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Risks associated with mother-to-child transmission of HIV infection

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Early infant diagnosis (EID) permits the detection of Human Immunodeficiency Virus (HIV) infection in exposed children from 4-6 weeks by polymerase chain reaction (PCR). The aim of this study was to assess some maternal and infant characteristics associated with HIV infected children in an EID program.

A retrospective study was performed using records of HIV exposed children enrolled in the EID program from 2009 to 2013. Patients recruited were from various health structures and at different clinical stages; some for the Prevention of Mother-to-Child Transmission (PMTCT) follow up, others with signs of HIV infection. Data was collected from completed hospital records of children aged 6 weeks to 18 months containing at least two PCR, one PCR and one serologic test, or one PCR test and viral load. HIV infection was considered if one of the of tests was positive.

In all, 130 (5.3%) exposed children with only one positive PCR test, and 1,442 (59%) others with information lacking in their record were excluded. A total 107 out of 871 infants enrolled (12.2%) were infected. Only, 32.7% of the mothers were on antiretroviral therapy (ART). Of these, 53.3% had their first PCR performed between 6 weeks and 6 months. Children were less likely to be HIV infected when their mothers received antiretroviral (ARV) (OR=0.15, 95% CI 0.07-0.30, P=0.000). Factors associated with HIV infection in the children were the lack of ARV prophylaxis (OR=2.07, 95%CI 1.05-4.09, P=0.035) and having mixed feeding (OR=3.91, 95% CI 1.66-9.24, P=0.002) in multivariate analysis.

The high rate of infection associated with the maternal and infant correlates of HIV infected children would result from the poor implementation of the PMTCT. Systematic screening of pregnant and breastfeeding women should be reinforced and the lifelong ARVs for PMTCT (Option B+) be promoted.

Key words: HIV, early infant diagnosis, infection, factors.

Pediatric human immunodeficiency virus (HIV) infection is most often acquired vertically from mother to child, either during pregnancy, delivery or breastfeeding.[1,2] It has been noted that combined interventions including antiretroviral (ARV) prophylaxis, caesarean section and the use of formula feeding has reduced the risk of mother to child transmission of HIV (MTCT) in high resources setting up to a rate of less than 2%.[1-3] Meanwhile, in low resource settings such as ours, the implementation of such interventions is low because of multiple barriers[4], so MTCT is still high with rates ranging from 3.6% to 15% where the Prevention of Mother-to-Child Transmission (PMTCT) program is not implemented.[5-7] The lack of antiretroviral treatment during pregnancy is among the main risk factors for transmission identified in many studies.[8,9]

Early infant diagnosis (EID) permits the

detection of HIV infection in an exposed infant from 4-6 weeks by Polymerase chain reaction (PCR).[10] It permits early initiation of ART in infected children and also helps to make decision concerning the follow up of uninfected HIV exposed children.[11] Newell et al.[12] noted that without any intervention, 35.2% of HIV infected children will die at the end of the first year in resource-limited settings, and the median survival of the infected infants was 23 months in Uganda.[13] Because of the high risk of death and given the increasing availability of pediatric ART in resource-limited settings, WHO recommends that national programs should provide early virological testing of infants for HIV.[11] In our milieu, the HIV status of most infants, born from infected mothers is frequently unknown at the early stage of life even though, EID of HIV is feasible.[14] In Eastern Cameroon, it was noted that the median age at first HIV testing was 4 months with 91.1% of infants and 65.2% of their mothers not receiving any ARV prophylaxis.[15] In a study at Yaounde, almost all mothers (98.2%) were aware of the need for EID, but only 67.1% were informed about the test and 47.9% knew the appropriate time at which it should be done[16]. The EID program provides an occasion for assessing the success of the implementation of PMTCT.[17] This study aims at assessing some maternal and infant characteristics found in HIV infected children in the EID program implemented since 2007 at the Mother and Child Center of the Chantal Biya Foundation in Yaounde, Cameroon.

Materials and Methods

This was a retrospective study. The target population was HIV-exposed infants enrolled in the EID program from 2009 to 2013. Patients recruited were from various health structures and at different clinical stages; some for the PMTCT routine follow up, others with suspected signs of HIV infection, or for the management of an already diagnosed infection.

