

Risk Factors for Mother to Child Transmission of HIV in Southwest Ethiopia

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ABSTRACT

Objective: One in four Ethiopian children born to human immunodeficiency virus (HIV) positive mothers were found to have acquired the virus, although the country has been implementing the World Health Organization's (WHO) four-pronged prevention approaches. This study was therefore aimed at identifying the factors responsible for mother to child transmission of HIV among children who received HIV exposure care.

Methods: An unmatched case-control study was conducted on randomly selected 64 cases and 256 controls from December 2011 to May 2012. The cases were HIV positive children less than 18 months of age, and the controls were HIV negative children less than 18 months of age born to HIV positive mothers. Data on the parents' sociodemographic characteristics and parents' clinical profiles before the final child's HIV status determination were collected. A logistic regression was used to identify predictors.

Results: The records of 60 cases and 235 controls were included for analysis. Mixed breastfeeding (adjusted odd ratio [AOR]: 22.03; 95% confidence interval [CI]: 5.31–91.49), maternal CD4 count <200 cells/mm³ before delivery (AOR: 17.14, 95% CI: 4.73–62.06), no maternal WHO clinical staging after delivery (AOR: 3.38; 95% CI: 5–35.76), children born to mothers from rural areas (AOR: 7.64; 95% CI: 2–29.22), and no paternal antiretroviral therapy (ART) enrollment or an unknown enrollment status (AOR: 11.11; 95% CI: 2.94–50) were factors independently associated with the child's HIV infection.

Conclusions: Mixed breastfeeding, maternal CD4 count, no maternal WHO clinical staging, children to mother from rural areas, and no paternal ART enrollment or an unknown status were independent predictors. Behavioral change communication should be intensified, and emphasis should be given for mothers with lower CD4 count and those from rural settings.

Keywords: Risk Factors, infectious disease transmission: vertical, HIV, Ethiopia

INTRODUCTION

In resource-limited settings, a marked decrease of mother-to-child transmission (MTCT) of HIV was documented, from over 570,000 in 2003 to an estimated 220,000 children in 2014. More than 90% of this infection among infants was from sub-Saharan African countries (1-3).

Several studies confirmed that almost all new child HIV cases resulted from perinatal transmission of HIV during pregnancy, childbirth, and breastfeeding. In the absence of preventive interventions, about one-half of HIV-exposed children will acquire the virus from their mothers. About one-fourth of exposed children will acquire the virus during childbirth, while one-fifth of the exposed children will acquire it during pregnancy and breastfeeding depending on presence/absence of other parental and child-related risk factors (4-6).

The rupture of the membrane for more than 4 hours, micro-transfusions across the placenta during labor contractions, genital tract infections, placental infection, and high maternal viral load/low CD4 cell count/advanced clinical stage, and mixed/prolonged breastfeeding were known to increase MTCT of the virus. However, the most important risk factors for MTCT of the virus are maternal plas-

ma and breast milk viral load followed by maternal immunologic status and clinical stage as suggested by several studies among both breastfed and non-breastfed children. Even among mothers on antiretroviral (ARV) agents and who do not breastfeed their infants, the maternal viral load is directly correlated to the MTCT of HIV. In addition, anemia, maternal mastitis, gastrointestinal tract lesion of infants, paternal enrollment to antiretroviral therapy (ART) care, and acute maternal sero-conversion during pregnancy or during breastfeeding were associated with MTCT of HIV (7-12).

To eliminate child HIV infection globally, The World Health Organization (WHO) recommended four-pronged MTCT of HIV preventive strategies to all its member states. The strategies include primary prevention of HIV infection among women of child-bearing age, prevention of unintended pregnancy among HIV positive women, prevention of MTCT of HIV from HIV positive mothers, and continued care/support for infected mothers/infants/partner. It was shown that appropriate ARV drugs prophylaxis or Highly Active Antiretroviral Therapy (HAART) to the mothers/infant, avoidance of breast milk, and elective cesarean section can reduce the risk of MTCT of the virus to less than 5% among breast fed, HIV exposed children, while to less than 2% among non-breastfed, HIV exposed children (8-12).

