

Reducing Pediatric HIV Infection: Estimating Mother-to-Child Transmission Rates in a Program Setting in Zambia

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Background: Vertical transmission of HIV remains the main source of pediatric HIV infection in Africa with transmission rates as high as 25%–45% without intervention. Even though effective interventions to reduce vertical transmission of HIV are now available and remarkable progress has been made in scaling up prevention of mother-to-child transmission (PMTCT) services, the effectiveness of PMTCT interventions is unknown in Zambia. In this study, we estimate HIV vertical transmission rates at different age bands among perinatally exposed children.

Methods: The study analyzed program data of DNA polymerase chain reaction results and selected client information on dried blood spot samples from perinatally exposed children aged 0–12 months sent to the polymerase chain reaction laboratory from 5 provinces between September 2007 and January 2009.

Results: Samples of 8237 babies between 0 and 12 months were analyzed, with 84% of the mothers having ever breastfed their children. The observed transmission rate was 6.5% (5.1%, 7.8%) among infants aged 0–6 weeks when both mother and infant received interventions compared with 20.9% (12.3%, 29.5%) where no intervention was given to either mother or baby. Observed HIV transmission with single-dose nevirapine (sdNVP) was 8.5% (5.9%, 11.0%) among infants aged 0–6 weeks, whereas zidovudine with sdNVP (zidovudine + NVP) and highly active antiretroviral therapy were associated with observed transmission rates of 6.8% (4.5%, 9.1%) and 5.0% (3.0%, 7.0%), respectively; whereas these estimates were not significantly different from one another, they were all significantly lower than no intervention for which the estimated rate was 20.9%. Regardless of the intervention, the observed transmission rates were higher among infants aged 6–12 months.

Conclusions: PMTCT interventions, including sdNVP, are working in program settings. However, postnatal transmission especially after 6 months through suboptimal feeding practises remains an important challenge to further reduce pediatric HIV.

Key Words: effectiveness, PMTCT, PCR, transmission rates, vertical transmission, Zambia

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INTRODUCTION

More than 90% of the world's 2.3 million children living with HIV get infected through vertical transmission.^{1,2} The infection is acquired during pregnancy, delivery, and/or breastfeeding. Without intervention, 25%–45% of births from HIV-positive mothers in developing countries compared with 15%–25% in industrialized countries are infected.³ With about 500,000 babies born annually in Zambia, around 88,000 HIV-positive pregnant women give birth to an average 28,000 HIV-positive children every year if there are no interventions.⁴

The coverage of prevention of mother-to-child transmission (PMTCT) interventions has been steadily increasing over the last 3 years⁵; most available data focus on process—number of pregnant women tested, number of pregnant women tested HIV+, and number of HIV+ pregnant women provided with prophylactic antiretroviral (ARV) drugs. Little is known about the effectiveness of PMTCT in program settings in

developing countries. In addition, measuring effectiveness of PMTCT, especially in early infancy, is challenging in resource-constrained settings because of poor follow-up after PMTCT interventions and limited availability of DNA polymerase chain reaction (PCR) technology. The Roche Amplicor HIV 1 DNA version 1.5 test is a highly accurate test for infant diagnosis^{6–8}; a single HIV PCR test at 6 weeks was 100% sensitive in diagnosing perinatally acquired HIV in the infant diagnostic study compared with gold standard diagnostic protocols.⁹

In the last few years, HIV-exposed children are increasingly accessing early infant HIV diagnosis even in developing countries like Zambia; this represents an opportunity to assess vertical transmission rates after PMTCT interventions, one of the accepted approaches to evaluate effectiveness of PMTCT in real life.

In this study, we use observational data to estimate HIV vertical transmission rates among perinatally exposed children aged 0–6 weeks, 6 weeks to 6 months, and 6–12 months after PMTCT intervention. We estimate transmission rates in situations where both the mother and the baby received PMTCT intervention and when the mother, the baby, or neither received PMTCT intervention. We also estimate the transmission rates for various ARV chemoprophylactic regimens in use in Zambia. Furthermore, we also determined transmission rates in mothers using different infant feeding options.

