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Research

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Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial

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Abstract

Objectives To investigate the impact of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV.
Design Two centre prospective double blind placebo controlled trial.
Participants Children aged ≥8 weeks with HIV.
Interventions Isoniazid or placebo given with co-trimoxazole either daily or three times a week.
Setting Two tertiary healthcare centres in South Africa.
Main outcome measures Mortality, incidence of tuberculosis, and adverse events.
Results Data on 263 children (median age 24.7 months) were available when the data safety monitoring board recommended discontinuing the placebo arm; 132 (50%) were taking isoniazid. Median follow-up was 5.7 (interquartile range 2.0-9.7) months. Mortality was lower in the isoniazid group than in the placebo group (11 (8%) *v* 21 (16%), hazard ratio 0.46, 95% confidence interval 0.22 to 0.95, P = 0.015) by intention to treat analysis. The benefit applied across Centers for Disease Control clinical categories and in all ages. The reduction in mortality was similar in children on three times a week or daily isoniazid. The incidence of tuberculosis was lower in the isoniazid group (5 cases, 3.8%) than in the placebo group (13 cases, 9.9%) (hazard ratio 0.28, 0.10 to 0.78, P = 0.005). All cases of tuberculosis confirmed by culture were in children in the placebo group.
Conclusions Prophylaxis with isoniazid has an early survival benefit and reduces incidence of tuberculosis in children with HIV. Prophylaxis may offer an effective public health intervention to reduce mortality in such children in settings with a high prevalence of tuberculosis.
Trial registration. Clinical Trials NCT00330304

Introduction

Tuberculosis and HIV are dual pandemics in children in sub-Saharan Africa. Tuberculosis accelerates the course of HIV, increasing morbidity, mortality, and the frequency of opportunistic infections.[1–4] It is an important cause of acute and chronic pneumonia in African children with HIV[5–7] and is responsible for a major proportion of mortality.[8] Infection with *Mycobacterium tuberculosis* confirmed by culture has been found in about 8% of children with HIV admitted to hospital for pneumonia in areas with high prevalence of tuberculosis and HIV.[5–7] In a postmortem study of Zambian children dying from respiratory disease *M tuberculosis* was found in 18% of children with HIV; in children older than 12 months with HIV, tuberculosis was second to pyogenic pneumonia as a cause of death.[8]

Prevention of tuberculosis in children with HIV through prophylaxis with isoniazid may be effective in reducing mortality in areas with a high prevalence of tuberculosis. In studies of adults with HIV, prophylaxis with isoniazid significantly reduced the incidence of tuberculosis and produced a favourable trend in mortality in those with a positive result on a tuberculin skin test.[9–11] The effect of such prophylaxis in children, however, is unknown.

We investigated the effect of isoniazid prophylaxis on mortality in children with HIV living in an area with high tuberculosis prevalence. We also looked at the incidence of tuberculosis, the susceptibility of *M tuberculosis* isolates, the occurrence of toxicity, and the impact of two different prophylactic regimens.

Methods

We carried out a prospective double blind placebo controlled trial of isoniazid versus placebo given with co-trimoxazole (CTX) either daily or three times a week in children with HIV in two centres in Cape Town, South Africa. The study started in January 2003; the placebo arm of the study was ended on 17 May 2004 on the recommendation of the data safety monitoring board (DSMB) on the basis of the results of interim analyses.

Participants

Participants were children aged ≥8 weeks with HIV who were attending the Red Cross Children's Hospital, University of Cape Town, or Tygerberg Children's Hospital, Stellenbosch University. Additional inclusion criteria were weight ≥2.5 kg, access to transport, and informed consent from a parent or legal guardian. Exclusion criteria were chronic diarrhoea, current use or need for prophylaxis with isoniazid, previous hypersensitivity reaction to isoniazid or to sulphur drugs, severe anaemia (haemoglobin <70 g/l), neutropenia (absolute neutrophil count <400 cells/μl), thrombocytopenia (platelet count <50 000×10^9/l), or non-reversible renal failure. Children who were receiving highly active antiretroviral therapy (HAART) were eligible for enrolment if they had been stable on treatment for two to three months. Children were enrolled during working hours from Monday to Friday. Written informed consent was obtained from a parent or legal guardian.

