FEEDING PATTERN, TRANSMISSION, MORBIDITY AND OUTCOMES AMONG HIV EXPOSED CHILDREN

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Abstract

Background: The risk of HIV transmission could persist despite preventive interventions. Feeding practices may continue to influence HIV transmission and morbidity-free survival amongst exposed infants.

Objective: To study the relationship between feeding, postnatal HIV transmission and morbidity amongst HIV exposed infants.

Methods: A cohort of consecutively enrolled HIV exposed infants was followed up from four weeks to 24 months of age at the Antiretroviral Clinic, ABU Teaching Hospital from April 2012. Data was collected using a structured questionnaire. HIV status was determined by DNA-PCR and rapid antibody tests.

Results: A total of 89 subjects, with a male/female ratio of 1:1.2 were studied, out of which 79 (88.8%) were exclusively breastfed (EBF), three (3.4%) formula-fed (FF), while seven (7.9%) were mixed-fed (MF) in the first six months. One subject in the EBF group tested HIV positive at six weeks of age. By 12 months, 42 (53.2%) amongst the EBF group stopped breastfeeding and were HIV negative 12 weeks thereafter. Of the 37 (46.8%) that continued, one tested HIV positive, and three out of seven MF subjects tested HIV positive. Overall postnatal HIV transmission was 4.55%, with an overall HIV free survival (HFS) rate of 95.45% (**98.73%, 100% and 57.12% amongst EBF, FF and MF groups respectively**). The exclusively breastfed group had significantly lower morbidities. By the end of follow-up five (5.6%) subjects were HIV infected, including the first detected at six weeks and four others detected after infancy.

Conclusions: The risk of HIV transmission still prevails despite proven interventions. Morbidities associated with feeding are lowest among exclusively breastfed infants. Adherence to infant feeding decisions remains a key determinant of HIV and morbidity free survival.

Key words: HIV, Postnatal Transmission, Exposed Infants, feeding, PMTCT.

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INTRODUCTION

A major goal of care for HIV exposed infants is to eliminate the risk of HIV transmission and ensure morbidity-free survival while implementing preventive interventions.¹ Studies have established that breastfeeding poses a risk of post-natal mother-to-child transmission (MTCT) but reduces morbidity and mortality,^{2,3,4} while longer periods of breastfeeding pose higher risks of MTCT.^{4,5,6} It is also established that formula feeding removes MTCT risk but predisposes to non-HIV morbidity and mortality.²⁻⁷

The current WHO recommendations on infant feeding in the context of HIV are to counsel HIV positive mothers and provide support to either breastfeed and receive ARVs, or completely avoid all breastfeeding, the rationale for which is to serve as a strategy to ensure the greatest chance of HIV-free survival.^{1,8} Nigeria adopted breastfeeding plus ARVs (also known as Option B) in 2010, which recommended stopping breastfeeding at 12 months conditional to availability of nutritionally appropriate replacement food.⁹

A number of reports on safety and risks of post-natal transmission of HIV studied large cohorts in the community setting for periods ranging between six and 18 months but few of these went up to 24 months.²⁻⁷ This report is from a facility-based observational study on a cohort followed up from four weeks to 24 months.

Objective was therefore, to study the relationships between infant feeding methods and risk of postnatal HIV transmission in a PMTCT setting.

SUBJECTS AND METHODS

The design was that of an observational prospective study of a cohort of HIV exposed infants enrolled into care at the Paediatric ART Clinic of Nasara Treatment Centre, a comprehensive HIV care facility at Ahmadu Bello

