ORIGINAL PAPER

A Descriptive Study of Outcomes of Interventions to Prevent Mother to Child Transmission of HIV in Lusaka, Zambia

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ABSTRACT

Objective: To determine the effectiveness of the Prevention of Mother-To-Child Treatment (PMTCT) interventions, in reducing mother-to-child transmission of Human Immune Deficiency Virus (HIV) infection in infants born to HIV infected women in two health centers Lusaka district (MTCT-Plus cohort) between 2002 and 2007.

Design: A **r**etrospective observational cohort study**.**

Main outcome measure: Transmission of HIV infection from mother to child, defined as proportion of infants born to HIV infected women that had taken prevention of mother-to-child interventions, who became HIV infected.

Results: A total of 534 infants had their final HIV status established, of which 101 (18.9%) were positive. A total of 372(67.7%) of 534 mother-infant pairs took single dose nevirapine, whilst 91 (17%) took triple therapy. The proportion of infants with a positive HIV test was much lower in infants where the maternal regimen was Highly Active Antiretroviral Therapy (HAART) at 6.6% (6/91), whilst that of infants where the maternal regimen was single dose nevirapine was 19.9% (74/372), (Chi-square test p-value 0.0005). Mixed feeding for six months was significantly associated with a positive infant HIV outcome (AOR 1.86[1.02-3.41], p-value 0.044).

Conclusion: This study indicates that the Prevention of Mother-to- Child Transmission of HIV treatment interventions in reducing transmission of HIV in infants and young children in two Lusaka urban clinics had been effective. Exclusive breastfeeding for 6 months, and use of triple therapy can reduce the transmission of HIV significantly.

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INTRODUCTION

Mother- to-child transmission of HIV remains a major problem worldwide. It is estimated that more than 90% of children living with HIV acquired the virus during pregnancy, birth or breastfeeding- forms of HIV transmission that can be prevented. In the absence of any interventions, the risk of transmission is 15-30% in non-breastfeeding populations. Breastfeeding by an infected mother increases the risk by 5-20% to a total of 20-40%.[1] The risk of MTCT can be reduced to less than 2% by evidence based interventions. [2]

Globally it is estimated that 3.4 million children under the age of 15 years were living with HIV in 2010. [3]

In 2009, it was estimated that 120,000 children aged 0-14 were living with HIV in Zambia.[4]

The HIV crisis has led to increased commitment and support for programs for the prevention of HIV infection in infants and young children. The program for Prevention of Mother to Child Transmission (PMTCT) has been implemented in Zambia for almost a decade; with an ultimate goal of preventing HIV infection in infants born to HIV infected mothers.

In 2002, the MTCT-plus Initiative, designed to promote wellness and to improve health care for infected mothers and their children was implemented in two clinics within Lusaka, namely Chelstone and Mtendere clinic. The entry point into the program was an HIV positive woman attending ante natal clinic.

Despite integration of the PMTCT activities in our ante-natal clinics, the outcome of these interventions at 18 months of age and beyond has not been widely described. The MTCT-Plus program did follow up children up to 18

months and beyond. Although data is available for long term follow up, this has not been analyzed. This study analyzed the data and the outcomes in the infants at 18 months.

The study determined whether the interventions have been of benefit to HIV exposed children, by reducing HIV vertical transmission from mother to child, at a local level. The proportion of infants born to HIV infected women who had either taken single dose nevirapine for PMTCT or combination therapy (for treatment), that became infected with HIV, and the proportion that did not become infected was determined.

METHODS

This was a Retrospective Observational cohort study, carried out in two primary health care centers under Lusaka District clinics, namely Chelstone and Mtendere clinics, which had implemented the MTCT-Plus initiative. The HIV pregnant women attending antenatal services at the two clinics and their children constitute the target population. All the mother-infant pairs in the target population that had accepted to be in the MTCT-Plus program were listed for enrollment.

