


Getting to under 1% vertical HIV transmission: lessons from a breastfeeding cohort in South Africa

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ABSTRACT

We report here on the transmission of HIV in a cohort of breastfeeding infants enrolled in a prevention of mother to child HIV transmission (PMTCT) programme at the epicentre of the HIV pandemic. South Africa implemented option B+ for PMTCT in 2015. Between 2013 and 2018, we enrolled 1219 infants born to HIV positive women into a non-inferiority trial assessing the current cotrimoxazole prophylaxis guidelines for HIV-exposed uninfected infants. Breastfeeding mothers and infants were enrolled and followed up at one of two clinics in eThekweni, KwaZulu-Natal, until 12 months of age. During the study period, 8 infants seroconverted (<1% transmission); these were likely four birth transmissions and four breastfeeding transmissions. It is critical in the post option B era to assess the reasons for vertical transmission of HIV to enable healthcare workers and policy makers to provide strategies to mitigate future infections. This report details the possible contributors to vertical transmission in this cohort and highlights the continued strategies that should be employed to further our goal towards reaching the elimination of mother to child HIV transmission

BACKGROUND

Several milestones are recommended for ending the global HIV epidemic by 2030, including the elimination of mother to child HIV transmission. This is defined by the WHO as a rate of <50 new paediatric HIV infections per 100 000 live births and a transmission rate <5% in breastfed infants, maintained for at least 1 year.¹ 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.² South Africa's national PMTCT guideline changed from single-dose nevirapine (NVP) for the mother to zidovudine (AZT) monotherapy from 28 weeks of gestation in 2008. In 2010, infants were able to receive 6 weeks of NVP 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

SUMMARY BOX

- ⇒ Vertical transmission under 1% is possible in the era of option B and option B+.
- ⇒ Vertical transmissions were mostly attributed to mothers' non-adherence to ARV regimens/not responding adequately to regimens, as well as poor monitoring of mothers' CD4 and viral load.
- ⇒ Further decreases to reach the <50 infections per 100 000 live births will require improved monitoring of mothers' CD4 and viral load during pregnancy and during breastfeeding, preferably with point-of-care technologies that enable immediate action on results.
- ⇒ Strengthening ARV adherence, breastfeeding and nutrition counselling during this vulnerable period could contribute to decreases in vertical transmission.

in South Africa decreased from occurring in 23.2% of mother–infant pairs to 2.4% of pairs.²

Based on clinical and programme evidence demonstrating the benefit of a single, standardised regimen for PMTCT, the WHO updated the PMTCT programme to include options B and B+ to augment option A in 2012.³ Option A encouraged mothers to use 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 however remains on lifelong ART.³ South Africa began implementation of option B+ in 2015, together with birth PCR testing for infants. We report here on the mother to child transmission of HIV in a cohort of infants born to women enrolled



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in a PMTCT programme 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.⁴

Context

Study population

Between 2013 and 2018, we screened 1570 infants and enrolled 1219 infants born to HIV-positive women attending PMTCT programmes at two clinics in Durban, South Africa into a non-inferiority trial assessing the current cotrimoxazole prophylaxis guidelines for HIV-exposed uninfected infants, the primary outcomes of which have already been published.⁴ The primary outcome paper also describes the screen out reasons for those not enrolled into the study. Of interest, only 3 of the 350 infants who were not enrolled were screened out due to being HIV-positive before the 6-week enrolment visit.⁴ Of the 1219 infants enrolled, 275 (22.6%) did not complete their 12 months of study visits, for reasons such as being lost to follow-up (15%), or relocating to another area (8.4%), in addition to 3 infant deaths. Due to the data safety monitoring board authorising early closure of the study, a further 103 infants (8.3%) 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 infants who completed study follow-up, or were well on study exit due to early study closure. As per the South African guidelines, all mothers received ART during pregnancy. From 2013 to 2014, maternal ART was discontinued after the infants stopped breastfeeding (WHO option B). From 2015 onwards, mothers remained on ART for life (WHO option B+). All infants received NVP prophylaxis for the first 6 weeks of life.

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 birth weight of 2.0 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. As per the South African treatment guidelines, all mothers received ART during pregnancy. Between 2013 and 2014, ART was discontinued after infants stopped breastfeeding (WHO option B). From 2015 onwards, mothers remained on ART for life (WHO option B+). This change in maternal ART did not result in a change in study recruitment, as mothers were all started on ART during pregnancy

and remained on ART for the breastfeeding period at a minimum.

