Scientific Research Publishing

Open Journal of Epidemiology, 2023, 13, 328-341
https://www.scirp.org/journal/ojepi
ISSN Online: 2165-7467
ISSN Print: 2165-7459

Deoxyribonucleic Acid-Polymerase Chain Reaction Status of HIV Exposed Infants in a Sub Regional Prevention of Mother-to-Child Transmission of HIV Programme during the Period 2009-2020

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How to cite this paper: Isaac, E.W., Ajani, A., Iliya, J., Manga, M., Difa, A.J., Oluwaseun, O.C. and Hassan, M.D. (2023) Deoxyribonucleic Acid-Polymerase Chain Reaction Status of HIV Exposed Infants in a Sub Regional Prevention of Mother-to-Child Transmission of HIV Programme during the Period 2009-2020. *Open Journal of Epidemiology*, **13**, 328-341.
https://doi.org/10.4236/ojepi.2023.134024

Received: August 2, 2023
Accepted: November 14, 2023
Published: November 17, 2023

Abstract

Introduction: Transitioning to more efficacious Antiretrovirals for HIV infected pregnant women and infant prophylaxis has reduced Mother to child transmission of HIV significantly. This study aimed to determine HIV infection status in HIVexposed infants who had their first DNA polymerase chain reaction test in our molecular Laboratory. **Subjects, Materials and Methods:** Dried Blood Spots for HIV DNA results from 5 states between 2009 and 2020 were analyzed in the PCR laboratory of the Federal Teaching Hospital, Gombe. **Results:** Nine thousand eight hundred and twenty-three Human Immunodeficiency Virus Deoxyribonucleic acid polymerase Chain Reaction results were analysed; 4937 (50.2%) were males. During the study period, there was an overall declining trend in the mother-to-child transmission rate from 3.8% in 2009 to 1.0% in 2020. 6120 (62.3%) of HIV + mothers received Highly active antiretroviral therapy HAART before pregnancy. 7845 (76.2%) of the infants received Nevirapine prophylaxis. Dried blood spot samples were collected from 4077 (41.5%) at 6 - 8 weeks. 8438 (85.9%) received co-trimoxazole. 9469 (96.4%) were ever breastfed. Of the 9823 HIV DNA PCR results, 255 (2.6%) were positive while 69/4077 (1.7%) and 109/2662 (4.1%)

were positive for HIV DNA at 6 - 8 weeks and > 12 weeks respectively. (p = 0.001). 86/747 (11.5%) of infants whose HIV-positive mothers received no ARVS were HIV DNA positive. (p = 0.001). 106/884 (12.0%) of infants who had no Antiretroviral prophylaxis had positive HIV DNA results; 7/413 (1.7%) with Zidovudine/Nevirapine prophylaxis had positive results. (p = 0.001). 246/9469 (2.6%) of infants that were ever breastfed were positive for HIV DNA; 11/354 (3.0%) that never breastfed had positive HIV DNA. **Conclusion:** Lack of maternal/infant ARVs and prolonged breastfeeding increased the risk of infant HIV infection.

Keywords

Mother to Child Transmission of HIV, Antiretrovirals, HIV Exposed Infants, Deoxyribonucleic Acid Polymerase Chain Reaction, Early Infant Diagnosis

1. Introduction

Mother-to-child transmission accounts for the vast majority of infections in children and is a significant contributor to the HIV pandemic, accounting for 9% of new infections globally. [1] Progress in reducing mother-to-child transmission of HIV has been dramatic since the introduction in 2011 of the "Global Plan towards the Elimination of New HIV Infections among Children and Keeping their Mothers Alive". This is largely because of increased access to PMTCT-related services and an increased number of pregnant women living with HIV being initiated on lifelong antiretroviral medicines. [2] Around 1.4 million HIV infections among children were prevented between 2010 and 2018 due to the implementation of PMTCT services. [3] Efforts to prevent mother-to-child HIV transmission have transformed the Paediatric HIV epidemic globally, thus reducing infant mortality, a pillar of the United Nations Sustainable Development Goal. Prevention of mother-to-child transmission of HIV interventions can reduce the risk of MTCT of HIV to less than 2%, and remains the most efficacious strategy for preventing pediatric HIV infection. [4] [5]