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Although all WHO member states, including Ethiopia, have been implementing the approach, pediatric HIV continued to be an important cause of child morbidity and mortality in the sub-Saharan African countries (12). In Ethiopia, the trends of HIV infection among pregnant women is declining, but their enrollment to ART care for MTCT of HIV remained very low compared to other sub-Saharan African countries (13).

For example, in 2012/13, there were 2.9 million expected pregnancies and 80% of them utilized antenatal care (ANC) in Ethiopia; 17,742 were found to be HIV positive, but <70% of these mothers and their infants received an ARV drug for the prevention of MTCT of HIV. It is evident that the prevalence of HIV among ANC attendants aged 15–24 years decreased from 3.5% in 2007 to 2.1% in 2012, and the rate of MTCT was reduced from 35% in 2007 to 25% in 2013 after the breastfeeding period. However, it is still far beyond the global expected prevalence in breastfed children and very slow decline rate for elimination of vertical transmission 2020 (12, 13).

As per the WHO recommendation of infant feeding in the context of HIV, Ethiopia adopted and promotes exclusive breastfeeding for the first 6 months of birth and complementary feeding plus breastfeeding until the child is two years of age (13). However, a study conducted in Zimbabwe indicated that breastfeeding for more than 6 months was responsible for over two-third of HIV infection among infants who were tested using DNA polymerase chain reaction (DNA PCR) negative at 6 weeks of birth, with a higher risk of HIV infection rate among mixed breastfed infants compared with exclusively breastfed infants (14). In another comparative cross-sectional study conducted in Addis Ababa, only 15% of HIV-exposed children were mixed breastfeeding. The study further revealed that mixed breastfeeding and maternal breast problem were associated with infant HIV infection (15, 16).

In conclusion, mixed breastfeeding practice among HIV positive mothers was low (15%), approaching WHO recommended level (5%). Similarly, enrollment of mothers/their infants to ART care of pregnant mother and their infants are encouraging. However, little is known about why the rate of child's HIV infection in Ethiopia is not declining as theoretically expected. We hypothesized that the parental clinical profile before childbirth, during breastfeeding periods, and breastfeeding by itself with incomplete maternal/child's HAART coverage throughout the breastfeeding period play a crucial role for MTCT of the virus.

The identification of those local factors is important to devise policy recommendations of HAART utilization to prevent MTCT of HIV in the context of the universal breastfeeding community. In addition, the identification of those factors will help healthcare providers to grade the risk of HIV infection for a given child and accordingly plan the management in more efficient ways. This study was therefore aimed at identifying parental and child-related risk factors for MTCT of HIV in the area.

METHODS

Study Area and Study Period

The study was conducted in two hospitals located 345–660 km away from Addis Ababa, Ethiopia. Both hospitals serve as teach-

ing and referral hospitals for an estimated 15 million population in the area. The hospitals in collaboration with International Centers for AIDS treatment and care Program, Ethiopia, provide HIV preventive and ART services since 2004. Between January 2004 and February 2012, a total of 683 children were born to HIV-positive mothers at both hospitals, and 86 of them were confirmed to be infected with HIV. The study was conducted between December 30, 2011, and May 05, 2012, on the original data generated for HIV exposed infants/children and their corresponding parents' care between January 2004 and February 2012.

Study Design, Study Population, and Sampling Design

A hospital-based unmatched case-control study was carried out on children aged 6 weeks–18 months. The cases were HIV positive children less than 18 months of age born to HIV-positive mothers, and the controls were HIV negative children less than 18 months of age born to HIV positive mothers. Children's and their parents' medical records and the HIV follow-up database was used as a data source. The clear HIV infection status of children and their mothers on either medical records or the databases were required for data extraction. However, the records or database that lacked information on maternal ARV prophylaxis status, child ARV prophylaxis, breastfeeding pattern, or at least one maternal CD4 count/WHO clinical staging before child HIV status determination were excluded. In cases where repeated measurements of predictor variables such as CD4 count, WHO clinical staging, were encountered, values measured nearest to the time at which infant was tested for HIV, was considered. Epi-info version 3.5.1 was used to determine the appropriate sample size using the following parameters: proportion of maternal breast problem among controls, 6.4%; proportion of maternal breast problem among cases, 21.1% (17); 5% significance level; power of 80%; control-to-case ratio of 4:1; and incomplete records/database of 15%, leading to 64 cases and 256 controls. A simple random sampling technique was applied to both cases and controls using a computer-generated a random number from sampling the frame created by child's treatment card number and the corresponding mother's records were obtained.