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 performed prior to the 6-week enrolment 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 months to 12 months. At each study visit, a nurse performed a clinical examination and took anthropometric measurements. Infants were assessed for weight and growth, and vaccines were administered as per the South African Department of Health schedule. Infants were evaluated for interval illnesses, signs and symptoms of study drug toxicity, mothers' antiretroviral (ARV) drug adherence, concomitant medications, breastfeeding status and HIV infection status. Most mothers' ARV regimens were managed by the antenatal and/or ART clinic and not the study clinic, making it challenging to monitor their programme adherence or non-compliance, therefore maternal ART adherence was self-reported. However, if mothers reported challenges, study staff would facilitate their care where possible and offer infant prophylaxis (as per Department of Health and WHO guidelines) if mothers had confirmed detectable viral load (VL).

Infant HIV testing

In 2013, HIV PCR testing was performed 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, or if clinically indicated. 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. Due to this change, the additional study PCR testing was only performed at 6 months and 12 months, or if clinically indicated.

Peer counselling

Peer counsellors provided breastfeeding, nutrition and ART adherence counselling 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.

All mothers provided written informed consent to participate.

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

Table 1 Biological demographics of the study cohort compared to infants who became infected with HIV.

	Baseline cohort (n=1219)	Baseline cohort excluding LTFU (n=944)	HIV seroconverters (n=8)	Birth transmissions (n=4)	Breastfeeding transmissions (n=4)
Infant sex					
Female (N (%))	566 (46)	441 (47)	5 (62.5)	2 (50)	3 (75)
Male (N (%))	653 (54)	503 (53)	3 (37.5)	2 (50)	1 (25)
Maternal age (median (IQR))	29.5 (25.9–33.7)	29.0 (26.0–34.0)	28.5 (25.8–33.6)	27.5 (25.0–30.0)	30 (26.8–33.3)
Maternal CD4 count (median (IQR))	450 (318.0–600.0)*	460 (324.0–601.5) †	228 (145.5–262.5)	195.5 (94.5–240.0)	233 (181.0–322.0)
Percentage of cohort with maternal CD4 <350 (N (%))	308 (32)*	203 (25)†	7 (88)	4 (100)	3 (75)
Vaginal delivery (N (%))	779 (64)‡	600 (63.5)	5 (62.5)	1 (25)	4 (100)
Caesarean delivery (N (%))	439 (36)	344 (36.5)	3 (37.5)	3 (75)	0 (0)
Infant birth weight kg (median (IQR))	3.1 (2.9–3.4)	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 count data were self-recalled from mothers (259 mothers either did not know or could not recall their most recent CD4 count at baseline).
 †CD4 count data were self-recalled from mothers (194 mothers either did not know or could not recall their most recent CD4 count at baseline).
 ‡Birth mode data missing for one infant.
 LTFU, Lost to follow up.

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).

While the main study cohort is not very different compared with the cohort with those lost to follow-up excluded, we compare the seroconverter group with the group that excludes those lost to follow-up. 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 for seroconverters was not different when compared with the main study cohort. Maternal age was 29.0 years (IQR: 26.0–34.0) 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 with 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 on maternal recall. Unsurprisingly, maternal CD4 was lower in the HIV seroconverter group compared with the main study cohort, respectively (228 cells/mm³ (IQR: 145.5–262.5) vs 460 cells/mm³ (IQR: 324.0–601.5)). Stratified by mode of transmission, maternal CD4 was 195.5 cells/mm³ (IQR: 94.5–240.0) in the birth transmission group versus 233 cells/mm³ (IQR: 181.0–322.0). If we compare mothers whose CD4 was <350 cells/mm³, 25% of the main cohort fell into this category, compared with 7/8 (88%) of the HIV transmission cohort (100% of birth and 75% of breastfeeding transmissions).

While HIV transmission in this cohort was low, it was similar to South African district health data, which also reported vertical birth transmission of under 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 KwaZulu-Natal).⁵ A meta-analysis of six studies in low-income settings in which mothers started ART before or during their most recent pregnancy, estimated a 6-month postnatal HIV transmission rate of 1.08%, with higher rates from mothers who commenced ART later in pregnancy.⁶ Similarly, the breastfeeding vertical transmission rate in this cohort was also low, but comparable to other studies. The *Promoting Maternal Infant Survival Everywhere* (PROMISE) Study in southern Africa reported a 0.7% breastfeeding transmission rate when mothers were on ART.⁷

