HIV-free survival among breastfed infants born to HIV-positive women in post-conflict northern Uganda: a perspective from two tertiary health facilities

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Abstract

Background Without interventions, the risk of mother-to-child transmission of HIV is up to 25% during pregnancy, labour and delivery with an additional risk of 5-20% during breastfeeding period, leading to an overall rate of up to 45%. Giving anti-retroviral therapy to the mother and anti-retroviral prophylaxis to the infant has been shown to significantly reduce the risk of HIV transmission through breastfeeding to less than 5%. According to the World Health Organization standard, the effectiveness of interventions towards prevention of mother-to-child transmission of HIV in any setting is measured by its HIV-free survival rate. We therefore carried out a study aimed at determining the HIV-free survival among breastfed infants in a resource poor setting in relation breastfeeding duration. Methods A cross-sectional retrospective study using routine clinical data and involving 365 HIV exposed infants followed up in two tertiary facilities in northern Uganda between 2014 and 2016. Data was analysed using Statistical Package for Social Scientists version 16 software package. Results Of the three hundred and sixty five (365) infants sampled for this study, 86.8% (317/365) were enrolled within the first 2 months of life, 12.1% (44/365) between 3-12 months of age and 1.1% (4/365) enrolled after 12 months of age. Almost all the infants (98.4%) were initiated on Nevirapine prophylaxis, 97.5% (356/365) of whom were initiated within 72 hours. The overall HIV-free survival rate in the current study was 93.7% (342/365), while 6.3% (23/365) were either HIV-infected (2.7%) or died (3.6%). The infants' age at enrolment was the single most important factor significantly associated with HIV-free survival. The overall duration of breastfeeding did not significantly affect the HIV-free survival: 98.1% (304/310) for children breastfed > 12 months versus 100% (15/15) for those breastfed ≤12 months, though exclusive breastfeeding for at least 6 months was protective. Conclusions Adherence to current approaches to prevention of mother-to-child transmission of HIV with support to breastfeeding in low income countries can greatly enhance HIV-free survival for breastfed infants, and supports the current infant and young child feeding recommendations. Key words: HIV-free survival, Mother-to-child transmission, Breastfeeding, Antiretroviral therapy

Introduction

It is estimated that about 1.8 million (1.3–2.4 million) children were living with HIV in 2017 who were infected by their HIV positive mothers during pregnancy, childbirth and breastfeeding (1), majority of who were in sub-Saharan African countries (2). Despite the fact that the incidence of paediatric HIV is falling as a result of an increase in effective methods to prevent mother-to-child transmission of HIV, an estimated 180,000 (110,000–260,000) new paediatric HIV–1 infections occurred in 2017, primarily through mother-to-child transmission, mainly in sub-Saharan Africa (1). In Uganda, a recent survey estimates that 95,000 children aged 0–14 years were living with HIV in 2017 (3), about 90% of them acquiring the infection through mother-to-child transmission (MTCT). An estimated 7,600 new paediatric HIV infections were registered in the country in 2017, with 3,800 AIDS-related deaths (1).

Without interventions for prevention of mother-to-child transmission of HIV (PMTCT), the rate of maternal-to-child transmission (MTCT) of HIV during pregnancy and delivery is estimated at 15–25%, and the additional risk through breastfeeding is estimated at 5–20% (4, 5). With interventions for PMTCT, transmission reduces to <5% in the breastfeeding population and to <2% in the non-breastfeeding

population, making the prevention of mother to child transmission of HIV (PMTCT) a major public health approach of reducing the scourge (6). Infant feeding recommendations in the context of HIV have evolved over the last decades (7–12) in response to emerging scientific evidence regarding the risk of postnatal transmission through breastfeeding (13–18), and the long-term benefits of longer duration of breastfeeding for both maternal and child health outcomes, highlighting the relevance of supporting breastfeeding in high- and low- income settings alike (12). Earlier reports from Kenya and Botswana demonstrated efficacy of continued ART during breastfeeding in reducing the risk of transmission to 1.1% and 4.2% at 1 and 6 months, respectively (19, 20). However, these studies showed some remaining risk of HIV transmission during breastfeeding, though small (20), and were based on shorter durations of breastfeeding (6–7 months).

In 2010, WHO recommended exclusive breastfeeding (EBF) for six months followed by complementary feeding (CF) and continued breastfeeding up to one year of age for infants of HIV positive mothers, under the cover of antiretroviral treatment (ART) to either the mother or the infant (10). Following this guidance, the Uganda ministry of health released guidelines on infant feeding recommending HIV positive mothers to exclusively breastfeed (EBF) for the first 6 months, introduce appropriate complementary feeds (CF) thereafter while being supported to adhere to ART and continue breastfeeding their infants for the first 12 months, breastfeeding should then only stop once a nutritionally adequate and safe diet can be provided (21, 22). This was in an effort to balance the risk of acquiring HIV through breastfeeding and the higher risk of death from diarrhoea (23), malnutrition and pneumonia among non-breastfed infants in developing countries, where replacement feeding does not usually meet the WHO recommended criteria of being Acceptable, Feasible, Affordable, Sustainable and Safe (AFASS), thus having implications on child survival. In 2016, WHO updated the infant feeding guidelines stating that mothers living with HIV should breastfeed for at least 12 months and may continue breastfeeding for up to 24 months or beyond (similar to the general population) while being fully supported for ART adherence (12), albeit very low quality of evidence. However, these recommendations were based on limited evidence in terms of final HIV-free survival.

Uganda rolled out nationwide implementation of PMTCT option B+ approach in 2013, a policy whereby all HIV-infected pregnant and breastfeeding women are started on combination ART for life, regardless of their WHO clinical stage and/or CD4 cell count, following the World Health Organization (WHO) guidance (11). This was later expanded in a 2016 update of the national guidelines (24) following release of new WHO guidelines in 2015 (25), with recommendation for lifelong ART for all HIV-positive individuals, including pregnant and breastfeeding women, regardless of clinical stage and CD4 count.

Although there are promising results on program effectiveness for the ever evolving interventions for elimination of mother-to-child transmission of HIV, data on the long-term effectiveness of these interventions through the duration of breastfeeding and HIV-free survival in the study setting is scarce. Furthermore, most previous studies in Uganda were mainly confined to centres of excellence, involving urban dwellers. This study therefore aimed to determine the HIV-free survival rate and associated factors among babies born to HIV positive mothers in a post-conflict setting of northern Uganda, in light of the current efforts to elimination of mother-to-child transmission of HIV (eMTCT).

