No HIV Transmission From Virally Suppressed Mothers During Breastfeeding in Rural Tanzania

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Background: To what extent antiretroviral therapy (ART) reduces mother-to-child HIV transmission (MTCT) during breastfeeding remains unclear. We assessed the MTCT risk from mothers on ART to their infants during breastfeeding.

Setting: Ifakara, rural Tanzania.

Methods: We included infants born between January 2013 and May 2016 to mothers who initiated ART before delivery, had a negative HIV DNA polymerase chain reaction at 4–12 weeks and exclusively breastfed for ≥6 months. Mothers' plasma HIV-RNA viral loads (VLs) were measured up to 11 months postdelivery. Infants were tested for HIV following national guidelines.

Results: Among 214 women with 218 pregnancies and 228 infants (10 twins), the median age at delivery was 33 years (interquartile range 28–36 years), and the mean time on ART was 23 months (interquartile range, 4–52 months). VL was measured twice in 53% (113/218) of pregnancies. During breastfeeding, 91% of mothers (199/218) had VL of <1000 copies per milliliter, and 75% (164/218) had <100 copies per milliliter. To November 2017, 8% (19/228) of infants were lost to follow-up (LTFU), 2% (5/228) transferred, and 8% (18/228) died before the determination of final HIV serostatus. Among the remaining 186 infants, 2 (1%; 95% confidence interval: 0.3% to 4%) were HIV positive: 1 born from a mother with high VL 1-month postdelivery and 1 from a mother who interrupted ART. Assuming a 15% MTCT risk through breastfeeding among the 42 infants LTFU, transferred, or dead, the overall MTCT risk would be 4%.

Conclusions: We found no MTCT from mothers who were retained in care and had suppressed VL. Breastfeeding signifies a very low risk when mothers adhere to ART. Adherence counseling, VL monitoring, and strategies to trace back those LTFU should be a priority.

Key Words: HIV, mother-to-child transmission, HIV-exposed infant, breastfeeding, sub-Saharan Africa

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INTRODUCTION

Worldwide, there were an estimated 2.1 million children living with HIV by the end of 2016.[1] More than 90% of pediatric HIV infections are acquired through mother-to-child transmission (MTCT), which can occur during pregnancy, labor and delivery, or breastfeeding. Without any preventive intervention, the MTCT risk among infants who breastfeed ranges from 25% to 40% (from conception to cessation of breastfeeding), 10%–15% during the breastfeeding period only.[2] The main determinant of MTCT risk is maternal plasma HIV RNA viral load (VL),[3] and its reduction is the aim of current prevention of mother-to-child transmission (PMTCT) guidelines. Since 2015, the World Health Organization recommends lifelong antiretroviral therapy (ART) for all pregnant and breastfeeding HIV-infected women regardless of their CD4 counts and clinical stage (Option B+ strategy).[4] Several studies demonstrate that an undetectable VL through pregnancy and delivery virtually eliminates MTCT during these periods.[5,6] However, studies indicating that viral suppression during breastfeeding leads to elimination, or at least dramatic reduction, of MTCT through breastfeeding are scarce and missing for rural Africa.[7]

We aimed to assess the MTCT risk from mothers on ART to their infants during a long breastfeeding period in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), a rural African HIV cohort.

METHODS

KIULARCO prospectively enrolls consenting HIV-positive patients seen at the Chronic Diseases Clinic of Ifakara,

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in southern Tanzania. The clinic and the cohort are a collaboration between the St. Francis Referral Hospital, the Ifakara Health Institute, the Swiss Tropical and Public Health Institute, and the Department of Infectious Diseases and Hospital Epidemiology of the University Hospitals of Basel and Bern. Ethical approval for KIULARCO was obtained from the Ifakara Health Institute ethical review board, the National Institute for Medical Research of Tanzania, the Tanzanian Commission for Science and Technology, and the ethical review board of Northwest Switzerland. Between 2004 and 2016, 9274 patients were enrolled. Since 2013, PMTCT and pediatric HIV services are delivered through a family-oriented and child-friendly unit integrated within the reproductive and child health clinic named the One Stop Clinic of Ifakara.[8,9] The KIULARCO cohort is described in detail elsewhere.[10,11]

For this prospective study, we included infants born between January 1, 2013, and May 31, 2016, to mothers enrolled in KIULARCO who initiated ART before delivery, exclusively breastfed for the first 6 months of life, and who had a negative proviral HIV DNA polymerase chain reaction (PCR) at age 4–12 weeks, and thus were not infected perinatally. Infants received postnatal prophylaxis with daily nevirapine during the first 4–6 weeks of life. Plasma HIV RNA VLs were measured from stored plasma samples of mothers. All breastfeeding mothers had VL measurements done once or twice, based on the sample availability, during the first 11 months after delivery. For proviral HIV DNA PCR, we used an in-house nested PCR protocol executed on a GeneAmp PCR System 9700 (Thermo Fisher Scientific, Waltham, MA), using GoTaq DNA Polymerase (Promega, Madison, WI). Viral RNA quantification was performed using a validated in-house protocol with the Taqman qPCR Master Mix (Applied Biosystems, Foster City, CA) using the StepOne Real-Time PCR System (Applied Biosystems), with a detection limit of 100 viral RNA copies per milliliter.