Researchers took each child's history, carried out a physical examination, and collected sociodemographic, clinical, and laboratory data at enrolment. Children were seen by the study team every four weeks for the first six months then every six weeks for the next six months and then every two to three months, depending on the medical and social circumstances.

Assignment
Pharmacists in each site labelled the trial drugs with sequential study numbers according to variable blocked randomisation lists prepared by the trial statistician. At enrolment children were also allocated a sequential study number by the research nurse and were then randomly assigned to one of the treatment combinations. Study investigators were blinded to the assignment. The research pharmacist dispensed the drugs.

Prophylaxis
Children were randomised to receive prophylaxis with co-trimoxazole either daily or three times a week on Monday, Wednesday, and Friday. As recommended by current South African guidelines, prophylaxis (5 mg/kg/dose of the trimethoprim component) was given until the age of 12 months after which it was continued in those with clinical category B or C disease (according to the Centers for Disease Control), in those with severe immunological impairment (CD4 count of $<15\%$ total lymphocyte count), or in those who had previous episode of *Pneumocystis jirovecii* pneumonia (PCP). The dose of isoniazid (100 mg tablets, Be-Tabs Pharmaceuticals, Johannesburg, South Africa) was 10 mg/kg/day with a variability of 8-12 mg/kg depending on whether half or quarter tablets were required. Placebo was manufactured to have an identical appearance to isoniazid tablets. Children received isoniazid or placebo according to the frequency of the co-trimoxazole schedule. The duration of prophylaxis was planned for two years but was subject to review depending on interim results.

Other medication
Multivitamin supplementation and immunisations were given according to a standard protocol. HAART was not widely available but was obtained for some children through participation in pharmaceutical trials or charitable donations. Standard guidelines for HAART in children in the Western Cape were developed during the study period; although these were not yet widely implemented, some children were able to access HAART according to medical and social criteria.

Investigations
HIV status was assessed at enrolment by two enzyme linked immunosorbent assays (Abbott AxSYM HIV antibody/antigen ELISA) in those aged >15 months and by polymerase chain reaction (Amplicor HIV-1, Roche Diagnostic Systems) in younger children. The CD4 cell count and percentage was measured at study entry and every six months. Full blood count, renal function (urea, creatinine), and alanine transaminase (ALT) were measured at baseline and every six months. A screening tuberculin skin test (PPD, 2 TU RT23, Staten Serum Institut, Copenhagen, Denmark) was done on enrolment and repeated every six months if previous results were negative. A positive result was regarded as ≥ 5 mm transverse induration. Children underwent screening chest radiography at enrolment and thereafter every six months. Blood tests, tuberculin skin tests, and chest radiography were performed more frequently if clinically indicated. In addition, for children receiving HAART, full blood count and alanine transaminase were measured one and three months after randomisation and thereafter every six months or more frequently if clinically indicated. If children were admitted to hospital or were ill between study visits, we took a detailed history and carried out clinical examination and laboratory tests as clinically indicated. The hospital or clinic records were obtained whenever possible for children who died; in the absence of these a verbal autopsy was performed when feasible.

Diagnosis of tuberculosis
Children were screened for tuberculosis on enrolment as described above. Any child who developed clinical signs of a lower respiratory tract infection underwent a tuberculin skin test and chest radiography. When chest radiography yielded abnormal results, three sequential gastric aspirates and sputum induction with nebulised hypertonic saline[12] were performed for acid fast staining and *M tuberculosis* culture. Additional specimens were sent for *M tuberculosis* staining and culture as clinically indicated. Children were classified as having confirmed tuberculosis if they were culture positive for *M tuberculosis*. Probable pulmonary tuberculosis was diagnosed when chest radiography suggested tuberculosis (lymphadenopathy, miliary pattern, pleural effusion, bronchial compression, or parenchymal infiltrate) and the child had at least one of: a positive tuberculin skin test result, a history of a close contact with tuberculosis, loss of weight or failure to gain weight within the previous three months, or a positive smear result for acid fast bacilli. The diagnosis of probable tuberculosis was subject to independent review by a blinded investigator.

