adults: results of a randomized controlled trial

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**Objectives:** To determine the efficacy of isoniazid 300 mg daily for 6 months in the prevention of tuberculosis in HIV-1-infected adults and to determine whether tuberculosis preventive therapy prolongs survival in HIV-1-infected adults.

**Design and setting:** Randomized, double-blind, placebo-controlled trial in Nairobi, Kenya.

**Subjects:** Six hundred and eighty-four HIV-1-infected adults.

**Main outcome measures:** Development of tuberculosis and death.

**Results:** Three hundred and forty-two subjects received isoniazid and 342 received placebo. The median CD4 lymphocyte counts at enrolment were 322 and  $346 \times 10^6/l$  in the isoniazid and placebo groups, respectively. The overall median follow-up from enrolment was 1.83 years (range, 0–3.4 years). The incidence of tuberculosis in the isoniazid group was 4.29 per 100 person-years (PY) of observation [95% confidence interval (CI) 2.78–6.33] and 3.86 per 100 PY of observation (95% CI, 2.45–5.79) in the placebo group, giving an adjusted rate ratio for isoniazid versus placebo of 0.92 (95% CI, 0.49–1.71). The adjusted rate ratio for tuberculosis for isoniazid versus placebo for tuberculin skin test (TST)-positive subjects was 0.60 (95% CI, 0.23–1.60) and for the TST-negative subjects, 1.23 (95% CI, 0.55–2.76). The overall adjusted mortality rate ratio for isoniazid versus placebo was 1.18 (95% CI, 0.79–1.75). Stratifying by TST reactivity gave an adjusted mortality rate ratio in those who were TST-positive of 0.33 (95% CI, 0.09–1.23) and for TST-negative subjects, 1.39 (95% CI, 0.90–2.12).

**Conclusions:** Overall there was no statistically significant protective effect of daily isoniazid for 6 months in the prevention of tuberculosis. In the TST-positive subjects, where reactivation is likely to be the more important pathogenetic mechanism, there was some protection and some reduction in mortality, although this was not statistically significant. The small number of individuals in this subgroup made the power to detect a statistically significant difference in this subgroup low. Other influences that may have diluted the efficacy of isoniazid include a high rate of transmission of new infection and rapid progression to disease or insufficient duration of isoniazid in subjects with relatively advanced immunosuppression. The rate of drug resistance observed in subjects who received isoniazid and subsequently developed tuberculosis was low.

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**Keywords:** Tuberculosis, isoniazid preventive therapy, isoniazid chemoprophylaxis, HIV-1, AIDS

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## Introduction

HIV is the single greatest risk factor for the development of tuberculosis (TB) with a 5–8% annual risk of developing TB and a 30% or greater lifetime risk in those infected with both HIV and TB [1]. In the pre-HIV era, 6 months of isoniazid therapy was shown to reduce the incidence of active TB by more than 80%, where adherence could be guaranteed [2]. Because of the underlying immune dysfunction [3] and increased susceptibility to new infection [4], the efficacy of isoniazid in the prevention of TB in the HIV-infected individual cannot be assumed. To date, three randomized placebo-controlled trials have been reported [5–7].

This study reports on the results of a randomized, double-blind, placebo-controlled trial which examined the efficacy of 6 months of daily isoniazid in the prevention of TB in HIV-1-infected adults in Kenya.

## Methods

The study was conducted at the Respiratory Diseases Research Unit, Kenya Medical Research Institute (KEMRI) in Nairobi, Kenya. Ethical approval was obtained from the KEMRI Ethical Review Committee and the London School of Hygiene and Tropical Medicine Ethics Committee.

Patients were eligible for the study if they were HIV-1-positive, aged between 14 and 65 years and were resident in Nairobi. Patients were excluded if they had a past history of TB, any suspicion of current TB (cough, fever, adenopathy greater than 2 cm in diameter or abnormal chest radiograph), abnormal liver enzymes, a life-threatening intercurrent illness or if they were pregnant.

Subjects were recruited at three study clinics within Nairobi between April 1992 and March 1994: group 1, University of Nairobi Majengo Research Clinic (recruited April 1992–November 1994); group 2, Owen House Counselling Centre (recruited October 1992–March 1994); group 3, a KEMRI research clinic (recruited October 1992–March 1994).