The primary outcome was the final HIV status of infants (either confirmation of HIV infection or exclusion of MTCT after at least 6 weeks after the cessation of breastfeeding) at the end of the study on November 6, 2017, overall and by virological suppression status of the mother. Infants were tested for HIV following the national guidelines: for infants of ≤9 months, proviral DNA PCR was used; for those aged 9–18 months, HIV rapid antibody tests (SD Bioline HIV-1/2 3.0, Standard Diagnostics, Inc, Yongin, South Korea; Alere Determine HIV-1/2, Abbot Laboratories Chicago, IL; and Unigold HIV, Trinity Biotech, Bray, Ireland) were used for screening, and, if positive, proviral DNA PCR was performed for confirmation. A negative HIV rapid antibody test at least 6 weeks after the cessation of breastfeeding was necessary to conclude that an infant was HIV uninfected.[12] We estimated 95% confidence intervals (CIs) for the proportion of infants infected,[13] ignoring correlation induced by twins or siblings; in sensitivity analyses, we restricted the analysis to single infants without siblings in this cohort.

RESULTS

We enrolled 228 infants born from 214 women with 218 pregnancies (10 twin pregnancies). At the time of delivery, the median age of mothers was 33 years [interquartile range (IQR), 28–36 years], the median time on ART was 23 months (IQR, 4–52 months), and 93% (203/218) of mothers were on a first-line ART regimen, most commonly a fixed-dose combination of efavirenz, tenofovir disoproxil fumarate, and lamivudine or emtricitabine (68%; 139/203). Fifty percent (113/228) of infants were female, 96% (219/228) were born at term (between 37 and 42 weeks of gestation), 83% (189/228) received postpartum antiretroviral prophylaxis, and 93% (211/228) were prescribed cotrimoxazole prophylaxis. The median duration of breastfeeding was 52 weeks (IQR, 41–54 weeks), and the median CD4 count of mothers during breastfeeding was 540 cells per cubic millimeter (IQR, 364–751 cells/mm^3). For all pregnancies, at least 1 VL was measured during the 11-month postpartum period. In 53% (115/218) of pregnancies, VL was measured twice. Figure 1 summarizes the maternal plasma HIV RNA VL measurements taken during the 218 postpartum periods. Overall, during breastfeeding, VL was <1000 copies per milliliter for 91% (199/218) and <100 copies per milliliter for 75% (164/218) of the postpartum periods.

At the end of the study, 8% (19/228) of infants were lost to follow-up, 2% (5/228) had been transferred to another clinic, and 8% (18/228) had died before the determination of their final HIV serostatus. Median age at death of the infant was 3 months (IQR, 3–7 months). The causes of death were pneumonia (4 cases), diarrheal disease (2 patients), sepsis (2 patients), unspecified neurologic disease (2 patients), spina bifida with hydrocephalus (1 patient), and in 7 infants, the cause of death was not documented. The final HIV serostatus was known for the remaining 186 (82%) infants, which was determined at a median age of 14 months (IQR, 12–16 months). Two infants (1%, 2/186; 95% CI: 0.3% to 4%) became HIV infected: 1 infant born to a mother with high VL (144,111 copies/mL) at 5 weeks after delivery, and 1 infant born to a mother who had undetectable VL at 6 weeks postdelivery but shortly after interrupted ART during breastfeeding. Similar results were found when restricting to single infants without siblings in the cohort, with 2/164 (1%; 95% CI: 0.3% to 4%) infections.

DISCUSSION

This is one of the first studies to document that viral suppression during breastfeeding successfully prevents MTCT in a rural African setting, indicating that breastfeeding in the context of effective Option B+ signifies a very low risk of HIV transmission. An important finding of our study is the prevalence of virological suppression (VL <1000 copies/mL) of 91% among mothers retained in care during breastfeeding. This is above the target set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) for 2020: 90% of people receiving ART being virally suppressed.[14] In a recently published study from South Africa, where VLs of postpartum women were measured repeatedly during 12 months after delivery, 22% of women had at least 1 VL of ≥1000 copies per milliliter.[15] Moreover, each additional month postpartum was associated with an 11% increase in the incidence of

