ORIGINAL ARTICLE

Primary Isoniazid Prophylaxis against Tuberculosis in HIV-Exposed Children

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ABSTRACT

BACKGROUND

The dual epidemic of human immunodeficiency virus (HIV) and tuberculosis is a major cause of sickness and death in sub-Saharan Africa. We conducted a double-blind, randomized, placebo-controlled trial of preexposure isoniazid prophylaxis against tuberculosis in HIV-infected children and uninfected children exposed to HIV during the perinatal period.

METHODS

We randomly assigned 548 HIV-infected and 804 HIV-uninfected infants (91 to 120 days of age) to isoniazid (10 to 20 mg per kilogram of body weight per day) or matching placebo for 96 weeks. All patients received bacille Calmette–Guérin (BCG) vaccination against tuberculosis within 30 days after birth. HIV-infected children had access to antiretroviral therapy. The primary outcome measures were tuberculosis disease and death in HIV-infected children and latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children within 96 to 108 weeks after randomization.

RESULTS

Antiretroviral therapy was initiated in 98.9% of HIV-infected children during the study. Among HIV-infected children, protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group and 53 (19.3%) in the placebo group (P=0.93). Among HIV-uninfected children, there was no significant difference in the combined incidence of tuberculosis infection, tuberculosis disease, or death between the isoniazid group (39 children, 10%) and the placebo group (45 children, 11%; P=0.44). The rate of tuberculosis was 121 cases per 1000 child-years (95% confidence interval [CI], 95 to 153) among HIV-infected children as compared with 41 per 1000 child-years (95% CI, 31 to 52) among HIV-uninfected children. There were no significant differences in clinical or severe laboratory toxic effects between treatment groups.

CONCLUSIONS

Primary isoniazid prophylaxis did not improve tuberculosis-disease–free survival among HIV-infected children or tuberculosis-infection–free survival among HIV-uninfected children immunized with BCG vaccine. Despite access to antiretroviral therapy, the burden of tuberculosis remained high among HIV-infected children. (Funded by the National Institutes of Health and Secure the Future; ClinicalTrials.gov number, NCT00080119.)

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Tuberculosis is highly endemic in sub-Saharan Africa, a situation aggravated by the ongoing epidemic of human immunodeficiency virus type 1 (HIV-1).[1] The increased burden of tuberculosis among adults in areas with a high prevalence of HIV infection is also associated with high rates of transmission of *Mycobacterium tuberculosis* (MTB) to household members and other contacts.[2-5] Therefore, it has been proposed that in areas such as South Africa, tuberculosis-prevention strategies with isoniazid chemoprophylaxis, which so far have targeted only household contacts of adults with positive sputum smears for MTB acid-fast bacilli, be expanded to include other high-risk groups.

Among otherwise immunocompetent children, MTB infection in the first 2 years of life is associated with a 43% risk of the development of tuberculosis during the next 12 months.[6] Also, the risk of culture-confirmed tuberculosis is increased by a factor of more than 20 among HIV-infected children under 2 years of age.[7,8] Furthermore, postmortem studies have identified tuberculosis as a leading cause of death in HIV-infected children in Africa, accounting for 12 to 18% of deaths in these children.[9,10] Isoniazid has shown effectiveness in preventing progression to tuberculosis disease in children who had known contact with persons with infectious tuberculosis,[11-13] but its role in preexposure prophylaxis has not been evaluated in HIV-infected infants or uninfected children exposed to HIV during the perinatal period — both groups at increased risk for tuberculosis.

Our study evaluated the safety and efficacy of isoniazid versus placebo for preexposure prophylaxis against tuberculosis in HIV-infected children and uninfected children exposed to HIV during the perinatal period, when treatment was started at 3 to 4 months of age and continued for 96 weeks.

METHODS

STUDY SITES

This multicenter, phase 2–3, randomized, double-blind, placebo-controlled trial of isoniazid was undertaken in three South African centers (Chris Hani Baragwanath Hospital, Johannesburg; Tygerberg Hospital, University of Stellenbosch, Cape Town; and King Edward VII Hospital, Durban) and one center in Botswana (Princess Marina Hospital, Gaborone). Enrollment at the Botswana site began shortly before the study was terminated. All sites had existing programs for the prevention of mother-to-child transmission of HIV. Children infected with HIV were given antiretroviral treatment, which primarily included stavudine, lamivudine, and lopinavir–ritonavir, per country-specific guidelines, or zidovudine, lamivudine, and lopinavir–ritonavir.