University Teaching Hospital, Zaria. At the time of this study the Centre was supported by the APIN/HARVARD PEPFAR Programme for provision of HIV/AIDS related services from 2007 to 2013. Monthly interviews and clinical evaluations were conducted with data collection using a standardized structured profoma. Consecutive HIV-exposed neonates who attended the clinic were enrolled from their first visits at 2-4 weeks of age over a 6-month period. Care services provided for infants were based on the National Guidelines for Prevention of Mother-To-Child Transmission (PMTCT) of HIV 2010.⁹ This included clinical evaluation, Nevirapine (NVP) prophylaxis from birth to six weeks and cotrimoxazole prophylaxis from six weeks till end of breastmilk exposure for those who were breastfed. Dried blood spot (DBS) samples were collected from heel prick samples of blood on Whatman filter paper at six weeks of age for each infant for HIV DNA-PCR testing (GeneAmp PCR System 9700 Perkin-Elmer, Norwalk, Conn, USA) using the manufacturer's instructions. Although further HIV DNA-PCR testing beyond this age as recommended in the National PMTCT Algorithm was planned, this was not possible due to limited availability of resources that allowed for just a single PCR testing for each infant. Rapid HIV antibody tests were employed using parallel testing strategy with Determine™ HIV-1/2 (Alere Medical Co. Ltd, Japan) and Unigold™ HIV (Trinity Biotech Plc, Ireland) rapid test kits, while HIV 1/2 Stat Packkit (Chembo Diagnostic Systems, Inc, USA) was used as tie-breaker kit (where necessary) 12 weeks after cessation of breastfeeding for those who breastfed irrespective of the duration and for all children at 18 and 24 months of age.

Infants were considered HIV infected if the sample for HIV DNA-PCR tested positive or had a positive HIV antibody test result twelve weeks after cessation of breastfeeding and at 18 months of age. If HIV antibody test result was negative

at 18 and 24 months, children were considered to be HIV free for the study period.

ART was commenced for infants who were eligible by a positive DNA-PCR result while cotrimoxazole prophylaxis was provided for all those that were breastfed. Treatment of co-morbidities was also provided for those children that presented with inter-current illnesses during scheduled as well as unscheduled visits. Follow-up care activities included group health education on disease prevention and nutrition as a routine aspect at each visit. Individual counselling was provided on breastfeeding, complimentary feeding and stopping breastfeeding at 12 months where appropriate, while counselling and appropriate support was provided for those who chose formula feeding.

The definitions of exclusive breastfeeding (EBF), replacement feeding (exclusive formula feeding (FF) and mixed feeding (MF) used in this study were as defined earlier.^{2,7} Mixed feeding was considered to have occurred when there was at least one episode of feeding an infant with any food/drinks apart from prescribed medication at age below six months. HIV transmission was considered as late postnatal (via breastmilk) for infants that were HIV (DNA PCR) negative at six weeks of age but tested HIV antibody positive twelve weeks after stopping breastfeeding and/or at 18 months of age. Informed consent was obtained from mothers while ethical approval was sought and obtained from the ABUTH Ethics & Scientific Committee.

The information obtained was captured into a standardized questionnaire. Data entry, cleaning and analysis were performed using Epi-info version 7.0 (2013) and results were presented as contingency tables. Chi-square test was used for comparisons of discrete data and p values of less than 0.05 were considered as statistically significant. For the analysis of morbidities the 24 months follow up period was divided into two periods of the first 12 months (birth to 12 months of age) and the second 12 months (13 to 24 months of age). The frequency of episodes of each illness collated during the monthly clinic visits were added up for each HIV status and infant feeding sub-categories to obtain the cumulative for each of these two follow up periods (before and after 12 months of age).

RESULTS

Eighty-nine HIV-exposed infants, all delivered by spontaneous vaginal delivery, were consecutively enrolled from birth, with a male/female ratio of 1:1.2. The initial infant feeding choice for seventy-nine (88.8%) was EBF, which was later continued with complimentary feeding from 6 months onwards, while three (3.4%) were exclusively formula-fed from birth and were never breastfed. Seven (7.9%) of the infants whose mother's chose EBF initially were later discovered to have had MF.

Maternal PMTCT Care and HIV [Transmission Outcomes

Considering maternal PMTCT care and risk of HIV transmission amongst infants, comparatively more infants became HIV positive amongst those whose mothers did not receive PMTCT care (Table 1). Three out of seven infants (42.9%) whose mothers did not receive PMTCT care were HIV positive by the end of the follow up. One of these was the only HIV DNA-PCR positive infant detected at six weeks, which suggests intrauterine or intra-partum transmission.