Children with confirmed or probable tuberculosis were randomised at enrolment but isoniazid or placebo was started only after they had finished standard tuberculosis treatment. Children who developed confirmed or probable tuberculosis during the study were unblinded; those in the placebo group were given standard tuberculosis treatment while those in the isoniazid group were treated with four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol or ethionamide). Treatment was modified according to the antimicrobial susceptibility of cultured isolates.

Toxicity
Clinical or laboratory events were graded 1 to 4 according to the toxicity criteria of the National Institutes of Health's division of AIDS (DAIDS). A grade 3 or 4 reaction was considered an important adverse event and managed according to a standard protocol.

Sample size and statistical analysis
The primary outcome measure was mortality. Using a survival analysis approach, we estimated that a sample size in each group of 196 with a 0.050 level one sided log rank test for equality of survival curves would provide 80% power to detect the difference between an isoniazid-placebo mortality proportion at time t of 0.100 and an isoniazid mortality proportion at time t of 0.050 (a constant hazard ratio of 0.769), assuming no dropouts before time t. Therefore, with an assumed 10% dropout rate, the estimated required sample size was 216 children per arm or a total sample size of 432.

All analyses were by intention to treat. We used the Kaplan-Meier method to analyse the time to event outcomes, made comparisons with a one sided log rank test, and used Cox proportional hazards regression to estimate hazard ratios after confirming the validity of the proportional hazards assumption. This assumption was tested with the Grambsch and Therneau test.[13] We did subgroups comparisons for severity of disease, dose, age, and study site to assess the consistency of the intervention effect. Tests for heterogeneity were done with the Cox regression model, except for tuberculin positivity as there were too few events in this subgroup. Anthropometric measurements were standardised with reference to standards from the National Center for Health Statistics.

Data safety monitoring board

A safety monitoring board comprising international and South African experts reviewed and monitored the study at regular intervals. Interim data analyses were undertaken every three to six months to ensure the safety of the study and review progress.

Results

At the first meeting of the monitoring board, data up to 30 September 2003 were analysed. Of the 129 children enrolled 13/61 died in the placebo group and 4/68 died in the isoniazid group (P = 0.009). The second meeting of the board in April 2004 considered data up to 30 December 2003. At that time, of the 148 children enrolled, 16 died in the placebo group and five in the isoniazid group (P = 0.002 by intention to treat and P < 0.001 for on treatment analysis). Both of these analyses met the O'Brien-Fleming rule for stopping a study, which requires P < 0.01.[14] As soon as the board recommended it, we terminated the placebo arm of the study. At this time, 277 children were enrolled. We excluded 14 children from the analysis (10 tested negative for HIV, four were lost to follow-up within a month after randomisation) and included 263 children (146 (56%) boys) in the analysis (fig 1). Of these, 132 were assigned to isoniazid (three times a week in 68 and daily in 64). Median follow-up time was 5.7 months (interquartile range 2.0-9.7 months).

Table 1 provides the baseline characteristics of the children. About half were younger than 24 months. Most children (231, 88%) were symptomatic, either Centers for Disease Control clinical category B or C. The median CD4 percentage was 20%; the proportion of moderate or severely immunosuppressed children was similar in both groups. Overall, children were malnourished with the median weight for age z score equal to −1.6 (interquartile range −2.5-−0.4) and the median weight for height z score equal to −0.2 (−1.1-0.9). Forty one (16%) children had a history of tuberculosis, with a similar number in both groups. Tuberculin skin test results were positive in 22 (9%); these children had previously received either prophylaxis or treatment for tuberculosis. At enrolment, 23 (9%) were receiving HAART, while 58 (22%) started HAART during the trial. The number of children who received HAART during the trial was similar both groups (41 in isoniazid group and 40 in placebo group).