Group 1 consisted of commercial sex workers, known to be HIV-1-positive, who were being followed at this clinic. HIV-1 positivity had already been confirmed at least twice using two different enzyme-linked immunosorbent assays (Organon Technika, Brussels, Belgium; and Behring Enzygnost Anti-HIV-1/HIV-2, Marburg, Germany) before recruitment to this study.

Group 2 consisted of clients of an HIV counselling centre. Patients were self-referred or referred by health

workers from sexually transmitted disease (STD) clinics, dispensaries or private clinics.

Group 3 consisted of patients referred by health workers from STD clinics, dispensaries or private clinics for HIV testing and treatment to a research clinic established to recruit subjects to this study.

Patients in groups 2 and 3 received pre-test counselling and were then tested for HIV-1 antibodies (Wellcozyme Recombinant VK 56/57, Wellcome Diagnostics, Dartford, Kent, UK). Those testing HIV-1-positive and confirmed with a second immunoassay (Behring Enzygnost Anti-HIV-1/HIV-2) received post-test counselling and were invited to be screened for the preventive therapy study.

Baseline screening for all subjects consisted of a questionnaire and physical examination, sputum fluorescence microscopy and culture for *Mycobacterium tuberculosis*, full blood count, bilirubin and liver enzyme assay and a chest radiograph. A tuberculin skin test (TST) was also performed with 0.1 ml intracutaneously of tuberculin purified protein derivative RT 23 SSI, 2 tuberculin units (TU)/0.1 ml (Statens Serum Institut, Copenhagen, Denmark). The area of induration was determined by palpation after 48 h and recorded as the mean of the long and short axes of induration. Lymphocyte subsets were determined using a FACScan flow cytometer (Becton Dickinson, Mountain View, California, USA).

The treatment arm consisted of isoniazid 300 mg daily for 6 months. No more than 1 month's supply of drug was issued at any one time. Isoniazid and placebo were supplied by Cosmos Limited, Nairobi packed in strips of 14 tablets. Both isoniazid and placebo were standard white, circular, uncoated tablets, indistinguishable in appearance. Drug quality and quantity was checked by the School of Pharmacy, University of London (London, UK) and conformed to British Pharmacopoeia standards [8]. Randomization was performed by a computer programme and randomly permuted blocks of 10 were used to ensure approximately equal numbers between the isoniazid and placebo groups throughout recruitment. The randomization code was passed on to an independent party who labelled the strip packs appropriately and did not disclose the code until the end of the study.

Serum bilirubin and liver enzymes were measured by a photometric autoanalyser (Vitalab 31, Vital Scientific N.V., Dieren, The Netherlands) at enrolment and at the 2- and 4-month visits during treatment. Adherence to treatment was assessed in three ways, using tablet counts at scheduled visits, an estimate of the total number of weeks of tablets missed during the 6-month period, and random urine testing for isonicotinic acid

and metabolites (Difco Laboratories, Detroit, Michigan, USA). Urine testing for isonicotinic acid and metabolites was performed by a technician who was blind to the drug code. Results were recorded and only known to the technician until the end of the study. The tablet counts were used to calculate the excess of tablets found over the number expected at each clinic visit, given the number of days since the subject's last visit and then the total excess found over the 6-month treatment period was calculated. At each clinic visit during the 6-month treatment period subjects were asked the number of days of tablets which they had missed. In addition, for those subjects who defaulted during the treatment period, the total number of weeks of tablets missed could be estimated. The total excess of tablets found on the subjects at their clinic visits and the estimated number of weeks they had missed were then grouped into a number of categories for the analysis to give a range of levels of adherence. The urine test results were used as a validity check for the other two measures of adherence in the isoniazid group and were found to correlate best with the estimate of number of weeks of tablets missed.

Follow-up was performed monthly during the 6-month treatment period and 3 monthly thereafter with a questionnaire and physical examination. A full blood count, lymphocyte subsets, TST and chest radiography were repeated annually.