Feeding Methods and HIV Transmission Outcomes

Out of the 79 infants that exclusively breastfed, 42 stopped all breastfeeding at 12th month of age and each of these consistently tested HIV antibody negative 12 weeks thereafter, at 18 and 24 months of age. The remaining 37 continued to breastfeed beyond 12 months, out of whom one stopped at 15 months following which HIV test was found to be positive at 18 months of age. All the three formula fed subjects consistently tested HIV negative at 12, 18 and 24 months. The seven mixed-fed subjects continued breastfeeding after the 12th month but stopped between 15th and 22nd months of age. HIV tests carried out 12 weeks after breastfeeding cessation and at 24 months of age revealed that three of these tested HIV positive within the period between 13 and 24 months of follow-up. The only subject positive by DNA-PCR earlier also continued breastfeeding till 20 months.

Overall, 85 subjects across all feeding categories (94.4% of 89) remained HIV negative by 24 months of age while additional four became HIV positive between 13 and 24 months. The HIV transmission rate for the entire cohort was thus 5.6% (five out of 89) and the late postnatal (breastmilk) transmission rate was 5.1% (four out of 78) amongst breastfed infants. The difference between the proportions of HIV infected subjects in the exclusively breastfed sub-group (two infants, or 2.5% of 79) and the mixed-fed sub-group (three infants, or 42.9% of 7) is statistically significant (Table 2).

Outcomes of Clinical Monitoring

There was no mortality amongst subjects during the study period. Table 3 shows the illnesses diagnosed and their frequency at the scheduled clinic visits. All of the illnesses were common infectious disease conditions that were managed as appropriate on outpatient basis.

Relationship between Frequency of Morbidities and HIV status sub-category

The total number of illness episodes experienced by the HIV positive subjects irrespective of feeding method by the end of the follow up was 68, while there were 21 illness episodes over the same period for HIV positive sub-group. Table 4, shows a comparison of frequency of clinic visits associated with illnesses out of the cumulative number of visits for HIV positive and HIV negative sub-categories. There were significantly more morbidity-associated visits amongst HIV infected subjects, which remained same after disaggregation to two periods of follow up (birth to 12 months and 13-24 months).

Relationship between Morbidities, HIV free Survival and feeding method sub-category

Table 5, shows a comparison of frequency of clinic visits with illnesses out of the cumulative number of visits for exclusively breastfed, mixed-fed and formula fed subjects. There were significantly more morbidity-associated presentations amongst mixed-fed and formula fed subjects compared to exclusively breastfed subcategory. The relationship remained significant for the mixed fed subgroup after the period of the visits were divided into two, i.e. before and after 12 months. The difference was however not significant for the period between 13 and 24 months for the formula fed sub-group.

There was no mortality amongst the cohort in this study.

Since four out of five HIV positive subjects amongst the total cohort (89) became HIV infected during the study period (i.e., excluding the only subject found to be HIV positive by DNA-PCR assuming intra-uterine or peripartum transmission) the overall postnatal HIV transmission rate is 4.55% (4/88), and an overall HIV free survival (HFS) rate of 95.45% (85/88). Among the 79 subjects of the EBF group one subject was found to be HIV positive after the infancy period and the transmission rate in this group is therefore 1.27% (1/79) and HFS of 98.73% (78/79). Among the seven subjects in the MF group three subjects became HIV positive after infancy, with a transmission rate of 42.86% (3/7) and an HFS of 57.12%. There was no transmission amongst the three subjects in the FF group and thus the HFS of this group is 100%.