Table 1 Comparison of children in isoniazid prophylaxis and placebo groups at randomisation. Figures are medians (interquartile range) for continuous variables or percentage (number) of children as shown

	Isoniazid (n=132)	Placebo (n=131)	Total (n=263)
Age (months):			
Median	29.6 (11.0-55.3)	22.1 (8.9-45.4)	24.7 (9.4-51.6)
<12 months	26% (35)	32% (42)	29% (77)
12-24 months	19% (25)	20% (26)	19% (51)
>24 months	55% (72)	48% (63)	51% (135)
Boys	55% (72)	57% (74)	56% (146)
Co-trimoxazole prophylaxis:			
Daily	49% (64)	46% (60)	47% (124)
Three times a week	52% (68)	54% (71)	53% (139)
Weight for age (z score)	−1.55 (−2.47-−0.44)	−1.62 (−2.61-−0.44)	−1.56 (−2.49-−0.43)
Weight for height (z score)	−0.07 (−1.07-0.88)	−0.19 (−1.14-0.92)	−0.15 (−1.08-0.88)
Centers for Disease Control classification :			
N	1% (1)	2% (2)	1% (3)
A	10% (13)	12% (16)	11% (29)
B	66% (87)	66% (86	66% (173)
C	24% (31)	21% (27)	22% (58)
Tuberculosis:			
Prior TB treatment	17% (23)	14% (18)	16% (41)
Positive tuberculin skin test	12% (15/128)	5% (7/129)	9% (22/257)
Immune classification:			
1	30% (40)	23% (30/129)	27% (70/261)
2	40% (53)	41% (53/129)	41% (106/261)
3	30% (39)	36% (46/129)	33% (85/261)
Laboratory tests:			
Alanine transaminase (U/l)	23 (7-30) (n=113)	22 (6-31) (n=111)	30 (22-43)
White cell count (10^9/l)	9.5 (7.0-13.4) (n=120)	10.7 (7.7-13.8) (n=122)	10.3 (7.2-13.4)
CD4 (% lymphocytes)	21 (14-29) (n=114)	19 (14-27) (n=118)	20 (14-28)
Receiving HAART at enrolment	10% (13)	8% (10)	9% (23)

HAART=highly active antiretroviral therapy.

Effect on mortality

Mortality (32 deaths in 263 children, 12%) was lower in the isoniazid group than in the placebo group (11/132 (8%) *v* 21/131 (16%), hazard ratio 0.46, 95% confidence interval 0.22 to 0.95,