STUDY ENROLLMENT AND PARTICIPANTS

Enrollment occurred between December 2004 and June 2008. Enrollment of the HIV-uninfected cohort was completed in June 2006. Infants born to HIV-infected women were identified through programs for the prevention of mother-to-child transmission of HIV. The HIV-infection status of infants was determined by means of HIV-1 DNA polymerase-chain-reaction (PCR) testing. HIV-uninfected infants had their negative status confirmed by a second negative DNA PCR assay 24 weeks after randomization and a negative HIV enzyme-linked immunosorbent assay (ELISA) at 18 months of age. Participants were enrolled between the 91st and 120th days of life. Eligibility criteria included receipt of the BCG vaccine by 30 days of age; no history of tuberculosis in the infant, known exposure to a microbiologically confirmed case of tuberculosis, or active antituberculosis treatment in the mother at the time of the infant's birth; and no evidence of failure to thrive, recurrent pneumonia, chronic diarrhea, or immunosuppressive conditions other than HIV infection.

Infants were randomly assigned to receive daily isoniazid, at a dose of 10 to 20 mg per kilogram of body weight, or placebo. Other aspects of their care, including trimethoprim–sulfamethoxazole prophylaxis, are detailed in the Supplementary Appendix, available with the full text of this article at NEJM.org.

STUDY OBJECTIVES AND END POINTS

The coprimary objectives were to compare the isoniazid and placebo groups with respect to tuberculosis-disease–free survival (hereafter referred to as disease-free survival) among HIV-infected children and tuberculosis-infection–free survival (hereafter referred to as infection-free survival) among HIV-uninfected children 96 weeks after randomization. The end point for disease-free survival was the first occurrence of death from any cause or tuberculosis disease, and the end point for infection-free survival was the first occurrence of death from any cause, tuberculosis disease, or MTB in-

Table 1. Algorithm Used to Screen for and Diagnose Clinical Tuberculosis.*

Feature	Score†				
	0	1	2	3	4
Weeks of illness (including cough)	<2	2–4		>4	
Nutritional status (% weight for age)‡	>80%	60–80%	<60% or a drop of ≥2 percentiles		
Family history of tuberculosis	None	Reported by family		Sputum-confirmed	
Tuberculin skin test	Negative			Reactive (≥5 or ≥10 mm)§	
Fever not responding to treatment for >2 wk	No		Yes		
Confirmed or suspected EPTB¶	No				Yes

* The algorithm is from the tuberculosis guidelines for South Africa.[14]
† Study participants with a score of 4 or more (excluding the tuberculin skin test) during screenings at their routine visits every 3 months were screened further by means of a tuberculin skin test and a chest radiograph.
‡ Evaluation for malnutrition was performed according to World Health Organization guidelines[15] on the basis of z scores and clinical and laboratory evaluations.
§ A reactive skin test was defined as an induration of at least 5 mm in horizontal diameter in HIV-infected children and an induration of at least 10 mm in HIV-uninfected children.
¶ Extrapulmonary tuberculosis (EPTB) included extrathoracic lymphadenopathy, joint or bone involvement, abdominal mass, meningitis, and tuberculosis of the spine, diagnosed according to criteria that were prespecified in the protocol.

fection. Secondary study objectives for the cohort of HIV-infected children were to determine whether isoniazid prophylaxis decreased the incidence of tuberculosis infection at 96 weeks and whether it reduced the risk of HIV disease progression, defined as the first occurrence of worsening of the Centers for Disease Control and Prevention (CDC) clinical categorization of HIV infection or death. A secondary objective for the cohort of HIV-uninfected children was to determine whether isoniazid prophylaxis improved disease-free survival.

TUBERCULOSIS INVESTIGATION AND OUTCOME CATEGORIZATION

Participants were screened for symptoms of tuberculosis at each study visit and assessed further if they had a score of 4 or more on the clinical algorithm scale (Table 1),[14] excluding scoring on the tuberculin skin test. Children were also assessed for pulmonary tuberculosis when presenting with clinical or radiographic evidence of pneumonia or at the discretion of the attending physician. For children with MTB exposure, the study drug was discontinued and open-label isoniazid was administered according to the guidelines in South Africa.[14]

Investigations for tuberculosis included collection of information on the status of sputum smears in the index case, a history taking for symptoms and signs suggestive of MTB infection, an intradermal tuberculin skin test with the use of RT23 2TU (Statens Serum Institut), a chest radiograph, and microbiologic or histopathological evaluation as clinically indicated. In children suspected of having pulmonary tuberculosis, two gastric washings, two induced-sputum samples, or both were tested by means of auramine staining and a mycobacterial culture was tested with the use of the Bactec method at nationally accredited laboratories. Mycobacterial isolates were analyzed for drug resistance with the use of the BACTEC 460 system (Becton Dickinson).