METHODS

Context

Since 2005, the Zambia Prevention, Care and Treatment Partnership has been supporting scale-up of PMTCT services in 5 of the 9 provinces in Zambia at all levels of health care—rural health centres to tertiary hospitals. All 210 supported health facilities have access to CD4 testing for all pregnant women attending antenatal clinic (ANC) that test positive either on-site where there is a laboratory with such capacity or off-site through a sample referral system for the smaller health facilities with no such capacity. Based on the CD4 results, the health care workers are able to triage the HIV-positive pregnant women to receive antepartum ARV regimen as per national guidelines. The national guidelines stipulate that women with CD4 less than 350 cells per milliliter should receive highly active antiretroviral therapy (HAART), whereas those with CD4 more than 350 should receive zidovudine (AZT) from 28 weeks with intrapartum single-dose nevirapine (sdNVP) and lamivudine (3TC). Single dose is offered as the last choice option when women for one reason or the other are unable to get AZT short course prophylaxis.⁴ Before the change in guidelines sdNVP was the main choice and the standard of care for PMTCT. The program does not provide free formula feeds. As a continuum of the PMTCT program to support early infant diagnosis and strengthen pediatric HIV care, Zambia Prevention, Care and Treatment Partnership in close collaboration with the Ministry of Health and Provincial Health Office, established the DNA PCR laboratory capacity at the Arthur Davison Children Hospital, a tertiary facility located in the Copperbelt Province in August 2007. Dried Blood Spot (DBS) samples are collected at the facilities by trained staff and then transported

periodically to a central hub using a motorcycle provided at the district for specimen referral of various laboratory investigations. At the central hub, the DBS packages are examined before being sent to the PCR Laboratory using Expedited Mail Service with the Zambia Postal Services. Test results are sent back to health facilities using the same process. DBS testing for DNA PCR is currently recommended at 6 weeks after birth, however in a program setting, it is sometimes done after 6 weeks when mothers bring their children to the postnatal clinic. In addition, DNA PCR testing is fairly recent compared to the PMTCT program and perinatally exposed children only accessed the services when it became available and they were above 6 weeks of age.

Study Design

This observational study analyzed all DNA PCR results and client information on all DBS samples from perinatally exposed children 0–12 months of age sent to the Arthur Davison Children's Hospital PCR laboratory from Copperbelt, Central, Northern, North-Western and Luapula Provinces from September 2007 to January 2009.

DNA PCR Testing Methodology

Testing is performed on 5 mm disks of the DBS which are punched into sterile 2 mL cryovials and washed in specimen wash solution for 30 minutes twice to remove hemoglobin. Working extraction solution, a detergent solution containing proteinase K and HIV-1 internal control (IC) is then used to extract and lyse the DNA containing leucocytes from the disks. 50 μ L of the extracted DNA solution is added to an equal volume of working mastermix and then amplified for 35 cycles with a final hold stage at 72°C for 15 minutes at which the amplified products are denatured. Denatured amplicon is hybridized in separate HIV-1 and HIV-1 IC target specific probe coated microwell plates, washed in buffer, conjugated to Avidin-Horseradish Peroxidase, washed again and a substrate added to give a colored complex. Detection is completed by colorimetric reading of the colored complex at 450 nm. Any values $< 0.2 A_{450}$ are considered negative, $\geq 0.2 A_{450}$ and $< 0.8 A_{450}$ are considered indeterminate and $\geq 0.8 A_{450}$ are positive. Duplicate repeat testing is performed on indeterminate specimen and results interpreted using 0.2 A_{450} as the cutoff point.

Data Collection, Entry, and Analysis

Health care workers at maternal, neonatal and child health units in the health facilities routinely filled the PCR requisition form for all babies who were perinatally exposed to HIV. The health care workers at the ANC are normally the same ones who conduct the post natal clinic. Information from the antenatal card on HIV status and intervention is transferred to the under five card at the post natal clinic. Children who are perinatally exposed are therefore systematically identified. The client information collected included age of child, maternal age, breast feeding status, type of ARV regimen given to mother and/or baby, mode of delivery and whether the mother disclosed her HIV status to her spouse.

A Microsoft Access database in the PCR laboratory was used to store and process data from the PCR request form and

the results from the PCR laboratory. Internal consistency of the data was assessed and electronic data were verified against paper records and cleaned where appropriate. Repeat samples were excluded from the analysis.