Data Collection Procedure and Data Analysis

Four trained nurses were recruited and trained to collect the data using a pretested questionnaire. The questionnaire was adapted from the Ethiopian HIV-exposed infant follow-up guideline, which consists of sociodemographic characteristics of the mother and child (age of the mother, sex of the child, address, and birth year), clinical profiles of the mother (HIV status known time, CD4, survival status, prevention of mother to child transmission (PMTCT) prophylaxis, WHO clinical stage, and breast lesion), clinical profile of the child (age of the child at enrollment, age of the child at status determination, birth place, birth weight, infant ARV prophylaxis, breastfeeding pattern, and breastfeeding duration), and paternal clinical profile (HIV status and ART enrollment status).

To maintain the quality of data, one health officer was recruited to supervise the data collection activities with the principal investigator. In addition, the questionnaire was pretested to estimate the time and simplicity of data transfer from data sources.

Table 1. Child's clinical profiles before HIV infection status determination associated with child HIV infection, in Southwest Ethiopia, January 2004–February 2012

Variables	Cases, N=60(%)	Controls, N=235(%)	COR(95%CI)
Child's HIV status confirmed the age			
6weeks–6 months	19(31.70)	146(62.10)	1
7–12 months	17(28.30)	50(21.30)	2.61(1.26,5.42)*
13–18 months	24(40)	39(16.50)	4.73(2.35,9.50)*
Birthplace			
Health facility	33(55)	193(82.10)	1
Home	27(45)	42(17.90)	3.76(2.05,6.91)*
Child's sex			
Male	15(25)	68(28.90)	0.82(0.43,1.57)
Female	45(75)	167(71.10)	1
Birth weight			
≤2500g	28(46.70)	105(44.70)	1
<2500 g	9(15)	37(15.70)	0.91(0.39,2.11)
Unknown	23(38.30)	93(39.60)	0.93(0.50,1.72)
Infant ARV			
Yes	40(66.70)	178(75.70)	1
No	20(33.30)	57(24.30)	1.56(0.85,2.89)
Breast Feeding pattern			
Exclusive	19(31.70)	157(66.80)	1
Mixed	23(38.30)	12(5.10)	15.84(6.80,36.87)*
Exclusive replacement fed	18(30)	66(28.10)	2.25(1.11,4.57)*
Breast Feeding duration when child's HIV status Confirmed			
≤6 months	43(71.70)	188(80)	1
>6 months	17(28.30)	47(20)	1.58(0.83,3.02)

*: $p < 0.25$; COR: crude odds ratio; CI: confidence interval; ARV: antiretroviral; HIV: human immunodeficiency virus

A 1-day training was given for data collectors and supervisors on the data collection procedure before data collection. Collected data were analyzed using the Statistical Package for Social Sciences for window version 16. Simple frequencies were used to see the overall distribution of the study subjects with regard to the variables under study. All variables with a P value less than 0.25 in a bi-variable analysis were entered into multiple logistic regression models using the backward likelihood ratio variable selection method. In addition, predictor variables that had shown a significant association with child HIV infection in the final model were evaluated for multi-collinearity using a variance inflation factor and standard error of the parameter estimate. In addition, each predictor variables in the final model were also evaluated for interaction.

An approval from the ethical committee was obtained from the institutional review board of Jimma University on October 6, 2011, through an approval letter number CPHMS/078/2011, and a letter of permission was also secured from the concerned hospital officials to access the patients' records. Confidentiality was assured through securing private rooms for data collectors

while extracting the data from the records, filled in the questionnaire were obtained on daily bases and kept in secure places. We did not obtain verbal or informed consent from study participant as we used secondary data (records) sources and patient records/information was anonymized and re-identified prior to analysis.

