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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 and is responsible for a major proportion of mortality.⁵ 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.⁶⁻⁸ The effect of such prophylaxis in children is unknown. We investigated the effect of isoniazid prophylaxis on mortality in children with HIV living in an area with high tuberculosis prevalence.

METHODS

We carried out a prospective double blind placebo controlled trial of isoniazid versus placebo given with co-trimoxazole 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.

Participants—Participants were children aged ≥ 8 weeks with HIV attending one of two hospitals in Cape Town. Researchers took baseline 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.

Treatment—Children were randomised to receive prophylaxis with co-trimoxazole either daily or three times a week. Placebo was identical in appearance to isoniazid tablets. Study investigators were blinded to the assignment. Children received isoniazid or placebo according to the frequency of the co-trimoxazole schedule for up to two years subject to review. Multivitamin supplementation and immunisations were given, but highly active antiretroviral therapy (HAART) was not widely available.

Investigations—HIV status was assessed at enrolment. The CD4 cell count and percentage was measured at study entry and every six months. A screening tuberculin skin test was done on enrolment and repeated every six months if previously negative. Children underwent screening chest radiography at enrolment and thereafter every six months. 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.

Diagnosis of tuberculosis—Any child who developed clinical signs of a lower respiratory tract infection underwent a tuberculin skin test and chest radiography, and where appropriate, further tests for the diagnosis of confirmed or probable tuberculosis (see bmj.com).

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 after they had finished standard tuberculosis treatment. Children who developed confirmed or probable tuberculosis during the study were unblinded.

Statistical analysis—The primary outcome measure was mortality. All analyses were by intention to treat. We analysed the time to event outcomes, and used regression to estimate hazard ratios. We did subgroups comparisons for severity of disease, dose, age, and study site to assess the consistency of the intervention effect.

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, and as soon as the board recommended it, we terminated the placebo arm of the study. At this time, 277 children were enrolled. We included 263 children (146 (56%) boys) in the analysis. Of these, 132 were assigned to isoniazid. Median follow-up time was 5.7 months (interquartile range 2.0-9.7 months).

About half of the children were younger than 24 months. Most children (231, 88%) were symptomatic. 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 to -0.4). 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 either previously received 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).

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, $P=0.015$ for the one sided log rank test and $P=0.226$ for the proportional hazards assumption). The benefit applied to children across all categories of severity of clinical disease

Table 1 | 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.

(test for heterogeneity $P=0.933$) and in all ages (test for heterogeneity $P=0.678$), table 1. 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). 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. 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.

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 2). The total child months of intention to treat follow-up in the two groups for the incidence of tuberculosis 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 2). All five cases of tuberculosis confirmed by culture occurred in the placebo group.

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. No child required permanent discontinuation of trial drug. No grade 3 or 4 toxicity occurred among children receiving HAART.

DISCUSSION

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, so we could not evaluate the impact of isoniazid prophylaxis on mortality in this subgroup. In contrast with our findings, a Cochrane review of prophylaxis in adults with HIV did not find a significant reduction in mortality.⁸ Our observed reduction in incidence of tuberculosis in children taking isoniazid prophylaxis was greater than that reported for adults with HIV⁸ 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%.⁸

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 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, depressed cell mediated immunity because of malnutrition, or early or lack of infection with *M tuberculosis*. Although all children were screened carefully for tuberculosis, diagnosis is notoriously difficult in those with HIV,^{3,9} raising the possibility that children with early or subclinical *M tuberculosis* infection were not detected.

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. Isoniazid prophylaxis may provide

Table 2 | 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.

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

longstanding protection by enhancing the host immune response.¹⁰ Alternatively, isoniazid may have effectively provided primary prophylaxis against *M tuberculosis* in an area where children are continuously at high risk of infection.¹¹

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.¹² Tuberculosis, however, may also be a direct cause of mortality.⁸ As confirmation of *M tuberculosis* by culture is difficult and positive in about a third of children with clinically suspected tuberculosis, it is possible that tuberculosis was underdiagnosed in our study.⁹ A further mechanism for the efficacy of isoniazid may be activity against organisms other than *M tuberculosis*.¹³⁻¹⁶ Current understanding of the molecular mechanism of isoniazid activity is incomplete.

Safety and tolerability

The safety and tolerability of isoniazid prophylaxis was excellent, even in the subgroup of children who were taking HAART. The optimal duration of prophylaxis, however, is not known and long term studies are needed. 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. Mortality among these children is much higher than that in children with HIV in the developed world. 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 and 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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