This population was selected as they had access to a comprehensive package of PMTCT care which included provision of anti retroviral therapy. Chelstone and Mtendere clinic at the time of inception of the MTCT-Plus program were the only health centers offering anti retroviral therapy in addition to PMTCT in a primary care setting, coupled with active treatment follow up. All the mother-infant pairs in the target population that had accepted to be in the MTCT-Plus program were listed for enrollment.

The information relating to the research question was extracted from the review of the clinical and laboratory records of the mother-infant pairs. The MTCT-Plus program used standardized forms for each clinical visit. The data collected from the maternal forms included age, education attained, employment status, PMTCT regimen and duration, WHO staging and CD4 count at enrollment. The infant data collected included mode of delivery that is whether caesarian section or spontaneous vaginal delivery, breastfeeding data; whether breast fed, or mixed feeding and duration, sex and final HIV status.

Data collection was done in January and February, 2012 by the researcher with the assistance of two trained assistants.

ANALYSIS

The outcome, the transmission of HIV infection from mother to child, defined as proportion of infants born to HIV infected women that had taken prevention of mother-to-child interventions, who became HIV infected was measured.

The Pearson Chi-square test was used for categorical variables to examine differences in transmission rates by maternal regimen.

Bivariate and multivariate regression analysis was used to identify predictors independently associated with two outcomes: a) positive HIV transmission, and b) positive HIV transmission and death. Crude odds ratios and 95% confidence intervals (95% CIs) were computed using logistic regression models, and adjusted odds ratios and their 95% CIs were generated using generalized estimating equations to account for clustering due to mother infant pairs. The statistical analysis was performed using S.A.S version 9.1.3 (SAS Institute Incorporated Cary, North Carolina)

RESULTS

A total of 534 HIV exposed children aged 0 to 9 years at enrollment (November 2002-December 2007) who had a documented final HIV result, and their 465 infected mothers were included in the cohort analysis. The mother-infant pairs' clinical and laboratory data were reviewed in the study. Amongst the 465 mothers, there were 9 sets of twins born, 56 enrolled a second child whilst 4 enrolled a third child. This accounts for the difference between the total infants' number and the total mothers' number (465).

The median age of the mothers was 28 years (23.7-31.1). A total of 146 (33.0 percent) mothers had a CD4 count of less than 250 cells per micro liter at enrollment. The median CD4 was 334(IQR: 200-502). Most of the women 372 (80.5 percent) had a WHO staging of I. The median of total pregnancies was 3 (IQR 2-4). At least 217 (46.9 percent) of the mothers lived within 30 minutes of the clinic, and for 201 (43.4 percent), time taken being between 30minutes and an hour. A total of 69 (12.9 percent) women did not take any anti-retroviral regimen.

The description of the maternal characteristics is given in Table 1.

Table 1: Description of Cohort -maternal characteristics

MOTHERS (n=465)	N	Value
Age at enrollment (median, range)	446	27.6 (23.7 – 31.1)
Enrollment CD4 Count (median, IQR)	442	334 (200 – 502)
Enrollment CD4 Count < 250	442	146 (33.0%)
	431	11 (9.9 – 12.1)
Enrollment Hg < 10 g/Dl	431	111 (25.8%)
Enrollment WHO (n, %) I II III IV	462	 372 (80.5%) 54 (11.7%) 32 (6.9%) 4 (0.9%)
Distance from Clinic (n, %) <30 minutes Between 30 and 60 minutes Between 1 and 2 hours 2+ hours	463	 217 (46.9%) 201 (43.4%) 40 (8.6%) 5 (1.1%)
Ever Attended School (n, %)	456	427 (93.6%)
Years of schooling completed (median, IQR)	433	9.0 (7.0 – 10.0)
Employed at Enrollment (n, %)	462	81 (17.5%)
Has Electricity at Home (n, %)	463	223 (48.2%)
Has Piped Water at Home (n, %)	462	116 (25.1%)
Marital Status at Enrollment (n, %) Legally Married Living with a partner Non-married with no partner Widowed	455	 353 (77.6%) 7 (1.5%) 78 (17.1%) 17 (3.7%)
Gravidity (median, IQR)	461	3.0 (2.0 – 4.0)
Parity (median, IQR)	461	2.0 (1.0 – 3.0)
On ARVs at Enrollment (n, %)	464	14 (3.0%)