Completed files of HIV-exposed children aged 6 weeks to 18 months containing at least 2 PCR tests or at least 1 PCR and 1 HIV serology, or 1 PCR with viral load considered, defining their HIV status were included.

We collected information regarding the socio-demographic profile of the mother, history of pregnancy and delivery, ARV prophylaxis or

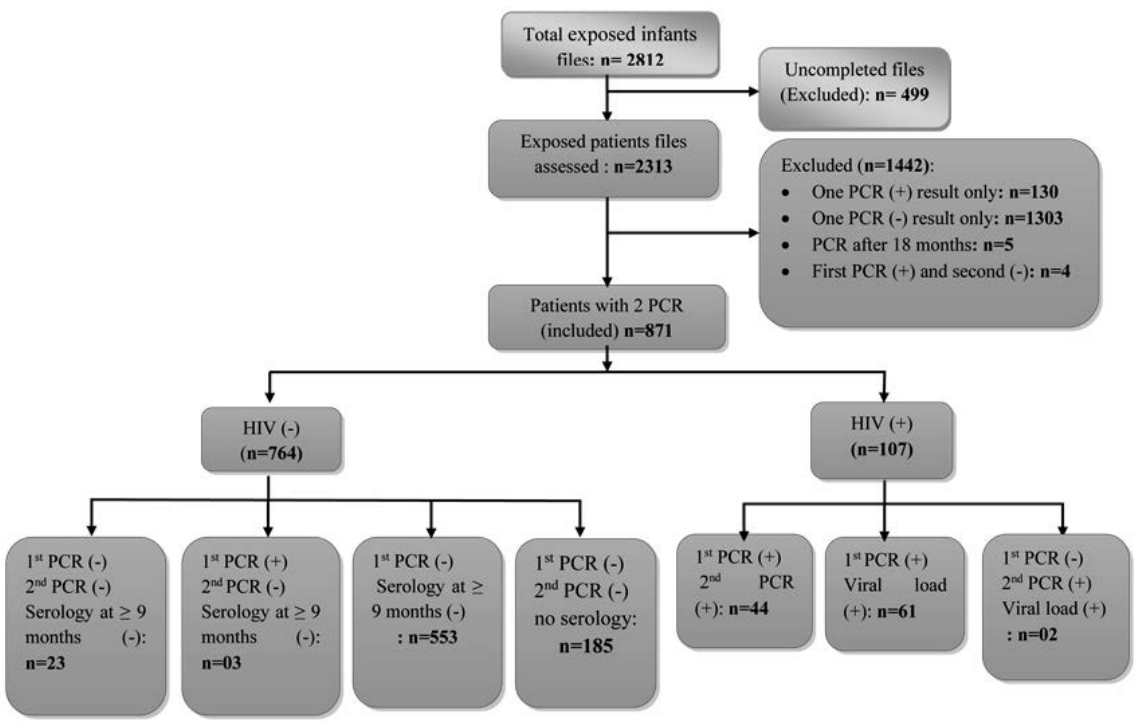

Fig. 1. Flow diagram of enrollment of patients in early infant diagnosis (EID) program

Table I. Baseline Characteristics of the Mothers.

Maternal Characteristics		Frequency	Percentage
Age group (years)	≤ 20	12	11.2
	21 - 30	66	61.7
	31 - 40	29	27.1
Marital Status	Cohabiting	50	46.7
	Single	43	40.2
	Married	11	10.3
	Widow	3	2.8
Profession	House wives	57	53.3
	Private sector	34	31.8
	Students	10	9.3
	Others	6	5.5
ARV during pregnancy (N=35)	ARV prophylaxis	24	68.6
	HAART before pregnancy	10	28.6
	Others	1	2.8

