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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

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ABSTRACT

Objective: To compare the HIV free survival and morbidity of breast- and formula-fed infants and young children of HIV infected women in the prevention of mother to child HIV transmission program.

Methods: Retrospective cohort study designs were employed from September 12, 2008 to February 28, 2014 to compare free HIV survival of exposed infants and young children whose age is < 18 months and were on breast-fed and formula-fed. Data were retrieved from 857 randomly selected study subjects (291 formula-fed and 566 breast-fed infants and young children). Morbidity and HIV infection (the counterpart of HIV-free survival) in the two feeding modalities were compared by using Kaplan-Meier time-to-event methods and log rank test was used to compare HIV free survival between the two groups. Cox regression analysis was employed to assess the independent predictors.

Results: Overall probability of HIV free survival in formula-fed infants and young children was significantly higher than breast-fed infants and young children (log rank test statistics = 6.13, *df* = 1, *P* = 0.013). Breast-fed infants and young children had four (adjusted HR = 3.8, 95% *CI* 1.3–11.1) times higher risks to acquire HIV infection as compared to formula-fed infants and young children. Mothers who didn't use any prevention of mother to child transmission of HIV intervention had five fold risk to transmit HIV infection to their infants than their counterparts (adjusted HR = 4.8, 95%*CI* 1.1–22.5). There was no statistically significant difference in the risk of developing any types of morbidity between the two groups.

Conclusions: The 18 months cumulative likelihood of HIV free survival was significantly lower in the breast-fed infants and young children as compared to formula-fed infants and young children.

1. Introduction

Globally, 36.7 million people were living with HIV and 35 million people have died from AIDS-related illnesses since the start of the epidemic[1]. In Saharan Africa, an estimated 13.8 million women of childbearing age were living with HIV in 2014. With the rapid global expansion of effective strategies to prevent mother-to-child transmission of HIV, more than one million HIV exposed uninfected infants were born during 2014. Similarly an increasing proportion of HIV-exposed children are born uninfected annually and HIV exposed uninfected children have been reported to have higher than expected risks of mortality and morbidity[2,3]. Even though the incidence of pediatric HIV acquisition is falling, over 240 000 children were newly infected with HIV primarily through mother-to-child transmission in 2013[4]. In sub-Saharan Africa, only 65% of HIV-infected pregnant women receive antiretroviral therapy and access to therapy during breastfeeding is still lower[5]. Ethiopia, with an estimated 1.1 million people living with HIV, has one of the largest populations of HIV infected people in the world. Though, there is lower prevalence HIV among adult population than in many sub-Saharan African countries[6].

The context of HIV infection, under the cover of antiretroviral treatment to either the mother or the infant, the 2010 World Health Organization (WHO) infant feeding guidelines recommended exclusive breastfeeding for 6 months followed by complementary feeding and continued breastfeeding for about 1 year[7]. However, these recommendations were relied on limited evidence in terms of

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HIV-free survival to infants where the infant received prophylaxis to prevent mother-to-child transmission[8].

HIV-free survival among HIV-exposed infants is likely to improve by extending the period of breastfeeding to 24 months or beyond, especially in settings with a significantly increased risk of infant and child mortality associated with replaced feeding as compared to exclusive breastfeeding. Nevertheless, if maternal antiretroviral therapy (ART) adherence is inconsistent, the potential for HIV transmission increases. In settings where health systems do not reliably provide ART and where maternal adherence is not high, this may result in transmitting HIV to children who are still breastfed[9]. Analysis of 2013 data shows that the risk of mother to child transmission rate was 7% for those breastfed for 6 weeks and 16% risk at the ends of breastfeeding. Depending on the duration of breastfeeding, the rate of HIV transmission from an HIV-positive mother to her child ranges between 30% and 45% if she is not receiving any antiretroviral[10].

Prevention of mother-to-child transmission has been proven to reduce the risk of mother-to-child transmission from 20%–45 % to 5% or less in breastfeeding populations and 2% in non-breastfeeding populations[11]. Despite the recent improvement in Prevention Of Mother To Child Transmission (PMTCT) service coverage from 10% in 2004 to 67% in 2013 in low and middle income countries, however, uptake and retention of mothers and newborn in PMTCT is below the target level[4,11]. In Southern and Eastern Africa, where child mortality rates are among the highest in the world, HIV infection is common and a leading cause of death. In these settings, use of commercial breast-milk substitutes and other replacement feeds among infants not exposed to HIV is associated with significantly increased morbidity and mortality. Moreover, the evidence for the long-term benefits of longer duration of breastfeeding for both maternal and child health outcomes, including child development and prevention of non communicable diseases, highlight the relevance of supporting breastfeeding in high- and low-income settings alike[9].