Methods

Study setting

This study was conducted at two tertiary referral hospitals in northern Uganda –Gulu regional referral hospital (GRRH), a public health facility and St. Mary's hospital Lacor, a private not-for-profit facility. These are the two largest hospitals in the district of Gulu and the sub-region at large, serving the population from the entire northern region and beyond. Gulu district is located approximately 340 kilometers North of Uganda's capital city, Kampala, and is bordered by Pader district in the East, Amuru district in the west, Kitgum district in the North East, and Omoro district in the south. The population of Gulu district was estimated at 443,733 (26). Both hospitals run antiretroviral therapy (ART) clinics which provide HIV services to the people of Gulu district and beyond. Northern Uganda is a region recovering from over two decades of insurgency with a high burden of HIV (7.2%) compared to the national prevalence (6.2%) (3) and access to health services still remains a challenge in the district and the region as a whole. Over 37% of the population moves a distance of more than 5 km to reach health services. High levels of poverty and illiteracy, especially among women, is exacerbated by high prevalence of preventable diseases, including HIV/AIDS.

Study design

This was a cross-sectional retrospective study using routine clinical data carried out at two tertiary referral hospitals in Gulu, northern Uganda. The study population comprised all HIV exposed infants who were enrolled and followed up at the two ART facilities between 2014 and 2016. Infants who had complete data and documented final outcome were included in the study, while those who did not complete the recommended period of follow up and whose outcome were not known were excluded. The minimum sample size was estimated using the formula for cross-sectional studies by Leslie Kish (1965) (27) and a standard error of 5%.

Determination of infants' HIV status

The infants final status was based on test results routinely performed using national procedures and algorithms for early infant diagnosis (EID) of HIV. The then Uganda national ART guidelines recommend that all infants born to HIV positive mothers be initiated on Nevirapine prophylaxis at birth according to their risk classifications. Infants were then routinely followed up at 6, 10, and 14 weeks, then monthly until 6 months of age and every 3 months until 18 months of age (24), with a final visit at 24 months. HIV status of infants were determined using national algorithms for early infant HIV diagnosis, and tested by polymerase chain reaction (PCR) for the detection of viral deoxyribonucleic acid (DNA) using dried blood samples (DBS) collected on filter paper at 4–6 weeks of age or at the earliest time thereafter (24). For infants with an initial negative DNA PCR test result, a second DNA PCR test is performed 6 weeks after cessation of breastfeeding. Infants with an initial HIV DNA PCR positive test result had a confirmatory PCR performed at the time of ART initiation. A rapid HIV antibody testing is done at 18 months of age for all infants who test negative at first or second PCR to determine the final HIV status. The national guidelines recommended that all children

below the age of 15 years who are confirmed HIV infected are referred for immediate ART initiation regardless of WHO clinical stage or CD4 count/percentage (22, 24). Infants with negative DNA PCR test results have a HIV rapid test performed at 18 months of age to determine the final status.

Sampling procedure and data collection

Infants' medical records in the Early Infant Diagnosis (EID) register were retrospectively reviewed and a sampling frame for all the eligible infants was written down using codes. A simple random sampling method was then used. Simple random sampling is a probability sampling in which each individual has an equal chance of being selected. The code numbers were written down on pieces of paper which were folded and put in a container. These were properly mixed and then randomly picked with replacement until the calculated sample size was reached.Data was collected using checklists designed in English and contained variables which were selected based on the study objectives. These were filled in by the researchers in relation to the available recorded data in the source documents of both hospitals. Data was double checked for completeness and accuracy at the end of each day of data collection, kept in a safe place out of reach of unauthorized people.

HIV-free survival in this study was defined according to WHO as "an infant or young child born to a mother living with HIV who remains both HIV uninfected (confirmed negative HIV status) and also alive over a defined follow-up period. It is commonly reported at 18 months (as used in the current study) or 24 months of age" (12).

Data analysis

Data were entered, cleaned and analysed using Statistical Package for Social Scientists (SPSS) version 16 software package. In univariate analysis, categorical variables were summarized as proportions, while continuous variables as means and standard deviations (SD). HIV-free survival rate was calculated as the proportion of study infants who were alive with final HIV-negative status at 18 months, the denominator being all infants enrolled in the study. In the bi-variate analysis, the chi-square test (for categorical variables) and student t-test (for continuous variables) were used to test if the factors among infants with negative HIV status at 18 months were different from those among infants with outcomes other than negative HIV status at 18 months. Odds ratios with 95% confidence interval (CI) were used to measure the strength of association between the outcome and predictor variables. Multivariate analysis using logistic regression was used to determine the factors that were independently associated with HIV-free survival. P-value <0.05 was considered for statistical significance. Results were summarized in bar graphs, tables, and texts.

Results

Description of the study population

Three hundred sixty five (365) infants enrolled in care between 2014 and 2016 were sampled from the two ART facilities for this study; 55.1% (201/365) from Gulu regional referral hospital (GRRH) and 164 (44.9%) from St. Mary's hospital Lacor (Figure 1). Over half 55.6% (203/365) of the infants were male and majority 86.8% (317/365) were enrolled within the first 2 months of age, while 12.1% (44/365) were enrolled between 3–12 months of age and 1.1% (4/365) after 12 months of age—with males predominating in each category (Figure 2). The mean age of enrolment of the infants into care was 2.03 (SD 1.91) and almost all, 98.6% (360/365) of the infants were initiated on Nevirapine prophylaxis, majority 97.5% (356/365) of whom were initiated within the recommended 72 hours of birth. Of the infants whose breastfeeding status could be ascertained, 94.5% (345/365) were exclusively breastfed. Overall, majority of the infants 95.4% (310/325) were breastfed for at least 12 months and more, and only 4.6% (15/325) were breastfed for a total duration of less than 12 months (Table 1).