POSSIBLE CONTRIBUTING FACTORS TO BIRTH TRANSMISSIONS

Each birth transmission had a possible causal factor. For infant 1, the mother had a partner from Central Africa from whom she contracted the virus. It is therefore possible that she was infected with HIV-2, rather than HIV-1, which does not respond as well to the ARV regimen she was taking, therefore resulting in a detectable viral load. The second infant tested positive with both cytomegalovirus (CMV) and HIV at 10 weeks of age. An active CMV infection could have resulted in the mother having an increased HIV viral load. Reactivation of latent viral infections such as CMV is thought to synergistically favour HIV shedding.⁸ Infant 3’s mother had initiated ARV treatment some time before pregnancy; despite this, her viral load was high throughout pregnancy. It is unknown if this mother’s viral load was high due to treatment fatigue and therefore non-adherence to her regimen, or due to not responding to her regimen. While adherence would have been probed by peer counsellors, the mother did not report non-adherence to her ART regimen. The mother of the fourth infant who was

a birth transmission had no CD4 or VL monitoring prior to birth. Thus, it would have been impossible to assess whether she was responding to treatment sufficiently.

POSSIBLE CONTRIBUTING FACTORS TO BREASTFEEDING TRANSMISSIONS

Similarly, each of the four infants whose HIV transmission could be attributed to breastfeeding transmissions, had circumstances that likely led to their transmissions. Infant 1 was born to a Zimbabwean mother who decided to return home for 3 months during the study, where she had no access to ARVs, per self-report. This likely led to the increased VL that resulted in the breastfeeding transmission. A second breastfeeding transmission was a Mozambican mother who also returned home for 3 months, where she was not adherent to an ARV regimen. Infant 3's mother missed several ARV clinic visits, and reported non-adherence to her ARV regimen. Infant 4's mother had a low CD4 count at birth (76 cells/mm³). Despite the birth VL being undetectable, the mother presented with a low, but detectable, VL at 6 months postpartum.

LESSONS LEARNT

While the low vertical transmission rates observed in this cohort show movement towards the elimination of vertical transmission, there is still much work to be done to improve these rates. We believe that several lessons can be learnt from vertical HIV transmission during this 5-year cohort study. *Strong and persistent peer counselling* (both ART adherence and breastfeeding counselling), together with widespread adoption of option B and option B+, likely contributed to the low mother to child HIV transmission 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. While viral load test results were not collected for this study, several studies have shown that viral load is linked to vertical transmission.⁹ Le Roux *et al*¹⁰ showed that infants born to mothers with lower CD4 counts (<350 cells/mm³) had higher morbidity than those born to mothers with higher CD4 counts.¹⁰ Hence *targeted ART adherence, health and nutrition counselling* could be directed towards these mothers. Mothers with a detectable viral load at birth could be provided with *additional ARV prophylaxis for the infant*, which could be extended until the mothers' VL is confirmed 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 with mothers receiving prophylaxis.⁷ Additionally, breastfeeding mothers need to have *regular VL testing, as recommended*, and need to be clearly counselled on these time points and the importance of adhering to them. 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, and are encouraged by the WHO.¹¹

RECOMMENDATIONS

Based on these lessons learnt, we recommend that the following be prioritised in countries where vertical transmission has not reached desired targets:

- ▶ Breastfeeding and ARV adherence counselling support for all mothers is critical during this vulnerable time for pregnant and breastfeeding mothers.
- ▶ Point-of-care viral load and CD4 testing for mothers in the last trimester, at birth and regularly while breastfeeding would facilitate real-time counselling and adjustment of mothers' and infants' prophylaxis regimens.
- ▶ Extend infant prophylaxis for mothers who are struggling to adhere to their ARV regimen or who are not responding appropriately, despite treatment adherence. Additionally, infant prophylaxis can be offered for those mothers who are changing to a second-line regimen, until their VL is undetectable.
- ▶ 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 (3–6 monthly) supplies should be considered for these mothers if they are stable on their current regimen.
- ▶ Regular refresher information sessions with health-care workers on the extended infant prophylaxis options when mothers are not responding or adherent to their ARV regimens could assist in protecting the vulnerable infants.

CONCLUSION

South Africa has made great strides in the prevention of vertical transmission. While the vertical transmission rate is under 1%, this does not yet translate to the <50 HIV transmissions per 100 000 live births. To reach this target, we will need to further improve routine testing for mothers and focus attention on those mothers with low CD4s and detectable viral loads. Additionally, improving counselling support during this vulnerable time will be critical to further reduce transmissions.

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