DISCUSSION

The rate of exclusive breastfeeding documented in this study is relatively high (88.7%), suggesting good compliance with recommendations to breastfeed infants while mothers receive antiretroviral interventions.^{1, 8, 9} This rate appears to contrast sharply with the national average reported in the 2013 Nigerian National Demographic and Health Survey (NDHS), which revealed a rate of 17% among infants.¹³ The disparity is probably because our findings were from a setting where ongoing infant feeding counselling was an integral component of the package of comprehensive care being provided for HIV exposed infants. The findings also vary widely with exclusive breastfeeding rates reported from some PMTCT and Paediatric HIV care provider facilities in other parts of Nigeria, e.g., a rate of 18.5% reported by Olatona, et al,¹³ in Lagos, 16.1% by Kalu, et al,¹⁴ in Nnewi, 10% by Oladokun, et al,¹⁵ in Ibadan and 36.3% reported by Anoje, et al,¹⁶ from a multi-centre study in Cross River and Akwa Ibom. All these studies also reported higher rates of infant formula use of between 20.2 and 93.5% in contrast to 3.4% in this report.

The wide disparity in rates of feeding methods for HIV exposed infants between our results and these other reports could be partly attributed to by the variable impact of transitions in infant feeding recommendations between 2006 and 2013. The 2006 WHO guidelines on infant feeding in the context of HIV recommended exclusive breastfeeding for HIV-infected mothers for the first six months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time and avoidance of all breastfeeding when these criteria were met.^{17, 18} Infant formula was then largely provided free to HIV infected women who opted for replacement feeding for their infants to prevent breastmilk transmission. However, subsequent guidelines from 2009 recommended exclusive breastfeeding for HIV exposed infants plus maternal ARV use for at least till when breastfeeding is discontinued (Option B Plus).^{1, 8, 9} This also led to a cessation of provision of infant formula in Nigeria and the choice for use of formula then became determined by affordability of formula milk by individual families. Our study was conducted after the provision of free infant formula has been discontinued in public health facilities in the country and the cost of infant formula became the burden of women (and/or their families) that chose this as their infant feeding option. Although we did not obtain information on determinants of choices of infant feeding, the relatively lower preference for formula feeding in

this study compared to reports from the southern parts of Nigeria,¹³⁻¹⁶ could have been partly due to lack of affordability for formula milk and avoidance of stigma associated with not breastfeeding. The 2013 Nigerian NDHS for instance, revealed a wide gap of wealth quintile distribution within the country, with up to 30-50% of the population in the south belonging to the highest quintile, in contrast to the north where up to 35-40% belong to the lowest quintile.¹² This socio-economic disparity suggests that families in the southern parts of Nigeria may be generally more likely to afford procurement of infant formula milk because of better wealth index compared to the north where this study was conducted.

With only one infant found to be HIV positive by six weeks of age and four others found to be HIV positive between 15-24 months, the postnatal HIV transmission rate amongst breastfed infants was 5.1% (4/79). The infant whose result was positive at six weeks of age most likely suggests either an intra-uterine or intra-partum HIV transmission. The mother of this infant was among those that did not receive PMTCT care. A major constraint that precluded identification of early postnatal transmission during the conduct of this study was lack of a second DNA-PCR test for infants with a first negative PCR result as recommended in National PMTCT Guidelines,⁹ due to limited availability of resources.

The postnatal transmission rate is lower than what has been observed in earlier community-based studies by Iliff, et al² and Read, et al,⁶ who reported transmission rates of 12.1% and 42% respectively, the majority occurring after 6 months of age. These reports had larger cohorts with data pooled from multiple study sites but were carried out with no ARV intervention (before policy on use of ARVs for PMTCT came into existence).^{2, 6} The recognizable risk factors identified among the four subjects found to have had late postnatal HIV transmission in this study included lack of maternal PMTCT care, mixed-feeding and prolonged breastfeeding. Similar risk factors for postnatal HIV transmission were earlier on observed by Peltier, et al,¹⁹ that also reported a cumulative risk of postnatal infection of 0.5% in their pioneer study that provided evidence for the effectiveness of maternal ART use to prevent postnatal HIV transmission.