Sputum was examined whenever available and subjects investigated for TB whenever symptoms or signs suggested TB. Examination of sputum or other relevant material was performed by fluorescence microscopy, and culture for *M. tuberculosis* by a modified Petroff's method [9] in the Respiratory Diseases Research Unit, KEMRI. Mycobacterial blood cultures were performed by adding 2 ml venous blood to 3 ml Kirchner medium and incubating at 37°C for 6 weeks and then sub-culturing on Lowenstein-Jensen medium for a further 3 weeks. Identification and susceptibility assays were performed in the same laboratory by standard methods [10,11]. Quality control was performed by the Mycobacterial Reference Laboratory, Public Health Laboratory Service (Cardiff, Wales, UK). Histology was performed on formalin-fixed tissue by the Department of Histopathology, Kenyatta National Hospital. Autopsy examination was performed at Kenyatta National Hospital whenever possible.

Tuberculosis was defined as follows: any subject with symptoms consistent with TB plus either (i) at least one culture positive for *M. tuberculosis* with greater than 10 colonies, or (ii) histology consistent with a diagnosis of TB, or (iii) a radiological pattern consistent with TB, and no response to broad-spectrum antibiotics for 7 days, and a response to anti-TB treatment as judged by resolution of symptoms and fever, and resolution of

radiographic findings by 12 weeks. The date on which the first culture-positive specimen was collected or a trial of anti-TB treatment commenced was considered the date of diagnosis of TB.

### Sample size estimation

An incidence of 3.5 cases of TB per 100 person-years (PY) was assumed in the placebo group and the efficacy of isoniazid was assumed to be 80%. With 2 years of follow-up after the 6-month treatment period, to obtain 90% power of obtaining a significant result ( $P < 0.05$ ) and allowing for a loss to follow-up of 10% per annum, the required sample size was estimated to be 350 in each group.

### Statistical analysis

Baseline characteristics between the isoniazid and placebo groups were compared using the  $\chi^2$  test for categorical variables or the Mann-Whitney test for continuous variables as appropriate. A non-parametric test was used for the continuous data as the distributions of these were skewed, in general. The main measure of the effect of isoniazid preventive therapy on the two major outcomes of TB and mortality was calculated as a rate ratio (RR). Since the length of follow-up varied widely between individuals, survival analyses that take this into account were performed. Kaplan-Meier survival plots were used to show the crude effect of isoniazid preventive therapy versus placebo. Cox proportional hazards regression analysis was used in order to obtain an estimate of the effect of isoniazid on the two major outcomes, adjusting for the effect of potential confounding factors.

## Results

Six hundred and ninety-six subjects were enrolled. Twelve of these subjects were excluded in retrospect leaving 684 subjects for analysis. Reasons for exclusion in retrospect were as follows: three subjects developed TB within 30 days of enrolment; three subjects had an abnormal chest radiograph at enrolment on review; one subject had abnormal liver enzymes at enrolment; four subjects were HIV-1-negative on retesting; and one subject required hospital referral shortly after enrolment. Three hundred and forty-two subjects received isoniazid and 342 received placebo. The mean age was 31.1 years in both groups with 63.5% women in the isoniazid group and 57.3% women in the placebo group. At enrolment, demographic, clinical and laboratory characteristics were similar between the two groups, except for slightly more women, more subjects with generalized lymphadenopathy and more subjects with a past history of herpes zoster in the isoniazid group (Table 1). The median CD4 lymphocyte count was 322 and  $346 \times 10^6/l$  in the isoniazid and placebo groups, respectively.

