High Burden of Morbidity and Mortality but Not Growth Failure in Infants Exposed to but Uninfected with Human Immunodeficiency Virus in Tanzania

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Objective To compare health and growth outcomes in children infected with HIV, children exposed to but uninfected with HIV, and children unexposed to HIV.

Study design Our cohort included 3554 Tanzanian children enrolled in 2 trials of micronutrient supplementation. Among infants born to mothers infected with HIV, 264 were infected with HIV and 2088 were exposed to but uninfected at 6 weeks of age. An additional 1202 infants were unexposed to HIV. Infants were followed until 18 months of age, death, or loss to follow-up. Morbidity and growth were assessed at monthly nurse visits.

Results Compared with unexposed infants, hazard ratios (95% CI) for all-cause mortality in infants infected with HIV and infants who were exposed to but uninfected with HIV were 28.99 (14.83-56.66) and 2.79 (1.41-5.53), respectively, after adjusting for demographic and nutritional covariates. Compared with infants unexposed to HIV, infants infected with HIV also had a significantly greater risk of all measured morbidities, while infants who were exposed to but uninfected with HIV were significantly more likely to suffer from cough, fever, unscheduled outpatient visits, and hospitalizations. Infants infected with HIV also were more likely to experience stunting, wasting, and underweight at baseline and during follow-up. Infants exposed to but uninfected with HIV were more likely to be underweight at baseline (adjusted relative risk, 2.05; 95% CI, 1.45-2.89), but on average, experienced slower declines in height-for-age *z*-score, weight-for-age *z*-score, and weight-for-height *z*-score as well as a lower rate of stunting over follow-up, compared with unexposed infants.

Conclusion In addition to preventing and treating HIV infection in infants, prevention-of-mother-to-child-transmission of HIV and child health services should also target children exposed to but uninfected with HIV to improve health outcomes in this vulnerable population. *(J Pediatr 2017;180:191-9).*

Trial registration Clinicaltrials.gov: NCT00197730 and NCT00421668.

Globally, 35.2 million people are estimated to be living with HIV, 3.2 million of whom are children.[1] One of the great health achievements in the past 2 decades has been the global expansion of prevention-of-mother-to-child-transmission of HIV services. In 2014, coverage of antiretroviral treatment for prevention-of-mother-to-child-transmission of HIV services reached 74% of pregnant women living with HIV, resulting in a 48% decrease in new pediatric HIV infections between 2009 and 2014.[2] As a result of expanded prevention-of-mother-to-child-transmission of HIV services, each year, almost one-quarter of infants born in several sub-Saharan African countries are born to mothers who are infected with HIV, and are thus "exposed" to HIV, but remain uninfected themselves.[3] Whether children exposed to but uninfected with HIV have the potential for similar health outcomes as infants who are not exposed to HIV, or whether they have outcomes "between" those of infants infected with HIV and infants unexposed to HIV, has not been determined.[3]

There are several mechanisms through which maternal HIV infection can lead to suboptimal child health. Children infected with HIV have a considerably higher risk of mortality, morbidity, and growth failure compared with infants not infected with HIV.[4-7] Even if an infant avoids HIV infection, however, prenatal exposure to HIV may influence developmental programming.[8] A handful of studies have documented impaired immune function[9-12] and an increased risk of morbidity and mortality[7,13-15] among infants exposed to but uninfected with

ART	Antiretroviral therapy	WAZ	Weight-for-age *z*-score
HAZ	Height-for-age *z*-score	WHO	World Health Organization
RR	Relative risk	WHZ	Weight-for-height *z*-score

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Supported by the National Institutes of Health (R01 HD043688-01, R01 HD048969-01, K24HD058795, and K24 DK104676). C.D. serves on the Editorial Board of *The Journal of Pediatrics*. The other authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.09.040

HIV compared with infants unexposed to HIV. Additional studies have also documented an increased risk of low birthweight—due to both intrauterine growth restriction and prematurity—among infants who were exposed to HIV but uninfected compared with infants who were not exposed to HIV.[7,16-19] Recent research also has indicated that maternal antiretroviral therapy (ART) during pregnancy may have independent negative effects on infant health and growth[20-22]; however, few studies have assessed the effect of HIV and/or ART exposure on long-term health outcomes such as growth.[5] Furthermore, much of the research on health outcomes in children exposed to but uninfected with HIV comes from cohorts in wealthy nations where antiretroviral access and underlying risk factors for poor growth, morbidity, and mortality are different than in the low-resource settings.[5,23] To better describe the unique health risks of children exposed to HIV in low-resource settings, we evaluated mortality, morbidity, and growth outcomes in children who were infected with HIV and children exposed to but uninfected with HIV in Dar es Salaam, Tanzania, compared with children who were not exposed to HIV from the same periurban community.