In settings in which diarrhea, pneumonia and under nutrition were still common causes of infant and child mortality, mothers were advised to exclusively breastfeed their infants for the first 6 months of life, to introduce appropriate complementary foods thereafter and to continue breastfeeding for the first 12 months of life. Mothers living with HIV should then consider stopping breastfeeding at 12 months if they are able to provide a nutritionally adequate and safe diet without breast milk[9]. The risk of mortality among young children after 12 months of age is lower than the risk of the first 12 months of life. Even though breastfeeding for longer periods has many other health benefits, it has less impact on mortality in this later period[12]. In the absence of ART, it is also associated with an increased risk of postnatal transmission of HIV. Breastfeeding is very acceptable to mothers living with HIV when antiretroviral (ARV) drugs are available and exclusive breastfeeding is promoted to reduce non-HIV-related morbidity and mortality. This would provide insight for the rationale and also help to promote exclusive breastfeeding[9]. The evidence suggests that breastfeeding may improve the growth and non-HIV infection outcomes of HIV-exposed infants[13]. Earlier cessation of breastfeeding among HIV-exposed infants whose mothers received ART was associated with dietary deficiencies[14]. Weight-for-height and length-for-age were comparable among HIV-exposed infants who were breastfed by mothers receiving ART and infants receiving quality complementary foods[15].

Estimates of HIV-free survival at 18 months were 89% for infants whose mothers were receiving ART to 6 months postnatally and 96.1% for infants with mothers receiving lifelong ART[16]. The relative risk of infant and child mortality associated with replacement feeding compared to exclusive breastfeeding and ART duration, the underlying infant, child and under-five mortality rates were found only to influence optimal breastfeeding duration. And in settings with low to moderate relative risk of replacement feeding, the optimal breastfeeding duration is 12 months, and at very high risk, the optimal breastfeeding duration is 24 months, regardless of the underlying child mortality rates[17]. If a net benefit in terms of HIV-free survival could be accomplished, the increased risks of mortality due to artificial feeding among HIV-exposed uninfected infants might be justifiable. The lower risk of HIV transmission for formula fed uninfected children was outweighed by the increased risk of mortality[18]. It is more difficult to quantify the instantaneous hazard of infection during early or later periods of breastfeeding because it is logical that the post-natal transmission rate increases as infections accumulate with each month of additional exposure with breastfeeding duration. Meanwhile breastfeeding tends to result in better nutritional outcomes, besides protecting wastage of under-fed and obesity in over-fed population; in addition, breastfeeding is a significant protector against respiratory disease, diarrheal disease and other infections[18]. The mortality reductions associated with breastfeeding became relatively greater than the risks of mother to child transmission of HIV, and HIV free survival was maximized with longer breastfeeding durations. At the extreme relative risk of replacement feeding, HIV free survival ranged from 64.7% to 88.8% and HIV free survival was maximized by breastfeeding durations[19]. Compared to the public health approach, individualized approach could lead to moderate benefits only when relative risk of replacement feeding is very low or very high or ARV availability is limited; some providers may already be individualizing feeding recommendation in such situations[20,21]. WHO 2010 and 2013 HIV and infant feeding guidelines emphasize a goal of infant HIV-free survival to simultaneously consider risks of HIV and those of infection-related deaths and address the dilemma facing HIV-infected women. The guidelines recommend the choice at country or program level between avoidance of breastfeeding where water supplies are safe and infant formula quantity is adequate, and 12 months of breastfeeding with infant or maternal ARV prophylaxis[22]. In Ethiopia, there is a shortage of data on mortality and HIV free survival of infants and young children of mothers who infected with HIV and the associated risk and benefit of formula and breastfeeding to enhance HIV-free survival of infants and young children. Therefore, this study tried to bring scientifically sound data on the aforementioned gaps and would have paramount importance for the evaluation of the various feeding and the effectiveness of PMTCT program.

2. Materials and methods

2.1. Study design, setting and period

A retrospective cohort study was employed from September 12, 2008 to February 28, 2014. The study was conducted in the capital city of Ethiopia, Addis Ababa and the city was divided into 10

administrative sub-cities. According to Ethiopian Central Statistical Authority July 2013 projection, Addis Ababa has a total population of 3 103 673, consisting of 1 478 890 men and 1 624 783 women. The adult HIV prevalence from 15 up to 24 years in Addis Ababa is estimated to be 8.8% of which the major HIV infections occur through heterosexual contact[23]. HIV prevalence in Addis Ababa is 6% based on the 2011 Ethiopian Demographic and Health Surveys report[24]. In Addis Ababa, a total of 32 public health facilities were providing PMTCT services and only 68% of deliveries were attended by skilled health personnel in 2010/11. In 2010/11, with the highest prevalence of HIV infection among women (11%) than men (7.3%), the prevalence of HIV among adults aged 15–49 years and among pregnant women attending ANC clinics were 9.2% and 5.8%, respectively. Of 3 643 HIV-positive pregnant women identified, only 46% were provided with ARV prophylaxis for PMTCT of HIV[25]. Moreover 18% and 9% of the respondents attended the facility for HIV counseling and testing (HCT) and received antiretroviral prophylaxis respectively. This was obtained from 94% of the pregnant women who visited the health facility for ANC check-up[26]. Integrated and "Opt-Out" approaches are re-enforced as the most appropriate strategies for expanding national access and sustainability of PMTCT services in the country. Ethiopia has adopted the WHO/UNICEF/UNAIDS 4-pronged PMTCT strategy as a key entry point to HIV care for women, men and families[27].