Table 1: Baseline children characteristics of the study population

Characteristics	Number	%
Mean age	2.03 (1.91)*	
Sex:		
Male	203	55.6
Female	162	44.4
Timeliness of enrolment:		
0-2 months	317	86.8
3-12 months	44	12.1
Above 12 months	4	1.1
Treatment facility		
Lacor	164	44.9
GRRH¥	201	55.1
NVP prophylaxis:		
Yes	360	98.6
No	5	1.4
NVP initiation:		
Within 72 hours	356	97.5
After 72 hours	2	0.5
Duration of EBF:		
At least 6 months	100	31.2
Less than 6 months	221	68.8
Total duration of B/feeding:		
12 months & more	310	95.4
Less than 12 months	15	4.6

** Mean and Standard deviation, ¥Gulu regional referral hospital*

Close to two third, 63.3% (231/365) of the mothers to the infants enrolled in this study were known HIV positives, 55.6% (203/365) of whom were on ART before conception. On the other hand, more than one third of the mothers only came to know their HIV positive status either during pregnancy 32.3% (118/365), or

after delivery 4.4% (16/365). One hundred forty four (39.5%) mothers were initiated on ART during pregnancy and 4.9% (18/365) after delivery. Overall, 99.7% (364/365) of the mothers on ART had good adherence. The mean CD4 count of the 240 mothers with documented CD4 test results was 592.94 (SD360.56). Only 12.0% (44/365) of the mothers had their viral load documented (Table 2).

Table 2: Baseline Maternal characteristics of the study population

Characteristics	Number	%
Mean CD4 count	592.94 (360.56)*	
§Viral load:		
≤1000cps/ml	39	88.6
≥1000cps/m	5	11.4
§CD4 Count:		
≥500cells/m3	133	55.4
<500cells/m3	107	44.6
HIV Diagnosis:		
Before pregnancy	231	63.3
During pregnancy	118	32.3
Postpartum	16	4.4
ART initiation:		
Before pregnancy	203	55.6
During pregnancy	144	39.5
Postpartum	18	4.9
Adherence to ART:		
Yes	364	99.7
No	1	0.3

**Mean and Standard deviation, §Only those with documented viral load & CD4 counts were considered).*

HIV-free survival

The HIV-free survival rate, depicted by the proportion of infants discharged HIV-negative was 93.7% (342/365). Majority, 304/310 (98.1%) of the infants who were breastfed for the recommended total duration of 12 months or more were discharged negative, while 1(0.3%) was infected and 5(1.6%) died (Figure 3). Majority of the infants with HIV-free survival at 18 months were males 186/342 (54.4%) and 156/342 (35.6%) were females.

Factors associated with HIV-free survival

The mean age of enrolment of the infants discharged negative (1.97, SD 1.66) was lower than that of the infants who either became HIV infected or died (2.99, SD 4.11) and this was statistically significant, P-value

0.014, $\chi 2 = 6.057$ (Table 3). The infants enrolled in Lacor were 3 times as likely to be discharged negative 97% (159/164) compared to those enrolled at GRRH 91% (183/201), and this was statistically significant, *P* = 0.021, OR = 3.128 (95%CI, 1.135–8.617). Generally, females were twice as likely to have a better outcome (discharged negative) compared to males (96.3% vs. 91.6%) who in contrast were more likely to become infected or die (8.4%Vs 3.7%), but this was not statistically significant, *P* = 0.068, OR = 2.37 (95%CI, 0.915–6.174).

Infants who received nevirapine prophylaxis were about 4 times as likely to be discharged negative 93.9% (338/360) compared to those who did not receive nevirapine prophylaxis 80% (4/5), but this was not statistically significant, *P* = 0.279, OR = 3.841 (95%CI, 0.412–35.839). Similarly, exclusive breastfeeding for at least 6 months was protective as compared to exclusive breastfeeding for less than 6 months, though this was not statistically significant, *P* = 0.407, OR = 1.856 (95%CI, 0.512–6.730). However, there was no difference in HIV-free survival with regards to overall duration of breastfeeding, *P* = 1.000, OR = 1.020 (95%CI, 1.004–1.036) (Table 3).

Table 3: Infants' characteristics associated with HIV-free survival

		HIV Free N=342(%)	Infected/Died N=23(%)	OR[α]	95% CI	*P*-value
¶Mean age		1.97 (1.66)	2.99 (4.11)	6.057[¤]		**0.014***
Enrolment:						
	0-2 months	300 (94.6)	17 (5.4)	2.521	0.941-6.752	0.058
	Above 2mo	42 (87.5)	6 (12.5)			
Sex:	Female	156 (96.3)	6 (3.7)	2.376		0.068
	Male	186 (91.6)	17 (8.4)		0.915-6.174	
Treatment facility:			5 (3.0)	3.128		**0.021***
	Lacor	159 (97.0)	18 (9.0)			
	GRRH	183 (91.0)			1.135-8.617	
NVP prophylaxis:			22 (6.1)	3.841		0.279
	Yes	338 (93.9)	1 (20.0)			
	No	4 (80.0)				
NVP initiation:			21 (5.9)	0.941	0.412-35.839	1.000
	Within 72hrs.	335 (94.1)	0 (0.0)			
	After 72hrs.	2 (100)				
Duration of EBF:			3 (3.0)	1.856		0.407
	At least 6mo	97 (97.0)	12 (5.4)		0.917-0.966	
	< 6months	209 (94.6)				
Total B/feeding:			6 (1.9)	1.020		1.000
	≥ 12 months	304 (98.1)	0 (0.0)			
	< 12 months	15 (100)			0.512-6.730	
					1.004-1.036	

*[α]Unadjusted Odds ratio, [¤]Chi-squared (d.f.=2) reported for categorical variables and unadjusted ANOVA (F statistic) for numerical values, ¶ Mean (SD), *P-value significant (<0.05)*

There was essentially no difference in HIV-free survival between infants whose mothers had viral loads 1000cps/ml 94.9% (37/39) and those whose mothers had viral loads ≥1000cps/ml 100% (5/5), *P* = 1.000. Infants whose mothers' CD4 count was ≥500cells/mm3 were more likely to be discharged negative 94.7% (126/133) than those whose mothers' CD4 count was 500cells/mm3 91.6% (98/107), but this was not statistically significant, *P* = 0.331, OR = 1.653 (95%CI 0.595–4.595). Mothers who were on ART before conception were also more likely to have their infants discharged negative 94.1% (191/203) compared to those who started ART during pregnancy or after delivery 93.2% (151/162), but this was not statistically significant, *P* = 0.731, OR = 1.159 (Table 4).