Methods

The study sample included 3554 children in Dar es Salaam, Tanzania, who participated in two micronutrient supplementation trials (Clinicaltrials.gov: NCT00197730 and NCT00421668). The first trial randomized infants born to mothers infected with HIV to either daily multivitamins (vitamins B complex, C, and E) or placebo at 6 weeks of age.[24] Children were tested for HIV infection at 6 weeks of age by using the Amplicor HIV-1 DNA assay version 1.5 (Roche Molecular Systems Inc, Pleasanton, California). Tests at 18 months of age were performed using HIV ELISAs followed by Enzygnost anti–HIV-1/2 Plus (Dade Behring, Deerfield, Illinois); discordant results were resolved by using a Western blot test. Samples from children who tested positive at 18 months of age were then backtested via polymerase chain reaction to estimate time of transmission. Infants confirmed to be infected with HIV at baseline (6 weeks of age) serve as the infected with HIV sample for analyses, and infants who were uninfected at baseline serve as the exposed but uninfected with HIV sample. If infants exposed to but uninfected with HIV tested positive for HIV at a later visit, they were censored after their last negative test.

The second trial was implemented with a 2 × 2 factorial design assessing zinc and multivitamins, zinc only, multivitamins only, or placebo among 2400 infants born to women not infected with HIV.[25] To enhance comparability with the first study, we restricted our current analyses to infants who received multivitamins alone or placebo. Multivitamin supplements in both trials were identical in composition and dosage.[24,25] Infants randomized to multivitamins consumed 1 capsule per day containing 150%-600% of the US Adequate Intake for children aged 0-6 months of age, and 2 capsules per day after 6 months containing 200%-400% of the Adequate Intake for infants 6-12 months of age and 133%-800% of the US Recommended Daily Allowance for children 1-3 years of age. The 2 studies were designed to allow for a pooled analysis; they were conducted in overlapping clinics with similar staff, identical inclusion/exclusion criteria (other than maternal HIV status), and they collected the same demographic and clinical data on all mothers and children.[24,25] The first trial did not show an effect of multivitamin supplements on morbidity and mortality,[24] or on growth.[26] The second trial, which was not powered to assess the effect of supplements on mortality in a population unexposed to HIV, also did not show substantial effects of multivitamins on morbidity[25] or growth.[27]

Approval for both trials was granted by the Harvard T.H. Chan School of Public Health Human Subjects Committee, the Muhimbili University of Health and Allied Science Committee of Research and Publications, the Tanzanian National Institute of Medical Research, and the Tanzanian Food and Drug Authority. All mothers provided written informed consent to enroll themselves and their infants in the studies.

In both trials, mothers were asked to bring children to the clinic for follow-up monthly. During follow-up visits, a trained study nurse performed a standardized assessment of child morbidity based on maternal recall aided by the mother's symptom diary that she received at the previous visit. The symptom diary was a pictorial aid of illness symptoms (eg, diarrhea, vomiting) where mothers were asked to check off which days their child had experienced these symptoms. A trained nurse also measured child anthropometry using standard techniques.[28] Weight was measured on a digital infant balance scale with 10-g precision (Tanita, Arlington Heights, Illinois) and length with 1-mm precision using a rigid length board with an adjustable foot piece. For our analysis, we calculated age- and sex-specific *z*-scores for 3 anthropometric indexes: weight-for-height (WHZ), height-for-age (HAZ), and weight-for-age (WAZ) using the 2006 World Health Organization (WHO) growth standards.[29] Children who missed their monthly follow-up appointment were visited at home by a study nurse, and their vital status was confirmed through contact with immediate family members.

Standard of Care

The medical care provided to mothers and children in both trials has been described previously.[24,25] In brief, mothers and children received medical care in accordance with Tanzanian guidelines. On the basis of earlier findings of the benefits of prenatal multivitamins among women infected with HIV who were not receiving ARTs,[29,30] all women infected with HIV received supplements containing high doses of vitamins B complex, C, and E during pregnancy and lactation. When the first trial began, ART medication was limited to nevirapine prophylaxis for maternal-to-child transmission.[21] As the trial progressed, access to ARTs expanded rapidly. Beginning in July 2005, women and children were screened for ART eligibility and treated according to national guidelines. For adults, eligibility was based on WHO stage IV disease, or CD4 cell count of ≤200 cells/mL, or WHO stage III and CD4 cell count of ≤350 cells/mL. For children, eligibility was based on CD4% < 20