**Table 1.** Characteristics of subjects at enrolment to the study

Baseline characteristic	Isoniazid (n = 342)	Placebo (n = 342)
Mean (SD) age (years)	31.1 (6.9)	31.1 (7.5)
Sex (female) [n (%)]	217 (63.5)	196 (57.3)
Occupation [n (%)]		
Unemployed/casual	144 (42.2)	153 (44.7)
Employed/skilled	119 (34.9)	112 (32.7)
Commercial sex workers	78 (22.9)	77 (22.5)
Study clinic [n (%)]		
Group 1	78 (22.8)	77 (22.5)
Group 2	150 (43.9)	149 (43.6)
Group 3	114 (33.3)	116 (33.9)
Mean (SD) weight (kg)	59.4 (9.6)	59.3 (9.9)
BCG scar [n (%)]	256 (74.9)	248 (72.7)
Generalized		
lymphadenopathy [n (%)]	40 (11.7)	26 (7.6)
Skin rash [n (%)]	37 (10.8)	34 (9.9)
Oral candida [n (%)]	27 (7.9)	31 (9.1)
Herpes zoster [n (%)]	103 (30.1)	80 (23.4)
TST skin test-positive [n (%)]		
≥5 mm induration*	67 (22.2)	69 (23.5)
Mean (SD) haemoglobin (g/dl)	13.6 (1.9)	14.0 (1.9)
Median (range)		
White blood count ( $\times 10^9/l$ ) <sup>†</sup>	5.5 (2.7–10.8)	5.5 (2.6–17.4)
Total lymphocyte count ( $\times 10^9/l$ ) <sup>†</sup>	2.6 (0.8–7.2)	2.5 (1.0–9.5)
CD4 count ( $\times 10^6/l$ ) <sup>††</sup>	321.5 (9–3352)	346.0 (3–1975)
CD4/CD8 ratio <sup>††</sup>	0.28 (0.01–1.47)	0.30 (0.01–2.29)

\*Tuberculin skin test (TST) data available for 302 isoniazid and 293 placebo subjects. <sup>†</sup>Median and range given for quantitative variables with a skewed distribution. <sup>††</sup>CD4 and CD8 counts available for 246 isoniazid and 242 placebo subjects. BCG, Bacille Calmette–Guérin.

The total period of follow-up of subjects in the study was 1178 PY of observation, 583 PY of observation in the isoniazid group and 595 PY of observation in the placebo group. Fourteen subjects failed to return after enrolment. At the end of the study, 356 (70.2%) out of 509 subjects (172 out of 253 on isoniazid and 186 out of 256 on placebo) who were expected to return had been seen within the previous 6 months.

### Effect of isoniazid on TB

TB was diagnosed in 48 subjects, 25 of whom had received isoniazid and 23 of whom had received placebo (Table 2). The incidence of TB in the isoniazid group was 4.29 per 100 PY of observation [95% confidence interval (CI), 2.7–6.33] and 3.86 per 100 PY of observation in the placebo group (95% CI, 2.45–5.79), giving a crude RR for isoniazid versus placebo of 1.11 (95% CI, 0.64–1.98). Adjusting for potential confounding factors (sex, generalized lymphadenopathy, herpes zoster, TST) gave an adjusted RR for isoniazid versus placebo of 0.92 (95% CI, 0.49–1.71). Crude RR for isoniazid versus placebo showed no significant pattern or trend with time when considered over 6-month time intervals throughout the study. Fig. 1a shows Kaplan–Meier plots which compare progression to TB in the isoniazid and placebo groups. The incidence of TB in the isoniazid and placebo groups, stratifying for skin test reactivity is shown in Table 3. The adjusted RR for isoniazid versus placebo for TST-positive sub-

**Table 2.** Distribution of outcomes and follow-up in the isoniazid and placebo groups.

Outcome	Isoniazid (n = 342)	Placebo (n = 342)	Total (n = 684)
Tuberculosis [n (%)]	25 (7.3)	23 (6.7)	48 (7.0)
Death [n (%)]	62 (18.1)	57 (16.7)	119 (17.4)
Withdrawal [n (%)]	11 (3.2)	11 (3.2)	22 (3.2)
Drug reaction [n (%)]	26 (7.6)	19 (5.5)	45 (6.6)
Weeks of tablets missed [n (%)]			
None	138 (40.6)	143 (42.8)	281 (41.7)
1–4	95 (27.9)	88 (26.3)	183 (27.1)
≥ 5	107 (31.5)	103 (30.8)	210 (31.2)
Follow-up from enrolment (person-years)			
Median	1.83	1.82	1.83
Range	0–3.41	0–3.37	0–3.41
Total	582.8	595.2	1178.0

**Table 3.** Incidence of tuberculosis per 100 person-years of observation (95% confidence interval).

Subjects	Isoniazid	Placebo
Total	4.29 (2.78–6.33)	3.86 (2.45–5.79)
TST-positive	5.59 (2.25–11.51)	8.03 (3.85–14.77)
TST-negative	3.28 (1.75–5.61)	2.73 (1.36–4.88)