Table 4: Maternal characteristics associated with HIV-free survival

	HIV Free N=342(%)	Infected/Died N=23(%)	OR$^{\alpha}$	95% CI	*P*-value
§Viral Load					
<1000cps/ml	37 (94.9)	2 (5.1)	0.949	0.882-1.021	1.000
≥1000cps/ml	5 (100)	0 (0.0)			
§CD4 Count					
≥500cells/m3	126 (94.7)	7 (5.3)	1.653	0.595-4.595	0.331
<500cells/m3	98 (91.6)	9 (8.4)			
HIV Diagnosis:					
Before pregn	218 (94.4)	13 (5.6)	1.352	0.576-3.175	0.487
ANC/PNC	124 (92.5)	10 (7.5)			
ART initiation:					
Before conception	191 (94.1)	12 (5.9)	1.159	0.498-2.701	0.731
ANC/PNC	151 (93.2)	11 (6.8)			
Adherence to ART					
Yes	342 (94.0)	22 (6.0)	0.060	0.040-.091	0.063
No	0 (0.0)	1 (100)			

$^{\alpha}$*Unadjusted Odds ratio, §Only those with documented viral load & CD4 counts.*

In the multivariate analysis using logistic regression, age at enrolment and treatment facility were the only independent predictors of HIV free survival. The only other factor that remained in the model even though not statistically significant was maternal adherence to ART (Table 5).

Table 5: Logistic regression for factors independently predicting HIV-free survival

Characteristics	AOR	95% CI	p-value
Age at enrolment	0.363	0.133-0.992	**0.048***
Treatment facility	0.333	0.119-0.927	**0.035***
Adherence	0.000	0.000	1.000

***** *P-value significant (<0.05), OR=Odds ratio, CI=95% confidence interval*

Discussion

This study was carried out to evaluate the HIV-free survival rate at 18 months and associated factors among HIV exposed infants enrolled and followed up between 2014 and 2016 in two tertiary health facilities in Gulu district, northern Uganda. Three hundred and sixty five (365) HIV exposed infants registered in the two facilities were sampled for this study using simple random sampling technique (Figure 1). The mean age of the infants at enrolment was 2.03 (SD 1.91), and more than half of the infants 55.6% (203/365) were males. Majority, 86.8% (317/365) of the infants were enrolled early within the recommended 2 months of age, while 12.1% (44/365) were enrolled between 3–12 months of age and 1.1% (4/365) were enrolled after 12 months of age (Figure 2). Timeliness of enrolment of infants in care as found in the current study shows a better trend compared to that reported by Hassan et al (2012) in rural Kenya where majority of the infants

(68%) were enrolled after 2 months of age (28). This is an important aspect of early infant diagnosis and an indicator which shows the effectiveness of the PMTCT processes. It is likely to relate, albeit as a proxy, to good antenatal attendance and facility delivery under skilled attendance where mothers get opportunities to receive appropriate and effective counselling and interventions for PMTCT.

HIV-free survival

The overall HIV-free survival rate in the current study was 93.7% (342/365), while 6.3% (23/365) of the infants were either HIV-infected (2.7) or died (3.6%) (Figure 3). This finding highlights the impact of the current effort to eliminate mother-to-child transmission of HIV implemented initially as PMTCT option B+, and now as test and treat or treat all (mothers tested and if HIV positive, initiated on lifelong ART regardless of CD4 count or clinical stage, and infants given ARV prophylaxis from birth for 6 or 12 weeks depending on risk classification while mothers are encouraged to exclusively breastfeed for at least 6 months). The 18-months HIV-free survival rate of 93.7% in the study setting therefore falls short of the >95% HIV-free survival rate recommended among breastfeeding populations, but compares well with the 93.2% 24-month HIV-free survival under similar Option B+ program in Rwanda (29). The current rate is also lower than the 95.9% reported in a community-based survey in Swaziland (30), but higher than the pooled estimates of 89.8% and 85.8% for 12-month and 24-month HIV-free survival respectively as reported by Chikhungu et al (2016) in a systematic review of 18 studies evaluating HIV-free survival among breastfed infants of HIV positive women on ART (13). The above differences could largely be explained by the differences in the duration of breastfeeding and maternal ART; timing of measurements of HIV-free survival, and the guidelines or PMTCT approaches used in the different studies. Notwithstanding, these findings seem to lay credence to the effectiveness of option B+ over the earlier approaches towards elimination of mother-to-child transmission (eMTCT) of HIV among breastfeeding population in developing countries.

The infants' age at enrolment was an important factor significantly associated with HIV free survival. Infants discharged negative (HIV-free survival) were six times more likely to have a lower mean age at enrolment into care compared to those who were HIV-infected or died, and this was statistically significant, $P = 0.014$, $\chi^2 = 6.057$. In the multivariate analysis (Table 5) age of enrolment remained a statistically significant independent predictor of HIV-free survival, $P = 0.048$, OR = 0.363. HIV-free survival also differed significantly by the care facilities. There was a significantly higher HIV-free survival rate for infants enrolled in Lacor 97% (159/164) as compared to those enrolled in GRRH 91% (183/201), and this was statistically significant, $P = 0.021$, OR = 3.128. We supposed this could relate to the fact that infants followed up in Lacor hospital were more likely to be enrolled earlier into care (mean age 1.91[SD 1.55]) –a factor positively associated with HIV-free survival, compared to those in GRRH (mean age 2.14[SD 2.16]). This is valid, and is in accord with the WHO recommendation for early infant diagnosis and a finding by Berhan et al (2014) in Ethiopia where infants with delayed DNA PCR tests had a 30% excess risk of mother-to-child transmission of HIV compared to those tested early (31). The mortality rate of 3.6% in the current study was relatively low but higher than the 1.1% reported in Mma Bana trial in Botswana (32), a difference possibly explained by the fact that infants in the Mma Bana trial breastfed for only shorter duration of 6 months (median 5.8 months).

