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High Incidence of Tuberculosis Infection in HIV-Exposed Children Exiting an Isoniazid Preventive Therapy Trial

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Abstract

Young HIV-exposed children are at high risk for TB infection. We performed QuantiFERON®-TB Gold (QFT) among HIV-exposed children in South Africa at enrolment and one year follow-up. The incidence of TB infection was high for HIV+ (11 cases/100 child-years) and HIV-exposed uninfected (HEU) children (15 cases/100 child-years). QFT may identify HIV-exposed children at risk for TB disease progression.

Keywords

tuberculosis; IGRA; HIV; children; tuberculin

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Introduction

Young children born to HIV-infected (HIV+) mothers in TB-endemic settings experience high rates of TB disease, despite maternal combination antiretroviral therapy (cART) and infant BCG vaccination.\textsuperscript{1,2} Isoniazid preventive therapy (IPT) administered to HIV-exposed children before TB exposure did not prevent TB disease in a randomized trial; however, IPT does decrease the risk of TB disease and is cost-effective in children and adults with well-documented TB exposure or evidence of TB infection.\textsuperscript{2,3}

Interferon gamma release assays (IGRAs) provide a mechanism to identify TB infection in young BCG-vaccinated children with better specificity than the tuberculin skin test (TST).\textsuperscript{4} Prior IGRA studies found an appreciable burden of TB infection in children born to HIV+ mothers in Kenya (11\%) and Uganda (4\%).\textsuperscript{5,6} While positive IGRA is an indicator of TB infection after exposure, many children with low magnitude of interferon (IFN)-\gamma in response to TB antigens will revert from a positive to negative result. In contrast, a recent study of children with a higher magnitude of IFN-\gamma values (>4.0 IU/mL) at the time of IGRA conversion had a greater than 40-fold increased risk of incident TB disease.\textsuperscript{7} We evaluated the incidence of TB infection by IGRA among a cohort of HIV-exposed children exiting an IPT trial and quantified longitudinal changes in IFN-\gamma.

MATERIALS AND METHODS

Study Population

The parent study, IMPAACT P1041, was a multi-centered, Phase II-III randomized, double-blind, placebo-controlled trial comparing pre-exposure IPT to placebo in HIV+ and HEU infants.\textsuperscript{2} BCG-vaccinated infants without reported TB exposure were randomized to receive daily INH or placebo for 96 weeks, and followed for an additional 96 weeks. This sub-study enrolled children followed in Cape Town who had either completed 96 weeks of study drug and were in follow-up, or who were receiving randomized study drug for planned discontinuation at the next scheduled study visit. Participants in the parent study for <12 weeks were excluded. Written informed consent was obtained for participation in the sub-study and the protocol was approved by the Research Ethics Committee at Stellenbosch University (HREC N08/08/234).

Data collection

At sub-study enrolment, sociodemographic (age, sex, ethnicity) and clinical data (HIV-infection status, cART use, TB exposure, prior TB diagnosis, anthropometric measurements) were collected. Participants had blood drawn for QuantiFERON®-TB Gold In-Tube ELISA (QFT; Cellestis Limited, Carnegie, Victoria, Australia) at enrollment and after one year of follow-up. Laboratory technicians blinded to clinical data completed QFT assays according to manufacturers’ guidelines.

Data analysis

Demographic and clinical characteristics of the HIV+ and HEU cohorts were summarized using descriptive statistics. Positive, negative, and indeterminate results for QFT assays were
defined according to manufacturer guidelines. Missing and indeterminate QFT results were excluded from analysis. Among children with positive QFT, we reported the median IFN-γ level (IU/mL) above background in response to ESAT-6, CFP-10 and TB7.7 at enrollment and follow-up. For QFT results after 1 year, the proportion of children converting from negative to positive and reverting from positive to negative were reported. Incidence rate of TB infection was estimated using positive QFT status at the one year follow-up visit among children with negative baseline QFT.

The impact of clinical and epidemiologic covariates on positive QFT at enrollment was assessed using univariable logistic regression. All statistical analyses were performed using Stata 14.0 SE (StataCorp 2015. Stata Statistical Software: Release 14. College Station, Texas, USA).

RESULTS

Of 412 children entering the P1041 parent study in Cape Town, South Africa between October 2008 and December 2009, 258 participants were screened for the sub-study. Of these, 217 children were enrolled, comprising 81 HIV+ and 136 HEU (Supplemental Digital Content 1). HIV+ children were more likely underweight and stunted (Supplemental Digital Content 2). A similar proportion of HIV+ and HEU children (12.4% versus 13.2%) reported TB exposure in the year before sub-study enrollment. The majority of HIV+ children (84%) were receiving cART and were not immunosuppressed (median CD4% 32%). As the HEU cohort accrued more quickly in the parent study, HIV+ children received less INH or placebo (median 38 versus 96 weeks), were younger and entered the sub-study sooner after completing study drug (median 16 versus 73 weeks).