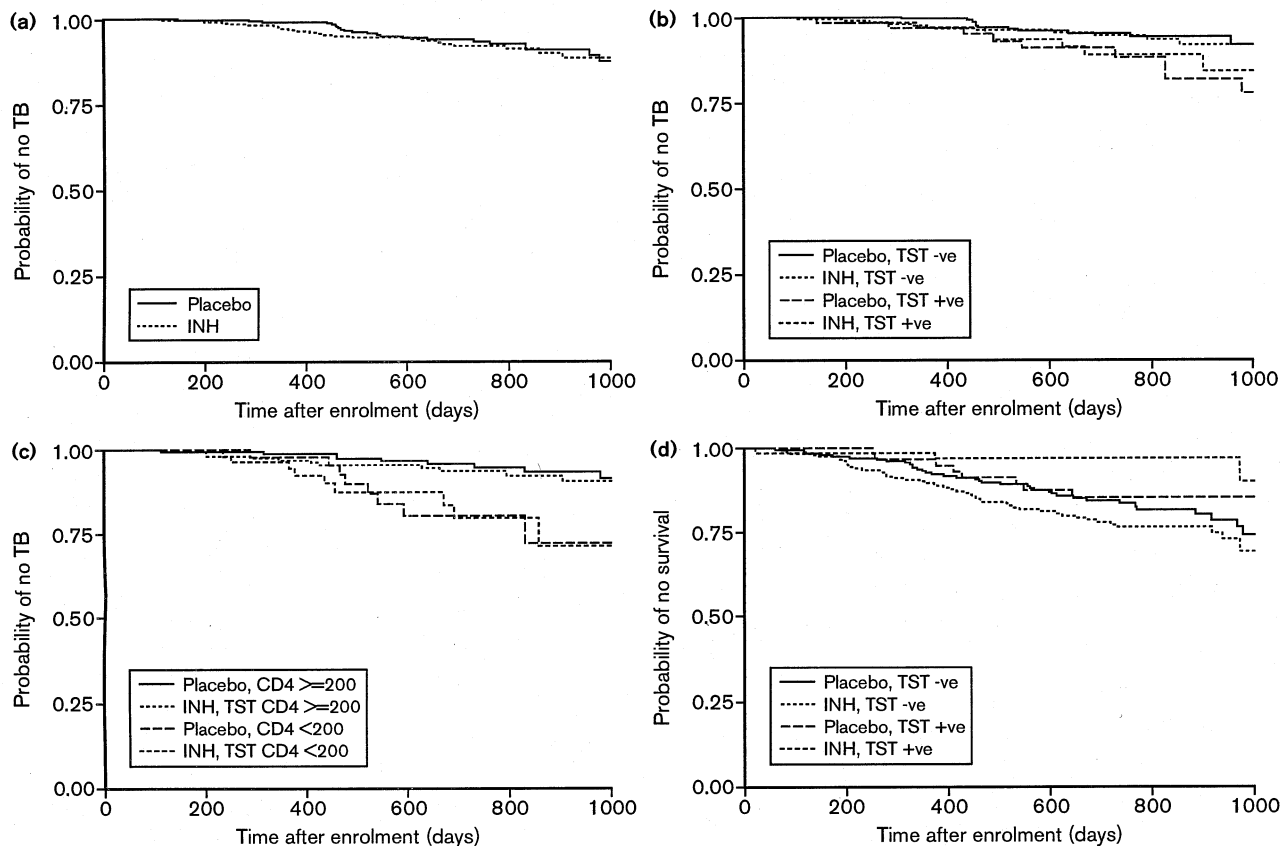
TST, Tuberculin skin test.

jects was 0.60 (95% CI, 0.23–1.60) and for the TST-negative subjects, 1.23 (95% CI, 0.55–2.76), although the difference in effect of isoniazid was not significant between the two TST groups ( $\chi^2 = 1.25$ ,  $P = 0.26$ ). The protective effect of isoniazid for TST-positive subjects was not significant at the 5% level (Fig. 1b). Similarly, stratifying for CD4 count showed no significant effect of isoniazid in the various categories of CD4 count, nor any difference in effect between the CD4 strata ( $\chi^2 = 0.05$ ,  $P = 0.97$ ; Fig. 1c).

