LESSONS LEARNED FROM A BREASTFEEDING HIV-EXPOSED UNINFECTED INFANT COHORT: GETTING TO UNDER 1% VERTICAL TRANSMISSION

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BACKGROUND

As one of the countries with the highest burden of HIV in the world, South Africa has a well-established Prevention of Mother to Child Transmission (PMTCT) programme. South Africa's national PMTCT guideline changed from single dose nevirapine for the mother to zidovudine monotherapy from 28 weeks of gestation in 2008. In 2010, infants were able to receive 6 weeks of nevirapine prophylaxis, instead of a single dose within 72 hours of birth. These two changes drastically improved the vertical transmission rates. Between 2003 and 2012, HIV transmissions from mother to child in South Africa decreased from occurring in 23,2% of mother–infant pairs to 2,4% of pairs (Sherman *et al.,* 2014).

Based on clinical and programme evidence demonstrating the benefit of a single, standardised regimen for PMTCT, the World Health Organization (WHO) updated the PMTCT program to include option B and B+ to augment option A in 2012. Option A encouraged mothers to use zidovudine (AZT) from 14 weeks' gestation, single-dose nevirapine (NVP) at birth, and 7 days of AZT/ lamivudine (3TC) postpartum for the mother, with daily NVP for the infant until breastfeeding cessation or until 4 - 6 weeks of age if the mother is receiving antiretroviral therapy (ART) or is not breastfeeding. Option B was simplified to ART for the mother from 14 weeks' gestation until birth or the cessation of breastfeeding, and the use of NVP for the infant until 4 - 6 weeks of age. While NVP prophylaxis for the infant remains the same for Option B+, the mother remains on lifelong ART (WHO, 2012). South Africa began implementation of option B+ in 2015, together with birth PCR testing for infants. We report here on the MTCT of HIV in a cohort of infants born to women enrolled in a PMTCT program at two public health clinics in Durban, South Africa between 2013 and 2018. These mothers and infants were a cohort of HIV-exposed, breastfeeding infants enrolled into a clinical trial examining the current relevance of the WHO cotrimoxazole prophylaxis guideline in a non-malaria area (Daniels *et al*. 2019).

DESCRIPTION

Study population: Between 2013 and 2018, we enrolled 1219 infants born to HIV positive women attending PMTCT programs at two clinics in Durban, South Africa into a non-inferiority trial assessing the current cotrimoxazole prophylaxis guidelines for HIV exposed uninfected infants. Of the 1219 infants enrolled, 275 (22.6%) did not complete their 12 months of study visits, either due to being lost to follow-up, relocating to another area or not being able to get leave from work to attend clinic, in addition to three infant deaths. Due to the study ending early, a further 103 infants were only followed up until they completed their 6-month visit. Therefore, while the full 1219 cohort was used for the baseline information, all seroconversion rates are calculated using the 944 who completed study follow up.

Inclusion criteria: Infants were included in the study if they were born to a woman living with HIV; tested negative for HIV by PCR before the 6-week enrolment visit; were breastfeeding at the screening and enrolment visits (and planning to breastfeed for at least 6 months); were a singleton birth with a birthweight of 2 kg or more; had no clinically observed genetic disorders; had no serious illnesses and had not received antibiotics or traditional medications (such as herbal remedies) prior to enrolment; and the mother, or the infant, or both were receiving a vertical transmission prevention regimen.

Study Procedures: Infants were assessed at screening visits before age 6 weeks, where study counsellors completed a demographic and screening questionnaire (including PMTCT information, questions about the infant's health and medicine intake, and infant feeding questions). An infant HIV PCR test was done if a previous test was unavailable. Infants and their mothers attended study visits at ages 6 weeks (enrolment and randomisation), 10 weeks, 14 weeks, and then monthly from 4 to 12 months. At each study visit, a nurse gave a clinical examination and took anthropometric measurements. Infants were assessed for weight and growth, and vaccines were administered as per the Department of Health schedule. Infants were evaluated for interval illnesses, signs and symptoms of study drug toxicity, mothers ARV drug adherence, concomitant medications, breastfeeding status and HIV infection status.

Infant HIV testing: In 2013, PCR testing for HIV was done at age 6 weeks and after cessation of breastfeeding according to the South African national protocol. Additional study PCR testing was done at screening (between age 1 week and 6 weeks) and at ages 4 months, 6 months, and 12 months. During the study (in August 2015), the South African national protocol changed to PCR testing at birth, at 10 weeks, and after cessation of breastfeeding. After this time, the additional study PCR testing was done at 6 and 12 months.

Peer Counselling: Peer counsellors provided breastfeeding and antiretroviral treatment adherence counseling for mothers at clinic visits. Both study clinics were accredited with Mother Baby Friendly Hospital Initiative status and all study staff were trained breastfeeding counsellors.

HIV Transmission: During the study period, eight (0.85%) infants were found to have acquired an HIV infection. Four infants (0.42%) tested positive for HIV at the 10-week PCR, which is indicative of either intrapartum or very early postnatal infections (hereafter referred to as "birth transmissions"), and the other four infants (0.42%) tested positive at the 12-month visit, which is indicative of postnatal breastfeeding transmission (**Table 1**). The national average for birth transmissions in South Africa has steadily declined from 4.3% in 2015/2016 to 0.7% in 2018/2019 (0.6% for the province of Kwa-Zulu Natal) (Massyn *et al*., 2020). The PROMISE study in southern Africa reported a 0.7% breastfeeding transmission rate when mothers were on ART (Flynn *et al*., 2018).