Nearly all young children newly infected with HIV are infected through mother-to-child transmission (MTCT); about 86% of the estimated 160,000 children newly infected with HIV in 2018 were in the WHO African Region. [6] With a PMTCT of HIV coverage of 46%, Nigeria harbours about 27 % of the global burden of mother-to-child transmission of HIV and is one of UNAIDS's 23 priority countries for PMTCT. [7] There is geographic disparity in PMTCT of HIV coverage among states and within regions in Nigeria. [8]

Early infant diagnosis uses Dried blood spot samples of HIV-exposed infants to detect HIV-DNA using the polymerase chain reaction technique in infants postpartum. Early Infant Diagnosis facilitates early linkage of HIV-infected infants to treatment care and support. [9] [10] Early initiation of antiretroviral therapy (ART) in the first 3 months of life reduces early infant mortality by 76%

and HIV disease progression by 75%. [11] Globally, in 2018, only an estimated 59% of HIV-exposed infants received early infant diagnostic (EID) nucleic acid test by age 2 months, and only 54% of children living with HIV received ART. [12] In Nigeria, EID coverage has remained low; it has increased from 15% in 2015 to 27% in 2019. [7] EID programs require coordination and management of multiple separate health facilities/systems as well as significant logistical, financial, and human investments thus making it complex process with multiple challenges, requiring effective specimen transport, laboratory testing and results delivery, and potential loss of HIV-exposed infants at many points along the EID cascade. [13] Low demand for EID, inefficient procedures to follow up; infrastructure constraints especially power supply; stock out of EID commodities; EID backlogs, inconsistencies in sample pick up, loss of EID results long turnaround time of test results have been identified as some of the myriad of issues facing the EID programme in Nigeria. [8] [14]

To guide Quality PMTCT implementation at all levels of health care, Nigeria has transitioned through seven PMTCT guidelines from 2001 through to 2020 with Single-dose Nevirapine to mother and Nevirapine prophylaxis to the infant as the first ARV in preventing vertical transmission of HIV. [15] Currently, more efficacious cART with viral load determination is the standard of care for all HIV-positive pregnant women with ARV prophylaxis and EID for their exposed infants. [16]

The MTCT rate provides a measure of the effectiveness of the programme for preventing infant infections in pregnant women living with HIV. [17] The earliest PMTCT effectiveness studies [18]-[23] conducted in Nigeria reported MTCT rates of between 2.4% [24] and 22%. [25]

Transitioning to more efficacious cART for PMTCT between 2010 and 2012, several studies [26]-[42] in the country reported MTCT rates of between 0% [43] [44] and 9.7% [45]. Most recent reports from Sokoto, [46] FCT/Nasarawa state, [47] Delta, [48] Rivers [49] and Imo state [50] showed MTCT rates of 0.9%, 1%, 4%, 1.1%, and 3.7% respectively. A very large subregional report of EID of HEI by Dakum *et al.* [51] reported a MTCT rate of 5.2% at 12 weeks postpartum. Khamofu *et al.* reported declining MTCT rates with more efficacious cART in Nigeria. [52]

While most of these MTCT rates were determined at 6 - 8 weeks, in breastfeeding women in small sample sizes and short-duration reports, they no doubt were significant contributions to the PMTCT effort in the country. The current 2020 National HIV guideline [16] recommends that all HIV-exposed infants should have DNA PCR testing or NAT at birth, 6 - 8 weeks of age, 9 months and 8 - 12 weeks after complete cessation of breastfeeding. If the baby is not being breastfed, DNA PCR testing should be done at birth and 6 weeks.

The aim of this study was to report HIV infection in HIV-exposed infants from 5 states in the North East and North Central regions of Nigeria from 2009

to 2020.