The transmission of HIV infection from mother to child was the outcome measure in the study. The final HIV status was determined at 18 months in the non breastfeeding or three months after cessation of breastfeeding. The feeding practices were self-reported as well as the infant HIV prophylaxis regimen. A total of 534 infants had their final HIV status established, of which 101 (18.9 percent) were positive. The median time to HIV diagnosis in weeks was 78(IQR: 47-89).

A total of 389 (72.9 percent) of the 534 infants were reported to have received single dose nevirapine as infant prophylaxis. There were 43 (8.0 percent) infant deaths reported during the period under review, of which 25 were HIV positive.

Table 2 gives the descriptive characteristics of the infants in the cohort.

Table 2: Description of cohort infant characteristics

INFANT INFORMATION (n=534)	N	Value
Infant Age in Weeks at Enrollment (median, range)	534	9 (5 – 21)
Infant Gender – Female (n, %)	534	271 (50.8%)
Ever Breastfed at 6 months (n, %))	363	312 (86.0%)
Ever Mixed Fed at 6 months (n, %)	308	113 (36.7%)
	519	388 (74.8%)
Ever Mixed Fed (all patients, regardless FU time)	530	206 (38.9%)
Maternal PMTCT Regimen (n, %) sdNVP HAART Other* None	534	 372 (69.7%) 91 (17.0%) 2 (0.4%) 69 (12.9%)
Infant Prophylaxis (n, %) sdNVP Other** None	534	 389 (72.9%) 2 (0.4%) 143 (26.8%)
HIV Positive (Final Result)	534	101 (18.9%)
Time to HIV Diagnosis, weeks (median, IQR)	530	78 (47 – 89)
Deaths	534	43 (8.0%)

The main exposure measured in the study was the ingestion of either single dose nevirapine for PMTCT or antiretroviral therapy for treatment where eligible for an HIV positive pregnant woman, and the ingestion of single dose nevirapine of the infant within 72 hours of delivery. However, some women had a short course of zidovudine given ante-partum beginning at 32 weeks (or at 28 weeks when regimen was later modified). Six of the infants had both single dose nevirapine and a short course of zidovudine.

The majority of the mothers (372, 67.7 percent) took single dose nevirapine for PMTCT whilst 91 (17.0 percent) were on Highly Active Antiretroviral Therapy (HAART) as they were eligible. The Pearson Chi-square test was used to examine differences in transmission rates by maternal PMTCT regimen. The proportion of infants with a positive final HIV test whose mothers took single dose nevirapine was 19.9 percent (74/372), whilst 6 out of 91(6.6 percent) infants whose mothers took HAART had a positive HIV result.

Table 3 shows the proportion of infants with a positive final HIV test in relation to the maternal regimen.

Table 3: Transmission Rates by Maternal Regimen (n=532)

Maternal PMTCT Regimen	Percent of Mothers on Regimen	Positive HIV Test Result (Final)
None	69 (12.9%)	21/69 (30.4%)
SdNVP	372 (67.7%)	74 / 372 (19.9%)
HAART	91 (17.0%)	6/91 (6.6%)

Chi-Square test p-value: 0.0005 note: 2 mothers who were on AZT based regimens are not included

A CD4 count of less than 250 cells per micro liter was significantly associated with a positive infant HIV outcome (adjusted odds ratio [AOR], 1.88 (1.07-3.31), p-value 0.029). A maternal PMTCT regimen of HAART was significantly associated with a significant reduction in a positive infant HIV outcome (AOR 0.16[0.05-0.53], p-value 0.003). Where a single dose nevirapine was taken as the maternal PMTCT regimen, a positive HIV outcome in the infant was less likely (AOR 0.77 [0.39-1.55], p-value 0.471), though this difference was not significant. The transmission rate where the mother did not take any anti retro-viral drug was 30.4 percent (21/69).