In those who were known to have developed TB, the median time to the development of disease from enrolment was 13.9 months (range, 3.5–38.2) and 17.1 months (range, 4.8–34.9) in the isoniazid and placebo groups, respectively. The median CD4 counts within 4 months of the diagnosis of TB were  $130 \times 10^6/l$  (range,  $17$ – $458 \times 10^6/l$ ) and  $121 \times 10^6/l$  (range,  $24$ – $514 \times 10^6/l$ ) in the isoniazid and placebo groups, respectively.

**Table 4.** Diagnostic category of tuberculosis.

	Isoniazid (n = 25)	Placebo (n = 23)	Total (n = 48)
Sputum, smear-negative, culture-positive	10	5	15
Sputum, smear-positive, culture-positive	7	11	18
Pleural effusion, culture-positive	0	3	3
Node, culture-positive	1	2	3
Autopsy tissue, culture-positive	1	1	2
Histology positive only	2	1	3
Response to trial of anti-tuberculosis treatment	4	0	4



**Fig. 1.** (a–c) Kaplan–Meier survival analysis of tuberculosis (TB), (b) stratified by tuberculin skin test (TST) positivity and (c) CD4 count ( $\times 10^6/l$ ). (d) Kaplan–Meier survival analysis of mortality stratified by TST positivity. INH, Isoniazid.

The diagnostic category of TB is shown in Table 4. Tuberculosis was pulmonary in 41 (85.4%) subjects (22 in the isoniazid and 19 in the placebo group), extrapulmonary in three (6.25%) subjects (one in the isoniazid and two in the placebo group) and concomitant pulmonary and extrapulmonary in four (8.3%) subjects (two in the isoniazid group and two in the placebo group). TB was confirmed by culture in 85.4% of cases (41 subjects; 19 in the isoniazid group and 22 in the placebo group), confirmed by positive histology only in 6.3% of cases (two in the isoniazid group and one in the placebo group) and presumed by a positive response to a trial of anti-TB treatment in 8.3% of cases (all four in the isoniazid group). When analysis was restricted to cases of TB confirmed either with at least two culture-positive specimens or with both one culture-positive specimen plus positive histology, there was some degree of protection by isoniazid, although it was not statistically significant (adjusted RR, 0.73; 95% CI, 0.37–1.44).

Drug susceptibility assay results were available for 38 subjects who developed TB (17 in the isoniazid group

and 21 in the placebo group). Two strains (both in the isoniazid group) were resistant, one to both isoniazid and streptomycin, and one to isoniazid only. Both of these resistant strains occurred after the 6-month treatment period.

Of 48 subjects with confirmed TB, TST at enrolment and within 3 months of the diagnosis of TB was available for 32 subjects. Of these 32, 13 (40.6%; seven in the isoniazid and six in the placebo group), had negative TST at enrolment and TST greater than 10 mm within 3 months of developing TB. Of the remaining 19 subjects, eight had a negative TST both at enrolment and within 3 months of the diagnosis of TB and 11 subjects had a positive TST greater than 10 mm at enrolment and within 3 months of the diagnosis of TB.

Of those with pulmonary or concomitant pulmonary and extrapulmonary TB ( $n = 45$ ) and an available chest radiograph ( $n = 44$ ), eight subjects had a pleural effusion, seven had a typical upper lobe infiltrate, 21 had an atypical pulmonary infiltrate or adenopathy, or both, and eight had a normal chest radiograph.

## Effect of isoniazid on disease progression and mortality

The median decline in CD4 lymphocyte count was 21.7 and 25.1  $\times 10^6/l$  per year in the isoniazid and placebo groups, respectively ( $z = -1.01$ ,  $P = 0.31$ ).

The mortality rate in the isoniazid group was 10.64 per 100 PY of observation (95% CI, 8.29–13.65) and in the placebo group 9.58 per 100 PY of observation (95% CI, 7.39–12.42) giving a crude mortality RR for isoniazid versus placebo of 1.11 (95% CI, 0.77–1.58). The effect of isoniazid prophylaxis on mortality was assessed using survival analysis methods, as for the outcome of TB. Cox proportional hazards regression was used to obtain the RR, adjusted for potential confounders (sex, generalized lymphadenopathy, herpes zoster, TST; RR, 1.18; 95% CI, 0.79–1.75). The effect of isoniazid on mortality was found to vary significantly ( $\chi^2 = 4.75$ ,  $P = 0.029$ ) between those with a positive and negative TST, and so adjusted RR were calculated separately for these two groups. The adjusted mortality RR for isoniazid versus placebo in those with a positive TST was 0.33 (95% CI, 0.09–1.23) and for those with a negative result, 1.39 (95% CI, 0.90–2.12). The Kaplan–Meier survival plot shows the comparison between the isoniazid and placebo groups separately for subjects who were positive and negative for the TST (Fig. 1d).