The prevalence of positive QFT was 11.8% (9/76) for HIV+ and 14.4% (19/132) among HEU children at enrolment. At follow-up, prevalence of positive QFT was 14.7% (10/68) for HIV+ and 24.0% (29/121) for HEU children. The median magnitude of IFN-γ response was higher in HEU compared to HIV+ children but the difference was not statistically significant at both time points (Supplemental Digital Content 2). Overall, of 23 children with positive QFT at baseline, 18 (78%) had consistent positive QFT results at follow-up. Of 158 children with negative QFT at baseline, 138 (87%) had consistent negative QFT results at follow-up. The proportion of children converting from a negative to positive QFT at 1 year of follow-up was 12.7% (20/158), and similar between HIV+ and HEU [6/59 (10.2%) versus 14/99 (14.0%), p=0.47]. The proportion of children reverting from a positive QFT at baseline to a negative QFT at 1 year was overall 21.7% (5/23) and was not significantly different in HIV+ and HEU children [2/5 (40.0%) versus 3/18 (16.7%), p=0.29]. Incidence of TB infection measured by QFT was 11 per 100 child-years for HIV+ and 15 per 100 child-years for HEU children. Quantitative changes in IFN-γ from baseline to follow-up are shown in Figure 1. Of children with incident TB infection, 50% (10/20) had QFT IFN-γ values >4.0 IU/mL. Notably, reversions generally occurred in participants who had low baseline positive QFT results [median 0.68 IU/mL (IQR 0.6, 1.9)].

Prior TB treatment was associated with a 5.9-fold higher odds of positive QFT for HIV+ children [(95% CI 1.31, 26.65), p=0.02] on univariable logistic regression. Lower HAZ was
associated with higher odds of positive QFT among HEU children [OR 1.69 (1.01-2.78), p=.04]. There was no association between INH study arm and QFT positivity among HIV+ or HEU children (Supplemental Digital Content 3).

DISCUSSION

We found a high incidence of TB infection among HIV+ and HEU, BCG-vaccinated young children after completing an IPT trial where TB exposure was an initial exclusion criterion. Our observed prevalence of TB infection at baseline was higher than other IGRA studies in HIV+ and HEU in East African children, likely reflecting the higher TB burden and transmission in South Africa. To our knowledge, our study is the first to report incidence of TB infection detected by IGRA in HIV+ and HEU children, and our findings highlight the ongoing high risk of TB exposure and infection in young children born to HIV+ women beyond infancy.

Current WHO guidelines recommend IPT for all children under 5 years of age with reported TB contact; however contact screening alone may miss many TB-exposed children living in TB high burden settings. Despite excluding children with TB exposure at enrolment, there was high incidence of TB disease in the parent trial (12.1 per 100 child-years in HIV+ and 4.1 per 100 child-years in HEU). In our sub-study, only 25% of children with positive QFT at baseline reported having a TB contact. Although prior studies in low TB burden settings show poor positive predictive value of IGRA for TB disease in children, a recent study performing serial IGRA in young South African children found that those with a high magnitude IFN-γ conversion (>4.0 IU/mL) had substantial increased risk of progressing to TB disease [incidence rate ratio (IRR) 42.5; p<0.0001]. Half the children in our study with incident TB infection had QFT values >4.0 IU/mL, suggesting that a significant proportion of HIV+ and HEU children with positive QFT are at high risk for TB progression. Future cost-effectiveness assessment of IGRA-targeted screening for TB preventive therapy in HIV-exposed children would be beneficial.

Our study had several strengths and limitations. We performed IGRA testing in an appreciable number of young HIV+ and HEU children at baseline and after a year. While our study adds to IGRA data for young HIV+ and HEU children, we have low power to detect small but potentially clinically significant associations. There is no gold standard to define TB infection, therefore estimates of test performance are not precisely known. Heterogeneity of the HIV+ and HEU cohorts may confound direct comparison of findings between the cohorts. Analyses by IPT arm were performed by intention-to-treat which may have under-estimated the effect of IPT. We did not collect data on TB disease history or evaluate for clinical TB disease at follow-up. In conclusion, we found a high incidence of TB infection in young children born to HIV+ mothers. A substantive proportion of HIV+ and HEU children with incident TB infection had high magnitude of IFN-γ values, indicating risk for TB progression. IGRA screening and targeted use of TB preventive therapy among young children in settings with high TB/HIV prevalence should be considered.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


Figure 1.
Longitudinal quantitative response of QFT IFN-γ to TB antigens above nil (IU/mL) in all HIV+ (N=76) and HEU (N=132) children. A. Consistent positive and negative responses; B. Conversions from a negative to positive response; C. Reversions from positive to negative response.