A positive infant outcome was less likely where there was some maternal education (AOR 0.42[0.17-1.004], p-value 0.062), in the married/with partner mothers (AOR 0.72[0.40-1.28], p-value 0.262) though not significant.

A total of 378 (74.8 percent) infants were reported to have ever breastfed, of whom 206 (38.9 percent) were mixed fed. Ever mixed feeding at six months was significantly associated with a positive infant HIV outcome (AOR 1.86[1.02-3.41], p-value 0.044). Single dose nevirapine in the infant was associated with a reduced risk of positive HIV outcome (AOR 0.89[0.50-1.60], p-value 0.698), but not significant.

The results of multivariate analysis predicting a positive HIV outcome are shown in table 4.

Multivariate analysis predicting positive HIV infant or death was also done. The results were comparable to those predicting positive HIV infant only, with maternal HAART regimen (AOR 0.19[0.06-0.57] P=0.004) and CD4<250 (1.88[1.07-3.31] P=0.029) being significantly associated with the outcome. Maternal education in the mother though not significant, showed a less likely hood of a positive HIV outcome or death (AOR 0.47[0.21-1.06] P=0.069.

However, mixed feeding though being a risk was not significantly associated with the outcome of HIV positive or death (1.53[0.88-2.65] P=0.132) as was observed in the outcome of HIV only.

	Crude OR (95% CI)	AOR^ (95% CI)	p-value (adjusted)
Age			
≥27 years old	1.27 (0.82 – 1.96)	1.25 (0.76 – 2.07)	0.383
< 27 years old	1.00	1.00	--
Education			
Ever Attended School	0.52 (0.24 – 1.12)	0.42 (0.17 – 1.04)	0.062
Never Attended School	1.00	1.00	--
Marital Status			
Married/Partner	0.76 (0.45 – 1.27)	0.72 (0.40 – 1.28)	0.262
Single/Widowed	1.00	1.00	--
Enrollment CD4			
< 250	1.21 (0.76 – 1.93)	1.88 (1.07 – 3.31)	0.029
≥ 250	1.00	1.00	--
Enrollment WHO Stage			
Stages III or IV	1.15 (0.53 – 2.49)	1.08 (0.40 – 2.90)	0.885
Stage I or II	1.00	1.00	--
Maternal PMTCT Regimen			
HAART	0.16 (0.06 – 0.43)	0.16 (0.05 – 0.53)	0.003
sdNVP	0.57 (0.32 – 1.00)	0.77 (0.39 – 1.55)	0.471
None	1.00	1.00	--
Infant Ever Breast Fed (6 mo)			
Yes	0.71 (0.43 – 1.17)	0.54 (0.26 – 1.11)	0.095
No	1.00	1.00	--
Infant Ever Mixed Fed (6 mo)			
Yes	1.12 (0.72 – 1.74)	1.86 (1.02 – 3.41)	0.044
No	1.00	1.00	--
Infant Regimen			
sdNVP	0.71 (0.44 – 1.13)	0.89 (0.50 – 1.60)	0.698
None	1.00	1.00	--

*Number of observations included in the model is 467, due to list wise deletion of missing values

^AOR = Adjusted Odds Ratio adjusting for all variables and for clustering due to mother-infant pairs, 95%CI = 95% Confidence Interval

Discussion

This study in two Lusaka urban clinics, has shown that Prevention of Mother-to-Child Transmission (PMTCT) of HIV treatment interventions have been effective in reducing transmission of HIV to infants and young children.