RESULTS

Socio-Demographic Characteristics and Children Clinical Profiles

After a stratified random selection of 64 cases and 256 controls, 4 case records and 21 control records were excluded from the analysis due to missing values. The male to female ratio was 1.2:1 in the reviewed records of children. HIV-infected children were enrolled on an average at 6.15 (± 3.40) months, while HIV-uninfected children were enrolled in ART care on an average at 3.51 (± 2.08) months of age. In total, 82% of HIV-uninfected children were born in a health facility compared to only 55% of HIV-infected children. Seventeen percent of mothers of HIV-infected children died compared to 10% of the uninfected cases. Forty

Table 2. Parents' clinical profiles before child HIV infection status determination, in Southwest Ethiopia, January 2004–February 2012

Variables	Cases, N=60(%)	Controls, N=235(%)	COR(95%CI)
Maternal address			
Urban	36(60)	146(62.10)	1
Rural	24(40)	89(37.90)	1.09(0.61,1.95)
Maternal HIV status confirmation time			
Before delivery	32(53.30)	146(62.10)	1
After delivery	28(46.70)	89(37.90)	1.44(0.81,2.54) [^]
Maternal CD4 before delivery			
<200 cells/mm ³	32(53.30)	22(9.40)	8.04(3.93,16.42) [^]
200–350 cells/mm ³	7(11.70)	97(41.30)	0.40(0.16,0.98) [^]
>350 cells/mm ³ or unknown	21(35)	116(49.40)	1
Maternal CD4 after delivery			
<200 cells/mm ³	10(16.70)	54(23)	0.65(0.29,1.44)
200–350 cell/mm ³	22(36.70)	83(35.30)	0.93(0.49,1.74)
>350 cells/mm ³ or unknown	28(46.60)	98(41.70)	1
Maternal survival status			
Died	10(16.70)	24(10.20)	1.76(0.79,3.91) [^]
Alive	50(83.30)	211(89.80)	1
Maternal PMTCT prophylaxis			
None or sdNVP	34(56.70)	138(58.70)	1
HAART or sdNVP+AZT+3TC	26(43.30)	97(41.30)	1.09(0.61,1.93)
Maternal WHO clinical stage before delivery			
I–IV	38(63.30)	149(63.40)	1
Not staged	22(36.70)	86(36.60)	1.00(0.56,1.81)
Maternal WHO clinical stage after delivery			
I–IV	15(25)	189(80.40)	1
Not staged	45(75)	46(19.60)	12.33(6.32,24.02) [^]
Maternal breast lesion			
Yes	17(28.30)	9(3.80)	9.93(4.15,23.73) [^]
No	43(71.70)	226(96.20)	1
Paternal HIV status			
Positive	15(25)	54(23)	1.15(0.57,2.31)
Negative	15(25)	57(24.20)	1.09(0.54,2.18)
Unknown	30(50)	124(52.80)	1
Paternal ART enrollment status			
Enrolled	14(23.30)	129(54.90)	0.25(0.13,0.48) [^]
Not enrolled or Unknown	46(76.70)	106(41.1)	1

[^]: p<0.25; COR: crude odds ratio; CI: confidence interval, HIV: human immunodeficiency virus; ART: antiretroviral therapy; HAART: highly active antiretroviral therapy; PMTCT: prevention of mother to child transmission; sdNVP: single dose nevirapine; AZT: Zidovudine; 3TC: lamivudine

percent of mothers of the HIV-infected children were from rural settings compared to only 38% for uninfected children (Table 1).

and unknown paternal ART enrollment status were more likely to transmit the virus to their children (Table 2).