ARV: antiretroviral treatment; HIV: human immunodeficiency virus; HAART: highly active antiretroviral treatment; PCR: polymerase chain reaction

treatment received during pregnancy. Infant variables collected included the birth weight, PMTCT measures, age at first PCR, feeding option and HIV status. The ARV prophylaxis was considered according to the different national guidelines in use at the time of follow-up. At our study site, the first PCR-DNA was done at the age of 6 weeks. Whole blood was collected and transferred to the virology laboratory of Centre Pasteur of Cameroon (CPC) when the child was selected under the ANRS 12140-Pediacam survey. The others samples sent for analysis at the Chantal Biya International Reference Centre for Research (CBIRC) were collected onto filter papers (DBS) and processed according to standard procedures[18] before transport to the laboratory. Occasionally viral loads were requested. Two PCR tests were required, and the first, if positive, was confirmed by a second before the exposed infant was declared HIV infected. For breastfed children, a second PCR was done at 6 weeks after complete cessation of breastfeeding[19]. The expected period for results to return was after 4 weeks. If positive, a second blood sample was collected for the second PCR and the infant was put on ART while waiting for confirmation. If the second PCR was positive, then the infant was declared HIV infected, and if it was negative, the third DBS sample was collected for the third PCR. For infants who were breastfed, if the first and the second PCR performed after the cessation of breast feeding were all negative, the infant was declared not infected. In those on formula who had the first PCR and HIV serology negative the infant was also declared not infected. Two discordant PCR results required a third to have a definite status of the patient. The serologic test was performed above 12 months. When there was a discordant serology result, a PCR was done and the exposed uninfected infants exited the EID program. Infants were uninfected when they had negative PCR test results with/without HIV negative serology.

Data analysis

For HIV-infected children, we described the maternal and infant characteristics with continuous variables using means; or median with inter-quartile range and categorical variables using the percentages. Univariate then multivariate stepwise logistic regression analysis was used to determine the significant maternal and infant variables as independent correlates of infection in HIV infected children. The Fisher test and the Odds ratio with a confidence interval at 95% was used to determine the factors correlated with HIV infection in children at a p-value <0.05.

The study was approved by the Ethics

Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I.

Results

In all, 871 HIV exposed children were enrolled, amongst which 107 (12.2%) were infected. We excluded 499 patients with only one positive PCR test, and 1,442 exposed children because information was lacking in their file (Fig. 1). The mothers of the infected children were aged 15-40 years with a mean age of 27.3 years. Only 32.7% benefited from ARV treatment during pregnancy, and in only 68.6%, ARV prophylaxis was given as recommended by the national guidelines (Table I). This consisted of single dose nevirapine (NVP) (2/107), zidovudine (AZT) from 28 weeks of pregnancy (5/107) and AZT from 28 weeks of pregnancy plus single dose NVP (17/107).

More than half (53.3%) of the HIV infected children had their first PCR test done between 6 weeks to 6 months, while the median age was 21 weeks. Most of them (58.0%) did not receive any ARV prophylaxis after birth (Table II). Feeding with formula was the most frequent option (43%) compared to exclusive breastfeeding (29%) and mixed feeding (28%).

The maternal risk factors of having an infected infant were living single (OR 1.68, 95%CI 1.12–2.55, P=0.009) and being less than 30 years old (OR 2.29, 95%CI 1.51–3.49, P=0.000). Others factors were per vaginal (OR 2.95, 95%IC 1.27–6.89, P=0.004) and home delivery (OR 5.76, 95%CI 2.36–14.01, P=0.000). Infants of mothers on highly active antiretroviral therapy (HAART) were less likely to have HIV infection; compared with those whose mothers were on ARV prophylaxis (OR 0.22, 95%CI 0.11–0.45, P=0.000); (Table III).

Factors related to the children were the PCR performed less than 6 weeks of the life, (OR 4.86, 95%CI 2.67–8.83, P=0.000) and mixed feeding (OR 24.52, 95%CI 12.31–48.83, P=0.000). On the contrary, ARV prophylaxis at birth protected children against infection (OR 0.06, 95%CI (0.04–0.09), P=0.000); (Table IV).

Factors associated with HIV infected children in multivariate analysis

HIV infection in children was less frequent when theirs mothers received HAART (OR 0.3, 95%CI 0.07–0.30, P<0.001), or ARV prophylaxis (OR 0.22, 95%CI 0.12–0.38, P<0.001). Among the infant correlates, age at first PCR, being exclusively breastfed, having mixed feeding and receiving ARV after birth were associated to their HIV status. It was 4 times more likely to have a positive PCR when it was done at an age beyond 6 weeks (OR 4.9, 95%CI 2.67–8.83, P=0.000). Infants on

Table II. Baseline Characteristics of the Children and the Prevention of Mother-to-Child HIV Transmission.