On the basis of positive results of these evaluations, children received a diagnosis of "definite," "probable," or "possible" tuberculosis (Table 2). Children whose health care providers initiated antituberculosis treatment but who did not fulfill protocol-defined criteria for a diagnosis of tuberculosis were classified as having "non-algorithm tuberculosis." Latent tuberculosis infection was diagnosed on the basis of a positive tuberculin skin test (induration ≥5 mm in horizontal diameter in HIV-infected children and ≥10 mm in HIV-uninfected children), in the absence of evidence of active tuberculosis disease, 96 weeks after randomization. An end-point review committee of study-team clinicians who were unaware of the study-group assignments reviewed all deaths and

Table 2. Protocol-Defined Criteria for Categorization of Tuberculosis Disease and Infection.

Tuberculosis Category	Microbiologic, Radiographic, Histologic, and Clinical Criteria
Definite tuberculosis	*Mycobacterium tuberculosis* cultured from any site, or positive auramine staining of a cerebrospinal fluid specimen
Probable tuberculosis	The presence of at least two clinical criteria in the algorithm shown in Table 1, plus either positive auramine staining of an induced-sputum or gastric-washing smear or suggestive histologic findings (caseating granuloma); or positive auramine staining of a gastric-washing or induced-sputum smear and a chest radiograph suggestive of tuberculosis*
Possible tuberculosis	An algorithm score ≥6 and a radiograph suggestive of tuberculosis, or a positive tuberculin skin test (induration ≥5 mm in horizontal diameter) and a chest radiograph suggestive of tuberculosis
Latent *M. tuberculosis* infection	A positive tuberculin skin test at week 96 after randomization in the absence of active tuberculosis (definite, probable, or possible)

* Radiographic findings that were considered to be suggestive of pulmonary tuberculosis included hilar lymphadenopathy, alveolar consolidation, a miliary pattern of lesions, and cavitations in the lung parenchyma.

potentially tuberculosis-related primary and secondary end points.

Screening for safety was undertaken at scheduled visits every 3 months while the participants were receiving the study drug. Screening included serum liver enzyme tests, complete blood counts, and clinical neurologic evaluations for peripheral neuropathy with the use of a modified Denver Developmental Screening Test, with severity grading based on criteria from the Division of Acquired Immunodeficiency Syndrome at the National Institute of Allergy and Infectious Diseases (NIAID).[16]

STUDY OVERSIGHT

The study was approved by the institutional review board of each participating center, the Medicines Control Council in South Africa, and the Division of AIDS at the NIAID. The study was conducted in accordance with Good Clinical Practices guidelines and the Declaration of Helsinki. Written informed consent was obtained from the legal guardians of the children before they underwent randomization. All authors vouch for the accuracy and completeness of the analyses presented and the adherence of the study and this report to the protocol, available at NEJM.org.

STATISTICAL ANALYSIS

The study was designed and powered to evaluate study outcomes independently in the HIV-infected and HIV-uninfected cohorts. A detailed description of the sample-size calculation (with a target sample of 500 HIV-infected and 800 HIV-uninfected children) and of oversight by the data and safety monitoring board is provided in the Supplementary Appendix.

Kaplan–Meier estimates were used to summarize the distribution of time to efficacy and safety end points. Data on end points were censored at week 96, with allowance for the inclusion of end points for 12 additional weeks (up to 108 weeks after randomization). Log-rank tests were used to compare these distributions between the study groups. Cox regression was used for hazard ratios and analyses adjusted for covariates.

Analyses followed an intention-to-treat approach unless otherwise specified. Data on children whose guardians declined further study follow-up before meeting a study end point were censored at the date of the last follow-up visit. All testing was two-sided at the 5% significance level. To maintain the significance level for each cohort at 5%, nominal P values of 0.0492 and 0.0493 for between-group differences in the HIV-infected and HIV-uninfected cohorts, respectively, were required in the final analysis of the primary end points. All P values presented were nominal. Data were analyzed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

A total of 548 HIV-infected and 806 HIV-uninfected infants were enrolled; the majority (65%) were enrolled in Johannesburg. Figure 1A shows the disposition of the 274 HIV-infected infants enrolled in each study group; the study drug was initiated within 4 days after randomization, except