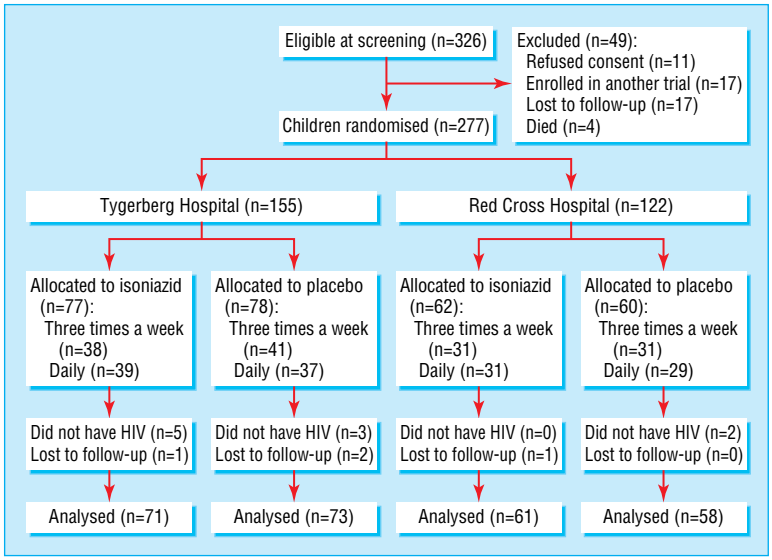

Fig 1 Allocation of participants and flow through trial

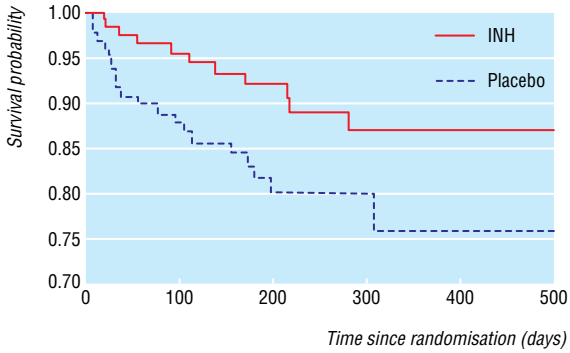

Fig 2 Survival in children on isoniazid (INH) or placebo

P=0.015 for the one sided log rank test and P=0.226 for the proportional hazards assumption; fig 2). The benefit applied to children across all categories of severity of clinical disease (test for heterogeneity P=0.933) and in all ages (test for heterogeneity P=0.678), table 2. The reduction in mortality was similar in children assigned to isoniazid three times a week compared with every day (test of heterogeneity P=0.943).

There were no deaths among children with positive results on tuberculin skin testing. The estimated hazard ratio for children negative for tuberculin was 0.51 (0.24 to 1.07). For children who received HAART at anytime during the study, three of 41 in the isoniazid group died with 195 months of exposure (the three children who died had a combined HAART exposure of 1.8 months) compared with none of the 40 children in the placebo group with 170 months of HAART exposure. The overall time without HAART was 577 months in the placebo group and 685 months in the isoniazid group. This converts to an annual non-HAART mortality of 43.6 per 100 in the placebo group and 14 per 100 in the isoniazid group.

Table 2 Mortality and hazard ratios (HR) in children allocated to isoniazid prophylaxis or placebo

	Isoniazid (%)	Placebo (%)	Total (%)	HR (95% CI)
Intention to treat	11/132 (8)	21/131 (16)	32/263 (12)	0.46 (0.22 to 0.95)
Frequency:				
Three times a week	5/68 (7)	9/71 (13)	14/139 (10)	0.44 (0.17 to 1.18)
Daily	6/64 (9)	12/60 (20)	18/124 (15)	0.49 (0.17 to 1.47)
Centers for Disease Control classification:				
A+N	1/14 (7)	2/18 (11)	3/32 (9)	0.82 (0.07 to 9.22)
B	6/87 (7)	11/86 (13)	17/173 (10)	0.45 (0.16 to 1.21)
C	4/31 (13)	8/27 (30)	12/58 (21)	0.41 (0.12 to 1.35)
Age group (months):				
<12	7/35 (20)	13/42 (31)	20/77 (26)	0.43 (0.17 to 1.09)
12-24	3/25 (12)	5/26 (19)	8/51 (16)	0.75 (0.18 to 3.13)
>24	1/72 (1)	3/63 (5)	4/135 (3)	0.26 (0.03 to 2.49)
Tuberculin skin test result (n=257):				
Positive	0/15 (0)	0/7 (0)	0/22 (0)	No estimate
Negative	11/113 (10)	20/122 (16)	31/235 (13)	0.51 (0.24 to 1.07)
Receiving HAART at enrolment:				
Yes	0/13 (0)	0/10 (0)	0/23 (0)	No estimate
No	11/119 (9)	21/121 (17)	32/240 (13)	0.46 (0.22 to 0.95)

HAART=highly active antiretroviral therapy.