Parental Factors Associated with MTCT of HIV

In a bi-variable analysis, cases of maternal CD4 count <200 cells/mm³ before delivery, no maternal clinical staging after delivery,

Factors Independently Associated with children HIV Infection

After controlling for the effects of other variables entered in to the multiple logistic regression, mixed breastfeeding, maternal

Table 3. Factors independently associated with child HIV infection, in Southwest Ethiopia, January 2004–February 2012

Variables	Cases, N=60(%)	Controls, N=235(%)	COR (95%CI)	AOR (95%CI)
Breastfeeding pattern				
Exclusive breastfed	19(31.7)	157(66.8)		1
Mixed breast fed	23(38.3)	12(5.1)	15.8(6.8,36.8)**	22.0(5.3,91.5)***
Exclusive replacement fed	18(30)	66(28.1)	2.3(1.1,4.6)*	0.5(0.1,3.0)
Maternal WHO clinical stage after delivery				
I–IV	15(25)	189(80.4)		1
Not staged at all	45(75)	46(19.6)	12.3(6.3,24.02)**	13.4(5,35.8)***
Maternal CD4 before delivery				
<200 cells/mm ³	32(53.3)	22(9.4)	0.7(0.3,1.4)^	17.1(4.7,62.1)***
200–350 cells/mm ³	7(11.7)	97(41.3)	0.9(0.5,1.7)^	1.0(0.3,3.7)
>350 cells/mm ³ or unknown	21(35)	116(49.4)	1	1
Maternal address				
Rural	24(40)	89(37.9)	1.1(0.6,1.95)^	7.6(2, 29.2)**
Urban	36(60)	146(62.1)	1	
Infant ARV				
Yes	40(66.7)	178(75.7)	1	1
No	20(33.3)	57(24.3)	1.6(0.9,2.9)^	4.7(0.9, 24.2)
Paternal ART enrollment status				
Enrolled	14(23.3)	129(54.9)	1	1
Not enrolled or unknown	46(76.7)	106(41.1)	4(2.1,7.7)***	11.1(2.9,50)***

***: p<0.001; **: p<0.01 and *: p<0.05; ^: p<0.25, COR: crude odds ratio; CI: confidence interval; AOR: adjusted odds ratio; ART: antiretroviral therapy; ARV: antiretroviral

CD4 count <200cells/mm³ before delivery, no maternal WHO clinical staging after delivery, children born to mothers from urban settings, and no paternal ART enrollment were identified as independent predictors of child HIV infection (Table 3).

DISCUSSION

Child HIV infection continued to be a major contributor to a preventable cause of morbidity and mortalities among Ethiopian children. The identification of child- and parent-related risk factors for MTCT of HIV is a workable approach to decrease the incidence of child HIV infection and thereby attain the global new child infection targets. Mixed breastfeeding, mothers with CD4 count <200cells/mm³ before delivery, mothers who were not staged after delivery, mothers from a rural setting, fathers who were not enrolled or with unknown enrollment status to ART care were found to be independently associated with child HIV infection.

The measurements of parent- and child-related factors were not subjected to recall bias, as the data was collected from records; misclassification of cases and controls is very unlikely since the DNA PCR was used on all of the study subjects, which have high sensitivity and specificity (18). However, all children were enrolled in follow-up care at various ages; this could lead to misclassifications of indicator factors as causal predictors. Therefore, the results should be interpreted with all these limitations in consideration.

HIV-exposed children who had been mixed breastfed were 22 times more likely (adjusted odds ratio [AOR]: 22.03, 95% confidence interval [CI]:5.31-91.49) to be infected with HIV compared to exclusively breastfed children. The finding implies that mixed breastfeeding is the predominant postnatal risk factor for MTCT of HIV in the studied population. This is consistent with the comparative cross-sectional study finding among HIV exposed children in Addis Ababa (AOR: 6.10, 95%CI: 1.40-25.70) and Zimbabwe (AOR: 3.79; 95%CI: 1.40-10.29) (14, 16). The difference in the magnitude of association might be attributable to social determinants, such as fear of status discovery by relatives or other community members by nonbreastfeeding mothers, (16, 17, 19, 20) which might have contributed to the difference. The other possible reason for the difference could also be due to differences in the study design, in which the comparability of cases and controls cannot be ascertained in a comparative study as that of a case-control study design. However, it was comparable with the study finding from Ivory Cost where mixed breastfed children in the first 6 months of life were 6 times more likely to be infected with HIV (AOR=6.3, 95% CI: 1.1-36.4) compared to exclusively breastfed children in the first six months of life (21). It was also comparable with other several studies in the sub-Saharan African countries, which had shown a reduction of HIV transmission to less than one-fourth among exclusively breastfed children compared to mixed breastfed (22).