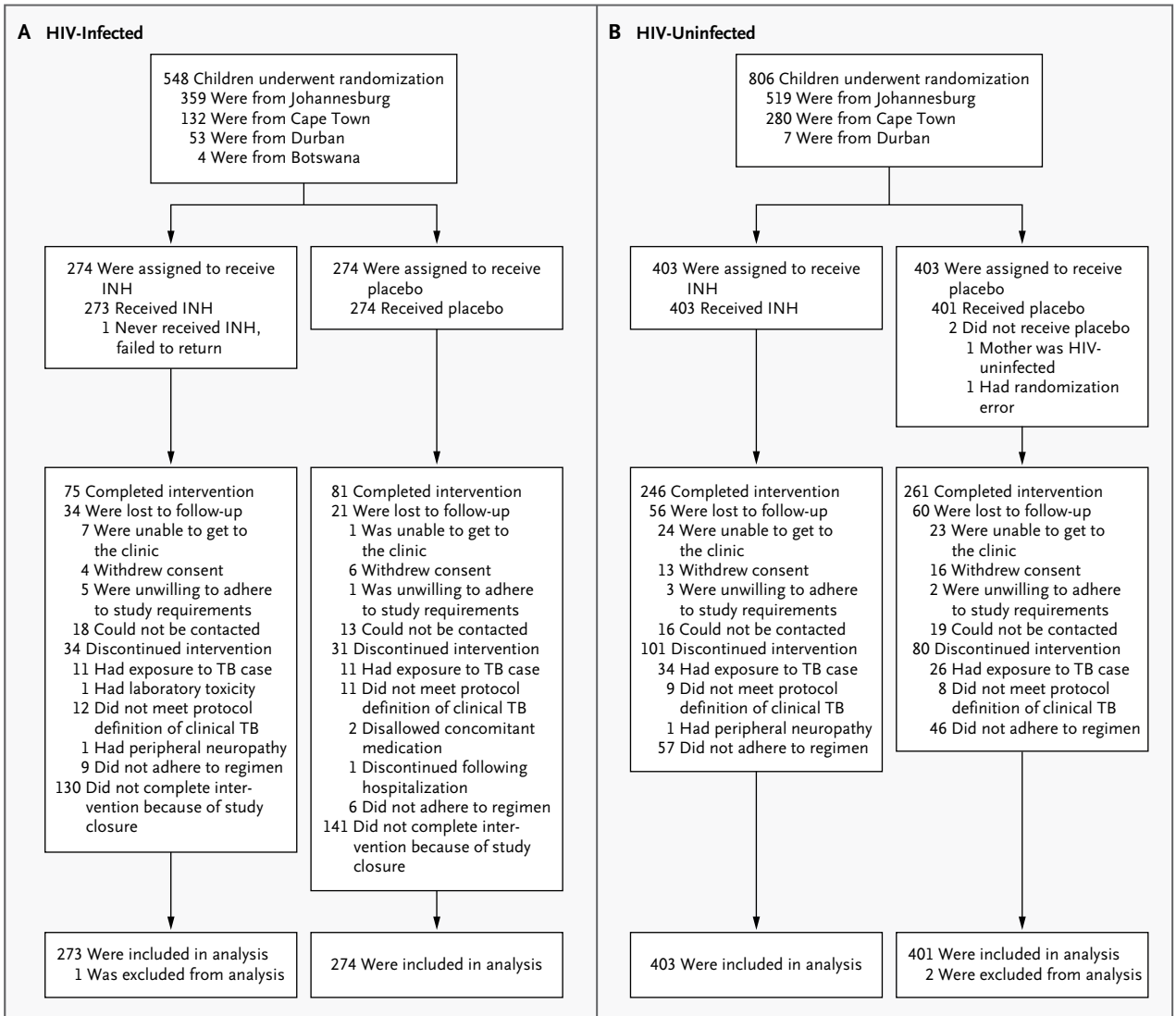

Figure 1. Enrollment, Randomization, and Follow-up of the HIV-Infected and HIV-Uninfected Study Cohorts.

Four HIV-infected children (one in the isoniazid group and three in the placebo group) who were positive for HIV at baseline were subsequently confirmed to be HIV-uninfected. Six HIV-uninfected children (two in the isoniazid group and four in the placebo group) who were negative for HIV at baseline were subsequently confirmed to be HIV-infected. The numbers of participants lost to follow-up or who discontinued the intervention denote those who were lost to follow-up or discontinued the intervention before a primary end point occurred. The reasons for discontinuing the intervention are enumerated only for those not lost to follow-up. INH denotes isoniazid, and TB tuberculosis.

in 1 child who never received it and was excluded from the analysis. The disposition of the HIV-uninfected infants, including 2 children who did not receive the study drug and were excluded from the analysis, is shown in Figure 1B.