The vertical transmission rates were estimated, along with 95% confidence intervals, separately for each age group and for specific subpopulations (e.g., among patients for whom both the mother and the infant received PMTCT). We applied multiple logistic regression models to assess the associations between vertical transmission rates and two PMTCT exposures, the first defined according to who received PMTCT intervention (mother, child, both, or neither) and the second defined according to which PMTCT intervention the mother received [HAART, AZT + nevirapine (NVP), NVP alone, or

none]; these models each controlled for province, infant breastfeeding status (never, stopped, or still breastfeeding), and delivery status (home, C-section in health facility, or health facility but no C-section). From these models, we estimated odds ratios along with 95% confidence intervals, separately for each age group. Missing data were ignored. Analyses were performed using SAS, version 9.2 (SAS Institute, Cary, NC).

Ethical Approval

Ethical Approval was granted by the University of Zambia Research and Ethics Committee and Protection of Human Subjects Committee of Family Health International, North Carolina, with final clearance from the Ministry of Health, Zambia.

TABLE 1. Mother and Child Characteristics

	Central	Copper-Belt	Luapula	North Western	Northern	All	
	n	n	n	n	n	n	%
Total	1700	4798	788	355	596	8237	100.0
PCR week age group							
0–6 wks	240	994	147	51	85	1517	18.4
6–12 mo	456	1049	203	83	175	1966	23.8
Client sex							
Female	862	2421	416	194	283	4176	50.6
Male	836	2369	372	160	312	4049	49.1
Missing	2	8	—	1	1	12	0.1
Mother disclosure status							
Did not disclose	102	210	65	18	53	448	5.4
Disclosed	1595	4582	719	335	543	7774	94.3
Missing	3	6	4	2	—	15	0.1
Child breastfeeding status							
Ever breastfed	1,588	3690	772	320	546	6916	83.9
Never breastfed	112	1097	16	33	49	1307	15.8
Missing	—	11	—	2	1	14	0.1
Infant feeding method							
Exclusive breastfeeding	1,029	2286	472	207	291	4285	52.0
Formula feeding	237	1,214	38	60	78	1627	19.7
Mixed feeding	412	1101	270	79	215	2077	25.2
None	1	2	—	—	—	3	—
Missing	21	195	8	9	12	245	2.9
Delivery location and mode							
Home	372	388	148	55	115	1078	13.0
Health facility, C-Section	48	316	18	11	11	404	4.9
Health facility, No C-Section	1278	4038	614	288	470	6733	81.7
Missing	2	11	8	1	—	22	0.2
Who received PMTCT?							
Both	1,052	3624	507	253	392	5828	70.7
Mother only	249	362	84	44	53	792	9.6
Infant only	43	151	18	2	15	229	2.7
Neither	331	548	143	45	128	1195	14.5
Missing	25	113	36	11	8	193	2.3
Mother's PMTCT regimen							
HAART	552	1493	172	96	152	2465	29.9
AZT + NVP	398	1177	144	81	197	1997	24.2
NVP	367	1375	292	127	102	2263	27.4
None	383	744	178	51	145	1501	18.2
Missing	—	9	2	—	—	11	0.1

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TABLE 2. Child Breastfeeding Status and Transmission Rates

Age Group	Child Breastfeeding Status	n (%)*	Number Detected	Transmission Rate (%)	95% CI
0–6 weeks	Still breastfeeding	1186 (78.5)	104	8.8	(7.2 to 10.4)
	Exclusive breastfeeding	1099	87	7.9	
	Mixed feeding	81	15	18.5	
	Stopped breastfeeding	47 (3.1)	9	19.1	(7.8 to 30.5)
	Exclusive breastfeeding	10	0	0	
	Formula feeding	27	6	22.2	
	Mixed feeding	8	2	25.0	
6 Weeks to 6 Months	Never breastfed	278 (18.4)	8	2.9	(0.9 to 4.9)
	Still breastfeeding	3575 (75.3)	541	15.1	(14.0 to 16.3)
	Exclusive breastfeeding	2886	389	13.5	
	Mixed feeding	668	150	22.5	
	Stopped breastfeeding	378 (8.0)	68	18.0	(14.1 to 21.9)
	Exclusive breastfeeding	17	2	11.8	
	Formula feeding	235	42	17.9	
6–12 Months	Mixed feeding	122	24	19.7	
	Never breastfed	794 (16.7)	49	6.2	(4.5 to 7.8)
	Still breastfeeding	913 (46.5)	276	30.2	(27.2 to 33.2)
	Exclusive breastfeeding	219	55	25.1	
	Mixed feeding	691	220	31.8	
	Stopped breastfeeding	816 (41.5)	171	21.0	(18.2 to 23.7)
	Exclusive breastfeeding	48	8	16.7	
Formula feeding	248	45	18.1		
Mixed feeding	506	116	22.9		
	Never breastfed	235 (12.0)	17	7.2	(3.9 to 10.6)