In the HIV seroconverter group, 5/8 (62.5%) of the infants were female and 5/8 (62.5%) were delivered via vaginal birth. Infant birth weight was not different to the overall cohort. Maternal age was 29.5 years (IQR: 25.9-33.7) in the main cohort and 28.5 years (IQR: 25.8-33.6) in the HIV seroconverter cohort. When stratified by mode of transmission, maternal age was 27.5 years (IQR: 25.0 – 30.0) in the birth transmission group compared to 30.0 years (IQR: 26.8 – 33.3) in the breastfeeding transmission group. The maternal CD4 captured was the most recent test result prior to birth. Unsurprisingly, maternal CD4 was lower in the HIV seroconverter group compared to the main study cohort, respectively [228 cells/mm^3 (IQR: 145.5 – 262.5)] vs 450 cells/mm^3 (IQR: 318.0 – 600.0)]. Stratified by mode of transmission, maternal CD4 was 195.5 cells/mm^3 (IQR: 94.5 – 240.0) in the birth transmission group vs 233 cells/mm^3 (IQR: 181.0-322.0). If we compare mothers whose CD4 was <350 cells/mm^3, 32% of the main cohort fell into this category, compared to 7/8 (87.5%) of the HIV transmission cohort (100% of birth and 75% of breastfeeding transmissions). Other noteworthy information collected regarding these eight mother-infant pairs is presented in **Box 1**.

Table 1: Characteristics of HIV seroconverter infants

	CTX Cohort N=1219	HIV Seroconverters N=8	Birth Transmissions N=4	Breastfeeding Transmissions N=4
Infant Female Sex [N (%)]	566 (46)	5 (62.5)	2 (50)	3 (75)
Maternal Age [Median (IQR)]	29.5 (25.9-33.7)	28.5 (25.8-33.6)	27.5 (25.0-30.0)	30 (26.8-33.3)
Maternal CD4 [Median (IQR)]	450 (318.0 – 600.0)	228 (145.5-262.5)	195.5 (94.5-240.0)	233 (181.0-322.0)
Vaginal Delivery [N (%)]	779 (64)	5 (62.5)	1 (25)	4 (100)
Caesarian Delivery [N (%)]	439 (36)	3 (37.5)	3 (75)	0 (0)
Infant Birth Weight [Median (IQR)]	3.1 (2.9-3.4)	3.2 (3.1-3.2)	3.2 (3.1-3.2)	3.5 (3.2-3.7)
CD4<350 [N (%)]	308 (32)	7 (87.5)	4 (100)	3 (75)

Box 1: Noteworthy information regarding HIV seroconverters

BIRTH TRANSMISSIONS

1. Mother had a partner from Central Africa from whom she contracted the virus. It is possible that she did not respond as expected to her ARV regimen due to HIV-2 infection.
2. Infant tested positive for Cytomegalovirus and HIV at 10 weeks of age.
3. Mother began ARVs prior to pregnancy and her viral load was high throughout pregnancy.
4. Mother's CD4 and VL not monitored prior to birth.

BREASTFEEDING TRANSMISSIONS

1. Mother was from Zimbabwe and returned home for several months where she was not adherent to ARV regimen.
2. Mother missed several clinic visits and was not adherent to her ARV regimen.
3. Mother had very low CD4 count at birth (76 cells/mm^3) and had low but detectable viral load at 6 months.
4. Mother was from Mozambique and went home for 3 months where she was not adherent to ARV regimen.

LESSONS LEARNED

This is the first large cohort that we are aware of in the epicenter of the HIV epidemic commenting on PMTCT rates in the era post Option B and B+ implementation. ***Strong and persistent peer counseling*** (both ART adherence and breastfeeding counselling) likely contributed to the low MTCT rate observed in this cohort. Both the ***mothers viral load and CD4 count monitoring*** is critical in the last trimester and at birth to prevent birth transmission and to ascertain whether the mother has responded adequately to her ARV regimen. Le Roux *et al.* (2020) showed that infants born to mothers with lower CD4 counts (<350 cells/mm^3) had higher morbidity than those born to mothers with higher CD4 counts. Hence ***targeted ART adherence, health and nutrition counselling*** could be directed toward these mothers. Mothers with a higher viral load at birth could be provided with ***additional ARV prophylaxis for the infant***, which can be extended until the mothers VL is undetectable. The PROMISE study showed that it was safe and just as effective at preventing HIV transmission to provide the infant with ARV prophylaxis for up to 12 months of age compared to mothers receiving prophylaxis (Flynn *et al*., 2018). Additionally, breastfeeding mothers need to have ***regular VL testing***. This will help determine which mothers are either not responding to their ARV regimen or not completely adherent to their regimen, facilitating the necessary steps to protect the infant from HIV transmission. Point-of-care testing for CD4 and viral load would assist in real-time assessment of mother's health and adherence/response to ART regimen, rather than waiting for lab results to return to the clinic.

RECOMMENDATIONS

- **Breastfeeding and ARV adherence peer counselling support is critical during this vulnerable time for pregnant and breastfeeding mothers.**
- **Point-of-care viral load and CD4 testing in the last trimester, at birth and regularly while breastfeeding would facilitate real-time counselling and adjustment of mothers and infants' prophylaxis regimens.**
- **Extended infant prophylaxis for mothers who are struggling to adhere to their ARV regimen or who are not responding appropriately, despite treatment adherence.**
- **Consideration must be given to foreign mothers who may not be able to obtain their ARVs when travelling to visit their home countries and extended (3 monthly) supplies should be considered for these mothers if they are stable on their current regimen.**

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