The baseline characteristics were generally well-balanced between the two groups (Table 3) in both cohorts. Infants underwent randomization at a median age of 96 days. All infants had received BCG vaccination by 30 days of age, before their positive HIV status was determined. The majority of infants were indigenous Africans (97.0%). By chance, in the HIV-infected cohort, a higher percentage of children of mixed ancestry were enrolled in the isoniazid group. A history of maternal tuberculosis was reported for 7.1% and 7.2% of HIV-infected and HIV-uninfected participants, respectively. Four participants in the HIV-

infected cohort, who initially had a positive HIV PCR test, were subsequently found to be HIV-negative on PCR assay. At study entry, 65.3% of HIV-infected infants were asymptomatic (CDC clinical category N) and 26.2% were mildly symptomatic (category A) (Table 3). Among children who were confirmed to be HIV-infected, the median CD4+ lymphocyte percentage and HIV-1 viral load were 28% and 625,000 copies per milliliter, respectively, at study entry, and 171 children (31.5%) had already started to receive antiretroviral treatment (Table 3).

EFFICACY

HIV-Infected Cohort

Primary end points are detailed in Table 4. Participants who reached more than one end point were categorized according to the first end point met. Eight participants with previous protocol-defined tuberculosis died, and only tuberculosis end points were included in the efficacy analysis for these participants. Either protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group as compared with 53 children (19.3) in the placebo group (hazard ratio, 0.98; 95% confidence interval [CI], 0.67 to 1.44) (Fig. 1 in the Supplementary Appendix). Tuberculosis accounted for 31 (59.6%) of the primary end points in the isoniazid group and for 38 (71.7%) in the placebo group (P=0.40); death accounted for 21 (40.4%) and 15 (28.3%) of the primary end points in the two groups, respectively (P=0.12). The results were similar when the analysis was adjusted for status with respect to antiretroviral treatment at baseline and maternal history of tuberculosis. Overall, 98.9% of HIV-infected children were initiated on antiretroviral treatment during the study. The results of analyses of the secondary end points

Table 3. Baseline Demographic and Clinical Characteristics of Children Randomly Assigned to Isoniazid or Placebo.*

Characteristic	HIV-Infected Children			HIV-Uninfected Children		
	Total (N=547)	Isoniazid Group (N=273)	Placebo Group (N=274)	Total (N=804)	Isoniazid Group (N=403)	Placebo Group (N=401)
Age — days						
Median	96	97	95	96	96	96
Range	91 to 120	91 to 120	91 to 120	91 to 120	91 to 120	91 to 120
Weight-for-age z score						
Median	−0.58	−0.61	−0.54	0.35	0.37	0.34
Range	−4.29 to 3.07	−3.44 to 3.07	−4.29 to 3.03	−2.83 to 3.95	−2.14 to 3.95	−2.83 to 3.64
Male sex — no. (%)	237 (43.3)	114 (41.8)	123 (44.9)	411 (51.1)	200 (49.6)	211 (52.6)
Race or ethnic group — no. (%)						
Indigenous African	536 (98.0)	264 (96.7)	272 (99.3)	775 (96.4)	389 (96.5)	386 (96.3)
Mixed ancestry or other	11 (2.0)	9 (3.3)	2 (0.7)	29 (3.6)	14 (3.5)	15 (3.7)
Biologic mother as primary caregiver — no. (%)	504 (92.1)	254 (93.0)	250 (91.2)	792 (98.5)	394 (97.8)	398 (99.3)
Housing type — no. (%)†						
Brick house	345 (63.3)	162 (59.3)	183 (67.3)	468 (58.2)	235 (58.3)	233 (58.1)
Shack or wooden structure	198 (36.3)	109 (39.9)	89 (32.7)	336 (41.8)	168 (41.7)	168 (41.9)
Hostel	2 (0.4)	2 (0.7)	0	0	0	0
Household size — no. of members						
Median	4	4	5	5	5	4
Range	2 to 15	2 to 15	2 to 15	2 to 21	2 to 21	2 to 16
Breast-feeding — no. (%)						
Ever breast-fed	73 (13.3)	37 (13.6)	36 (13.1)	48 (6.0)	24 (6.0)	24 (6.0)
Breast-fed at baseline	29 (5.3)	15 (5.5)	14 (5.1)	7 (0.9)	3 (0.7)	4 (1.0)

Table 3. (Continued.)