Mothers with a CD4 count of <200cell/mm³before delivery were 17 times more likely (AOR: 17.14, 95% CI: 4.73-62.06) to transmit

HIV to their children compared to mothers with a CD4 count >350 cells/mm³ or with an unknown CD4 count. This is because the maternal CD4 count is inversely related to the viral load in the maternal body fluids, including breast milk, which in turn affects the child's viral exposure during pregnancy, delivery, and breast-feeding, as reported elsewhere (20, 23–25). A lower maternal CD4 count before delivery implies prolonged child exposure to higher maternal viral load during pregnancy and child birth. It implies that HIV positive pregnant mothers are coming to health institutions at an advanced stage of the disease probably because of lower PMTCT service uptake of the mothers (13).

A nested case-control study conducted in France also indicated a comparable finding, in which mothers with a higher viral load or lower CD4 count before delivery were 23 times more likely (AOR: 23.2; 95% CI: 3.5–553) to transmit the virus to their children compared to mothers with a lower viral load or higher CD4 count (20). It was also consistent with other study findings elsewhere in Africa and America (20, 25).

Children from mothers with no WHO clinical stage after delivery were 13 times more likely (AOR: 13.38; 95% CI: 5–35.76) to be infected with HIV compared to those whose mothers were staged. This might be related to low postnatal service uptake in the general population of Ethiopia, which could also hold true for HIV-positive mothers and thus allow mothers miss the follow-up schedule for WHO clinical staging and other services (26). This is roughly comparable to mothers who received no preventive measures at all among mothers in developing countries (12). In addition, more than three-fourth of the mothers who were staged after delivery had been on HAART, while only a one-fourth of the mothers who were not staged had been on HAART; a retrospective cohort study conducted in Mozambique indicated that mothers who had been on HAART before delivery were more likely (AOR: 3.15; 95% CI: 1.02–9.73) (27) to bring their children for an early diagnosis and thereby have the opportunity for staging for their own health as well. Hence, mothers who were staged are in a better position to be evaluated for child- and parent-related risk factors and receive the corrective measures which will, in turn, decrease HIV infection risks in children.

Children born to mothers from rural settings were 7 times more likely (AOR: 7.64; 95% CI: 2–29.22) to be infected with HIV compared to children to mothers from urban settings. This might be due to poor PMTCT service utilization among rural mothers and poor quality of maternity care in primary healthcare facilities where most rural mothers get the services.

Children whose fathers were not enrolled or had an unknown enrollment status to ART care were 11 times (AOR: 11.11; 95% CI: 2.94–50) more likely to be infected with HIV compared to children whose fathers were enrolled. Although the direction of a relationship was similar and the CIs overlap, there is a stronger association when compared with the finding from a prospective cohort conducted in Nairobi (Adjusted Hazard Ratio (AHR) = 1.79; 95% CI: 1.02–3.03) (15). In Ethiopia, fathers enrolled in HIV chronic care when their sexual partners disclose their HIV positive status. Studies indicated that a female partner who disclosed her

status and helped her partner enroll in ART care is more likely to participate in PMTCT of HIV services and more likely to adhere to ART for her own health (16, 17, 20). This could, in turn, decrease the risk of MTCT. But the non-disclosure issue of the mother to her male partner is commonly reported in the studied area (16).

CONCLUSION

Mixed breastfeeding, maternal CD4 before delivery, no maternal WHO clinical staging after delivery, children to mothers from rural settings, and no paternal ART enrollment or an unknown enrollment status were independent predictors of child HIV infection. Behavioral change communication should be intensified to address mixed breastfeeding, paternal ART enrollment, and postpartum retention in care for clinical staging. In addition, service providers in the studied hospitals need to devise strategies to enhance postpartum retention in care for clinical staging and give special attention for mothers with a lower CD4 count before delivery and for mothers from rural settings.

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