2. Subjects, Materials and Methods

2.1. Study Design

This was a retrospective analysis of the results of Dried Blood Spot samples for DNA PCR testing of HIV-exposed infants.

2.2. Study Setting

Dried Blood Spot sample test results for HIV DNA from 5 states (Gombe, Yobe, Bauchi, Benue and Kaduna) in the Northern Region of the country from 2009 to 2020 were analyzed in the regional Polymerase Chain Reaction laboratory in the Federal Teaching Hospital, Gombe. DBS samples were from all levels of health care facilities including public and private, private profit and nonprofit and faith-based facilities in both rural and urban Nigeria. All HIV-exposed infants with positive DNA PCR were referred to the Paediatrics ART clinic.

This Molecular laboratory is one of the earliest DNA PCR Laboratories established in the country to support the Early Infant Diagnosis of HIV in the country. Cobas AmpliPrep (CAP)/Cobas TaqMan 96 (Roche Molecular Systems NJ) was used to detect HIV DNA. Molecular methods of DNA determination were used in accordance with the Manufacturer's guide. The Quality Control and Assurance were ensured and maintained as recommended by the Federal Ministry of Health. The sample size was all consecutive Dried Blood spot samples that were analysed with their results from 2009 to 2020 in the Molecular laboratory in our health facility.

The following information was retrieved from the Laboratory forms and analyzed: Maternal ARV, ARV and Cotrimoxazole prophylaxis given to the infant, age at DBS Sample collection, sex, infant breast-feeding status and HIV DNA PCR test result.

Laboratory forms with incomplete information were excluded from analysis.

2.3. Ethical Clearance

Ethical clearance was received from the research and ethics committee of the Federal Teaching Hospital, Gombe (NHREC/25/10/2013).

2.4. Data Analysis

Data was analyzed using Epi info version 3.5.1. All data were analyzed with a statistical significance level set at $p < 0.05$. Frequencies, proportions, confidence intervals were computed. Results were summarized using tables and figures. Hypothesis testing was performed using Pearson Chi-Square as appropriate.

3. Results

Table 1 shows that 9,823 PCR DNA results were analysed during the study period. There was an over-all declining trend in the MTCT rate from 3.8% in 2009

Table 1. Yearly DBS sample collection 2009-2020 and HIV DNA PCR results.

Variable	HIV DNA (%) Positive	HIV DNA (%) Negative	Total (%)
Year of DBS sample collection			
2009	2 (3.8)	50 (96.2)	52 (0.5)
2010	0 (0.0)	63 (100.0)	63 (0.6)
2011	4 (3.7)	103 (96.3)	107 (1.1)
2012	40 (3.7)	849 (98.3)	889 (9.1)
2013	10 (3.1)	317 (96.9)	327 (3.3)
2014	27 (3.1)	839 (96.9)	866 (8.8)
2015	4 (1.7)	233 (98.3)	237 (2.4)
2016	93 (4.7)	1899 (95.3)	1992 (20.3)
2017	36 (1.7)	2124 (98.3)	2160 (22.0)
2018	0 (0.0)	224 (100.0)	224 (2.3)
2019	27 (1.3)	1702 (98.7)	1729 (17.6)
2020	12 (0.8)	1165 (99.2)	1177 (12.0)
TOTAL	255 (2.6)	9568 (97.4)	9823 (100)

X^2: 84.047, $p < 0.001$.

to 0.8% in 2020 with blips in 2011 and 2016. Of the 9823 HIV DNA PCR results, 9568 (97.4%) had Negative DNA PCR while 255 (2.6%) were Positive.

Table 2 shows the distribution of maternal ARVs and Infant HIV DNA status; 6120 (62.3%) of HIV + mothers were receiving ART before pregnancy; 25.2 % (2475) started ART in pregnancy; 747 (7.6%) and 285 (2.9%) of HIV positive pregnant women did not receive and had unknown ARV status respectively. Regimen received by HIV-positive women was AZT + 3TC at 34 - 36 weeks gestation, AZT from 14 weeks gestation and single dose NVP in labour. Table 2 shows that 86 (11.5%) infants whose HIV-positive mothers received no ARVS were HIV DNA PCR positive; 98/6120 (1.6%) of mothers;32/2475 (1.3%); 10/98 (10.4%); 3/69 (4.5%) and 26/285 (9.1%) of infants whose HIV positive mothers had ART before pregnancy; ART during pregnancy; AZT mono-therapy; NVP Mono-therapy and those with unknown ARV status were HIV DNA PCR positive respectively ($p = 0.001$).