Characteristic	HIV-Infected Children			HIV-Uninfected Children		
	Total (N=547)	Isoniazid Group (N=273)	Placebo Group (N=274)	Total (N=804)	Isoniazid Group (N=403)	Placebo Group (N=401)
Maternal history of tuberculosis — no. (%)						
During index pregnancy	2 (0.4)	0	2 (0.7)	6 (0.7)	4 (1.0)	2 (0.5)
Before index pregnancy	37 (6.8)	14 (5.1)	23 (8.4)	51 (6.3)	29 (7.2)	22 (5.5)
Any history of tuberculosis	39 (7.1)	14 (5.1)	25 (9.1)	57 (7.1)	33 (8.2)	24 (6.0)
BCG vaccination — no. (%)						
Within 7 days after birth	513 (93.8)	255 (93.4)	258 (94.2)	787 (97.9)	395 (98.0)	392 (97.8)
8 to 29 days after birth	34 (6.2)	18 (6.6)	16 (5.8)	17 (2.1)	8 (2.0)	9 (2.2)
CDC clinical HIV category — no. (%)‡						
N	354 (65.3)	178 (65.7)	176 (64.9)			
A	142 (26.2)	74 (27.3)	68 (25.1)			
B	37 (6.8)	16 (5.9)	21 (7.7)			
C	5 (0.9)	2 (0.7)	3 (1.1)			
HIV-uninfected	4 (0.7)	1 (0.4)	3 (1.1)			
Missing data	5	2	3			
CD4+ cells — %§						
Median	28	29	28			
Range	6 to 58	6 to 53	6 to 58			
CD4+ category — no. (%)¶						
<20%	111 (21.5)	56 (21.7)	55 (21.3)			
20–24%	86 (16.7)	40 (15.5)	46 (17.8)			
25–34%	187 (36.2)	90 (34.9)	97 (37.6)			
≥35%	132 (25.6)	72 (27.9)	60 (23.3)			
Missing data or HIV-uninfected	31	15	16			
Plasma HIV-1 RNA — copies/ml¶						
Median	625,000	710,000	482,000			
Interquartile range	46,000 to 750,000	97,905 to 750,000	258,000 to 750,000			
Antiretroviral treatment at or before study entry — no. (%)‖	171 (31.5)	78 (28.7)	93 (34.3)			

* Percentages may not add to 100 because of rounding. BCG denotes bacille Calmette–Guérin, CDC Centers for Disease Control and Prevention, HIV human immunodeficiency virus, and HIV-1 human immunodeficiency virus type 1.
† Housing type was not provided for two HIV-infected participants in the placebo group.
‡ Category N denotes asymptomatic, A mildly symptomatic, B moderately symptomatic, and C severely symptomatic.
§ Participants with missing data and HIV-uninfected participants were excluded from the percentages.
¶ Excluded were seven and six HIV-infected participants with missing data from the isoniazid and placebo groups, respectively. HIV-uninfected participants were excluded from the percentages. The range was ≤400 to ≥750,000 for both study groups.
‖ HIV-uninfected participants were excluded from the percentages.

were consistent with lack of efficacy. In addition, a post hoc analysis of the composite end point of "probable" or "definite" tuberculosis showed no significant difference in incidence between the isoniazid group (10 participants, 3.7%) and the placebo group (11 participants, 4.0%; P=0.83). The overall incidence of tuberculosis was 121 cases per 1000 child-years (95% CI, 95 to 153).

Table 4. Summary of First End Point Met toward Primary Outcome Measures in Children Randomly Assigned to Isoniazid or Placebo.*

End Point	HIV-Infected Children				HIV-Uninfected Children			
	Total (N=547)	Isoniazid Group (N=273)	Placebo Group (N=274)	P Value†	Total (N=804)	Isoniazid Group (N=403)	Placebo Group (N=401)	P Value†
		no. (%)				*no. (%)*		
Primary end point: tuberculosis disease or death	105 (19.2)	52 (19.0)	53 (19.3)	0.93‡	84 (10.4)	39 (9.7)	45 (11.2)	0.44
Specific end points								
Protocol-defined tuberculosis§	69 (12.6)	31 (11.4)	38 (13.9)	0.40	59 (7.3)	28 (6.9)	31 (7.7)	
Definite PTB	8 (1.5)	5 (1.8)	3 (1.1)		14 (1.7)	8 (2.0)	6 (1.5)	
Probable PTB	8 (1.5)	5 (1.8)	3 (1.1)		9 (1.1)	3 (0.7)	6 (1.5)	
Possible PTB¶	48 (8.8)	21 (7.7)	27 (9.9)		36 (4.5)	17 (4.2)	19 (4.7)	
Definite EPTB	3 (0.5)	0	3 (1.1)		0	0	0	
Probable EPTB and possible PTB	2 (0.4)	0	2 (0.7)		0	0	0	
Death without prior tuberculosis	36 (6.6)	21 (7.7)	15 (5.5)		4 (0.5)	2 (0.5)	2 (0.5)	
Latent tuberculosis‖					21 (2.6)	9 (2.2)	12 (3.0)	