*Numbers in subcategories may not sum to the whole as child-feeding status was missing for some patients.

RESULTS

Characteristics of Study Population

In all, 8237 samples from babies aged between 0 and 12 months from 206 facilities in 39 districts in the 5 provinces were analyzed.

Forty-nine percent of the infants were males, 18% were aged 0–6 weeks, 58% were aged 6 weeks to 6 months, and 24% were aged 6 months to 12 months.

Ninety-four percent of the mothers disclosed their status to their spouses, whereas 83.9% ever breast fed during the postnatal period.

Overall, 52% of women were practising exclusive breastfeeding, whereas 25% practised mixed feeding at the time samples for PCR was taken. Twenty percent fed their babies with formula (Tables 1 and 2).

Of those who ever breastfed, 96.2% were still breastfeeding at age 0–6 weeks, and 52.8% were still breastfeeding after 6 months. This included exclusive breastfeeding and/or mixed feeding. Transmission rates were highest among the mixed feeding groups in all the age bands. Transmission rates among those who never breastfed regardless of intervention was 2.9% at 0–6 weeks (Table 2). Among 259 babies who were never breastfed and for whom both mother and baby received intervention, the transmission rate was estimated at 2.3% (data not shown).

Transmission Rates: Overall and by Type of Intervention

When both mother and infant received interventions (Fig. 1), the estimated transmission rate was 6.5% among

infants aged 0–6 weeks ($n = 1253$) and 15.1% among infants aged 6–12 months ($n = 1098$).

When neither the mother nor the infant received a PMTCT intervention, the estimated vertical transmission rate was 20.9% among infants aged 0–6 weeks ($n = 91$) and 39.3% among infants aged 6–12 months ($n = 514$). There was a 69% reduction in transmission rate if mother and infant received intervention compared with no intervention among infants aged 0–6 weeks.

When only the infant received an intervention and not the mother, the observed transmission rate was 21.2% among infants aged 0–6 weeks ($n = 33$) and 28.1% among infants aged 6–12 months ($n = 64$).

The odds ratio after adjusting for province, breastfeeding status, mode and location of delivery was 0.34, 0.38, and 1.22 at 0–6 weeks for PMTCT exposure to both mother and baby, mother only, and baby only, respectively (Table 3).

When the mothers received a PMTCT intervention but their infants did not, the observed transmission rate was 8.7% among infants aged 0–6 weeks ($n = 104$) and 27.2% among infants aged 6–12 months ($n = 232$).

General Transmission Rates By Type of Chemoprophylactic Regimen

Transmission varied depending on the type of ARV prophylaxis received by the mother.

The use of sdNVP was associated with an estimated transmission rate of 8.5% among infants aged 0–6 weeks ($n = 472$). More efficacious regimens such as (AZT + NVP) and