Duration of breastfeeding and HIV-free survival

Without intervention, the absolute risk of a mother transmitting HIV to her child during pregnancy and delivery is estimated at 15–25%, with an additional risk through breastfeeding estimated at 5–20%. However, with interventions for prevention of mother to child transmission of HIV, the transmission rate reduces to less than 5% in the breastfeeding population. In this study 95.4% (310/325) of the infants were breastfed for 12 months or more and only 4.6% (15/325) were breastfed for less than 12 months. This finding correlates well with the current national and WHO recommendations of infant and young child feeding in the context of HIV where mothers living with HIV are advised to continue breastfeeding while receiving complementary foods until 12–24 months of age just like the general population while both mother and infant are receiving ARV interventions for PMTCT (12). The overall duration of breastfeeding did not significantly affect the HIV-free survival; 98.1% (304/310) for children breastfed >12 months vs. 100% (15/15) for those breastfed ≤12 months, P = 1.000, OR = 1.020. This finding compares well with that reported by Alvarez-Uria et al (2012) in India (33) and Peltier et al (2009) in Rwanda (34) where there was no significant difference in HIV-free survival with breastfeeding status, though HIV-free survival was significantly higher among breastfed than formula-fed children in the two reports. In addition, the Rwandan study estimated HIV-free survival at an earlier time interval of 9 months during a different approach to PMTCT and the infants were breastfed for only 5–6 months (exclusive breastfeeding) followed by rapid weaning. In contrast, Mekonnen A, et al (2017) reported a significantly lower 18 months cumulative probability of HIV-free survival in the breast-fed infants and young children (84%) than formula fed counterparts (97%) (35).

While majority (87.9%) of the infants had exclusive breastfeeding (EBF), only 27.4% were exclusively breastfed for at least 6 months as per the guidelines. The overall rate of exclusive breastfeeding in this study, though lower, nears that reported by Okafor et al (2014) in Nigeria of 91.8% (36). However, by implication, the fact that only very few mothers (27.4%) in the study setting are exclusively breastfeeding their infants adequately for at least 6 months should be of concern since it could be a precursor of prevailing misinformation and inherent negative perception about breastfeeding in the context of HIV which calls for more awareness and counselling. By and large, exclusive breastfeeding for at least 6 months in the current study was protective and associated with a better chance of HIV-free survival 97% (97/100) compared to EBF for <6 months 94.6% (209/221), although this was not statistically significant, P = 0.407, OR = 0.539. The above findings could be attributed to the fact that regardless of breastfeeding duration, maternal ART and timely infant ARV prophylaxis are critical factors in prevention of mother-to-child transmission of HIV, in line with the current guidelines.

In the current study, mothers who were on ART prior to pregnancy were more likely to have an HIV-free child compared to those who initiated ART during pregnancy or after delivery, though this was also not statistically significant, P = 0.487, OR = 1.352. This result is similar to that reported in a Cameroonian study in which the 12-month HIV transmission rate where 51% of women were receiving ART prior to pregnancy was low at 1.2% (37), and also compares relatively well with that reported in a study by Hoffman *et al* (2010) where MTCT rate was lower in women who were on HAART before pregnancy (0.7%) compared to women who initiated HAART during pregnancy (5.7%), P = 0.01 (38). Similarly, Oluwayemi et al (2015) in

Nigeria reported a significantly lower risk of HIV transmission among babies whose mothers commenced HAART before pregnancy (3.4%) compared to those whose mothers initiated HAART during pregnancy (5.4%) and after delivery (28.6%) (39). The above results could be explained by the fact that one of the hypothesized benefits of lifelong ART is protection against HIV transmission in subsequent pregnancies, resulting from greater chances of virologic suppression, as also suggested by Gill et al (2017) in a Rwandan study where the substantial proportion of women on ART prior to pregnancy with suppressed viral load (VL) was thought to have contributed to the high effectiveness of PMTCT (29).

Likewise, available evidences also point to the fact that long duration of ART may be associated with high viral load (VL) or viral rebound postpartum which could be associated with increased risk of mother-to-child transmission (29, 40, 41), supporting the importance of VL monitoring during pregnancy and breastfeeding, and continued adherence counselling (29). In the current study, data on maternal viral load suppression and CD4 were very limited, making comparison of HIV-free survival based on these parameters unrealistic. This could probably explain the paradoxical finding seen in table 4 contrary to the well documented evidences that lifelong HAART for mothers with achievement of significant virologic suppression is an important determinant for reducing the risk of MTCT of HIV- the rationale for the current guidelines. VL was not widely available in Uganda within the period for which data was collected for this study.

Infants who received NVP prophylaxis were about 4 times more likely to have a HIV-free survival outcome 93.9% (338/360) compared to those who did not receive NVP prophylaxis 80.0% (4/5), who were in turn more likely to get infected or die, although this was not statistically significant, $P = 0.279$, OR = 3.841. This finding compares well with that by Mandala et *al* (2012) where the estimated 24 month HIV-free survival among those who received Nevirapine prophylaxis was 82% compared to 61% among those who did not receive Nevirapine (42). It is also consistent with the finding from a study by Jamieson *et al (*2012) (43) which showed that infant Nevirapine for 28 weeks was effective in reducing HIV transmission during breastfeeding (43). According to a report by Kahungu et al (2018) and Fisseha and Bereket (2016), infants who did not receive ART prophylaxis at birth had a five-fold risk of being HIV infected compared to those who received prophylaxis (44, 45). Similarly in an Ethiopian study, infants who did not receive ARV prophylaxis were about seven times as likely to test HIV positive compared to ARV-protected infants (31). The above findings are not surprising and are in line with the already known benefits of early infant ARV prophylaxis for PMTCT.

Limitations of the Study

Being a retrospective study with use of secondary data, the information retrieved was incomplete for some infants. Some of the maternal potential factors for vertical transmission could not be exhaustively explored in the study because they were lacking. Our estimates may be an overestimate or underestimate since some infants with undocumented final outcome were not considered.

Conclusion

The overall HIV-free survival rate for breastfed infants in the study setting of 93.7% was below the WHO goal of >95% HIV-free rate in breastfeeding population (virtual elimination of HIV). Overall duration of breastfeeding did not significantly affect HIV-free survival, though exclusive breastfeeding for at least 6 months showed positive relationship with HIV-free survival.To improve on the outcome of HIV free survival, early enrolment of HIV exposed infants into comprehensive care should be emphasized and adhered to. In addition, adherence to the infant feeding guidelines should be encouraged with emphasis on exclusive breastfeeding for at least 6 months, while both mother and infant are on ART and ARV prophylaxis respectively.

List Of Abbreviations

WHO: World Health Organization; HIV: Human Immunodeficiency virus; ART: Antiretroviral Therapy; ARV: Antiretroviral; GRRH: Gulu Regional Referral Hospital; MTCT: Mother-to-child transmission; PMTCT: Prevention of mother-to-child transmission; eMTCT: Elimination of mother-to-child transmission; AIDS: Acquired Immunodeficiency Syndrome; EBF: Exclusive Breastfeeding; CF: Complementary Feeding; AFAAS: Acceptable, Feasible, Affordable, Sustainable and Safe; DNA: Deoxyribonucleic Acid; PCR: Polymerase Chain Reaction; DBS: Dry Blood Spot; EID: Early Infant Diagnosis; HAART: Highly Active Antiretroviral Therapy; VL: Viral Load.