Characteristics		Frequency	Percentage
Sex	Male	60	56.1
	Females	47	43.9
Birth weight (grams) (N=99)	< 2500	19	19.2
	2500 - 4000	71	71.7
	> 4000	9	9.1
ARV prophylaxis (N=107)	Yes	45	42.0
	No	62	58.0
Age at first PCR (N=107)	6 weeks	13	12.1
	6 weeks - 6 months	57	53.3
	6 - 18 months	37	34.6
Feeding option	Exclusive breastfeeding	31	29.0
	Mixed feeding	30	28.0
	Formula feeding	46	43.0

ARV: antiretroviral treatment HIV: human immunodeficiency virus; PCR: polymerase chain reaction

Table III. Maternal Socio-Demographic and Obstetric Correlate of HIV Infection: Univariate Analysis.

	HIV positive, n(%)		Total n(%)	Odd Ratio [95% CI]	P
	Yes	No			
Marital status of the mother					
Living singly*	46 (16.3)	236 (83.7)	282 (32.4)	1.678[1.117 - 2.548]	0.009
Living as a couple**	61 (10.4)	528 (89.6)	589 (67.6)		
Maternal age					
< 30 Years	68 (17.1)	330 (82.9)	398 (45.7)	2.293[1.508-3.486]	<0.001
Mode of delivery					
Per vaginal	101 (13.4)	650(86.6)	751 (86.2)	2.952[1.265 - 6.889]	0.004
Caesarean section	6 (5.0)	114 (95)	120 (13.8)		
Place of delivery					
Home	9 (42.9)	12 (57.1)	21 (2.4)	5.755[2.364-14.008]	<0.001
Health facility	98 (11.5)	752 (88.5)	850 (97.6)		
Prolonged rupture of membrane					
Yes	8 (21.1)	30 (78.9)	38 (4.4)	1.977[0.882-4.434]	0.083
No	99 (11.9)	734 (88.1)	833 (95.6)		
CD4 cell count					
≤ 350 / mm^3	16 (8)	185 (92)	201 (32.4)	1.423[0.739-2.744]	0.187
ARV treatment during pregnancy					
HAART	10 (2.2)	451(97.8)	461 (63.3)	0.215[0.101 –0.454]	<0.001
ARV prophylaxis***	25 (9.4)	242(90.6)	267 (36.7)		

HIV: human immunodeficiency virus; ARV: antiretroviral treatment; HAART: high active antiretroviral treatment; PCR: polymerase chain reaction; CD4: Cluster of differentiation 4.
* Living singly (never been married, divorced, widow); **Living as a couple (married, cohabiting), ***Recommended ARV prophylaxis

mixed feeding were 24 times more likely to be infected than those who were on formula (OR 24.5, 95%CI 12.31–48.83, P<0.001). On the contrary, an infant who received ARV prophylaxis at birth (42.1%), had a protective effect (OR 0.1, 95%CI 0.04–0.09, P<0.001) against HIV infection (Table V).

Discussion

Our study was retrospective, performed on HIV exposed infants registered in the EID program during a period of 5 years; from 2009 to 2013. Many children were excluded and the PCR tests were not performed at the study site; furthermore, the results were collected by the parents. This renders our sample size less representative.

The prevalence (12.2%) of HIV infection in the EID program was high in our study compared to 3.7% shown by Tejiokem et al.[14] in two cities that included our site. Unlike ours, their study was a multicenter prospective cohort and its results were based on 2 positive PCR tests. On the contrary, our study involved patients at various stages; some of the infants were recruited just for follow up after birth. Some came already with signs of HIV infection. The prevalence was also high (18.9%) in Brazil and the diagnosis was based on 2 detectable viral loads and persistent positive HIV serology.[20] According to some authors, the confirmatory PCR2 could be left out if on the same DBS sample a PCR1 and viral load was performed.[21]

Concerning the adherence to the EID program, lack of partner support could be the main hindrance to PMTCT uptake.[22-28] In the present study, about half (46.7%) of the mothers were cohabiting and 40.2% were single. Married mothers, may have adequate knowledge of PMTCT, as compared to those who are not[29], however, the knowledge is not often put into the practice. Our study revealed also that the

Table IV. Infant Correlates of HIV Infection: Univariate Analysis.