2.2. Sample size and sampling procedure

All HIV exposed infants and young children whose feeding type is determined as breast or formula feeding and 18 or less months of age that have completed the PMTCT follow up were included in this study. However, infants and young children who were transferred in, mixed feeding and those whose feeding practice were unknown were excluded from this study. The size of the sample was determined by using two-population proportion formula according to the following assumptions: 5% level of significance (two-sided), a power of 80% and a 1:1 ratio of exposed group to unexposed, estimated proportion of HIV free survival 57.5% for breast fed and 70% formula fed infants and young from the study conducted in Kenya has been considered[28]. Therefore, the calculated total sample size was anticipated by taking the design effect of 1.5 and considering 10% incomplete or inconsistent data. However, in practice, 566 breast-fed and 291 formula-fed infant and young children were included. Thus, the total sample size was 857. To recruit the pre-determined sample size, simple random sampling technique was used and the study subjects were selected from the clinic computerized registry. Then computer generated random number was used to select study subjects among the eligible cards by considering the registration number.

Data extraction form was prepared in English and it consists of four sections: Maternal socio-demographic characteristics, maternal clinical conditions, infant feeding types and infant clinical characteristic variables.

2.3. Data collection tools and procedures

Six clinical nurses and one public health expert were used as data collectors and supervisor respectively. To assure the data quality, training was given for data collectors and supervisor for a day. The data collection instrument was pre-tested on 2% of the eligible study subjects from Bole 17 Health Center and the supervisors and principal investigator was closely monitored the data extraction process.

2.4. Operational definition

Breast feeding: Exclusive breastfeeding for the first 6 months and introduce complementary feeding at 6 months and continue breastfeeding until 12–18 months.

Formula feeding: Exclusive replacement of feeding for the first 6 months and adequate complementary feeding and formula thereafter for those who fulfill the AFASS criteria.

HIV-free survival-child is alive without acquiring HIV infection.

Any types of morbidity – In this study if infants and young children developing at least one types of morbidity from the following: GLP, diarrhea, acute gastro enteritis (AGE) with or without dehydration, pneumonia or lower respiratory tract infection (LRTI), otitis media or hepatomegaly during the follow up time.

2.5. Data management and analysis

Epi info for window version 3.5.3 software was used for data entry and then data were exported into SPSS version 16 and STATA version11 statistical software for cleaning and analysis. The HIV free survival status of infants and young children were presented by using actuarial life table analysis. Infants and young children morbidity and the complement of HIV free survival *i.e.* HIV infection in the two feeding modalities were compared by using Kaplan-Meier time-to-event methods. HIV free survival of breast-fed and formula-fed infants and young children was compared by using log-rank test. Multivariate Cox regression analysis was performed to see the independent effects of determinant variables after the Cox proportional hazard assumption was checked. All explanatory variables with P-value of < 0.2 on the bivariate Cox regression analysis were fitted into multivariate Cox regression model after the multicollinearity assumption was assessed.

2.6. Ethical consideration

We obtained ethical approval from research and ethics committee of Addis Ababa University, School of Public Health and written permission was obtained from Addis Ababa City Administration Health Bureau (AACAHB). Then the school of public health wrote support letter for each health facilities where this study was conducted. Verbal permission had been obtained from respective health facilities. Since medical records of the clients were reviewing for this study, the individual child was not imposed to any damage as far as the confidentiality is maintained. Assent was obtained from mothers or care takers who were in the hospital during record review. Moreover, no personal identifiers were used on data extraction form.

3. Results

3.1. Maternal Socio-demographic characteristics

Mother-infant pair data were retrieved from 857 (97.2%) of 882

records; 566 from breast-fed and 291 formula-fed infants and young children. The mean (± SD) age of the mothers were 29 (± 4.4) years among breast-fed group and 29.4 (± 3.9) among formula-fed group. Majority of the mothers 373 (79.2%) in breast-fed group and 180 (80.4%) in formula-fed group were married and 205 (57.4%) and 62 (35.0%) of mothers were unemployed in breast-fed and formula-fed group, respectively. From the total of 608 women, more than a third 154 (37.7%) in breast-fed and more than half 105 (52.5%) in formula-fed group had secondary level education, respectively. There was no statistically significant difference between the two cohorts of each attributes of socio-demographic variables except mothers' employment status and level of education (χ^2 = 24.9, P = 0.000 1 and χ^2 = 18.0, P = 0.0001), respectively (Table 1).