With there being no mortality amongst the cohort in this study the overall HIV free survival (HFS) rate of the cohort is thus 95.45% at the end of follow up. The HFS rate amongst the EBF group was 98.73%, 100% amongst the FF group and 57.12% amongst the MF group, the latter being the poorest rate. These findings compare somehow with those of a study of 801 HIV exposed infants in Makurdi, North Central Nigeria reported by Anígilájé, et al,²⁰ one of the few published studies on HIV free survival (HFS) in the country and probably the only one from the Northern part. That study reported 196 (24.5%) subjects in the EBF group of subjects, 544 (67.9%) in the FF and 61 (7.5%) in the MF group, with the latter group shown to have the poorest HFS rates of 69.8% at the end of follow up, compared to 92.5% for the EBF group and 86.2% for the FF group.²⁰ Contrary to our finding of HFS rate of 100% among the FF group however (which should be expected if formula feeding was truly exclusive), the HFS rate reported in that study was just 86.2% amongst the FF group, which the authors attributed to undisclosed mixed-feeding. Anígilájé's study,²⁰ also in contrast, had a retrospective design and was conducted at a

time when breast milk substitutes were provided free and before the change in infant feeding recommendations that favour exclusive breastfeeding along with maternal use of highly active antiretroviral drug combination to prevent HIV transmission.

The most common morbidities observed were respiratory tract infection, acute diarrhoeal disease and malaria, which were in keeping with findings reported by Becquet, et al,²¹ who observed similar morbidities in their cohort of HIV exposed infants. Nacro, et al,²² in Burkina Faso, also observed these medical conditions being the commonest but with no difference in their frequency between infant feeding sub-categories.

The cumulative frequency of clinic visits associated with morbidities is significantly higher amongst the five children that were HIV positive compared to that among the 84 un-infected children. The relationship still prevailed regardless of feeding method and even when the follow up period was disaggregated to before and after 12 months of age. Similarly, there was significantly higher cumulative frequency of morbidities amongst mixed-fed children compared to those exclusively breastfed, but with no significant difference between formula-fed and exclusively breastfed groups after 12 months of age. The high rate of EBF perhaps explains the finding of a lower frequency of morbidities amongst exclusively breastfed compared to that in mixed-fed sub-group of infants in this study. The lack of significant difference in morbidity between exclusively breastfed and formula-fed infants could have been because the number (three) of the latter sub-group was rather too small for a valid statistical comparison. However, the advantages of exclusive breastfeeding in the context of HIV has been reported in earlier studies that found higher morbidity and mortality rates amongst mixed-fed as well as formula-fed HIV exposed infants compared to those exclusively breastfed.^{7,10,11.}

Although mothers were instructed to report back to our facility whenever their infants became ill in between scheduled visits, the methodology may have missed some unreported illnesses, likely to have occurred at home during these intervals resulting in data not captured. However, in a review Motarjemi, et al²³, observed that most studies reported generally higher diarrhoeal morbidity and mortality among mixed-fed than exclusively breastfed infants. Other studies from Bangladesh,²⁴ Peru¹¹ and multi-centre study in India, Ghana, and

transmission and compelled us to use of HIV antibody tests for diagnosis of HIV contrary to recommendation of 18 months and over in the guidelines.

In conclusion, although ARV interventions reduce the risk of postnatal HIV transmission the method of infant feeding of exposed infants is an important determinant of the risk of morbidity. The risks of postnatal HIV transmission and that of associated morbidity are lowest amongst exclusively breastfed infants.

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Peru,⁷ also reported lower morbidity rates in exclusively breastfed than formula fed infants, with no difference in the rates between predominantly breastfed and exclusively breastfed infants, attributing the lack of difference to undisclosed mixed-feeding by mothers who chose to exclusively breastfeed.

The limitations of this study include uncertainty of account of adherence to choice of infant feeding. The morbidity information was only limited to presenting illnesses at the clinic visits, with potential for loss of information on illnesses that occurred during intervals between scheduled appointments. The limited availability of DNA-PCR facilities precluded early identification of confirmatory late postnatal

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