## Adverse events

There were 4.75 adverse drug reactions per 100 PY of observation (95% CI, 3.10–6.96) in the isoniazid group and 3.37 per 100 PY of observation (95% CI, 2.03–5.26) in the placebo group during treatment (RR, 1.41; 95% CI, 0.78–2.54). Biochemical hepatitis, defined as a serum aspartate transaminase or alanine transaminase concentration greater than twice the upper limit of normal, occurred in 18 subjects while on isoniazid and 12 subjects while on placebo. In all subjects the hepatitis was mild and reversible. No subject developed jaundice or clinical hepatitis. There were three subjects who developed peripheral neuropathy in the isoniazid group. All other reactions were mild. Drugs were stopped because of an adverse drug reac-

tion in 11 of the isoniazid group and five of the placebo group. These subjects were still included in the analysis but classified according to their level of non-adherence.

## Adherence

Tablet counts during the 6-month treatment period were available for 554 subjects, of whom 406 (73%) were found with an excess of seven or fewer tablets during the whole 6-month treatment period. Ninety-eight (18%) subjects were found with between eight and 14 tablets more than expected, and 50 (9%) subjects were found with greater than 14 tablets than expected. The total number of weeks of tablets missed during the 6-month period could be estimated for 674 subjects. Of these 674, 281 (42%) missed less than 1 week of tablets, 183 (27%) missed between 1 and 4 weeks, and 210 (31%) missed at least 5 weeks of tablets. There was no statistically significant difference between the isoniazid and placebo groups in the number of tablets found more than expected or in number of weeks of tablets missed (Table 2). Urine tests for isoniazid were available for 630 subjects (315 isoniazid and 315 placebo) and the median number of tests per subject was four (range, one to 10). One hundred and forty-three out of 315 subjects who received isoniazid (45%) had all tests positive for isoniazid, and 70% of these 315 had at least 50% positive tests. There were no statistically significant differences in the effect of isoniazid on the incidence of TB between the levels of adherence for any of the three measures. Similarly, when subjects were classified into categories of adherence (adherent, mildly and moderately non-adherent) separately for each of the three measures, there remained no significant differences in the incidence of TB between the different levels of adherence (Table 5).

## Discussion

Overall this study showed no efficacy of daily isoniazid for 6 months in the prevention of HIV-associated TB.

**Table 5.** Incidence of tuberculosis (TB) in the isoniazid group according to category of adherence for the three measures.

Measure of adherence	Category of adherence			Trend test for incidence of TB	
	Adherent	Mildly non-adherent	Moderately non-adherent	$\chi^2$	<i>P</i>
Excess tablets	$\leq 2$	3–7	$\geq 8$		
TB incidence rate per 100 PYO	3.5	5.7	2.8	0.05	0.823
Weeks missed	0	1–4	$\geq 5$		
TB incidence rate per 100 PYO	5.2	3.8	3.3	0.69	0.405
Urine tests (% positive)	100	50–99	< 50		
TB incidence rate per 100 PYO	3.2	5.9	4.2	0.49	0.486

PYO, Person-years of observation.

However, in the TST-positive subjects, there was some protection against TB and some reduction in mortality, although this was not statistically significant.

The rationale for the possible efficacy of isoniazid in the HIV-infected individual assumes sufficient reduction of a latent bacillary load to remove the possibility of reactivation of infection as immunity decreases in an individual who is infected with *M. tuberculosis*. A second mode of action may be to prevent establishment of latent infection; however, once isoniazid is discontinued this effect can no longer operate. The major effect of isoniazid can therefore only occur in those individuals who are infected with *M. tuberculosis* and have a positive TST or in those individuals who are infected but anergic and therefore have a negative TST. Why then did we fail to demonstrate a protective effect of isoniazid?