Table 1

Socio-demographic characteristics of mothers on selected health facilities in Addis Ababa, September 2008 to February 2014.

Variables	Breast-fed [*n* (%)]	Formula-fed [*n* (%)]	χ^2, *df*	*P*-value
Age of mother [*n* (mean ± SD)]	482 (29.0 ± 4.4)	235 (29.4 ± 3.9)[#]		
No. of rooms			1.4, 1	0.2
Living in 1 room	110 (42.8%)	43 (36.4%)		
Living in ⩾ 2 rooms	147 (57.2%)	75 (63.6%)		
No. of peoples in the HH			2.2, 2	0.3
1 person	11 (3.7%)	5 (3.4%)		
2–3 persons	157 (52.9%)	88 (60.3%)		
⩾ 4 persons	129 (43.4%)	53 (36.3%)		
Source of drinking water			0.3, 1	0.6
Pipe water	4 (1.3%)	3 (1.9%)		
Running water	297 (98.7%)	151 (98.1%)		
Mothers marital status			5.6, 2	0.06
Never married	61 (13.0%)	18 (8.0%)		
Married	373 (79.2%)	180 (80.4%)		
Separated/divorced/ Widowed	37 (7.9%)	26 (11.6%)		
Mothers employment status			24.9,2	0.000 1[*]
Working full time	93 (26.1%)	63 (35.6%)		
Working part time/not Working due to ill	59 (16.5%)	52 (29.4%)		
Unemployed /others	205 (57.4%)	62 (35.0%)		
Mothers levels of education			18.0, 3	0.000 1[*]
No education	50 (12.3%)	15 (7.5%)		
Primary	183 (44.9%)	63 (31.1%)		
Secondary	154 (37.7%)	105 (52.5%)		
Tertiary	21 (5.1%)	17 (8.5%)		
Mothers religions			3.3, 3	0.3
Orthodox	296 (72.7%)	155 (78.7%)		
Protestant	69 (17.0%)	28 (14.2%)		
Muslims	41 (10.1%)	13 (6.6%)		
Catholic	1 (0.2%)	1 (0.5%)		

[*]: Significant at α = 0.05; [#]: *T*-test statistics for independent sample test used; HH: Household.

3.2. Delivery and clinical characteristics of infants and young children

The majority of the infants were delivered at hospital 528 (94.1%) in breast-fed group and 268 (92.7%) in formula-fed groups. And 436 (81.8%) of breast-fed infants and 203 (74.1%) of formula-fed infants were delivered through spontaneous vertex delivery, respectively. Three quarter of infants 421 (77.2%) in breast-fed and 207 (75.0%) formula-fed infants groups were on SD NVP + AZT for 7 days ARV prophylaxis. There was a statistically significant difference on place of delivery and mode of delivery (χ^2 = 5.6, P = 0.02 and χ^2 = 8.7, P = 0.003), respectively between the two cohorts (Table 2).

Table 2

Delivery and clinical characteristics of infants and young children in Addis Ababa, September 2008- February 2014

Variable	Breast-fed [*n* (%)]	Formula-fed [*n* (%)]	χ^2, *df*	*P*-value
Place of delivery			5.6, 1	0.02[*]
Home	10 (1.8%)	2 (0.7%)		
Hospital	528 (94.1%)	268 (92.7%)		
Health center	18 (3.2%)	10 (3.5%)		
Others[a]	5 (0.9%)	9 (3.1%)		
Mode of delivery			8.7, 1	0.003[*]
SVD	436 (82.9%)	203 (74.1%)		
C/S	90 (17.1%)	71 (25.9%)		
Infant sex			0.8, 1	0.4
Male	298 (53.0%)	145 (49.8%)		
Female	264 (47.0%)	146 (50.2%)		
Infant birth weight			0.9, 1	0.3
< 2500 (g)	64 (12.8%)	40 (15.3%)		
⩾ 2500 (g)	437 (87.3%)	222 (50.2%)		
Gestational age			2.7, 1	0.1
< 37 weeks	84 (19.2%)	54 (24.8%)		
⩾ 37 weeks	353 (80.8%)	164 (75.2%)		
Infant ARV prophylaxis			4.9, 4	0.3
SD NVP + AZT for 7 days	421 (77.2%)	207 (75.0%)		
AZT for 7 days	70 (12.8%)	49 (17.8%)		
Sd NVP	16 (2.9%)	5 (1.8%)		
None	10 (1.8%)	3 (1.1%)		
Others[b]	28 (5.1%)	12 (4.3%)		
Immunization			0.1, 1	0.7
Not immunized	83 (14.7%)	40 (13.7%)		
⩾ 1 immunization	483 (85.3%)	251 (86.3%)		
Developmental milestones			0.7,1	0.4
No red flags	551 (97.3%)	286 (98.3%)		
Red flags	15 (2.7%)	5 (1.7%)		
Growth pattern	544 (96.1%)	281 (96.6%)	0.1, 1	0.7
Normal growth	22 (3.9%)	10 (3.4%)		
Growth flatter				