Declarations

Ethics approval and consent to participate

The study was approved by Gulu University Research and Ethics Committee (GUREC) and permission to conduct the study and access records was granted by the respective research committees of the respective hospitals. Being a retrospective study the patient consent was deemed unnecessary. However, the identity of the participants was kept confidential by using participants' codes and not names.

Consent for publication

Participants' consent to publish this manuscript was not applicable since the manuscript does not contain any participants' personal data.

Availability of data and materials

The dataset supporting the conclusions of this article is available on request to the corresponding author.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to design of the study. AI, KC, AP and MS participated in data collection and entry. NR performed the statistical analysis. All authors participated in drafting the manuscript. All authors read and approved the final manuscript.

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References

1.UNAIDS data 2018. available at: https://www.unaids.org/en/resources/documents/2018/unaids-data–2018.

2.Dube Q, Dow A, Chirambo C, Lebov J, Tenthani L, Moore Ma, et al. Implementing early infant diagnosis of HIV infection at the primary care level: experiences and challenges in Malawi. Bulletin of the World Health Organization. 2012;90(9):699–704.

3.Uganda Population-based HIV Impact Assessment (UPHIA 2016–2017), August 2017; available from: https://www.afro.who.int/sites/default/files/2017–08/UPHIA%20Uganda%20factsheet.pdf.

4.WHO, UNICEF, UNAIDS, UNFPA. HIV Transmission Through Breastfeeding A Review of Available Evidence An Update from 2001 to 2007; available from: www.who.int/nutrition/topics/Paper_5_Infant_Feeding_bangkok.pdf.

5.UNAIDS: Global Report: UNAIDS Report on the Global AIDS Epidemic. Geneva: 2012. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120 unaids_global_report_2012_with_annexes_en.pdf.

6.World Health Organization, WHO antiretroviral therapy for infants and children. Report of the WHO Technical Reference Group, Paediatric HIV/ART Care Guideline Group meeting. Geneva: World Health Organization; 2008.

7.World Health Organization. Consensus statement from the WHO/UNICEF consultation on HIV transmission and breastfeeding, Geneva, 30 April–1 May 1992. Geneva: World Health Organization; 1992.

8.World Health Organization. New data on the prevention of mother-to-child transmission of HIV and their policy implications: conclusions and recommendations: WHO technical consultation on behalf of the UNFPA. In: WHO technical consultation. Geneva: World Health Organization; 2001.

9.World Health Organization. HIV and infant feeding: update based on the technical consultation held on behalf of the inter-agency task team (IATT) on prevention of HIV infections in pregnant women, mothers and their infants, Geneva, 25–27 October 2006. Geneva: World Health Organization; 2007.

10.World Health Organization. Guidelines on HIV and infant feeding 2010: principles and recommendations for infant feeding in the context of HIV and a summary of evidence. Geneva: World Health Organization; 2010.

11.World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2013.

12.World Health Organization. Guideline Updates on HIV and infant feeding: the duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV. Geneva: World Health Organization; 2016.

13.Chikhungu LC, Bispo S, Rollins N, Siegfried N, Newell ML. HIV-free survival at 12–24 months in breastfed infants of HIV-infected women on antiretroviral treatment. Tropical Med Int Health. 2016;21(7):820–8.

14.Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med. 2010;362(24):2282–94.

15.Chikhungu L, Bispo S, Newell M. Postnatal HIV transmission rates at age six and 12 months in infants of HIV-infected women on ART initiating breastfeeding: a systematic review of the literature. Commissioned for the guideline review. In: guideline: updates on HIV and infant feeding: the duration of breastfeeding, and support from health services to improve feeding practices among mothers living with HIV. Edn. Geneva: World Health Organization. 2016.

16.Bispo S, Chikhungu L, Rollins N, Siegfried N, Newell M-L. Postnatal HIV transmission in breastfed infants of HIV-infected women on ART: a systematic review and meta-analysis. J Int AIDS Soc. 2017;20(1):21251.

17.Coutsoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM. Method of feeding and transmission of HIV–1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. AIDS. 2001;15(3):379–87.

18.Iliff PJ, Piwoz EG, Tavengwa NV, Zunguza CD, Marinda ET, Nathoo KJ, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV–1 transmission and increases HIV-free survival. AIDS. 2005;19(7):699–708.

19.Thomas T, Masaba R, Borkowf C, Ndivo R, Zeh C, Misore A, et al. Triple-antiretroviral prophylaxis to prevent mother-to-child HIV transmission through breastfeeding-the Kisumu Breastfeeding Study, Kenya: a clinical trial. PLoS Med 2011:8: e100105.

20.Shapiro R, Hughes M, Ogwu A, Kitch D, Lockman S, Moffat C, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. N Engl J Med 2010;362:2282–94.

21.Ministry of Health of the Republic of Uganda. The new National Guidelines (2010) for PMTCT and infant feeding in the context of HIV. In: Ministry of Health knowledge management portal; 2010.

22.Ministry of Health, Uganda. Addendum to the National Antiretroviral Treatment Guidelines, December 2013.

23.Kafulafula G, Hoover DR, Taha TE, Thigpen M, Li Q, Fowler MG, et al. Frequency of gastroenteritis and gastroenteritis-associated mortality with early weaning in HIV–1-uninfected children born to HIV-infected women in Malawi. J Acquir Immune Defic Syndr. 2010;53(1):6–13.

24.Ministry of Health, Uganda. Consolidated Guidelines for Prevention and Treatment of HIV in Uganda, December 2016. Available from: https://aidsfree.usaid.gov/sites/default/files/uganda_hiv_gl_2016.pdf.

25.World Health Organization. Guidelines on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. Geneva, Switzerland: World Health Organization; 2015. Available from: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.

26.Uganda bureau of statistics (UBOS). Findings from the national population and housing census 2014. Available from; https://www.ubos.org/…/03_20182014.

27.Leslie Kish. Survey Sampling. John Wiley and Sonsa. New York. 1965:59–60.