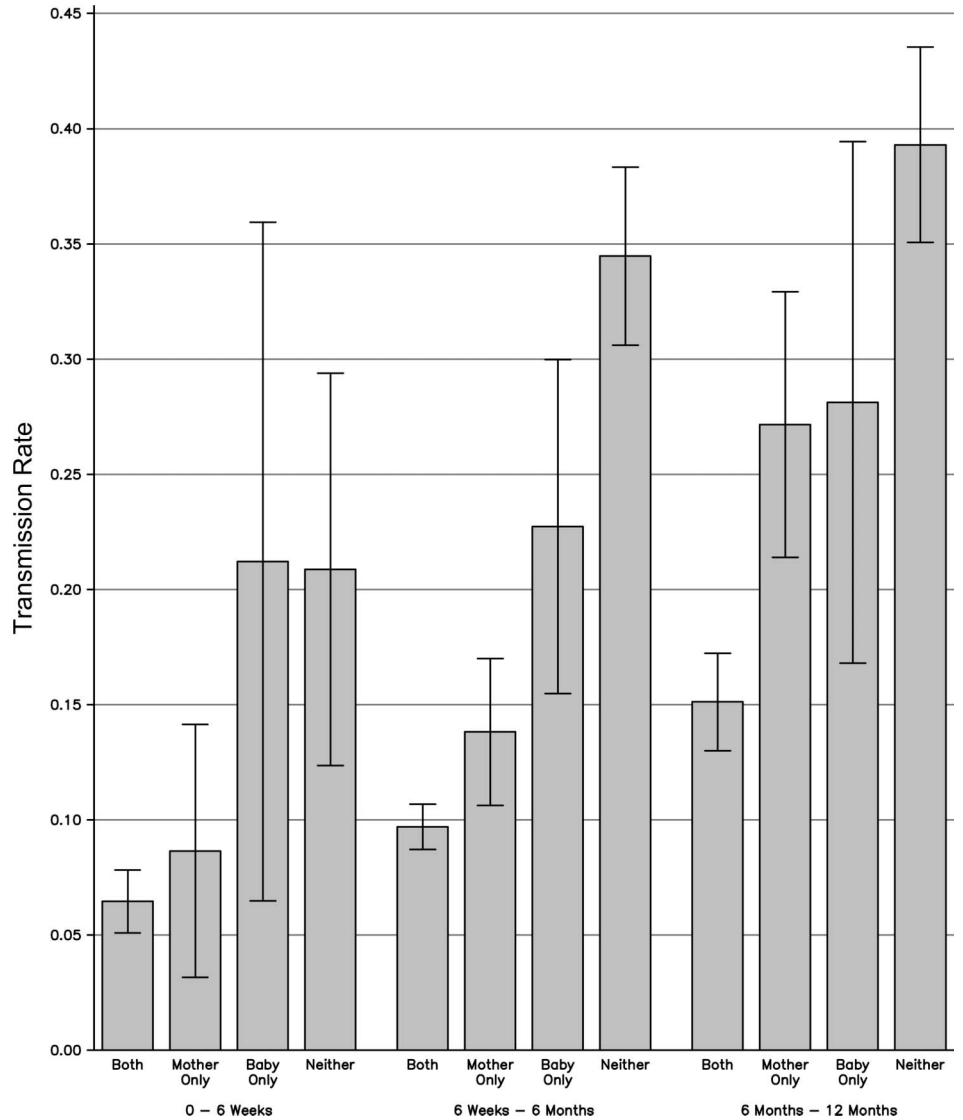


FIGURE 1. HIV vertical transmission rates following intervention, by age group and intervention status.

TABLE 3. Estimated Adjusted Odds Ratios* and 95% Confidence Intervals for PMTCT Exposures, by Age Group

PMTCT Exposure	Age Group		
	0–6 Weeks	6 Weeks to 6 Months	6–12 Months
Who received intervention?			
Both	0.34 (0.18 to 0.63)	0.22 (0.18 to 0.28)	0.30 (0.23 to 0.38)
Mother only	0.38 (0.16 to 0.90)	0.31 (0.23 to 0.43)	0.61 (0.43 to 0.86)
Baby only	1.21 (0.43 to 3.43)	0.59 (0.38 to 0.93)	0.67 (0.37 to 1.20)
Neither	1.0	1.0	1.0
Mother’s chemoprophylactic regimen			
Highly-active ARV therapy	0.26 (0.14 to 0.50)	0.13 (0.10 to 0.17)	0.33 (0.25 to 0.45)
AZT plus sdNVP	0.33 (0.18 to 0.60)	0.28 (0.22 to 0.36)	0.37 (0.26 to 0.52)
sdNVP	0.42 (0.24 to 0.75)	0.38 (0.30 to 0.48)	0.44 (0.33 to 0.59)
None	1.0	1.0	1.0

*Logistic regression models adjusted for province, infant breastfeeding status (never, stopped, or still breastfeeding) and delivery status (home, C-section in health facility, or health facility but no C-section).