[*]: Significant at α = 0.05; [a]: Private clinic, on the street; C/S: Cesarean section; SVD: Spontaneous vaginal delivery; b: Zidovudin.

3.3. HIV infection

There was a statistically significant difference of HIV transmission between the two cohorts with incident rate ratio of 2.54 (95% *CI* 1.2–6.3, P = 0.009). About 60% of HIV infection in breast-fed infants and young children were attributable to breast milk. The overall incident rate of HIV infection for both cohorts during the follow up time was 0.17 per 1 000 infant days.

The cumulative probability of HIV free survival for breastfed infants and young children in the first 180 and 360 days were 95% and 93%, respectively, but it was 97% in the two above mentioned durations for formula-fed infants and young children. The 18 months' cumulative probability of HIV free survival in breast-fed and formula-fed infants and young children were 84% and 97%, respectively. To compare the survival probabilities of the two groups, we have used Kaplan-Meier analysis and log rank test. There was statistically significant difference on HIV free survival time between the two groups (log rank test statistics = 6.13, P = 0.013) *i.e.* the overall probability of HIV free survival in formula-fed cohort was significantly greater than the breast-fed group.

3.4. Cox regression analysis

Infant breastfed duration, mothers' duration on HAART, mothers' duration on ARV prophylaxis and father HIV/ART care enrollments were excluded from the multivariate Cox regression analysis even if these variables had a *P*-value < 0.2 on bivariate Cox regression analysis on HIV infection because there were few valid cases for those variables, so the number of missing values were high and this may reduce the power of the study if they are included in the analysis. Infants and young children from mothers who didn't take any types of prevention of mother to child transmission of HIV intervention were 4.8 (95% *CI* 1.1–22.5) times higher risk of HIV infection than to infants and young children whose mothers were on HAART intervention. Breastfed infants and young children were 3.8 (95% *CI* 1.3–11.1) times higher risks to HIV infection than formula-fed infants and young children (Table 3).

Table 3

Multivariate Cox regression analysis for determinants of HIV transmissions on selected health facilities in Addis Ababa, September 2008 to February 2014.

Variables	Breast-fed (*n*)	Formula-fed (*n*)	Crude HRN (95% *CI*)	Adjusted HR (95% *CI*)
Mothers status				
Alive	552	286	1	1
Dead	2	4	11.6 (2.8–48.8)	0.0
Fathers status				
Alive	534	276	1	1
Dead	7	6	7.0 (2.5–19.8)	1.0 (0.08–12.1)
No. of ANC visit				
1–3 visits	381	205	1.8 (0.9–3.7)	1.6 (0.7–3.7)
⩾ 4 visits	185	86	1	1
Mothers HIV/ART care enrollment				
Enrolled	510	264	1	1
Not enrolled	17	16	4.6 (1.9–11.0)	3.2 (0.7–13.2)
Mothers PMTCT interventions				
HAART	364	186	1	1
AZT + SD NVP + 3TC	132	70	0.9 (0.4–2.1)	0.5 (0.2–1.5)
Sd NVP	8	5	3.9 (0.9–16.8)	3.2 (0.6–17.1)
None	14	3	13.6 (6.0–30.8)	4.8 (1.1–22.5)*
Others[a]	28	22	2.1 (0.7–6.0)	1.4 (0.3–6.1)
Infant place of birth				
Hospital	528	268	1	1
Home	10	2	5.8 (1.7–18.9)	1.5 (0.2–9.9)
Health center	18	10	2.4 (0.7–7.8)	0.6 (0.09–5.2)
Others[b]	5	9	2.4 (0.6–10.3)	0.2 (0.01–3.5)
Infants ARV prophylaxis				
SD NVP+AZT for 7 days	421	207	1	
AZT for 7 days	70	49	0.8 (0.3–2.2)	0.5 (0.1–1.6)
SD NVP	16	5	4.2 (1.2–13.9)	2.5 (0.6–10.2)
None	10	3	8.7 (3.0–25.1)	1.6 (0.2–9.8)
Others[c]	28	12	1.3 (0.3–5.6)	0.7 (0.1–5.6)
Infant feeding type				
Breast-fed	566	0	2.5 (1.2–5.4)	3.8 (1.3–11.1)*
Formula-fed	0	291	1	1
Developmental milestones				
No red flags	551	286	1	1
Red flags	15	5	4.3 (1.5–12.1)	3.6 (0.8–15.7)
Growth pattern				
Normal growth	544	281	1	1
Growth flatter	22	10	2.5 (0.9–7.0)	0.9 (0.2–4.8)

*: Significant at α = 0.05; [a]: AZT; [b]: Private clinic, on the street; c: Zidovudin.