Our objective in planning this study was to detect a significant overall reduction in TB. It was expected that the proportion of the population infected would be high and it seemed reasonable to expect that isoniazid might therefore have an overall protective effect. However, the number of TST-positive individuals recruited was lower than expected, hence the lack of a statistically significant effect in this subgroup may have been due to lack of power to detect a significant effect. We were not able to determine the number of infected but anergic subjects and so the effect of isoniazid could not be examined in this group.

There are several other reasons why the benefit of isoniazid may have been limited in the TST-positive group and masked by the rate of disease in the TST-negative group. These include a high rate of transmission of new infection, an insufficient duration of therapy to eradicate latent infection in an immunosuppressed host, non-adherence to therapy and a high prevalence of primary isoniazid resistance.

Once preventive therapy is discontinued, acquisition of new infection with rapid progression to active TB is possible [4,12,13]. High rates of recent transmission have been documented in San Francisco [14] and New York [15] where recent transmission is believed to contribute up to 40% of cases of TB. This proportion is even higher in HIV-infected individuals. In sub-Saharan Africa where the annual risk of infection exceeds 1%, the risk of newly transmitted infection is likely to be as high or higher than in San Francisco or New York. Therefore, once preventive therapy is discontinued some persons who were protected from reactivation by isoniazid may have subsequently been re-exposed, acquiring new rapidly progressive infection. Uninfected persons are equally susceptible to new rapidly progressive infection and this is the likely explanation for the lack of effect overall.

Insufficient duration of therapy in an immunocompro-

mised host may also have reduced the protective effect of isoniazid in the infected group. Macrophage and lymphocyte function, which is deficient in HIV infection [3], provide the major host defence mechanism in TB. One might therefore expect that a longer period of preventive therapy may be required to sufficiently reduce or eradicate a population of latent bacilli in the HIV-infected individual to prevent reactivation.

Non-adherence is a further factor to consider as a possible explanation for the lack of efficacy of isoniazid in this study. Thirty-one per cent of subjects missed at least 5 weeks of tablets during the 6-month treatment period. However, when the incidence of TB was compared in adherent and less adherent groups it was not found to be significantly different.

A high prevalence of primary isoniazid resistance would reduce the efficacy of isoniazid in preventing the progression of latent infection to TB. In this study, only two (11.8%) out of 17 subjects who developed TB, who had received isoniazid and had susceptibility tests available, were resistant to isoniazid. This excludes primary isoniazid resistance as the sole reason for failure of preventive therapy.

In the pre-HIV era, there was no increase in the rate of isoniazid-resistant TB seen in subjects who had received isoniazid preventive therapy [2]. Despite this, the possibility that isoniazid preventive therapy might result in the emergence and spread of isoniazid-resistant strains has been of concern. Although the two cases with isoniazid-resistant strains occurred in the isoniazid group and none in the placebo group, this was not significantly different and is not significantly increased above 8.5% found in HIV-1-infected persons with TB in Kenya [16].

There are several important differences between the Haiti study [5] and ours that may account for the different outcome. The Haitian study recruited subjects with asymptomatic HIV infection and had a TST positivity rate of 66 and 42% in the isoniazid and vitamin groups, respectively. At this early stage in HIV disease, reactivation is likely to be the dominant pathogenetic mechanism causing TB, possibly accounting for the efficacy of isoniazid demonstrated. The proportion of disease caused by reactivation and newly acquired infection may differ geographically, resulting in a varying efficacy of preventive therapy world-wide. The Haitian study also used isoniazid for 12 months instead of 6 months in our case. The Ugandan negative-therapy study [7] used 6 months of isoniazid, although details of the entry criteria and degree of immunosuppression are not yet available as results were preliminary and in abstract form.

In conclusion, this study suggests that 6 months of daily isoniazid is unlikely to be useful as preventive therapy

for TB for all HIV-infected persons, regardless of TST status, but suggests that it may be useful in those who are TST-positive, although the likely size of the effect is unclear. However, identification of such individuals remains problematic and the implementation of preventive therapy provides a major hurdle. Further studies to elucidate the efficacy of isoniazid preventive therapy at different levels of immunosuppression, the efficacy of alternative preventive therapy regimens and the feasibility of implementation of preventive therapy are awaited.

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