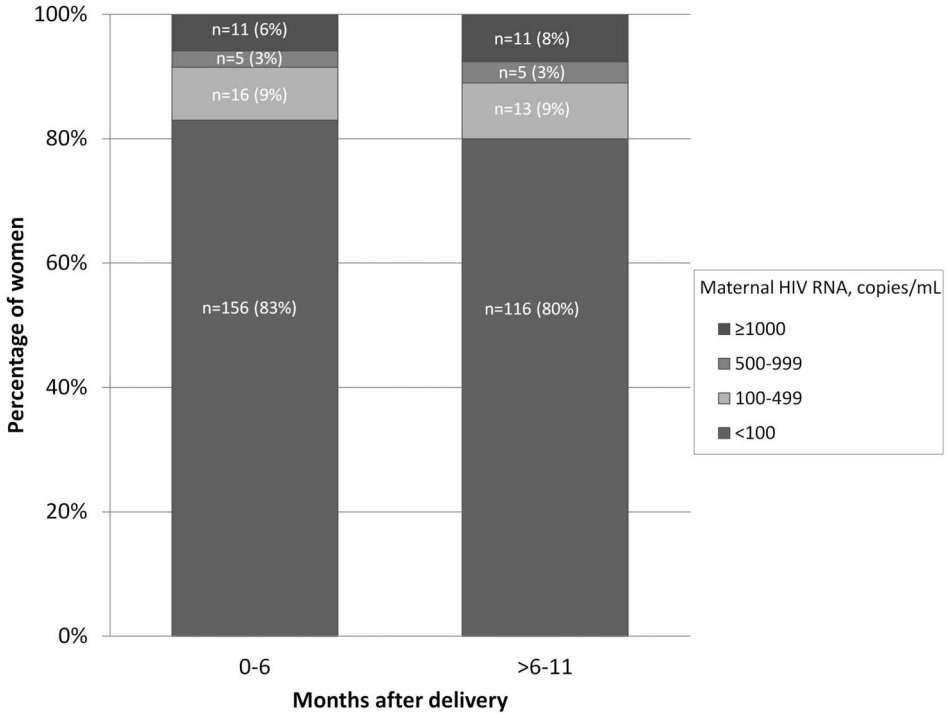

FIGURE 1. VL results of 333 samples from 218 postpartum periods in 214 women.

viremia. That study did not assess the MTCT events associated with viremic episodes.

Two infants became HIV infected in our study. Their mothers had either a documented high VL or had interrupted ART for a long period, rendering a significant viremic episode very probable. This finding is in line with recent analyses of the large Malawi Breastfeeding, Antiretrovirals and Nutrition (BAN) study assessing the benefits and safety of maternal and infant antiretrovirals to prevent HIV transmission during breastfeeding. In that study, all transmitting mothers had detectable plasma VL immediately preceding transmission.[16] Nevertheless, it should be highlighted that even if 25% of breastfeeding mothers in our study had detectable viremia (≥100 copies/mL) during the postpartum period, only 2 MTCT events occurred. This finding can be explained by the average 10%–15% transmission risk during breastfeeding in the absence of PMTCT measures and the possibility of temporary viral episodes during breastfeeding.[2,15]

Despite the high proportion of viral suppression among mothers and the very low MTCT risk observed in our study, some caution is needed when interpreting these findings: 8% of infants were lost to follow-up before the cessation of breastfeeding, and therefore, their final HIV status was not established. The lost to follow-up rate in our cohort is much lower than in other sub-Saharan African settings.[17,18] In contrast, the mortality rate observed in our cohort is similar to that described in a recent systematic review, where mortality of HIV-exposed uninfected infants at 24 months was 11%.[19] Although a consistently higher risk of mortality among HIV-exposed uninfected infants compared with unexposed infants is well documented,[20] the underlying mechanisms remain unclear, and research is needed to elucidate them. Assuming a 15% transmission of HIV among infants for whom we did not have final serostatus (infants lost to follow-up, transferred or dead), the overall MTCT rate during breastfeeding would be 4%.

Low adherence to ART and retention in care are the main downsides of the Option B+ strategy.[21] In a recently published review, Myer and Philips[22] propose a framework that recognizes the fundamental drivers of disengagement from care and suboptimal adherence to ART during pregnancy and breastfeeding periods. The authors discuss factors related to the health system, patients, the biology, and psychosocial environment. In our setting, where the drug supply chain integrity was maintained during the whole study period, strategies to identify women at risk of poor adherence and to enhance ART counseling are needed. An additional concern of Option B+ is the possible toxic effects of different antiretrovirals on fetuses and infants exposed from conception through breastfeeding. To date, data on the effects of ART exposure during breastfeeding on the health of infants are limited, and surveillance systems for toxicities are necessary.[23–25]

This study has some limitations. First, because we measured VL only once or twice during the 11 months after delivery, we may have failed to detect maternal temporary viremic episodes during breastfeeding. Second, the proportion of infants lost to follow-up or transferred, despite being low compared with similar cohorts, prevents us from knowing the exact MTCT risk during breastfeeding. The strengths of our study lie in its prospective character, the rural sub-Saharan African setting, for which little information is available, and the long breastfeeding period assessed.

ART and the consequent high prevalence of viral suppression successfully prevented MTCT through

breastfeeding in a rural Tanzanian setting under programmatic conditions. However, this success is threatened by postpartum attrition from HIV care and suboptimal treatment adherence. Strategies to ensure retention in care and treatment adherence during the postpartum period need to be developed along with an effective rollout of universal VL monitoring to timely detect mothers at the risk of transmitting HIV to their infants.

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APPENDIX 1. Members of the KIULARCO Study Group

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