Table 3 Incidence of tuberculosis in children allocated to isoniazid prophylaxis or placebo

	Isoniazid n=132 (%)	Placebo n=131 (%)	Total n=263 (%)	HR (95% CI)
Intention to treat	5/132 (4)	13/131 (10)	18/263 (7)	0.28 (0.10 to 0.78)
Frequency of dose:				
Three times a week	3/68 (4)	5/71 (7)	8/139 (6)	0.45 (0.11 to 1.90)
Daily	2/64(3)	8/60(13)	10/124 (8)	0.16 (0.03 to 0.76)
Centers for Disease Control classification:				
A+N	0/14 (0)	1/18 (6)	1/32 (3)	No estimate
B	4/87 (5)	11/86 (13)	15/173 (9)	0.22 (0.07 to 0.70)
C	1/31 (3)	1/27 (4)	2/58 (3)	0.86 (0.05 to 13.8)
Age group (months):				
<12	0/35 (0)	0/42 (0)	0/77 (0)	No estimate
12-24	2/25 (8)	5/26 (19)	7/51 (14)	0.50 (0.10 to 2.60)
>24	3/72 (4)	8/63 (13)	11/135 (8)	0.26 (0.07 to 0.98)
Tuberculin skin test result (n=257):				
Positive	0/15 (0)	1/7 (14)	1/22 (5)	No estimate
Negative	5/113 (4)	12/122 (10)	17/235 (7)	0.32 (0.11 to 0.90)
Receiving HAART at enrolment:				
Yes	0/13 (0)	1/10 (10)	1/23 (4)	No estimate
No	5/119 (4)	12/121 (10)	17/240 (7)	0.31 (0.11 to 0.87)

HAART=highly active antiretroviral therapy.

In most children (27, 84%) the cause of death could be reliably determined. Clinical sepsis was the cause in 14 (44%); 10 (31%) had bacteraemia confirmed by culture. Most cultures were Gram negative bacteria (*Klebsiella pneumoniae* in four, acinetobacter in two, citrobacter in two, *K xanii* in one, enterobacter species in one, *Escherichia coli* in one), and *Staphylococcus aureus* was isolated in two children. Three children had polymicrobial sepsis, and one child had concomitant cryptosporidial diarrhoea. Other causes of death included pneumonia (7, 22%), gastroenteritis (3, 9%), and wasting syndrome, HIV encephalopathy with respiratory depression, and Burkitt's lymphoma in a single case each. In five (16%) children the cause of death could not be ascertained: three died at home and two died at a local day health facility.

Incidence of tuberculosis

The incidence of confirmed or probable tuberculosis cases by intention to treat analysis (18 cases in 263 children, 7%) was lower in the isoniazid group than in the placebo group (5/132 (4%) *v* 13/131 (10%), hazard ratio 0.28, 0.10 to 0.78, P=0.005 for the one sided log rank test and P=0.919 for the proportional hazards assumption, table 3). The total child months of intent to treat follow-up in the two groups for the incidence of tuberculosis (total time from randomisation until a positive tuberculosis event or censoring event for each child) was 667 months in the placebo group and 839 months in the isoniazid group. This translated into 7.2 cases of tuberculosis annually per 100 children in the isoniazid group compared with 23.4 cases in the placebo group and an incidence rate ratio of 0.31 (0.09 to 0.91). The protective effect of isoniazid on incidence of tuberculosis occurred in all categories of severity of clinical disease in children aged >1 year and in both dose regimens (table 3). All five cases of tuberculosis confirmed by culture occurred in the placebo group. All *M tuberculosis* isolates were sensitive to anti-tuberculosis drugs including isoniazid.

Toxicity

The incidence of grade 3 or 4 toxicity was low with five (4%) in the isoniazid group and eight (6.1%) in the placebo group. Of

these, two were increases in alanine transaminase activity, both in the placebo group, while 11 were haematological events including neutropenia, thrombocytopenia, or anaemia. Alternative causes of haematological events included infections, other drugs, and HIV infection. No child required permanent discontinuation of trial drug. No cutaneous or neurological toxicity was observed. No grade 3 or 4 toxicity occurred among children receiving HAART.