28.Hassan AS, Sakwa EM, Nabwera HM, Taegtmeyer MM, Kimutai RM, Sanders EJ, et al. Dynamics and Constraints of Early Infant Diagnosis of HIV Infection in Rural Kenya. AIDS Behav 2012;16:5–12; DOI 0.1007/s10461–010–9877–7.

29.Gill MM, Hoffman HJ, Ndatimana D, Mugwaneza P, Guay L, Ndayisaba GF, et al. 24-month HIV-free survival among infants born to HIV-positive women enrolled in Option B+ program in Kigali, Rwanda. The Kabeho Study. Medicine. 2017;96:51.

30.Caspian Chouraya, Rhoderick Machekano, Simangele Mthethwa, Krysia Lindan, Munamato Mirira, Kwashie Kudiabor, et al. Mother-to-Child Transmission of HIV and HIV-Free Survival in Swaziland: A Community-Based Household Survey. AIDS and Behavior 2018;22:S105–S13.

31.Berhan Z, Abebe F, Gedefaw M, Tesfa M, Assefa M, Tafere Y. Risk of HIV and associated factors among infants born to HIV positive women in Amhara region, Ethiopia: a facility based retrospective study. BMC Research Notes. 2014;7:876: http://www.biomedcentral.com/1756–0500/7/876.

32.Shapiro RL, Kitch D, Ogwu A, Hughes MD, Lockman S, Powis K, et al. HIV transmission and 24-month survival in a randomized trial of HAART to prevent MTCT during pregnancy and breastfeeding in Botswana (The Mma Bana Study). AIDS. 2013;27(12):1911–20.

33.Alvarez-Uria G, Midde M, Pakam R, Bachu L, Naik PK. Effect of Formula Feeding and Breastfeeding on Child Growth, Infant Mortality, and HIV Transmission in Children Born to HIV-Infected Pregnant Women Who Received Triple Antiretroviral Therapy in a Resource-Limited Setting: Data from an HIV Cohort Study in India. ISRN pediatrics 2012;2012:763591.

34.Peltier CA, Ndayisaba GF, Lepage P, van Griensven J, Leroy V, Pharm CO, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. AIDS (London, England) 2009;23(18):2415–23.

35.Mekonnen Assefa, Alemayehu Worku, Aman Yesuf. HIV-free survival and morbidity among breast-fed and formula-fed infants and young children in a prevention of MTCT of HIV program in Addis Ababa, Ethiopia, 2014. Asian Pac J Trop Dis. 2017;7(4):225–32.

36.Okafor II, Ugwu EO, Obi SN, Odugu BU. Virtual elimination of mother-to-child transmission of human immunodeficiency virus in mothers on highly active antiretroviral therapy in Enugu, South-Eastern Nigeria. Ann Med Health Sci Res. 2014;4:615–8.

37.Altan AM, Taafo F, Fopa F, et al. An assessment of Option B implementation for the prevention of mother to child transmission in Dschang, Cameroon: results from the DREAM (Drug Resource Enhancement against AIDS and Malnutrition) cohort. Pan Afr Med J. 2016;23:72.

38.Hoffman R, Black V, Technau K, van der Merwe KJ, Currier J, Coovadia A, et al. Effects of Highly Active Antiretroviral Therapy Duration and Regimen on Risk for Mother-to-Child Transmission of HIV in Johannesburg, South Africa. J Acquir Immune Defic Syndr. 2010;54(1):35–41. doi:10.1097/QAI.0b013e3181cf9979.

39.Oluwayemi IO, Olatunya SO, Ogundare EO. PCR Results and PMTCT Treatment Outcomes among HIV-Exposed Infants in a Tertiary Hospital in Nigeria, 2010–2014. International Journal of MCH and AIDS 2015;3(2):168–73.

40.Gill MM, Hoffman HJ, Bobrow EA, et al. Detectable viral load in late pregnancy among women in the Rwanda option B+ PMTCT program: enrollment results from the Kabeho study. PLoS One 2016;11:e0168671.

41.Huntington S, Thorne C, Newell M-L, et al. The risk of viral rebound in the year after delivery in women remaining on antiretroviral therapy. AIDS. 2015;29:2269–78.

42.Mandala J, Moyo T, Torpey K, Weaver M, Suzuki C, Dirks R, et al. Use of service data t inform pediatric HIV-free survival following prevention of mother-to-child transmission programs in rural Malawi. BMC Public Health. 2012;12:405; doi:10.1186/471–2458–12–405.

43.Jamieson DJ, Chasela CS, Hudgens MG, King CC, Kourtis AP, Kayira D, et al. Maternal and infant antiretroviral regimens to prevent postnatal HIV–1 transmission: 48-week follow-up of the BAN randomised controlled trial. Lancet. 2012;379(9835):2449–58. doi:10.1016/S0140–6736(12)60321–3.

44.Kahungu MM, Kiwanuka J, Kaharuza F, Wanyenze RK. Factors associated with HIV positive sero-status among exposed infants attending care at health facilities: a cross sectional study in rural Uganda. BMC Public Health. 2018;18:139; DOI 10.1186/s12889–018–5024–6.

45.Fisseha Wudineh, Bereket Damtew. Mother-to-Child Transmission of HIV Infection and Its Determinants among Exposed Infants on Care and Follow-Up in Dire Dawa City, Eastern Ethiopia. AIDS Research and Treatment. 2016:6; http://dx.doi.org/10.1155/2016/3262746.

