Maternal Antiretroviral Therapy Is Associated with Lower Risk of Diarrhea in Early Childhood

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Objectives To identify risk factors, including maternal antiretroviral therapy (ART), for diarrhea in Tanzanian children exposed to HIV during the first 2 years of life.

Study design Using generalized estimating equations, we analyzed data from a cohort of 2387 Tanzanian children exposed to HIV from age 6 weeks to 2 years, as well as data from their mothers, to determine risk factors for diarrhea in children. Mothers recorded diarrhea in a diary and reported results at visits scheduled every four weeks.

Results Body mass index was ≥18.5 in 95.6% of mothers. World Health Organization HIV stage was 1/2 for 1255 (87.8%) mothers. ART was received by 24.3% of mothers, most initiating ART during pregnancy. At baseline (6 weeks of age) 264 (11.3%) children were infected with HIV. In children whose mothers received ART, the relative risk of diarrhea in children was 0.79 (95% CI 0.68-0.92), after we adjusted for multiple factors, including child HIV status and exclusive breastfeeding duration. Exclusive breastfeeding (relative risk 0.67, 95% CI 0.56-0.80) also was protective.

Conclusion Our results provide additional support to increase ART coverage for all pregnant mothers, to control clinical HIV progression, reduce perinatal HIV infection, but also to reduce the risk of a major cause of death and morbidity in young children worldwide. *(J Pediatr 2016;175:54-60)*.

Trial registration ClinicalTrials.gov: NCT00197730.

Diarrhea in children younger than 5 years of age is a major global health problem, causing an estimated 760 000 deaths annually, and accounts for almost 10% of postnatal child deaths[1] and up to 17% of child deaths in Tanzania.[2] Diarrhea episodes in the first 2 years of life may have many effects, including negatively impacting adult height, IQ, and school attendance.[3-5] Every 5 episodes of diarrhea during childhood may stunt a child by 13%.[3] Stunting remains a measure of poor nutritional status. Furthermore, multiple episodes of diarrhea also lead to impaired catch-up growth.[3] Poor nutritional status and impaired growth are associated with poor neurocognitive outcomes, immune deficiencies, and greater risk of death in children.[6] In addition, most child deaths from diarrhea occur in the world's poorest regions, with about 90% of related deaths in sub-Saharan Africa and South Asia.[7] The incidence of diarrhea is most prevalent in areas also heavily impacted by HIV, including sub-Saharan Africa.

Antiretroviral therapy (ART) is lifesaving therapy for people infected with HIV, including pregnant women and mothers. The effects of ART for mothers may include improved nutritional status, greater hemoglobin, and improved economic status.[8] In children, ART for mothers reduces the rate of HIV transmission,[9] but there is controversy about the benefits of ART on other child outcomes such as birth weight[10] and prematurity in children exposed to HIV.[8,11,12] These are critical questions, given the size of the affected population. In 2013, 16 million women were infected with HIV, and 240 000 children were newly infected with HIV,[13] and with mother-to-child HIV transmission rates as low as 5%,[9] many hundreds of thousands more were exposed to HIV.

Despite its evident public health importance and wide use in mothers with HIV, the potential for maternal ART to protect against infant infectious diseases including diarrhea has received little attention. Breastfeeding reduces diarrhea in children exposed to HIV[14,15]; however, few other maternal factors that reduce diarrhea have been identified for children exposed to HIV. There has been

ART	Antiretroviral therapy
BMI	Body mass index
HR	Hazard ratio
RR	Relative risk
WHO	World Health Organization

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very limited research that examines maternal predictors such as ART use on diarrhea in young children at risk of HIV infection.[15,16] In areas with high burdens of infectious disease and high HIV prevalence, identifying factors that influence the incidence of diarrhea in the first 2 years of life could provide opportunities for intervention to reduce diarrhea and to prevent short- and longer-term diarrhea-associated morbidity and mortality. To better understand risk factors for diarrhea in children exposed to HIV early in life, we examined data from a cohort of Tanzanian mothers infected with HIV and children exposed to HIV followed prospectively from birth to 2 years of age.