The cumulative probability of not developing any types of morbidity for the first 6 months of follow up period of breast-fed and formula-fed infants and young children were 97%. The cumulative probabilities of not developing any types of morbidity at 540 days follow up time were 33% and 48% for breast-fed and formula-fed infants and young children, respectively. The median time to develop any types of morbidity for breast-fed infants and young children was 506 days while it was 565 days for formula-fed infants and young children. There was no statistically significant difference on the incident rate of development of any types of morbidity (IRR = 1.25, 95% *CI* 0.9–1.7, *P* = 0.15). To compare the morbidity of breast-fed and formula-fed infants and young children, we have used the Kaplan-Meier analysis and log rank test. As a result, there were no statistically significant difference on risk of developing any types of morbidity in breast- and formula-fed groups (log rank statistics = 0.92, *P* = 0.34).

3.5. Determinants of morbidity of breast- and formula-fed infants and young children

Those variables in bivariate Cox regression with a *P*-value of < 0.2 were fitted into multivariate Cox regression after the multi co linearity were assessed. Multivariate Cox regression was stratified by mothers ANC visit, mothers HIV disclosure status and infant place of birth because of violation of Cox proportional hazard assumption. But none of the stratification was improved the final multivariate Cox regression model as compared to the model computed by excluding them. Infants and young children from mothers who disclosed their HIV status to other than their husband to their parents, brother/sister, relatives and friends were decreasing the risk of the development of any types of morbidity by 30% (adjusted HR = 0.7, 95% *CI* 0.5–0.9). Infants who did not take any types of ante retroviral prophylaxis were 3.8 (95% *CI* 1.3–10.6) times higher risk of developing any types of morbidity as compared to the reference group. Those infants who did only take SD NVP at the time of delivery had 4.8 (95% *CI* 1.9–12.0) times higher risk to develop any types of morbidity as compared to those infants who were on SD NVP + AZT for 7 days ARV prophylaxis. As compared to infants on SD NVP + AZT for 7 days ARV prophylaxis, infants on other forms of ARV prophylaxis had a hazard ratio of 5.8 (95% *CI* 3.5–9.8) (Table 4).

Table 4

Multivariate Cox regression analysis for determinants of development of morbidity in infants and young children on selected government and private health facilities in Addis Ababa, September 2008 to February 2014.

Variables	Breast-fed (*n*)	Formula-fed (n)	Crude HR(95% *CI*)	Adjusted HR (95% *CI*)
Mothers HIV disclosure status				
Disclose to husband	348	170	1	1
Disclose to others[c]	216	121	0.7 (0.5–1.0)	0.7 (0.5–0.9)*
No. of ANC visit				
1–3 visit	381	205	1.3 (0.9–1.7)	1.3 (0.9–1.8)
⩾ 4 visit	185	86	1	1
Mothers PMTCT Intervention				
HAART	364	186	1	1
AZT+SD NVP+3TC	132	70	0.9 (0.6–1.4)	1.0 (0.7–1.4)
SD NVP	8	5	1.1 (0.4–3.5)	1.8 (0.5–6.1)
None	14	3	1.6 (0.7–3.7)	0.9 (0.4–2.5)
Others	28	22	0.5 (0.2–1.2)	0.6 (0.2–1.4)
Infants place of birth				
Hospital	528	268	1	1
Home	10	2	0.0	0.9 (0.2–4.6)
Health center	18	10	4.5 (1.0–19.6)	0.8 (0.2–2.6)
Others[a]	5	9	2.8 (0.3–21.5)	0.5 (0.1–2.1)
Infants ARV prophylaxis				
SD NVP + AZT for 7 days	421	207	1	1
AZT for 7 days	70	49	1.3 (0.8–2.0)	1.3 (0.8–1.9)
SD NVP	16	5	5.1 (2.0–12.6)	4.8 (1.9–12.0)*
None	10	3	5.4 (2.5–11.6)	3.8 (1.3–10.6)*
Others[c]	28	12	5.5 (3.4–8.9)	5.8 (3.5–9.8)*
Growth pattern				
Normal growth	544	281	1	1
Growth flatter	22	10	1.8 (0.9–3.2)	1.3 (0.6–2.7)
Developmental milestone				
No red flags	551	286	1	1
Red flags	15	5	2.2 (1.0–4.5)	1.5 (0.6–3.6)

*: Significant at α = 0.05; [c]: Disclosure to parents, brothers/sisters, friends, relatives and neighbors; [a]: Private clinic, on the street; e: Zidovudin.