The use of triple therapy –Highly Active Anti-retro viral Therapy (HAART) was the most effective in reducing transmission of HIV to the infant, with a transmission rate of 6.6 percent (6/91), P=0.0005, a reduction of 83 percent from the expected 39.5 percent in the absence of any interventions. Single dose nevirapine was also effective by reducing the transmission by 49 percent, (19.9 percent [74/372], P=0.0005). These findings are in line with other studies like the HIVNET 012 [5] In mothers that did not take

any anti retro-viral, the transmission rate was 30.4 percent, a result that has been observed by studies done by De Cock.[1]

In the study, 69 (12.9 percent) mothers were reported as not having taken any anti-retroviral drug for PMTCT. A further analysis of this number of mothers showed that 41 denied having received any PMTCT regimen. This raises concern on non adherence to prescribed counseling and self administration of PMTCT drugs. A study by Stringer J et al in 2005[6], to determine the population effectiveness of a city wide perinatal HIV prevention program showed a 32 percent maternal non-adherence to ingestion of prescribed nevirapine. This study could have shown a lower non adherence as the information was based on self reporting whereas the study by Stringer was based on an anonymous surveillance of new born cord blood for HIV serology and nevirapine. However, it gives an indication of maternal non-adherence being a factor to effectiveness of the program. Temmerman M et al[7] in an observational study in Kenya 2003 also recommended further qualitative research on the determinants of MCH services coverage and compliance, and the need for improvement in mother-child follow up in order to improve effectiveness of single dose nevirapine.

Predictors associated with a positive HIV outcome were a CD4 count of less than 250 cells per micro-liter and mixed feeding in the infant. This is consistent with other studies. A study in France showed a gradual increase in risk of transmission from 15 percent of counts greater than 600 CD4 cells, to 43 percent at counts less than 200 CD4 cells[8]. Shapiro, Smeaton and Lockman et al[9] in a study in Botswana found CD4 to be an independent predictor of HIV transmission among others. The HIV RNA viral load is significantly associated with increased risk of transmission as seen in most studies; however this study did not have data on this as HIV RNA was not being done until a later stage of the MTCT-Plus program.

Breast feeding significantly increases the risk of MTCT of HIV substantially[10]. Mother-to-child transmission of HIV remains a challenge in resource poor settings. In developing countries, nearly all infants are initially breastfed, and most continue to breast feed until at least six months of age but frequently into the second year of life [11]. In settings where avoidance of breast feeding is feasible, affordable, and culturally accepted, as in the United States of America, complete avoidance of breast feeding has been advised since the 1980s.[12]

An observational study in India in 2003 by Phadke M A et al [13]showed an increased risk of hospitalization for replacement fed (animal milk diluted with water) infants born to HIV infected mothers who had received pre-natal ZDV for PMTCT compared to breast fed infants.

In another study by Fawzy A et al 2011[14], it was found that continued breast feeding is associated with a reduced risk of diarrhea related morbidity and mortality among uninfected children born to HIV infected mothers, compared to those with early weaning.

Maternal education though not significant was associated with reduced HIV transmission

Exclusive breast feeding up to six months should continue to be encouraged in all HIV infected women The MTCT-Plus model of family centered care where the mother infant-pairs are reviewed in the same clinic should be encouraged as it makes it easier to follow up the infant right up to the time the final HIV status is determined. Single dose nevirapine, though it reduces the risk of transmission as shown by this study is no longer considered as a PMTCT regimen

In conclusion, this study has shown that the Prevention of Mother-to- Child Transmission of HIV treatment interventions in reducing transmission of HIV in infants and young children in two Lusaka urban clinics had been effective. The use of HAART had the lowest reduction in transmission in a breastfeeding population. Exclusive breast feeding up to six months should continue to be encouraged in all HIV infected women. There is need for studies locally to determine the duration of triple therapy as PMTCT in women that are not eligible for treatment.

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