Methods

The parent study for these analyses was a randomized, placebo-controlled clinical trial to determine the effects of micronutrient supplementation on morbidity and mortality in Tanzanian children exposed to HIV (ClinicalTrials.gov: NCT00197730). The methods and main results have been documented in detail previously.[17] In brief, pregnant mothers were enrolled before 32 weeks' gestation and children randomized to placebo or supplementation at 6 weeks of age. A total of 2387 infants were enrolled; 1193 were randomized to receive multivitamin and 1194 to receive placebo. As part of standard medical care, mothers were provided with micronutrient supplements, and all children received growth monitoring, immunizations, routine medical care for illnesses, and periodic high-dose vitamin A supplementation per Tanzanian Ministry of Health guideline (100 000 IU at 9 months and 200 000 IU at 15 and 21 months of age).

All antiretroviral medications were prescribed according to Tanzanian Ministry of Health national guidelines. Nevirapine was given as single dose to the mother at the onset of labor and also to the infant within 72 hours of birth. In July 2005 the availability of ART expanded as the result of funding from HIV treatment support programs such as the US President's Emergency Plan for AIDS Relief.[18] During the study period, ART eligibility included mothers with World Health Organization (WHO) stage 3 HIV disease or CD4+ cell count <350 cells/μL and children with WHO stage 3 HIV.[19] Children age <18 months were eligible for ART with CD4+% <20, or if age ≥18 months, with CD4+% <15. First-line therapy for mothers included stavudine or zidovudine, lamivudine, and nevirapine, and for children included zidovudine, lamivudine, and nevirapine. Once started, ART was not stopped. Alternative drugs were available as needed.

Documentation of child morbidities, including diarrhea, was performed via a nurse visit of mothers and their children every 4 weeks at a central clinic site on the campus of Muhimbili University of Health and Allied Sciences. At these visits, mothers and nurses reviewed the data in a symptom diary from the previous 4 weeks that was collected via pictorial representations of symptoms of common morbidities including diarrhea. Nurse visits occurred every 4 weeks and physician visits occurred every 12 weeks or when requested for sick child visit. Acute diarrhea was defined as 3 or more loose or watery stools within 24 hours with or without blood or mucus. Persistent diarrhea was defined as watery or loose stools for more than 14 sequential days. Dysentery was defined as any diarrhea with blood, pus, or mucous. A positive report for any of these definitions was used as the primary outcome in our analysis. Diarrhea reports within 14 days of a previous report were counted as a single episode to avoid multiple counting of diarrhea events. In breastfed infants more than 12 weeks postnatal age who commonly have several loose stools per day at baseline, diarrhea was defined as a change in stool pattern according to the mother. Children with illnesses (including diarrhea) unable to be managed by nurses were referred to a study physician, where additional clinical data were collected.

Exclusive breastfeeding was defined as feeding a child with breast milk only, without supplemental foods. HIV treatment was provided to all participants according to standard of care per the Tanzania Ministry of Health. Written informed consent was obtained from all subjects at enrollment. All procedures were approved by institutional review boards at both Muhimbili University of Health and Allied Sciences and Harvard T.H. Chan School of Public Health.

Statistical Analyses

Examination of associations of potential risk factors with incident diarrhea was performed with the use of generalized estimating equations in the GENMOD procedure of the Statistical Analysis Systems statistical software package, version 9.2 (SAS Institute Inc, Cary, North Carolina). The binomial distribution with the log link function and a working exchangeable covariance structure was specified for repeated diarrhea episodes. A data structure with one record per child-visit was used to facilitate the handling of time-varying covariates.

For inclusion in the model, we considered potential risk factors for diarrhea from a list of known[14,20] and suspected risk factors. These variables were categorized as follows: maternal age (<25, ≥25 years), education level (none, 1-7, 8 + years), employment (housewife without income, housewife with income, others), daily food expenditure (≤500, >500 Tanzanian Shillings), marital status (single, married/living with partner), number of previous pregnancies (0, 1-3, 4+), maternal WHO HIV stage (1/2, 3/4), time-varying ART (yes/no), maternal body mass index (BMI <18.5, 18.5 to <25.0, 25.0 to <30, 30+ kg/m^2), maternal hemoglobin level (<11.0, ≥11.0 g/dL), maternal CD4+ counts (<350, ≥350 cells/μL), child sex (male/female), birth weight (<2500, ≥2500 g), preterm birth (<37, ≥37 weeks), time-varying exclusive breastfeeding (yes/no), time-varying breastfeeding (yes/no), and child time-varying HIV status (yes/no). Exposure to the treatment arm of the parent study was included in the multivariate models. Relative risks (RRs) and their corresponding 95% CIs are used to estimate their associations with incident diarrhea. Variables with P value <.2 in univariate analysis were selected for multivariate analysis. The significance tests were 2-sided, and differences were considered significant at $P < .05$.