Infants who received ARV prophylaxis but whose mothers did not receive ART in pregnancy 747 (8.1%) had significantly more infection ($p = 0.000$) compared to infants who had received ARV with maternal ART ($p = 0.971$).

Table 2 shows that 7485 (76.2%) of HIV-exposed infants received NVP prophylaxis; 884 (9.1%) had no prophylaxis; 560 (5.6%) received AZT; 413 (4.2%) AZT/NVP and 481 (4.9%) of infants had unknown ARV (prophylaxis) status; 106/884 (12.0%) of HIV exposed infants who had no ARV prophylaxis; 10 (1.8%), 120/7485 (1.6%); 7/413 (1.7%) infants who received AZT mono-prophylaxis; NVP

Table 2. Maternal ARV status and infant HIV DNA PCR test results.

Variable	HIV DNA (%) Positive	HIV DNA (%) Negative	Total (%)	X^2	P = value
ARV received by HIV-positive mother					
HAART during pregnancy	32 (1.3)	2443 (98.7)	2475 (25.2)	343.797	0.000
HAART before pregnancy	98 (1.6)	6022 (98.4)	6120 (62.3)		
AZT + 3TC at 34 - 36 weeks	0 (0.0)	29 (100.0)	29 (0.3)		
AZT + sdNVP in labour	10 (10.4)	88 (89.6)	98 (1.0)		
sdNVP in labour	3 (4.5)	66 (95.5)	69 (0.7)		
Nothing	86 (11.5)	661 (88.5)	747 (7.6)		
Unknown	26 (9.1)	259 (90.8)	285 (2.9)		
ARV Prophylaxis given to infants					
Nothing	106 (12.0)	778 (88.0)	884 (9.1)	338.129	0.000
AZT	10 (1.8)	550 (98.2)	560 (5.7)		
NVP	120 (1.6)	7365 (98.4)	7485 (76.2)		
AZT + NVP	7 (1.7)	406 (98.3)	413 (4.2)		
Unknown	12 (2.5)	469 (97.5)	481 (4.9)		

mono-prophylaxis and AZT/NVP dual prophylaxis had positive HIV DNA PCR result. (p = 0.000)

Dried Blood Spots samples were collected in 2514 (25.6%) of HIV exposed infants at <6 weeks of age; 41.5% (4077) at 6 - 8 weeks; 5.8% (570) at >8 - 12 weeks and 27.1% (2662) at >12 weeks postpartum. Table 3 shows that (58/2514) 2.3% 1.7% (69/4077); 3.3% (19/570) and 4.1% (109/2662) were positive for HIV DNA PCR at <6 weeks of age; 6 - 8 weeks; 8 - 12 weeks and >12 weeks respectively. There was an increasing likelihood of positive DNA PCR test results with a delay in DBS sampling and this was statistically significant (p = 0.000).

Table 3 also showed that 96.4% (9469/9823) infants were ever breastfed and 3.6% (354) had never breastfed. Daily cotrimoxazole was received by 85.9% (8438/9823) of the infants. About 2.6% (246/9469) of infants that were ever breastfed were positive for HIV DNA PCR and 2.5% (9/354) of infants that were never breastfed were positive for HIV DNA PCR (P = 0.348) (Table 3). In Table 3 more male infants than females had positive DNA PCR tests and was statistically significant p = 0.001. At the time of DBS sample collection infants of mothers who were not breastfeeding were DNA PCR positive compared to infants whose mothers were breastfeeding. However, this was not statistically significant (p = 0.295)

4. Discussion

This study showed that the HIV infection rate using the first DNA PCR at 6 - 8

Table 3. HIV-exposed infants' profile and HIV DNA PCR result.