* Percentages for specific outcomes may not add to the total percentages because of rounding.
† P values are for the log-rank test.
‡ P=0.85 in an analysis adjusted for status with respect to antiretroviral treatment at baseline and maternal history of tuberculosis.
§ Protocol-defined tuberculosis included any episode that fulfilled the protocol-specified criteria for possible, probable, or definite tuberculosis, as confirmed by the end-point review committee. EPTB denotes extrapulmonary tuberculosis, and PTB pulmonary tuberculosis.
¶ One HIV-infected participant with possible pulmonary tuberculosis later fulfilled the criteria for probable pulmonary tuberculosis.
‖ Latent tuberculosis was evaluated at 96 weeks of age by means of a tuberculin skin test (with an induration ≥10 mm in horizontal diameter considered to be reactive). The outcome was not evaluated for HIV-infected children because most children had not completed 96 weeks in the study when the study ended.

Details on compliance with study follow-up, HIV-AIDS disease progression, and mortality rates and causes of death are provided in the Supplementary Appendix. Self-reported compliance at scheduled visits (defined as no missed doses since the last visit) ranged from 74 to 92% across visits and did not differ significantly between the study groups.

HIV-Uninfected Cohort

The rate of loss to follow-up at 96 weeks was 14.4% (95% CI, 12.0 to 17.0) in the cohort of children without HIV infection, with no significant difference between the isoniazid and placebo groups (P=0.58). Eighty-four children (10.4%) reached a primary end point, a composite of tuberculosis disease, latent tuberculosis infection, or death. The estimated hazard ratio for the isoniazid group as compared with the placebo group was 0.85 (95% CI, 0.55 to 1.30) (Table 4, and Fig. 1 in the Supplementary Appendix). There was no significant difference between study groups (P=0.44) (Table 4). Analyses of all secondary end points showed lack of efficacy of isoniazid prophylaxis as compared with placebo. The overall incidence of tuberculosis was 41 cases per 1000 child-years (95% CI, 31 to 52). Six HIV-uninfected children (three each in the isoniazid and placebo groups) died of either gastroenteritis or unknown reasons (Table 1 in the Supplementary Appendix). Survival did not differ significantly between the study groups (P>0.99). Self-reported compliance at scheduled visits ranged from 62 to 82% across visits and was similar in the two groups.

DRUG-SUSCEPTIBILITY TESTING

Overall, isoniazid resistance was identified in 5 of 19 children (26.3%; 95% CI, 9.2 to 51.2) with culture-confirmed tuberculosis who were tested for susceptibility. Of these 5 children, 2 children (1 HIV-infected and 1 HIV-uninfected) were in the isoniazid group and 3 (all HIV-uninfected) were in the placebo group.

SAFETY

Rates of grade 3 or higher clinical or laboratory abnormalities were similar in the two study groups, stratified according to HIV status (Table 2 in the Supplementary Appendix). With the exception of

grade 3 peripheral neuropathy in one HIV-infected child in the isoniazid group, all grade 3 or higher toxic effects resolved, allowing for the resumption of treatment with the randomly assigned study drug. All reportable serious adverse events are shown in Table 3 in the Supplementary Appendix.

DISCUSSION

The prevention of tuberculosis in perinatally exposed HIV-infected and HIV-uninfected infants in areas with high incidences of tuberculosis and HIV infection, such as southern Africa, is a major public health challenge. The only current alternative to BCG vaccination for preventing tuberculosis is chemoprophylaxis, especially with isoniazid. Our study showed no benefit of isoniazid as preexposure prophylaxis in improving disease-free survival among HIV-infected children or infection-free survival among HIV-uninfected children. Similarly, a post hoc analysis that included the composite outcome of protocol-defined tuberculosis, death, or non-algorithm tuberculosis showed no significant differences in outcome between the isoniazid group (24.2%) and the placebo group (24.1%, P=0.93) among HIV-infected children.

A meta-analysis of trials of tuberculosis prophylaxis in HIV-infected adults showed that isoniazid reduced the incidence of tuberculosis (by 62%) in those with a positive tuberculin skin test but was ineffective in those with a negative test,[17] suggesting that prophylaxis does not prevent primary tuberculosis. In addition, the meta-analysis showed no significant overall reduction in mortality.[17] These data are corroborated by our study, in which isoniazid prophylaxis failed to prevent tuberculosis among HIV-infected children without a history of MTB exposure.