Discussion

Efficacy of isoniazid prophylaxis

Isoniazid prophylaxis significantly reduced mortality in children with HIV who were living in an area with a high prevalence of tuberculosis. The impact on mortality was evident in all categories of clinical disease, across age groups, and for varying degrees of immune suppression. The effect on survival occurred within six months of the initiation of prophylaxis and was in addition to that provided by co-trimoxazole. Furthermore, isoniazid prophylaxis reduced the incidence of tuberculosis by about 70%. The impact on survival and incidence of tuberculosis was similar for isoniazid three times a week or once a day. Few children were taking HAART at randomisation, reflecting the poor access and unaffordability of antiretroviral therapy for most children in sub-Saharan Africa, so we could not evaluate the impact of isoniazid prophylaxis on mortality in this subgroup. The three deaths that occurred in children taking isoniazid and HAART occurred soon after HAART initiation, suggesting that it was started too late in these children with advanced HIV disease.

The Western Cape area of South Africa has one of the highest incidences of tuberculosis in the world, with reported rates of 988/100 000 population in 2004[15] and an estimated annual risk of infection of 3.8%.[16] Children aged <15 years contribute about 20% of the case load.[17] In addition, the incidence of HIV infection, as reflected by the prevalence in pregnant women, has increased exponentially from 8.6% in 2001 to 15.4% in 2004.[18] In contrast with our findings, a Cochrane review of prophylaxis in adults with HIV did not find a significant reduction in mortality, although a favourable trend on survival was reported for adults with positive results on tuberculin skin test.[11] Furthermore, our observed reduction in incidence of tuberculosis in children taking isoniazid prophylaxis was greater than that reported for adults with HIV[11] and also occurred in children with negative tuberculin results. In contrast, chemoprophylaxis in adults with HIV has been found to be significantly effective only in those with positive results on tuberculin skin test, reducing the risk of active tuberculosis by about 60%.[11]

In our study, only a few children had positive results on tuberculin skin test. The impact of isoniazid on mortality and incidence of tuberculosis could therefore be reliably assessed only in children with a negative result on a tuberculin skin test, in whom we found a consistently protective effect of isoniazid. The high number of children with negative results on tuberculin skin tests may reflect anergy as a result of HIV mediated immunosuppression (most children had moderate or severe immunosuppression by CD4 counts), depressed cell mediated immunity because of malnutrition (most children were also malnourished), or early or lack of infection with *M tuberculosis*. Tuberculosis in young children with HIV differs from adult disease in that it usually reflects primary infection and may often develop into severe or disseminated disease, which may cause death.[3] Although all children were screened carefully for tuberculosis, diagnosis is notoriously difficult in those with HIV,[3 12] raising the possibility that children with early or subclinical *M tuberculosis* infection were not detected.

Possible mechanisms of isoniazid efficacy

The effect of isoniazid prophylaxis on incidence of tuberculosis may therefore have been because of treatment of early, subclinical, or latent *M tuberculosis* infection. In addition, ongoing isoniazid treatment may have provided primary or secondary prophylaxis against infection. Recently it has been reported that treatment for latent tuberculosis with isoniazid (but not rifampicin) alters the immune response, resulting in an increase in the number of interferon γ producing T cells within a month of therapy.[19] Therefore isoniazid prophylaxis, by enhancing the host immune response, may provide longstanding protection. This mechanism may explain the long term protection (in excess of 19 years) provided by nine months of isoniazid prophylaxis in Alaskan people without HIV.[19 20] The ability of isoniazid to stimulate such immunity in people with HIV is not known. Alternatively, isoniazid may have effectively provided primary prophylaxis against *M tuberculosis* in an area where children are continuously at high risk of infection.[16]