4. Discussion

In this study, morbidity and HIV free survival of breastfed and formula-fed infants and young children of HIV infected mothers were assessed. As a result, the 18 months cumulative probability of HIV free survival was significantly lower in the breast-fed infants and young children than formula fed counterparts (84% *vs.* 97%). This is analogous with the randomized intervention cohort study conducted in KwaZulu Natal (KZN) showed that by 18 months of age an estimated 25% of infants ever exclusively breast-fed born to HIV infected mothers would have acquired HIV infection or have died, compared to 20% of never breast-fed infants. This difference is mostly due to acquisition of infection through breastfeeding[29]. But the proportion is much lower than the current findings may be because of the study done in rural and semi-urban antenatal clinics and those mothers who chose to formula feed for their infants were visited at home antenatally and shown how to safely prepare feeds which is not an ideal circumstance for formula feed preparation. The current finding is also in line with the study conducted in rural Haiti which showed that the overall HIV-free survival rate of exclusively formula-fed infants were 93.7%, and rates of HIV transmission (3.2%) and HIV infection or death (8.6%) were lower[30]. Our finding is consistent with the study on individualizing the WHO HIV and infant feeding guidelines on optimal breastfeeding duration to maximize infant HIV-free survival showed that HIV free survival was maximized (93.0%) by replacement feeding from birth for all combinations of maternal CD4 and ARV availability. And any duration of breastfeeding led only to increased MTCT risk, without reducing the replacement feeding associated mortality. HIV free survival, therefore, declined steadily with increasing breastfeeding duration, to the lowest values ranging from 72.7% (maternal CD4 350/μL, no ARVs) to 89.0% (maternal CD4 > 350/μL, maternal ART). And the WHO notably recommended that outcome of HIV free survival reflects an implicit valuation of infant HIV infection to be "equal" to death[19].

The result of the current study is not consistent with the study done in Rwanda which showed that there was no statistically significant difference between breast-fed and formula-fed groups in their nine month cumulative HIV free survival that was 95% (95% *CI* 91%–97%) and 94% (95% *CI* 91%–96%) respectively without difference in the adjusted analysis (adjusted hazard ratio for BF: 1.2 (95% *CI* 0.5%–2.9%)[31]. There is also other studies which are inconsistent with this result [31-33].

The current findings are inconsistent with a systematic review from 18 published studies on HIV-free survival in breast-fed infants of HIV-infected women on antiretroviral treatment showed that HIV-free survival in breast-fed and formula-fed infants ranged from 87% to 96% and 67% to 97.6%, respectively[34]. Free-of-HIV survival was also significantly higher in breast-fed children (96.2%) than in formula-fed ones (86.1%). This may be due to their use of interventional cohort study on pregnant women and these HIV-infected pregnant women initiated triple antiretroviral therapy (ART) regardless of the CD4 lymphocyte count. To reduce the risk of HIV transmission at birth, all women deliveries were carried out by caesarean section, unless they had an HIV viral load below 1 000 copies/mL in the third trimester of pregnancy. The cumulative 12-month mortality was 9.6% for formula-fed infants versus 0.68% for breast-fed infants. This high number of infants' death in formula-fed group may be due to the fact that the study was conducted in a rural district of India which may be confounded by lack of adequate and safe water supply since it was a community cohort study[33].

Based on our findings, the probabilities of cumulative transmissions risk of HIV from infected mother to their child was 16% for breast fed infants and 3% for formula fed infants and young children. And 60% of risk differences in the breast fed arms were contributed from mothers' breast milk. Likewise by 18 months, an estimated 21% (19%–23%) of children born to HIV-infected mothers would have acquired HIV infection and the overall estimated risk exposure for breastfeeding over this period was 9.1 cases per 100 child-years of breastfeeding. In combination, the overall probability of remaining free from HIV infection and death by 18-month was 0.76 (0.73–0.78)[29]. In the scenario with highest MTCT risk (maternal CD4 $\leqslant$ 350/μL and no ARVs), infant HIV free survival was maximized with 3 months of breastfeeding (87.1%); beyond 3 months of breastfeeding, the risk of HIV infection outweighed the risk of mortality associated with the replacement feeding. In maternal CD4/ARV scenarios with lower MTCT risks, longer breastfeeding durations were preferred[19]. A study conducted in India showed that the effects of breast feeding and formula feeding on infant mortality, child growth and HIV transmission in children born to HIV infected pregnant women of formula-fed infants had significantly higher risk of death compared to breast-fed infants though breastfeeding added a 3.1% additional risk of HIV acquisition[33].