Figures

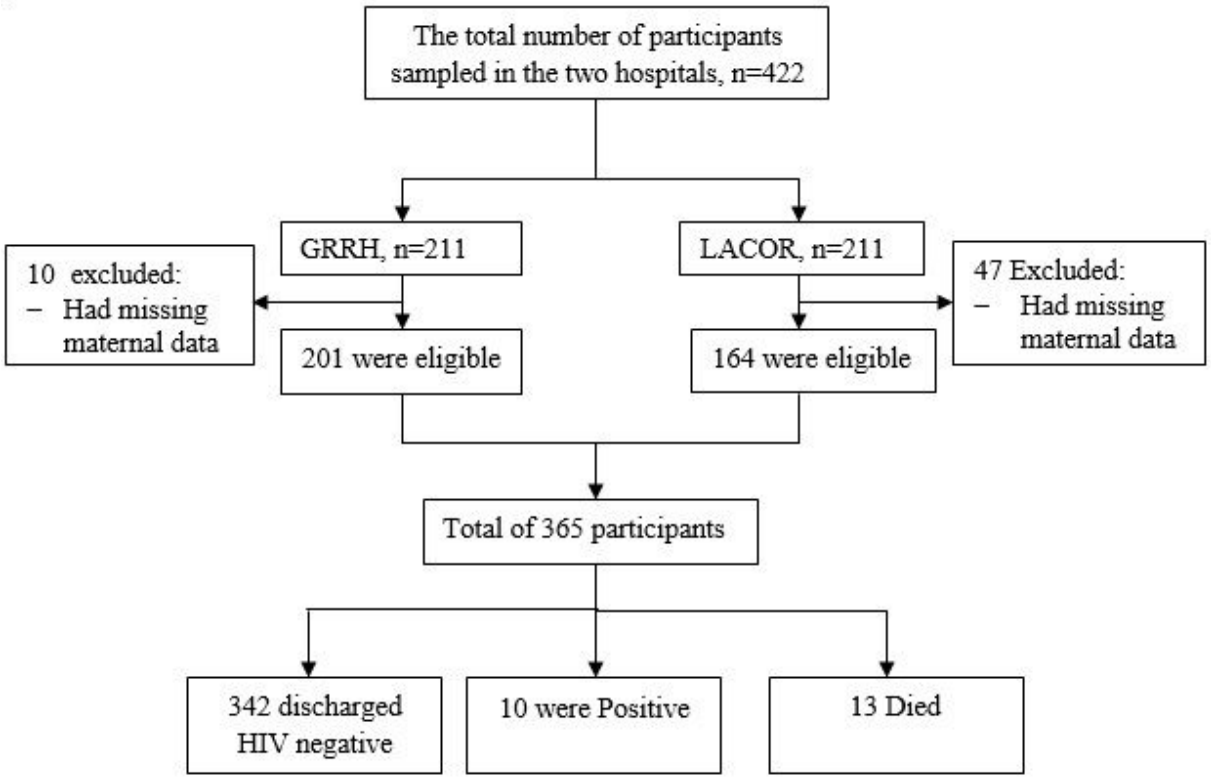

Figure 1

Study profile

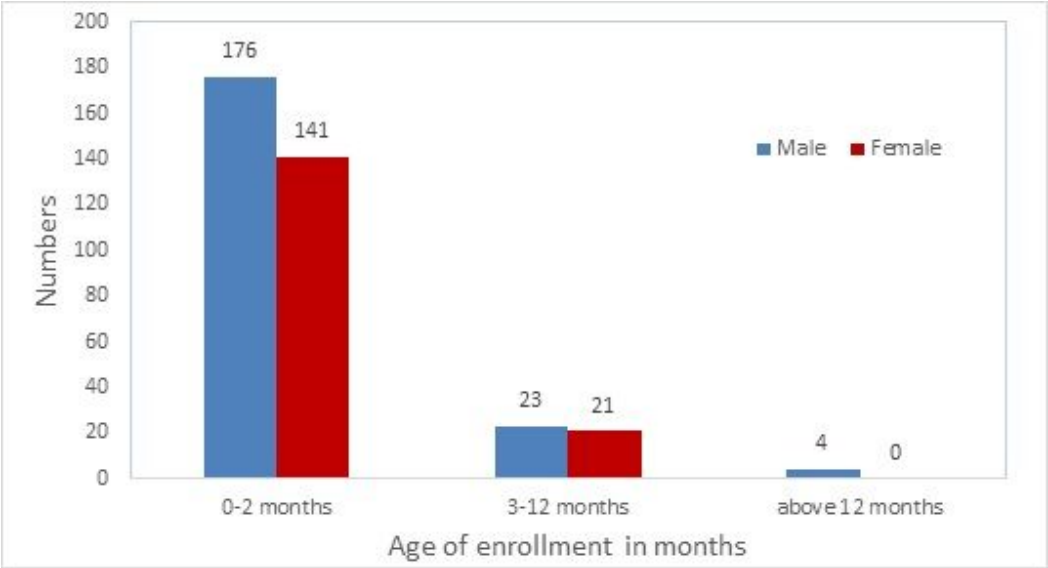

Figure 2

Age-Sex distribution of the study population.

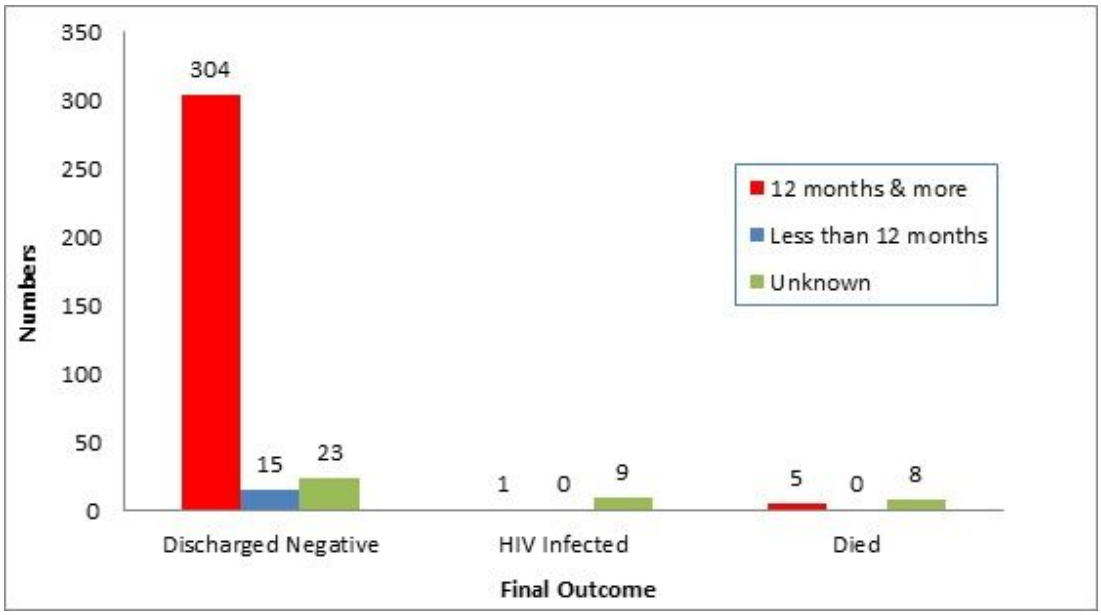

Figure 3

Final outcome disaggregation by duration of breastfeeding.