Variable	HIV DNA Positive (%)	HIV DNA Negative (%)	Total (%)	X^2	P = value
Ages of infants at DBS Sample collection					
<6 weeks	58 (2.3)	2456 (97.7)	2514 (25.6)	38.865	0.001
>6 - 8 weeks	69 (1.7)	4008 (93.3)	4077 (41.5)		
>8 - 12 weeks	19 (3.3)	551 (96.6)	570 (5.8)		
>12 weeks	109 (4.1)	2553 (95.9)	2662 (27.1)		
Sex					
Male	143 (2.9)	4794 (97.1)	4937 (50.2)	76.055	0.001
Female	112 (2.3)	4774 (97.7)	4886 (49.8)		
Cotrimoxazole prophylaxis given to infant					
No Cotrimoxazole	51 (3.7)	1334 (96.3)	1385 (14.1)	7.696	0.006
Yes, receiving cotrimoxazole daily	204 (2.4)	8234 (97.6)	8438 (85.9)		
Breastfeeding status at the time of DBS sample collection					
Yes, breastfeeding	214 (2.5)	8342 (97.5)	8556 (87.1)	1.095	0.295
Not breastfeeding	41 (3.2)	1226 (96.8)	1267 (12.9)		
Was HIV-exposed infant ever breastfed?					
Yes	246 (2.6)	9223 (97.4)	9469 (96.4)	0.348	0.556
No	9 (2.5)	345 (97.5)	354 (3.6)		

weeks in HIV-exposed infants was 2.6%. This rate is less than 5% expected in breastfeeding women on ART. [4] [5] Significantly there was a trend of declining MTCT rate over the years as the country transitioned to more efficacious combination ART. This similar trend was demonstrated earlier by Itiola [45] and Khamofu [52] in the country and Olana in Ethiopia. [53] These studies however had smaller number of mother-infant pairs and shorter study duration. Efficacious cART with viral load determination is the standard of care for all HIV-positive pregnant women with ARV prophylaxis and EID for their exposed infants. [10] [15] [16]

Increased DBS samples from 2016 in this study were as a result of additional logging to our laboratory from non-functional PCR laboratories in some parts of in the country.

In this study, forty-two percent of the first DBS samples were obtained within the 6 - 8 weeks period as recommended by the National guideline; [10] [15] [16] a third of DBS were taken after this period with increasing possibility of positive DNA test result. (p = 0.01). This finding is similar to the report by Dakum *et al.* [51]; however, the proportion of DBS sample obtained at 6 - 8 weeks in our

study is twice as high as reported by Dakum *et al.* [51] and Itiola *et al.* [45] in the country. Reports on fairly large number of HIV-exposed infants in the country by Anoje *et al.*, [28] Olerigbe *et al.*, [41] Ibobo *et al.*, [48] did not report 6 - 8 weeks age of DBS sample collection. Higher DBS collection rates at 6 - 8 weeks of 67.3%, 50%, and 79% have been reported in Ethiopia, [53] Malawi, [54] and Kenya, [55] respectively. HIV DNA PCR testing through DBS collection at 6 - 8 weeks has a very high sensitivity and is considered programmatically more efficient and therefore reported. [10] [15] [16] [56]

Overall, more than three-quarters of HIV-positive women in our report had received ART and had lower MTCT rate compared to women who had less efficacious ARV consisting of two or less ARVS. This is in agreement with the findings of Khamofu *et al.* [52] and Itiola *et al.* [45] with however much smaller sample sizes and shorter study duration. Highly Active Antiretroviral therapy or combination ART with at least three antiretroviral have more durable and sustained maternal viral suppression with reduced risk of MTCT of HIV. [23] [26] High Maternal viral load in Pregnancy is a major risk factor for MTCT. [10] [15] [16]