The mechanism whereby isoniazid prophylaxis improves survival in children with HIV is unclear but could occur in several ways. Co-infection with *M tuberculosis* and HIV results in more rapid deterioration of immune dysfunction, viral replication, and progression of HIV.[21] Such immune decline has been reported to result in more frequent, severe infections such as bacterial sepsis,[22] which was the cause of death in most of our children. Tuberculosis, however, may also be a direct cause of mortality, as has been reported in a postmortem study of Zambian children in which tuberculosis was the second commonest cause of death in children aged >1 year with HIV who died from respiratory disease.[8] As confirmation of *M tuberculosis* by culture is difficult and positive in about a third of children with clinically suspected tuberculosis, and, as bacterial co-infection may occur, it is possible that tuberculosis was underdiagnosed in our study.[12] A substantial number of children (22%) died from clinical pneumonia, some of whom may have had tuberculosis. A limitation of our study is that we were unable to perform postmortem studies to investigate this. A further mechanism for the efficacy of isoniazid may be activity against organisms other than *M tuberculosis*. For example, isoniazid in combination with rifampicin has been reported to be effective against leishmaniasis,[23] and isoniazid has been shown to inhibit development of the malaria parasite.[24] Current understanding of the molecular mechanism of isoniazid activity is incomplete, though the drug has been shown to interfere with fatty acid metabolism.[25] Although isoniazid has not been shown to have activity against other bacteria, this pathway has been postulated to affect microbes such as *E coli* and other gram negative bacteria.[26] Furthermore, isoniazid blocks the lethality of endotoxin in mice[27] and is an efficient scavenger of free radicals.[28] Finally, co-trimoxazole prophylaxis has been reported to improve survival in African children with HIV[29]; isoniazid may have an additive antimicrobial effect.

Safety and tolerability

The safety and tolerability of isoniazid prophylaxis was excellent, even in the subgroup of children who were taking HAART. Data from adults have confirmed the safety of isoniazid, with reported hepatotoxicity in only 0.3% of people treated for latent tuberculosis.[30] The optimal duration of prophylaxis, however, is not known and long term studies are needed. Limited studies in adults with HIV suggest that prolonged use may be associated with longer protection.[31 32] Careful screening of children for

tuberculosis before prophylaxis is started is important. Reassuringly, the incidence of resistant *M tuberculosis* infection did not increase in children on prophylaxis, suggesting that it did not promote the development of resistance. Ongoing monitoring of this is needed.

Most children with HIV currently live in sub-Saharan Africa, where tuberculosis is highly prevalent and where there is limited access to antiretroviral therapy. Mortality among these children is much higher than that in children with HIV in the developed world, with infant mortality and mortality in those aged <5 around 25% and 65%, respectively.[33] Prophylaxis with isoniazid offers an available, well tolerated, and effective means for improving survival in these children in addition to that provided by co-trimoxazole. Tuberculosis prophylaxis is cost effective, extends life expectancy, reduces the incidence of tuberculosis, and provides savings in medical and social costs in adults with HIV who are tuberculin skin test positive.[34] Therefore, isoniazid prophylaxis may be an important public health intervention for children with HIV living in areas with high prevalence of tuberculosis, particularly when antiretroviral therapy is not available. Our results support the routine use of isoniazid prophylaxis in such children who cannot access HAART. Further studies in children of the cost efficacy of this intervention, the long term durability of protection, the efficacy in areas with low prevalence of tuberculosis, and the applicability of our findings to those receiving HAART is needed.

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Contributors: HJZ and MFC conceived the study, wrote the protocol and grant application, and supervised the study. SS and JK were trial physicians. HSS and GH assisted with design, supervision, and coordination of the study. HSS also reviewed clinical diagnoses. HR supervised trial management. CJL contributed to study design and was responsible for development of the database and statistical analysis. HZ drafted the paper and is guarantor, and all authors contributed to the final manuscript.

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What is already known on this topic

Prophylaxis with isoniazid significantly reduces the incidence of tuberculosis in adults with HIV and a positive tuberculin skin test result

There are no published data on the impact on mortality or incidence of tuberculosis in children with HIV

What this study adds

Prophylaxis with isoniazid in children significantly reduced mortality by about 50% and incidence of tuberculosis by about 70%

The reduction in mortality occurred in all categories of clinical disease, in children in all age groups, and for varying degrees of immune suppression

Such prophylaxis may offer an effective public health intervention to reduce mortality in children with HIV

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