	HIV Positiven, (%)		Total n(%)	Odd Ratio (95% CI)	P
	Yes	No			
Age at first PCR					
6 Weeks	13 (4.1)	307 (95.9)	320 (36.7)	4.857 [2.672-8.831]	<0.001
> 6 Weeks	94 (17.1)	457 (82.9)	551 (63.3)		
Infant on ARV prophylaxis					
Yes	45 (6.0)	707 (94.0)	752 (86.3)	0.059 [0.037-0.094]	<0.001
No	62 (52.1)	57 (47.9)	119 (13.7)		
Birth weight					
< 2500 g	19 (15.7)	102 (84.3)	121 (14.5)	1.481[0.861-2.547]	0.104
≥ 2500 g	80 (11.2)	636 (88.8)	716 (85.5)		
Feeding option					
Exclusive breastfeeding	31 (14.4)	185 (85.6)	216 (26.2)	2.055 [1.265-3.336]	0.003
Formula	46 (7.5)	564 (92.5)			
Mixed feeding	30 (66.7)	15 (33.3)	45 (6.9)	24.522 [12.314-48.832]	<0.001
Formula	46 (7.5)	564 (92.5)	610 (93.1)		

HIV: human immunodeficiency virus; ARV: antiretroviral treatment; PCR: polymerase chain reaction

Table V. Mother and Infants' Correlates of HIV Infection in Exposed Children: Univariate and Multivariate Analysis.

Characteristics	Univariate Analysis		Multivariate Analysis	
	Odd Ratio	P	Adjusted Odd Ratio	P
Maternal correlates				
Marital status (couple/single)	1.69	0.009	0.70	0.176
Age of the mothers	2.29	<0.001	1.01	0.972
Per vaginal delivery	2.95	0.004	0.71	0.475
ARV (HAART/ARV prophylaxis)	0.22	<0.001	0.15	<0.001
Place of delivery : Home/Health facility	5.76	<0.001	1.85	0.330
Infant correlates				
Age at first PCR >6 weeks	0.06	<0.001	0.22	<0.001
ARV prophylaxis	4.86	<0.001	2.07	0.035
Exclusive breastfeeding	2.06	0.003	0.67	0.155
Mixed feeding	24.52	<0.001	3.91	0.002

ARV: Antiretroviral Treatment; HAART: High Active Antiretroviral Treatment; PCR: Polymerase Chain Reaction

risk of HIV infection was high, when the mother was less than 30 years old. In South Africa, more than half of MTCT involved young women[30]; although authors noticed that maternal age was not associated with HIV MTCT.[31]

Concerning the obstetric factors, the type of ARV regimen during pregnancy[8,9], the mode and the place of delivery were associated with HIV infection in children. Per vaginal delivery has been associated with a higher risk of MTCT.[9,20] in our study, it was the main mode of delivery (94.4%). With respect to the place of delivery, we found that the risk of the children being HIV infected was increased by 5-fold when they were born at home. Home

delivery is characterized by the lack PMTCT interventions[32] and inadequate post natal follow up of the mother-infant pair.

Children of mothers who had received HAART before pregnancy or ARV prophylaxis were at low risk of being HIV infected. We found out that the risk of being HIV positive was higher in children whose first PCR was done beyond 6 weeks of age. Other authors found the risk to be 4.8 times higher when the infant was enrolled to follow up to an age above 6 weeks.[27,32] Mixed feeding exposes children to a higher risk of HIV infection. As in others studies, ignorance of the HIV status of the mothers among others factors could have influenced their feeding choices.[8,9]

The high rate of infection associated with the maternal and infant correlates of HIV infected children would have result ed from the poor implementation of PMTCT in our setting. Systematic screening of pregnant and breastfeeding women should be reinforced and the Option B+ be promoted.

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