The other major published study of isoniazid prophylaxis in HIV-infected children was undertaken in Cape Town, South Africa. Isoniazid prophylaxis was associated with a 54% reduction in all-cause mortality and a 72% reduction in the incidence of tuberculosis, prompting early trial termination by the data and safety monitoring board.[18] There were marked differences between the HIV-infected children enrolled in our study and those in the Cape Town study, limiting a direct comparison of the findings from the two studies. The children enrolled by Zar et al. as compared with our cohort were older (median age, 24.7 months vs. 96 days), had been treated for tuberculosis in some cases before enrollment (16% vs. 0%), were more likely to be severely immunocompromised (CDC category B or C, 88% vs. 8%), were less likely to be receiving antiretroviral treatment at study entry (9% vs. 31%), had lower CD4+ percentages (20% vs. 28%), and were more severely malnourished at study entry (median z score, −1.56 vs. −0.58). In addition, 9% of children in the study by Zar et al. had a reactive tuberculin skin test at study entry, possibly indicating previous MTB infection.

Contrary to the findings of the meta-analysis of antituberculosis prophylaxis in HIV-infected adults with a nonreactive tuberculin skin test,[17] the study by Zar et al. showed a 49% reduction in mortality and a 68% reduction in the incidence of tuberculosis among children with a nonreactive tuberculin skin test.[18] A clinically relevant aspect of the findings by Zar et al. is that the causes of death in both groups were primarily attributed to sepsis (44%), pneumonia (22%), and gastroenteritis (9%), not directly to tuberculosis. However, tuberculosis could have predisposed the children to bacterial infection.[19] In addition, the greatest difference in survival observed between the groups occurred primarily within 30 days after randomization, with marginal differences between the groups thereafter. The study also enrolled 44.8% of the children during the course of hospitalization for an acute illness.[20]

Because the progression from MTB infection to active disease takes 1 to 3 months to be manifested,[21] the mechanism by which isoniazid prophylaxis prevented tuberculosis and improved survival in the study by Zar et al. remains unexplained. It is possible, however, that the reduction in the incidence of tuberculosis observed in the isoniazid group by Zar et al. was the result of treatment of unrecognized underlying primary tuberculosis in the enrolled children, as was observed in early studies of isoniazid,[22] rather than the result of prophylaxis against MTB infection and its progression, which was the objective in our study.

Possible reasons why isoniazid prophylaxis was ineffective in children without known MTB exposure in our study include a suboptimal dose of the drug, isoniazid resistance, lack of compliance with the medication regimen, and issues regarding the specificity of the study end points. A discussion of these factors is available in the Supplementary Appendix.

Finally, a limitation of our study is related to possible changes in the epidemiology of tuberculosis and in mortality among HIV-infected children

because of increased access to antiretroviral treatment. The overall rate of a primary end point among HIV-infected children in our study was 22% over a period of 96 weeks, which is below the 40% rate that we originally estimated. We therefore continued enrolling children after the initial target enrollment of 500 participants had been reached. The futility analysis, nevertheless, indicated that even with the most optimistic estimates, it was unlikely that the study was adequately powered to show significant differences in the primary end points between the two groups. Our study was adequately powered (91.7%) to detect a 50% relative reduction in primary end points among HIV-infected children on the basis of an estimate that 25% of the children in the placebo group would reach a primary end point over the 96-week period, an incidence similar to that observed in our study.

In conclusion, in our study isoniazid prophylaxis as compared with placebo was safe but ineffective as preexposure prophylaxis against tuberculosis in HIV-infected and HIV-uninfected children. However, the results of our study are specific to a setting such as South Africa with a high dual burden of tuberculosis and HIV infection. Much insight has been gained into the epidemiology of tuberculosis in southern Africa in the era of antiretroviral treatment. In a study conducted in Cape Town from 2004 to 2007, the incidence of culture-confirmed tuberculosis was 1596 cases per 100,000 HIV-infected infants.[7] In addition, the incidence of hospitalization for culture-confirmed and all categories of pulmonary tuberculosis in Johannesburg, before the introduction of antiretroviral treatment, was 3028 per 100,000 and 10,016 per 100,000, respectively, in children under 5 years of age.[8] The burden of tuberculosis among HIV-infected children (121 cases per 1000 child-years) in our study remained high despite access to antiretroviral treatment. A high burden of tuberculosis was also identified among HIV-exposed uninfected children (41 cases per 1000 child-years). These findings underscore the need to explore alternative options for the prevention and management of tuberculosis in HIV-exposed children.

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