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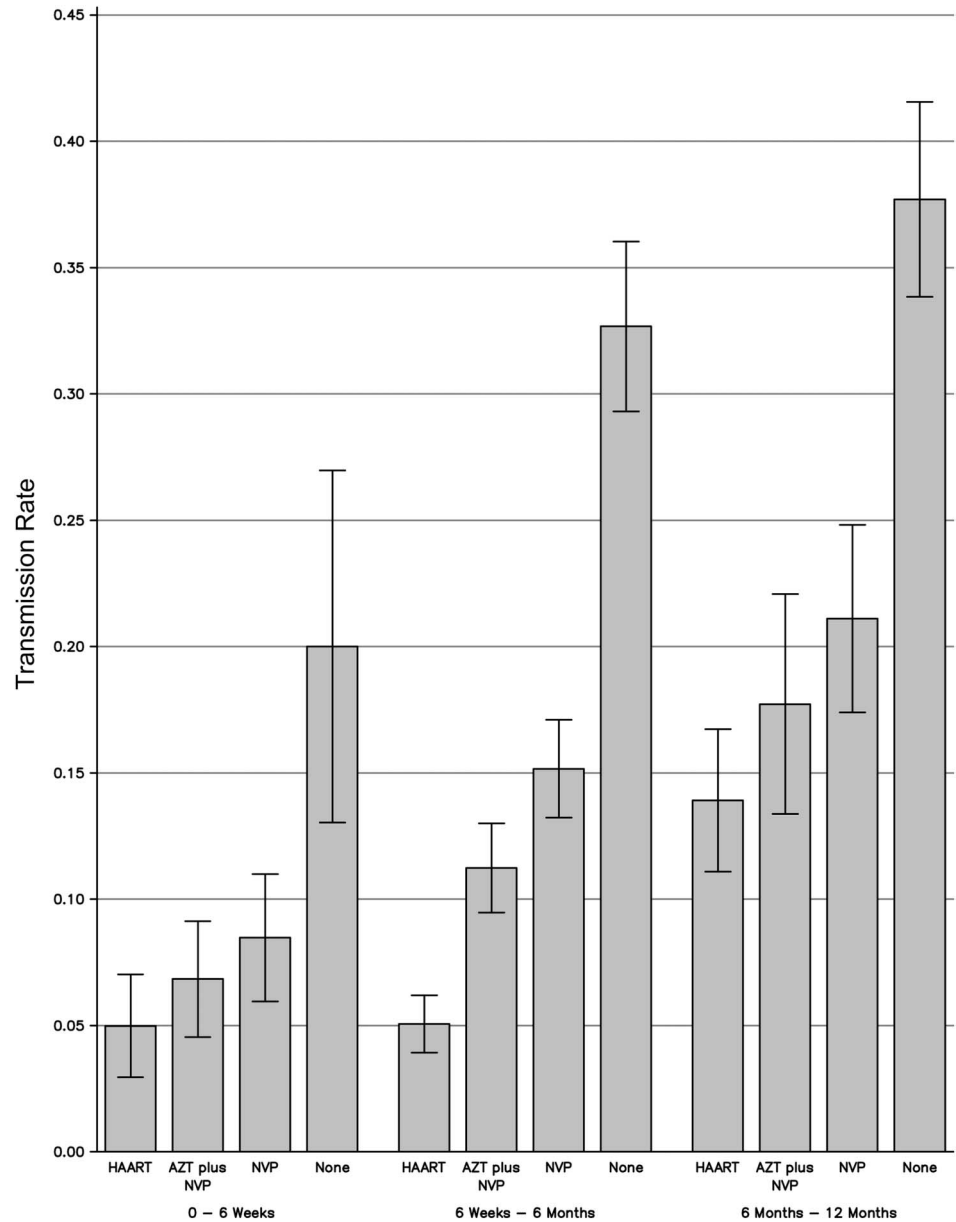


FIGURE 2. Vertical transmission rates by age group and mother's chemoprophylactic regimen.

HAART were associated with estimated transmission rates of 6.8% and 5.0%, respectively, among infants aged 0–6 weeks (AZT + NVP; $n = 468$, HAART; $n = 441$), although these results were not significantly different from NVP alone. The transmission rates regardless of the type intervention were higher among infants aged 6–12 months, ranging from 13.9% when the mother received HAART to 39.3% when the mother received no intervention.