In this study, the median breast-fed duration was 7.3 months with IQR of 3.8 months which is inconsistent with other studies[29,35]. This may be because of all these studies had different duration of breast-fed and follow up time. Breast-fed infants and young children had 3.8 (adjusted HR = 3.8, 95% *CI* 1.1–11.1) time higher risk of HIV infection as compared to formula-fed infants and young children. In the current study it was difficult to determine the effect of mothers' CD4 count at the time of delivery for the risk of HIV transmissions, even though it shows no significant association on the bivariate Cox regression analysis for the risk of transmissions as there were only 459 (53%) of mothers who had CD4 count during delivery. But the relationship between maternal CD4 cell count around the time of delivery and risk of postnatal HIV transmission have been consistently reported by other studies.

Based on our findings, infants and young children from mothers who were not initiated to any types of PMTCT intervention had 4.8 (95% *CI* 1.1–22.5) times higher risk for the acquisition of HIV than those infants and young children whose mother was on highly active antiretroviral therapy. This result is in line with the study done in Rwanda which showed that when compared with children whose mothers did not take any ARV intervention during pregnancy, children born to HIV positive women who received HAART during pregnancy were 60% (AOR: 0.4, 95% *CI*: 0.1–0.96) less likely to be infected with HIV[36]. In this study, we assessed the overall incident of any types of morbidity which includes: diarrhea, acute gastro enteritis (AGE) with or without dehydration, pneumonia or lower respiratory tract infection (LRTI), ear discharge, oral candidacies, skin lesion, hepatomegally, persistent fever and GLP. There was no statistically significant difference on the incident rate of development of any types of morbidity (IRR = 1.25, 95% *CI* 0.9–1.7, *P* = 0.15). The current finding was consistent with the study done in South Africa[37]. But it is inconsistent with study

done in South Africa which showed that the risk of morbidity (*e.g.* diarrhea, lower respiratory tract infection, ear infection) was two times higher among those who had never breastfed as compared to those who had reported ever breastfeeding[30].

According to the ZVITAMBO trial study, all-cause hospitalization was significantly higher in the first 28 days of life (IRR 1.5, 95% *CI* 1.2–2.0) among HIV-exposed uninfected compared to HIV-unexposed infants, with a trend towards increased all cause hospitalization through 6 months of age. Hospitalization for malnutrition or diarrhea was common overall, but was not increased in HIV-exposed uninfected compared to HIV-unexposed infants. Hospitalization was 50% more frequent among HIV exposed uninfected infants in the first month of life, and mortality rates were higher over the 24-month follow-up period[38]. A systematic review and meta analysis report on optimal breastfeeding practices and infant and child mortality showed that non breast-fed children of 6–11 and 12–23 months of age had 1.8- and 2.0-fold higher risk of mortality respectively when compared to those who were breastfed. pertinent to exclusively breast-fed infants, the risk of infection-related mortality in 0–5 months were higher in predominantly (RR 1.7), partially (RR 4.56) and non breast-fed (RR 8.66) infants[39].

There was no statistically significant difference for 18 months' cumulative probabilities of not developing any types of morbidity in the two cohorts. In our study, infant and young children feedings types did not have statistically significant association with the development of morbidity which was supported by other studies[37]. In this study, infants and young children from mothers who disclose their HIV status to parents, brothers/sisters, friends, relatives and neighbors decreased the risk of developments of any types of morbidity by 30%.

The findings of this study were also interpreted by revising its strengths and limitations. Taking relatively larger sample size from a relatively longer period of retrospective follow-up and the use of both mother and infant paired data for clinical and nonclinical characteristics of the clients were considered as strength. And as a limitation, this study used routinely collected data which might have been introduced under estimation of HIV free survival due to many unrecorded cases. On the other hand, the data were secondary data whose analysis was restricted only on the variables recorded on the clients' card. Therefore, the interpretation and conclusion of the findings should take these limitations into account.

The cumulative risk of HIV transmissions during the infants feeding period from infected mothers to their infants and young children were significantly higher for those breast-fed infants and young children than formula-fed infants. As a result, the 18 month cumulative probability of HIV free survival was significantly lower in the breast-fed infants and young children as compared to formula-fed infants and young children. The majority of HIV infection occurred in the early period of breastfeeding duration before 6 months. In this study, there were no statistically significant difference for the risk of development of any types of morbidity for breast- and formula-fed infants and young children.

Providing infants ARV prophylaxis was the important determinant factors for the development of any types of morbidity for breast-fed and formula-fed infants and young children. As a result, infant who didn't take any forms of ARV prophylaxis had significantly higher risk for the developments of any types of morbidity.

Conflict of interest statement

We declare that we have no conflict of interest.

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