In this study, 7.6% of HIV-positive pregnant women did not receive ARVs and therefore had higher MTCT rates. This is similar to 7% reported by Dakum *et al.* [51] but lower than the 13% and 38.5% reported by Itiola *et al.* [45] and Anoje *et al.* [28] respectively. A much lower proportion of HIV-positive pregnant women did not receive ARVs in the report of these workers. [41] [48] While this study showed 2.9% of HIV-positive mothers with missing data on ARVs, these workers [49] [51] reported 17.4% and 12.2% respectively. Similarly, 9.1% of HIV-exposed infants did not receive ARV prophylaxis and 4.9% had missing data on ARVs. Infant HIV infection was highest in the former category in our study. A much higher proportion of 17.1% [45] and 38.2% [28] of HEI did not receive ARV prophylaxis. This infant status was not reported by Dakum *et al.* [51] Infant ARV prophylaxis is an indicator of the quality of PMTCT service delivery. [10] [15] [16] Increased odds of infant HIV infection with lack of Maternal ARV and infant HIV prophylaxis have also been reported. [53] [54] [55]

Missing data, unknown status and non-administration of ARVs in PMTCT programme remain significant challenges in the country traceable to gaps in training, human resource constraints, monitoring and evaluation and lack of electronic medical records. [7] [8] [12] [14]

At the time of DBS sample collection, 87% of HEI were breastfeeding and overall, 96.4% of these infants reported ever breastfed. In this study, there is a significant relationship between the duration of breastfeeding and positive DNA PCR test result with prolonged Breastfeeding increasing the risk. This relationship between prolonged breastfeeding and infant HIV infection has also been reported by workers in Nigeria [41] [45] [48] [51] and in Ethiopia [53] and Kenya. [55]. The risk of postnatal transmission through breastfeeding is associated with clinical, immunological and virological maternal factors and

infant feeding patterns. [57] Maternal seroconversion during breastfeeding, low maternal CD4 cell count, increased maternal RNA viral load in plasma and breast milk are strongly associated with increased risk of transmission. Breast pathologies such as clinical and subclinical mastitis, nipple bleeding, and abscesses, fissures or lesions are also associated with a higher risk of transmission through breastfeeding. [57] Mother-to-child transmission rates of HIV through breastfeeding is 13% at six weeks rising to 23% at the end of breastfeeding. [7] Breastfeeding remains and will be the topmost item on the agenda of child survival globally and especially in low- and medium-income countries. [1] [2] [16]

5. Limitations

There are several limitations in this study; this is the first HIV DNA PCR results analyzed and therefore we are unable to determine subsequent and final HIV infant outcomes. Our study did not report other maternal and infant characteristics like CD4 + cell count, viral load, WHO clinical stage, follow-up infant status, or cessation of breastfeeding that would affect final infant outcomes. As a retrospective study, information may have been incomplete and the MTCT rate therefore and estimation and not the actual. In spite of its limitations, the large sample size, the long duration of review and evidence of PMTCT effectiveness through different ART regime remain the strength of this study.

6. Conclusions

Mother-to-child transmission of HIV infection rate has declined with the use of efficacious combination ARV therapy in five states of Northern Nigeria.

Prolonged breastfeeding is associated with the risk of transmission of HIV especially in the absence of maternal and infant ARV.

7. Recommendation

PMTCT requires strengthening, especially the provision of maternal and infant ARV in northern Nigeria and the country in general.

Author Contribution

Elon Warnow Isaac: Conceived of the study and study design, developed the first manuscript draft and critically reviewed all drafts of the manuscript.

Dr Iliya Jalo, Dr. Abubakar Joshua Difa, and Ms. Oyeniyi Christianah Oluwaseun: Conducted quantitative data analysis and reviewed all drafts of the manuscript.

Dr Mohammed Manga and Mr. Muhammad Danlami Hassan: Reviewed and commented on the data.

Acknowledgments

We wish to acknowledge Hajiya Fatima Y Aliyu, Hajiya Zainab Dan-Malam and

Hafsat Sabo of the Data unit of Paediatrics department for extracting the data.

Funding

There was no funding received for this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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