When the logistic regression model is adjusted for province, infant feeding, mode of delivery and where delivery took place, reduction in transmission was highest in mothers who took HAART followed by AZT + sdNVP and sdNVP (Fig. 2; Table 3).

DISCUSSION

The results of this study indicate that PMTCT interventions are effective in real-life setting. The PMTCT program data compares favorably with other series reported in Africa. The estimated transmission rate for sdNVP among infants aged 0–6 weeks of 8.5% was lower than the rate in the NVP arm in the HIVNET 012 and SAINT trial which were 11.8% and 12.3%, respectively.^{10–12} The transmission rate attained with use of AZT-based regimen with sdNVP (6.8%) was similar to results of the DITRAME Plus study in Cote D'Ivoire (6.5%).¹³ Regardless of the duration, HAART during the antenatal period was associated with lowest transmission rate, although the comparison was only significant among infants aged 6 weeks to 6 months.

Creek et al¹⁴ in a similar study in a program setting in Botswana showed a transmission rate of 5% at less than 8 weeks in a predominantly (97%) nonbreastfeeding population. In another study in South Africa in almost exclusively formula feeding population (96%), the overall transmission rate at 4–6 weeks was 5.8%.¹⁵ This compares favorably with our rate of 6.5% where both mother and baby received intervention in a population where about 84% ever breastfed.

In our study, we observed vertical transmission of HIV was not significantly reduced compared with receiving no intervention if only the infant and not the mother received prophylaxis. ARV drugs, especially regimens that maximally suppress viral replication, are essential in reducing the transmission risk. An ARV drug is a cornerstone to prevent antepartum and intrapartum transmission of HIV. Infants born to mothers who took HAART and more efficacious regimen are more likely to have better outcomes. However, sdNVP, though a last tier option, significantly reduced vertical transmission compared with no intervention. Excellent postnatal management to prevent transmission will be a futile exercise if the infant is already infected at birth.

Stringer et al,¹⁶ in a study conducted in 10 public sector delivery centers in Lusaka, Zambia, assayed NVP levels in the cord blood after birth. Sixty-eight percent had NVP detected in the cord blood indicating a nonadherence rate of 32%. Clearly it is important that mothers accessing ANC services have access to ARV drugs to reduce vertical transmission. Even though drug availability does not necessarily mean ingestion, nondrug availability will certainly lead to noningestion. The World Health Organization's 3-tiered approach recommends the use of HAART when the mother has a CD4 less than 350 cell per cubic millimeter, and combination therapy AZT + 3TC and NVP when not eligible for treatment. SdNVP is offered in cases where the other more effective options are impractical or not feasible.¹⁷ Availability of ARVs or SdNVP at first contact creates a safety net for pregnant women who do not return to the clinic.

Though our study provides evidence of the effectiveness of PMTCT interventions, postnatal infections account for a significant number of new infections in children especially aged 6–12 months. Our data show that 52.8% of the mothers were still breastfeeding (includes mixed feeding) after 6–12 months, which has the potential to wipe out the benefits of PMTCT interventions. This is supported by results from the MASHI study in Botswana.¹⁸ Results of recent studies have shown that the use of extended ARV prophylaxis and HAART during the breastfeeding period has the potential of reducing postnatal transmission.^{19–21} Although a great deal of progress has been made in reducing vertical transmission, aggressive and sustained efforts are required to reduce the levels of postnatal infections arising of infant feeding practices. This includes promotion of exclusive breastfeeding and exclusive formula feeding which is acceptable, feasible, affordable, safe, and sustainable. In addition, the use of HAART or extended ARV prophylaxis should be recommended. However, further studies are required to understand infant feeding practices in Zambia to reduce postnatal infections.

Our study, though very informative, has some limitations. It did not include samples from HIV-exposed children

who died before 6 weeks and those who did not bring their children to health facility for their immunization.

Furthermore, given the repeated cross-sectional nature of our data, we are unable to distinguish any effects of age from cohort or history effects; for example, the effect of age is masked with any changes in PMTCT regimens that occurred over time. In addition, using observational data precludes making strong causal statements when comparing estimates of transmission rates.

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